Praise for *The Secret Language of Cells*

"*The Secret Language of Cells* takes us on an exciting journey into a world where we can visualize elaborate conversations among immune cells, brain cells, gut cells, bacteria, and even viruses. Dr. Lieff gives a wealth of examples for his thesis that this cellular signaling is the basis of life. It is a must read for anyone seeking to understand modern biology and advanced medical science. It is equally important for those of us who wonder, as I do, how this ubiquitous information transfer in the form of cellular conversations might be related to the emergence of intelligence and consciousness."

—Ray Kurzweil, inventor, author, and futurist

"*The Secret Language of Cells* explains the complex ways that cells in the body communicate and presents a new paradigm for understanding health and disease. It also suggests new possibilities for treatment and for promoting healing. I'm pleased that my former Harvard colleague, Jon Lieff, has written this important book."

—Andrew Weil, MD, director of the Andrew Weil Center for Integrative Medicine, professor at University of Arizona College of Medicine, and author

"Through a brilliant synthesis of cellular biology, microbiology, immunology, and neuroscience, *The Secret Language of Cells* offers a lucid explanation of the marvelous intricacies of cellular life. The result is a masterful exploration of the profound implications of cellular intelligence for understanding pathophysiology, human health, and even our origins."

—William B. Miller, Jr., MD, physician, biologist, author of The Microcosm Within: Evolution and Extinction in the Hologenome, *and internationally recognized expert on Cognition-Based Evolution*

"Jon Lieff's description of cellular communication is insightful, provocative, illuminating, and engaging and provides deep and novel observations into the remarkable symphony of how life happens. Mimicking the cellular world he describes, Dr. Lieff is the great communicator and muse of living things. An inspiring and informative read."

—Ted Kaptchuk, professor of medicine at Harvard Medical School

"This journey into the dynamic realm of cellular conversations is a tour-deforce—fascinating, vital, and especially timely for understanding emerging viruses. As we learn about intelligence in smaller and smaller animals, it's not surprising that the tiniest creatures—microbes and even viruses—exhibit elaborate communication and complex decision making. Read *The Secret Language of Cells*!"

—Marc Bekoff, PhD, professor emeritus of ecology and evolutionary biology at the University of Colorado, Boulder and author of Canine Confidential: Why Dogs Do What They Do

"As a storyteller, my imagination is sparked by the insights Dr. Lieff brings to our innermost world and the mysteries at the edge of our understanding. *The Secret Language of Cells* reveals how the micro world reflects

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INTRODUCTION

THE GREATEST SECRET of modern biological science, hiding in plain sight, is that all of life's activity occurs because of conversations among cells. During infections, immune T cells tell brain cells that we should "feel sick" and lie down. Long-distance signals direct white blood cells at every step of their long journey to an infection. Cancer cells warn their community about immune and microbe attacks. Gut cells talk with microbes to determine who are friends and enemies. Instructor cells in the thymus teach T cells not to destroy human tissues.

This key to modern medical science is hidden because it is impossible for most of us to understand the best current technical journals in neuroscience, genetics, molecular biology, immunology, and microbiology. Filled with incomprehensible names of molecules, signals, receptors, and cells, the secret of cellular communication is concealed by jargon.

UNDERSTANDING THE CONVERSATIONS

Taking away the mystery, *The Secret Language of Cells* provides a clear way to understand medical research—and life itself. Explained in everyday English, the many languages of cells and how they operate are laid bare. Sections of this book focus on cells from the body, the brain, microbes, and communication inside cells between cell compartments. By describing the lifestyle of each cell, *Secret Language* makes advanced biology understandable.

And whether you speak jargon or not, *The Secret Language of Cells* will make clear the extent and significance of this pervasive communication. Perhaps, like me, you will gain a greater sense of awe about the nature of cell signaling, which we are just beginning to tap into, and how it influences the life of every organism

on the planet.

The overwhelming conclusion of the best current research is that all processes in the human body, in all animals and plants, and in microbe communities as well, are based on conversations and group decision making among cells. By understanding how determinations are made among a wide range of cells from the immune system, blood vessels, barrier cells of the gut and skin, brain tissue, and microbes, it becomes clear how cellular communication determines health and disease.

In fact, understanding cellular communication will allow you to keep up with the latest, most advanced modern medical treatments—such as new immune therapies for cancer. Experimental treatments using microbes and immune cells against any number of cancers take advantage of natural conversations among these cells. Elaborate discussions in the gut determine how microbes might affect treatments related to metabolism, weight loss, anxiety, gut diseases, food allergies, and brain diseases. Results of cellular conversations between immune cells and brain cells determine possible treatments for stress, inflammation, depression, anxiety, trauma, brain disease, and microbe invasions.

SAME LANGUAGE, DIFFERENT APPROACHES

Chapters in *The Secret Language of Cells* demonstrate the many different cells that use multiple signals at the same time. All of the following can serve as signaling devices:

- secreted chemicals
- launched sacs filled with genetic instructions
- electric currents
- electromagnetic waves
- physical contact by cells
- biological nanotubes between cells

Remarkably, all levels of cells throughout nature—humans, animals, plants, and microbes—use these same languages with the same vocabulary.

You are likely aware that neurons use one type of signal in brain circuits. Neurons produce electrical currents along an axon, which triggers the release of neurotransmitter molecules as a signal to another neuron. In fact, neurons use all of these other language techniques just mentioned—and at the same time. Neurons don't just talk with other neurons; they talk with three other types of supportive brain cells, multiple immune cells, and cells from all other human

tissues—simultaneously. In chronic pain syndromes, neurons communicate through complex connections, sometimes including ten different cell types at once. Another recently discovered neuron trick is sending messages to local immune cells sideways from the axon into the tissue, rather than at the usual connection to the next neuron in a circuit.

Neurons also communicate with brain waves. Groups of neurons vibrate together, sending particular frequencies of electromagnetic oscillations as messages to other brain regions. For messages between two primary brain memory centers, one frequency provides spatial information about the memory, and a different frequency supplies time-related information.

The science of cell signaling demonstrates that the immune system and the brain can't really be separated. Both perceive stress, social isolation, trauma, and infections and talk together constantly about all of these. The brain is built on a dynamic, but fairly fixed, structure of circuits. This "wired" brain sends signals rapidly to particular locations throughout the body. Immune cells, on the other hand, travel freely throughout tissue and blood, constantly signaling to each other, to brain cells, and to bodily organs. This "wireless brain" can send signals through blood and tissue to other locations that are hard to reach.

By reading *The Secret Language of Cells*, you will understand how the wired and wireless brains work constantly together through elaborate conversations. This type of communication between mobile immune cells and stationary nerves is described in the book as a way to explain the wide-ranging effects of acupuncture.

Another example of the brain and immune system working together occurs when the master immune regulator T cell travels into the fluid that bathes the brain. From that vantage point, T cells send signals to brain cells explaining whether there is an infection or not. Signals from these immune T cells normally stimulate ordinary cognition. When an infection occurs, T cells alter their signals to trigger "the sick feeling" we all experience when ill. They tell the brain it is time to slow down and rest so that healing can occur.

UNDERSTANDING THE BASIS OF HEALTH AND DISEASE

The Secret Language of Cells puts together and organizes a large amount of information not available in one place anywhere else. Based on the latest findings from the top scientific journals, it is a modern view of biological science whose time has come. As medical science becomes increasingly complex, many people find it more challenging than ever to understand what maintains health and what causes disease.

Each chapter of *The Secret Language of Cells* provides insight into critical new

areas of immunity, cancer, and the physiology of the brain, gut, and skin. Anyone interested in microbes; how the body and brain work; how immune, blood, and gut cells work; and how cancer works will find this book essential reading.

By following stories of each major cell type, you will understand these conversations firsthand. Cells that provide a border for an organ might seem to be boring, but in fact, lining cells in the gut have elaborate conversations and make many of the most important decisions. Large numbers of microbes in the gut talk to these barrier cells, as well as immune cells, local neurons, and each other. All through the long gut, these conversations determine which specific microbes are allowed to live as residents to help us in many different ways.

The lining cells of skin, lung, blood vessels, and brain fluid are also engaged in conversations with cells from every other part of the body. In the brain, gatekeeper cells determine which specific cells can enter the brain and which are needed to heal brain trauma and infections. Surprisingly, capillary lining cells not only line the smallest blood vessels but also have major roles in instructing each organ how to produce cells to build tissues. Special cells in each organ that produce all other cells are called stem cells, and they sit right next to capillaries. Both capillary cells and stem cells engage in back-and-forth conversations about how to supply new cells for the tissue as needed.

DAILY CONVERSATIONS AND THE QUESTION OF INTELLIGENCE

The Secret Language of Cells describes multiple kinds of cellular conversations. Cells talk about every aspect of life—where they should be in an organ, what time of day activity must occur, how big they should grow, how they can fight microbes together, how to rebuild and heal tissue, and how to cooperate to provide necessary functions for our daily activity. Conversations determine types of inflammation, how food is digested, and chronic pain. Almost every aspect of physiology is determined by back-and-forth signaling among groups of cells. Often, the discussion group is large and includes blood cells, tissue lining cells, immune cells, and brain cells, all at the same time. Microbes and cancer cells take part as well.

Conversations also occur between small components inside cells. These organelles are tiny parts of cells, just as organs are smaller parts of the body. Signals are sent between organelles, such as mitochondria and the nucleus. Some complex molecules appear to send signals as well—gathering data, making decisions, and signaling back-and-forth with organelles. Signals inside cells between organelles and molecules are much harder for scientists to observe, and these conversations are just now being discovered.

Are cellular conversations "intelligent"? Since no one can really define intelligence in nature, it is not possible to answer this question. Certainly, lifestyles of cells are complex and intriguing. Cells use back-and-forth discussions to ask questions, get answers, give feedback, gather information, call for each other, move through the body, and make decisions based on multiple inputs. Signals stimulate very specific actions, which are altered as situations change. The question about the implications of ubiquitous cellular communication explaining intelligence in nature is discussed in the concluding chapter.

THE BLOG AND REALIZATION

The central place of cellular signaling in nature dawned on me gradually. For forty years as a neuropsychiatrist, I witnessed the interactions of medical and mental events—effects of medical conditions on the brain and the actions of mind on the body. After extensive research, it became apparent that no one could say what the mind is or where it could be in the brain. This led to the question of where mind, or intelligence, might reside in nature.

Eight years ago, I began an exploration of mind in nature through my website, Searching for the Mind with Jon Lieff, M.D. Presenting detailed blog posts on the website each week was the best way for me to keep up with the most current scientific information and receive immediate feedback from readers. Daily interactions with many readers increased with a Facebook page (Searching for the Mind) and a Twitter account—@jonlieffmd. A large community of people, including top scientists, joined me in attempting to find where intelligence might be in nature.

Multiple blog posts considered remarkable functions of the human brain. Because of these, I was asked to write two guest blog posts for *Scientific American* about the close relationship of the wired and wireless brains and the creation of new cells in the adult brain. Other blog posts described amazing capacities in other animals' brains—even the tiniest. For example, bees have the ability to retain kaleidoscopic memories of five miles of travel, use abstract concepts and symbolic language, and intelligently self-medicate. Another honor occurred when a top animal scientist, Marc Bekoff, asked me to write a joint guest post on his blog for *Psychology Today*. The article described unique types of intelligence in birds, lizards, and bees, whose brains are all quite different from humans'.

In all of these different brains, the same types of vital conversations occur among cells, but in different patterns. Similar cellular conversations are also found in plants talking with microbes to build nitrogen factors. One of the most intriguing plant discoveries in the new science of cellular communication is that

almost all trees and shrubs in a forest are connected by conversations sent along long, microscopic threads of fungus cells, which function as wires. Through this internet of fungal wires, trees and other plants send signals to nourish and defend each other.

Perhaps most remarkable of all is communication among microbes. Unicellular microbes display unusual abilities for single-celled creatures, almost as if they have a brain. Somehow, they are able to make decisions from multiple simultaneous inputs. They demonstrate elaborate back-and-forth communication with each other, but, even more surprisingly, with much larger and more complex human cells.

Synthesizing and writing about the most current research from the best scientific journals led me to the startling conclusion that cellular communication is the basis of all current medical science, and of life itself. Everywhere we look, cells are talking to each other. This includes blood cells, immune cells, gut cells, brain cells, plant cells, and all microbes—even viruses, which some scientists don't classify as being alive. It became apparent to me that signaling among cells is the way biology works.

I noticed that an overarching synthesis of conversations among cells is nowhere to be found in any books or journal articles. The time had come to put forth this thesis and the overwhelming evidence—hence *The Secret Language of Cells.* It synthesizes eight years of intensive analysis of the scientific literature and makes research understandable for the general science reader.

As science progresses, more and more detailed information becomes available —with a greater ability to observe smaller and smaller events in nature. Just recently, it has become possible to observe the specific conversations among cells. Even more recently, the first signals sent between viruses have been observed.

CELLULAR VIEWPOINTS

The Secret Language of Cells is divided into four sections. Each section can be read by itself. However, reading all sections gives a deeper understanding of the interrelationships of all the cells and how physiology works in health and disease.

The first section is about cells in the body—T cells, capillary cells lining the smallest blood vessels, traveling blood cells, platelets, gut cells, skin cells, and cancer cells. While each organ is unique and fascinating, the particular cells in this section are chosen as important examples that give insight into how all organs operate through cell communication.

The second section is about the brain—neurons, three types of supportive brain cells, two types of guardian barrier cells protecting the brain, and a chapter

on the unique conversations that produce various chronic pain syndromes. The third section describes the world of microbe communication—among microbe species, with plants, and with humans.

A fourth section explains conversations inside cells—among organelles and other cellular components, such as mitochondria and protein factories. Section four also includes the description of a molecule that appears to send signals to these components. The conclusion begins to grapple with the implications of these ubiquitous cellular conversations.

SECTION I

THE BODY

CHAPTER 1

CELLS—THEY TALK ABOUT EVERYTHING!

CELLULAR COMMUNICATION is inherently complicated, with an immeasurable number of signals going in all directions at once. In the midst of billions of cells, a particular cell can rapidly make complex decisions and send signals that direct the efforts of many other cells to make our bodies work in amazing ways.

Before we delve into how specific types of cells—blood cells, gut and skin cells, cancer cells, brain cells, microbes, and more—use signals to perform their unique physiological functions, we'll devote this chapter to discussing four areas that all cells appear to converse about, which was once unfathomable to even the most ardent researchers. These cellular conversations allow each cell to function with other cells in tissue throughout the body by knowing their appropriate size, their age, the time of day, and their own location.

While it is clear that individual cells are able to use the information that is described throughout this chapter in a variety of important ways, the mechanisms by which they do so are just now beginning to be discovered, and there is still much to learn. Finding individual minuscule molecules used as signals inside cells and tissues is extremely difficult, even as advanced imaging technologies are enabling us to view ever smaller details of cells. In further chapters, it will be seen that more detailed information is becoming available for many of the cells described.

DETERMINING THEIR PROPER SIZE

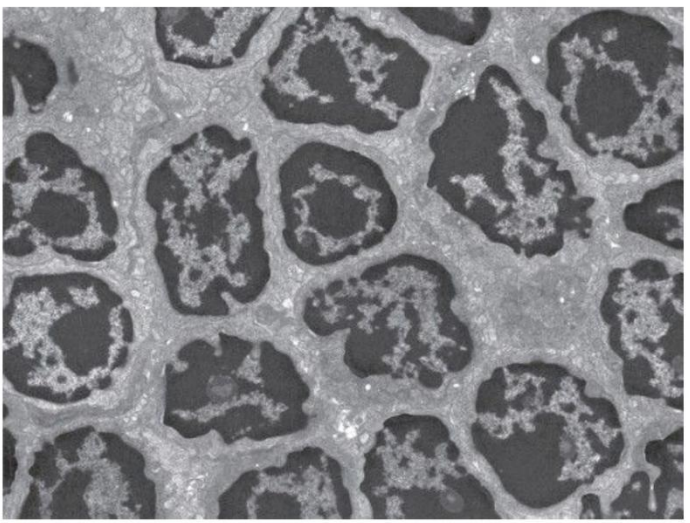
Cells come in many different shapes and sizes, but particular types of cells are usually produced within a narrow size range. For example, at least a thousand diverse types of neurons have specific sizes and shapes to fit into particular neural

circuits. In other organs, it is not as obvious why cells are certain sizes.

Many influences determine cell sizes, such as input from the environment and signals from other cells. Cell sizes can be altered by signals from food particles or from molecules that are part of ordinary metabolic cycles. Cells can also increase size in new circumstances. Pancreatic cells, for instance, increase their size to make more insulin during pregnancy. But when these cells die because of the effects of diabetes, cell size stays the same, and the number of cells decreases.

Liver cells also increase in size during pregnancy. When fat cells enlarge, they signal changes in the extracellular matrix. Lymphocytes and microglia change size when immune cytokine signals trigger them to perform different functions. (Lymphocytes, microglia, and cytokine signals are all explained in the chapters ahead.)

Organs, too, have multiple techniques to maintain exact cell sizes, but these are not yet well understood. Even with differing environmental factors, they know what size the new cells should be. Cells produced from stem cells are not the size of the stem cell itself and can be ten times larger. The number of human cells, not the average cell size, makes one person larger than another. Even during rapid growth, organs maintain cell sizes. Two pancreatic cell types that are right next to each other are maintained at different sizes. Bone cells increase size by ten times when bone is growing.



Lymphocytes in a lymph node. Electron micrograph. *(Steve Gschmeissner/Science Source)*

For an individual cell, size is determined by activity in phases of the multi-staged reproduction cycle for new cells. When new cells emerge, only certain-sized cells can proceed to the next stage in the process. For example, cells measure

protein production as they go through different phases of the cycle. These levels of proteins become signals to tell a too-small cell that it has to stay in a particular phase longer to catch up in size. Cellular size is often increased between stages of DNA copying and the separation of the two DNA strands, for instance.

Sending secreted signal molecules from one cell to another is another technique used to alter cell size. These signals activate receptors on the second cell that signal internally to the nucleus to adjust the cell's size. Signals include immune cytokine signals and growth factors (often proteins or hormones) that trigger cells to divide in order to produce new, smaller cells. Some signals increase growth and others decrease it. These factors have varied effects in different organs and are not yet well understood.

CELLS INFLUENCE THEIR OWN AGING PROCESS

Cells also can directly influence their own aging process. Cell aging has multiple distinct steps, and cells can make choices along the way. They can proactively use different rates of aging for various purposes. When healing a wound, for example, particular cells can age rapidly and die off to avoid producing severe body scars. In the fetus and during regeneration in adult organs, cells can use a rapid aging process to avoid making too many cells as a particular structure, such as an organ, is being developed. They can also preplan a tidy cleanup of dead-cell debris.

Cells use different genetic pathways to alter aging, including modifying how they reproduce. Cells can increase the rate of aging by shortening appendages (called telomeres) at the ends of DNA molecules. Cancer cells do the opposite—they enlarge the appendages to make themselves grow out of proportion.

Cells also produce an enzyme that can make the appendages longer or shorter, and new research has found a switch that turns this enzyme on and off. Multiple internal signaling pathways trigger the switch. These are pathways related to the repair of damaged DNA and they provide protection from destructive oxygen-based molecules produced in various metabolic processes that are related to cell stress.

Other major influences on cellular aging are pathways related to preprogrammed cell suicide, and these pathways are housed in mitochondria, the subcompartment of cells that provides energy and other important functions. The preplanned cell suicide pathway is used in a variety of circumstances in which maintaining the cell would be dangerous to the organism, such as a cell that has been infected by too many viruses and could spread infection.

With internal signals, cancer cells avoid triggers from mitochondrial metabolic pathways that stimulate the suicide pathway, enabling them to live much longer.

With chronic stress, the opposite occurs in which cells use alternative metabolic pathways, triggered by mitochondria, to self-destruct. Also, immune signals can alter the normal cell-suicide mechanisms.

Two types of cell aging exist—acute and chronic. Acute aging is highly regulated during wound healing and in embryos to eliminate cells when their jobs are done. Signals are produced that stimulate aging for a particular group of cells in a section of tissue, but not the entire organ. They can trigger programmed cell-suicide pathways. Targeted cells rapidly age and die. This stops excessive scarring and other problems in the repair of organs, such as the liver.

Chronic aging occurs with cellular distress over time. It is random and generally considered to be "natural" cellular aging. For example, neurons that do not divide and can live for a century gradually accumulate random DNA damage and are eventually hurt by immune cytokine signals and inflammation. Aging cells gradually increase overall tissue aging by making it less functional. Then the entire body ages when cells stop multiplying, causing problems for the entire organism. Aging cells damage stem cell niches and destroy extracellular matrixes. Faulty cells impair structures. Aging cells stimulate damaging inflammation and send signals to make other cells begin to age. Signals for cellular division can stem this aging briefly. However, in the end, many stressors cause deterioration.

CELLS KNOW THE TIME OF DAY

Every cell has its own clock, and each type of tissue has its own specific set of internal clocks. Signals from the central brain clock coordinate physiological functions, such as metabolism and immune responses, with clocks in cells and tissue.

Single cells coordinate with the brain's central clock as it responds to light and darkness cycles, bodily movements, and cycles of eating and fasting. Genetic loops in individual cells create oscillations that sync with other bodily rhythms. The brain coordinates and plans for specific activity related to the environment with these signals. Signals from the central brain clock to all cellular clocks anticipate the major activities of the total organism, such as eating and sleeping.

The first individual cell clock in evolution was developed in bacteria two billion years ago, and this was based on sun availability. In addition to enabling these bacteria to produce energy by photosynthesis, sun rays break DNA. At the same time, most cellular DNA repairs occur when the sun is bright. The first clock allowed microbes to plan ahead with resources for DNA repair when the sun was brightest.

Clock mechanisms and signals are complex and not yet fully understood. A

mechanism in the gut that coordinates the cycles of two cells was discovered recently. Friendly microbes living near gut cells move in a timed pattern—a micrometer to the left, then right, then back. Back-and-forth signals from each position keep the microbes in sync with the cellular rhythms of the nearby gut lining.

An individual cell's clock mechanism is based on timed feedback loops of interacting genes. Clock genes, components of the body's internal timekeeping system, are both stimulated and inhibited by RNA and protein molecules. A gene is triggered, producing a protein or RNA, which then triggers a second gene in the circuit. The second gene product stimulates a third gene, and so on. These events form a cycle that lasts twenty-four hours.

Molecular tags are an important type of signaling device described throughout the book. Tags placed on proteins to protect DNA are also part of these clock loops. Tags can open or close the availability of particular genes that produce RNAs and proteins related to clock functions.

While all cells have the same basic genetic clock machinery, various RNAs and proteins specific to each type of cell and organ are signals that produce various clock functions. A huge amount of all RNAs—at least 10 percent—are related to tags and signals for clocks. Multiple layers of genetic regulation influence these cycles. For example, very recently a new form of regulation was discovered that alters three-dimensional structures of the DNA molecule in the nucleus. When the structure changes, it alters how physically close particular genes are to each other. Bringing certain genes near each other can synchronize clock functions.

Multiple influences affect clock rhythms. Signals from metabolic cycles alter specific RNAs and proteins to influence clock genes. Various chemicals in particular organs affect clocks in different ways. Global factors, such as temperature and other environmental conditions, alter gene function. Many of these complex clock signals for individual cells are not yet understood.

When tissue cannot sync with the central brain mechanisms, illness can occur. One issue that needs to be addressed is our twenty-fourhours-a-day, seven-days-a-week online culture, which pays no attention to the rhythms corresponding to daylight that were established in our distant evolution. Multiple other influences on our bodily clock functions are not yet well understood. For example, we don't understand the clock cycles in the liver and pancreas, which operate on opposite schedules. We also don't know how cancer cells are able to respond to particular rhythms to help them grow.

CELLS TALK ABOUT THEIR LOCATION

Cells need to know where they are in order to make multiple decisions. For example, a white blood cell needs to know its current location when traveling to an infection at another location. Cells near an infection send signals to these traveling immune cells along blood vessels, which then provide the directions for travel. This type of signaling for traveling white blood cells is described in chapter two.

Importance of Gradients

For cells in a developing tissue, location is often derived by using a chemical gradient as a measuring tool. In a fetus, for instance, a traveling neuron or stem cell must know where it is and where it must end up in the developing brain. Also, when cells participate in the growth of an organ or a limb, they need to know how they fit into the final shape, such as determining where the edges are.

When we measure something, we use a measuring rod that spans a distance. Cells can measure the distance that certain molecules have traveled, such as measuring these chemicals across groups of cells and the spaces in between. Cells located throughout the gradient determine where they are by picking up the gradient molecule with receptors, which measure the concentration of the molecule at their position. But for this measurement to be accurate, the gradient has to be steady and not fluctuating.

Establishing a steady state in a molecular gradient is based on many different factors, including the rate of molecular production, how rapidly the molecule diffuses through the tissue medium, and the rate of elimination of the gradient molecule when it is picked up by various receptors on cells. Other influences, such as temperature, metabolism, and inflammation, can affect gradient levels as well.

For a growing organ, a row of cells can produce gradient molecules at the same rate. Every cell in the path of the gradient takes up the molecules with receptors. Signaling molecules that form chemical gradients trigger particular genes inside the cell to determine the cell's actions in relation to the growing tissue. This technique is used in forming a fly's wing, for example, where signals from cells at the center of the tissue continue to stimulate new cells until there is a steep drop-off of the gradient that determines the edge. Gradients are an important way that body organs and types of tissue of very specific shapes are formed, but scientists are just learning exactly how this happens.

Gradients, Retinoic Acid, and Signaling

One important gradient that is beginning to be understood forms the structure of the fetal brain. It is based on various levels of retinoic acid, which is produced in two steps from dietary vitamin A picked up by cells. This metabolic pathway that produces retinoic acid is highly regulated by molecular signals, which makes maintaining the gradient and the cell's calculations easier.

Regulation involves feedback loops of various proteins that regulate the multiple enzymes synthesizing the gradient molecule. In addition, cells produce a variety of diverse protein receptors with different sensitivities to eliminate the gradient molecule. These varied receptors are also regulated by feedback loops. In laboratory experiments, when the amounts of ingredients are altered, these cellular pathways adjust to maintain the gradient and produce the precise receptors needed. Somehow, neurons use this information to find their place in the developing fetus and build the brain precisely.

Stem cells in the fetus also compare the retinoic acid gradients with gradients of several other molecules. Cells can switch between measuring the two different molecular gradients. One cellular process is maintained until the switch occurs, and then the other begins. This recurs until the cell eventually makes a decision based on information from both. Stem cells use this mechanism to decide whether to divide in a particular spot in the developing brain. It is not yet clear how the switching technique is regulated.

It is quite remarkable that cells are able to know the exact shapes of organs, perform these location measurements, and send signals about these measurements. It is not yet understood how all of this works. But what is clear is that the daily maintenance of all tissue structures in the body is dependent on measurements and signals. As more is learned, perhaps we will find a way to exploit the stimulation of these signals to rebuild damaged organs.

CHAPTER 2

SIGNALS FOR MIGRATING WHITE BLOOD CELLS

AN ABUNDANT VARIETY of white blood cells respond to immune cellular conversations that identify invasions of microbes and injuries to tissues. These problems can be in skin, kidneys, liver, brain, lungs, or gut, among other organs. The first line of defense includes platelets, local capillary lining cells, and cells located in damaged organs. They begin the fight by first calling for help. Later, other immune cells and even neurons join in. A large number of white blood cells respond as fast as possible.

The most prominent white blood cells are neutrophils, which contain vesicles with large amounts of toxic molecules to fight microbes, scavenger cells living in blood and tissues, and lymphocytes (discussed in the next chapter). Responding to specific cellular signals, white blood cells are called to address trouble spots. Travel is not always easy, and their tasks are not simple when they arrive at the site. But they manage by using complex navigation modes to transit through drastically different environments, sometimes without nutrients and oxygen. They need constant help via signals from many other cells for these journeys.

RESPONDING TO AN EMERGENCY

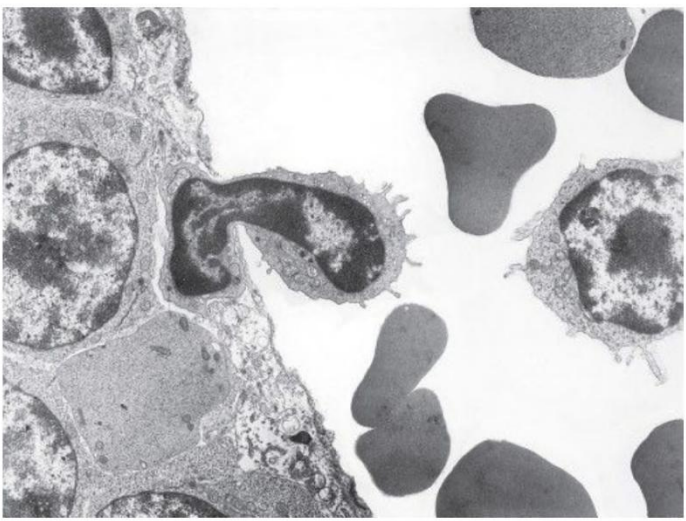
The first phase of signal and response involves getting to the site. As white blood cells start to travel, they also join in the signaling by sending their own messages for more reinforcement cells to follow. Depending on the need, messages from tissue, capillaries, and traveling blood cells may tell bone marrow to trigger production of new cells. The assembled army is soon marching through blood and

tissue.

White blood cells produce diverse receptors to receive signals related to multiple aspects of this trip. Signals from T cells alter other white cell behavior for the ensuing battle. Signals stimulate production of particular toxic molecules to kill the identified microbes. Because some signals only last a short time, tissue and cells that make up capillaries need to continue repetitive signaling until enough helper cells arrive at the site. Different situations require varied responses, such as those for trauma or infections. Infections need a large number of white blood cells. But in a clean wound, too many white blood cells can cause more problems.

Traveling cells keep up chatter with capillaries that are calling for help from the site of infection or damage. They also reach out to cells that line the larger blood vessels for assistance along the way. Cells in their path use chemical gradients to attract or repel them. Signals from these conversations create "sticky" protein molecules that enable the blood cells to grab onto lining cells as they move. This allows travel even against the flow of blood. Traveling cells may tether themselves to a lining cell and even rest there for a while. They may roll or crawl along lining cells and also grab on, as if pulling themselves up a rope.

Quite a lot of communication is necessary to get white blood cells to the problem area. Conversations include not just capillary lining cells but also the lining cells in gut and skin, neurons, supportive brain cells, and even molecular signals from the matrix outside of cells. Neuronal signals provide regulation of blood flow by directing it to the distressed region as much as possible. Neurons also signal to all local cells that white blood cells are coming.



After permission is given, a white blood cell exits through a lining cell. Electron micrograph. *(Don W. Fawcett/Science Source)*

Many Ways to Travel

White blood cells are masters of traveling within the extracellular matrix in between cells. They move with coordinated actions produced by dynamic internal scaffolding molecules. These flexible, rapidly changing cytoskeleton filaments constantly alter internal cell structures to produce "arms" and "legs" that propel white blood cells forward like amoebas. The filament structures also use motors that produce cellular movement similar to the motors that propel lengthening and shortening in muscle cells. These motors can alter the force in a variety of different ways needed for diverse terrain. Methods include rolling, tethering, and firm attachment.

Traveling cells can fluctuate between different techniques, such as pulling or pushing the cell body forward, in order to navigate on different surfaces—some sticky and others smooth. The leading edge can move in a gliding fashion. The filament structures in the cell are rapidly shoved to the front leading edge to provide an enlargement that moves the cell forward. After this, motors working on the fibers pull the rear to catch up. Motors also pull the nucleus along. In addition, external attachment molecules between the blood cell and capillary pull the cell forward.

Another travel technique uses various types of internal motors that push the cell's inner substance forward into multiple protruding round areas, propelling the entire cell headlong. For this, molecular motors can also reach outside of the cell and attach to the lattice of molecules between cells, with molecules alternately grabbing and disengaging in rapid succession. Basically, the cell walks forward stepwise with two "feet" below that alternately adhere and release at different places.

By rapidly changing shape, white blood cells move quickly through many different environments. The round cell transforms into a polarized flat directional cell with a distinct front and a rear. In low-density matrixes, they use less motor activity. When tissue is compact, they need stronger motors in the rear. To get through a small crevice, they shrink and elongate the nucleus.

T cells (described at length in the next chapter) use all of these traveling techniques and more. They must find a small particle in large spaces, often with few helpers. They need even better homing signals and movement techniques in dense inflammation sites. T cells scan an entire region and can use simpler attraction techniques than other white blood cells. T cells also elongate their shape in unusual ways to move in even tighter matrixes. Unlike most other white blood cells, T cells change shape often and can find paths where they can become round again.

Arrival at the Site

One main category of white blood cells is scavenger cells, responsible for destroying bacteria and eating other foreign particles. There are several different types of scavenger cells—some embedded in tissues and others circulating in the blood.

When trauma has occurred in tissue—a wound in the arm, for instance—scavengers immediately respond by gobbling up some of the microbes that have lodged in the wound. As they do so, they signal to the lining cells in the nearby capillaries that an infection has occurred. In turn, the lining cells usher in neutrophils, the most abundant type of white blood cells that are considered "first responders." Floating around the blood, neutrophils get the signal that danger is occurring, attach to the capillaries, and squeeze through the blood vessels to help attack the bacteria. In order for the neutrophils to get out of blood vessels and directly into tissue, signals from other immune cells have to loosen the barriers that normally contain the blood vessel. Even more signals are necessary in blood vessels near the brain, which have the most elaborate barriers.

Getting themselves out of the blood vessels and into tissue is just the beginning for the neutrophils. Traversing through tissue might require them to use other special travel techniques that rely on helpful signals from local cells. When more traveling cells finally arrive at the infected or injured site, neutrophil signals enable them to form clusters near the epicenter of the problem. First, several scouts move in, producing a strong signal for others to follow. Neutrophils relay these signals to those behind. Clusters build until several hundred cells have joined together into a mass. With larger numbers of cells, the entire area can be walled off.

SWARMING NEUTROPHILS

Neutrophils in the tissue have a wide range of attack options. In some situations, neutrophils form large moving clumps of cells that have been likened to insects swarming around a hub. As part of neutrophil swarming, they remodel a dense extracellular matrix, allowing clusters of cells to stay close to the action. Signals help coordinate clusters for positioning that can wall off the trouble spot. Some of the original cells in the center die, sending further signals that enlarge the swarm.

Neutrophils can each produce more than three hundred different toxic chemicals, store them in sacs inside themselves, and then release them against a target. These sacs are called granules because they looked like grains when first seen by microscopes. Another tactic uses enzymes that cut proteins to remodel

the lattice between cells. Products of these incisions can also serve as new signals to call for help.

Toxic molecules to kill microbes often provide chemical reactions based on the instability of oxygen in the body. Oxygen is highly reactive and is dangerous if not carefully monitored. Producing unstable oxygen-based molecules that are highly reactive is a tactic to increase inflammation and to kill more microbes. These oxygen products are also used as regulatory signals, letting immune cells understand what is occurring. Another neutrophil technique is to make special traps for microbes. These netlike structures, which consist of DNA pieces and proteins, grab onto microbes to help destroy them.

Killer T cells use many different strategies in their work as well. They can chase viruses by dividing into two cells that move in different directions at once. One type grows many long arms and crawls between cells to slowly find cells infected by the virus. To maximize their search, sometimes T cells accumulate information by briefly touching multiple cells, one at a time. T cells store this gathered information from contacts by placing molecules in their nuclei, which produces more accurate navigation.

TAMPING DOWN ACTIVITY AND CHRONIC INFLAMMATION

As the fight with microbes is won, new signals provide different messages. They can tell white blood cells to slow inflammation in various ways, leave the scene, or, in some cases, help maintain chronic inflammation. Just as T cells produce special regulatory cells to stop excessive scarring, all white blood cells at the inflammation site tamp down their activities when the battle is over. Some signals for this endgame come from dying and dead neutrophils. These instructions alert scavenger cells to eat the debris and switch from the aggressive mode that produces inflammation to one of healing and repair of tissue. When there are too many blood cells left over, signals stimulate them to commit a programmed form of suicide.

Billions of white blood cells are produced each day. Until recently, they were thought to live only six hours, and most were thought to die by suicide. Recently, it was found that a select group lives much longer (perhaps months, although research is just emerging). Once inflammation is under control, new signals tell this surviving group to reverse direction and travel backward out of the inflammation site. A wide variety of signals from inside the wound and from the blood vessels shows that it is time for white blood cells to pack up. Cleanup scavenger cells tell them by direct contact or via secreted signals.

A small group of longer-living neutrophils travels back into the blood, where

signals from other cells stimulate them to go work at another trouble spot. Capillaries on this new route and tissue cells at the new site take up the signaling. Finding signals that cause neutrophils to leave the scene of injury is a current research focus. It will help scientists develop medications to control dangerous infections by removing white blood cells that could contribute to debris at the wound site.

Even more recently, cellular conversations have been found that tell an even smaller group of neutrophils not to kill themselves or leave the site, but to stay and maintain chronic inflammation. Diseases of chronic inflammation have been closely tied to abnormal activity of the scavenger cells that are supposed to mop up the site when the battle is tamping down. Now, these diseases are also found to be related to neutrophil activity going awry.

Before, it was thought that both dead and dying white blood cells secrete signals, directing scavenger cells to eat them. As it turns out, there is a big difference between a dying neutrophil and a dead neutrophil. Only dead cells send these signals to tamp down activity. Dying cells send a recently discovered type of signal to maintain inflammation indefinitely.

Signals from dead white blood cells help to avoid scars and chronic infections. But when they are constantly dying for a long time, neutrophils continue to push for more aggressive behavior rather than cleanup. This produces chronic, damaging inflammation. Understanding these conversations of slowly dying cells is vital for future treatments of atherosclerosis, arthritis, and bowel disease.

Surprisingly, a friend of the white blood cell is the humble platelet cell, which, it turns out, is much more than a plug for bleeding. Chapter five shows how, even without a nucleus and DNA, tiny platelets are able to engage in elaborate communication, helping white blood cells migrate as well as regulating responses to inflammation.

CHAPTER 3

T CELLS—MASTERS OF IMMUNITY

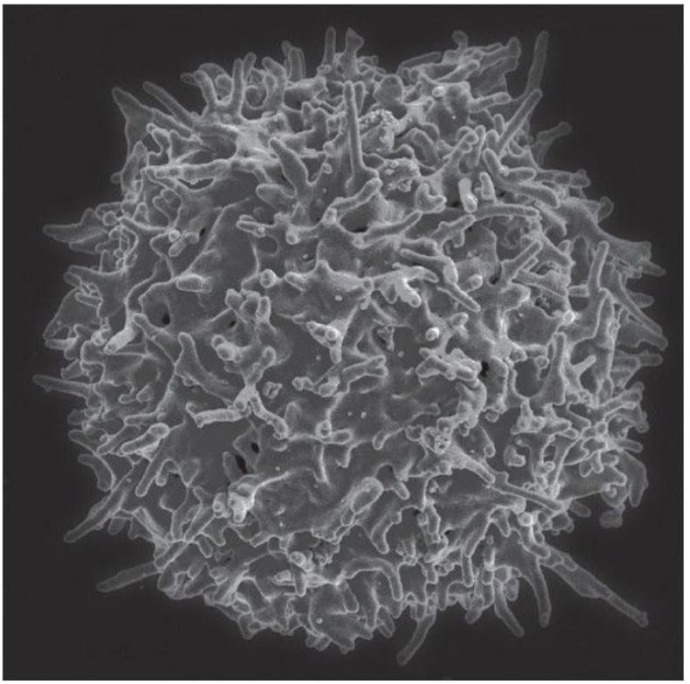
T LYMPHOCYTES—white blood cells known as T cells—are the master cells of the immune system. They communicate with almost every other cell in the body. T cells constantly converse among themselves and with the many different kinds of cells they directly influence, including all other immune cells, blood cells, lining cells, and even some friendly microbes.

All organ cells turn to the T cell for help with trauma and infections. T cells chase and kill microbes and attack cancer cells. T cells also morph into a wide range of subtypes that analyze situations, attack problems, and support other cells in a variety of ways. They can rapidly become a large army of fighting cells. T cells are also able to remember for years the particular signals that were successful in defeating a viral invasion.

A primary job for T cells is to evaluate pieces of material that shouldn't be in the body—microbes, cancer cells, debris, and chemicals. When they find these foreign molecules on the surface of other cells, T cells organize campaigns to eliminate them by directing the activity of traveling blood cells, other immune cells such as B lymphocytes (B cells), lining cells, neurons, supportive brain cells, gut lining cells, skin cells, and many other cells.

A NEW FRONTIER FOR FIGHTING DISEASE

Scientists are largely still learning about T cell communication and the sources by which this communication takes place. Researchers hope that new discoveries will allow the development of a wide range of new medical treatments to stimulate actions against infections and cancers by modifying these natural conversations.



A healthy T lymphocyte. Electron micrograph. *(NIAID/Science Source)*

Some approaches could involve producing entirely new signals and receptors placed on cells. Treatments could include delivery of signals via microbes that normally talk with each other and with cancer cells. Intercepting signals from T cells will be vital for the treatment of a host of autoimmune diseases. By modifying T cell behavior via new signals, new treatment avenues could open up for diabetes, arthritis, pain, lupus, and multiple sclerosis, among many other diseases.

T cells can now be energized by inserting engineered viruses or other microbes inside them. We call these kinds of T cells superkillers. This genetic engineering technique uses microbes to stimulate new receptors, which unleash a heightened immune response to eradicate cancer and other diseases.

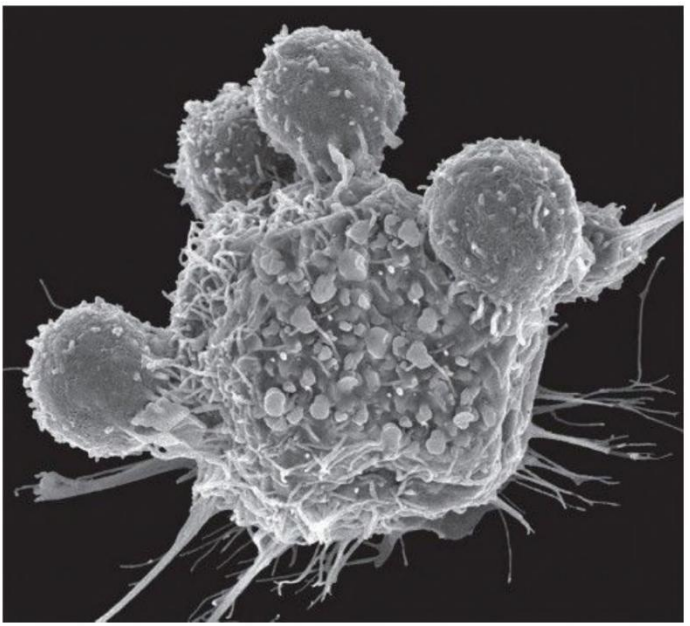
In general, however, it has been found that T cells are naturally better at fighting microbes than cancer. This is because fighting an infection usually involves one intense battle. For cancer, with multiple mutated stem-cell subtypes and various stages of development, a longer, more sequential war must be waged. T cells often become exhausted in such a prolonged battle. Future research could strengthen T cells for a longer-lasting, multifaceted approach to attack various cancer subtypes during multiple stages of the cancer life cycle.

Researchers hope new discoveries into the ways that internal T cell signals

alter their own behavior will also lead to medical treatments for food allergies and even cancer. T cells can be very aggressive in producing inflammation and then change entirely to tamp down inflammation activity. This progression from aggressor to helper occurs when a microbe infection is neutralized or after traumatized tissue is rebuilt. The change can halt further damage to tissue that could lead, for example, to scar tissue.

After the battle is over, T cells alter their external signals to modulate the behavior of the entire variety of cells engaged against microbes. This same type of T cell regulatory behavior occurs on a daily basis in the gut, where T cells inhibit immune cells from attacking food particles and friendly microbes.

Understanding how these signals work for these regulatory actions could enable treatments for runaway infections and for alleviating food allergies. On the other hand, finding ways to alter this signal behavior could enable T cells to fight a full battle for a longer period of time as a cancer treatment. In addition, scientists have recently discovered that T cells leave long-lasting offspring at the site of a battle with microbes. These memory T cells stay vigilant in the trouble spot for years. Future treatments based on these memory cell signals could enhance the prevention of infections of all types.



Four T cells fighting a larger cancer cell. Electron micrograph. *(Steve Gschmeissner/Science Source)*

FROM BIRTH TO GRADUATION

T stands for thymus, which is a small but central gland that contributes to both the lymphatic and endocrine systems. The thymus, little more than two inches long and weighing about a half ounce at its peak, is situated in front of the heart and behind the breastbone. It consists of a left and a right lobe, which in turn consist of smaller sections called lobules, which account for the gland's bumpy appearance.

Starting life in bone marrow, T cells migrate to the thymus and other lymph tissues. In lymph tissue, dozens of different T cell types can arise. In the thymus, T cells undergo their extensive education with a gradual maturation into fully functioning masters. Only 2 percent graduate. The other 98 percent that do not meet the exact qualifications required by a series of checkpoints are eliminated by their instructors.

After T cells are tested and approved, graduation consists of a change in their status. Mature T cells are released to investigate each cell they meet while traveling in all regions of the body. These T cells can rapidly change themselves into multiple varieties of cells and can trigger various kinds of inflammation. They can transform into fearsome killer cells that fight disease wherever needed in the body.

The Training Process—Meet the Lineup of T Cell Teachers

Thymus teacher cells are a distinct class of lining cells and are different from any other cell in the body. These thymus lining cells organize the structure and functions of the thymus and provide the "training" and pruning of young T cells.

Teacher cells exist in two broad categories, each with many subsets that are just being discovered. One category organizes the outer thymus region into a precise, brainlike, three-dimensional structure of concentric circles. The other exists in an amorphous center region.

It appears that most T cells need training from both types of teacher cells. Some receive training in the outer layers first and are then transferred to the center. Others start in the center and then travel to the edge layers.

The outer thymus cells first attract immature T cell precursor cells that begin to travel through the blood from their birth in the bone marrow. The teacher cells send specific signals with instructions on how to travel to the thymus and enter.

One unusually large teacher cell in the outer region is called a nurse cell. It takes up a student T cell entering the thymus, engulfs it, and forms a cage around it, separating it from the rest of the thymus environment. In this isolated state, the nurse cell tests the immature T cell by bombarding it with a wide variety of signals. In response, the student begins to produce a large number of different

receptor types.

Cells that fail at this point are liquidated in the garbage-disposal compartment of the nurse cell. Others are rerouted into a less complex pathway to become regulatory T cells, which focus on specific tasks, rather than a full master T cell that is able to respond to almost any stimuli. Student cells that pass tests in the periphery of the thymus are then sent into the center, where the second set of teacher cells also has several unusual cellular characteristics.

Just as there are a large number of different T cell receptors and an almost infinite number of different antibodies, recently it was found that there are many types of teacher cells in the center of the thymus. These teacher cells use their DNA to maximize training for the T cells. Although most cells use only selected genes to function at particular moments, these special teacher cells in the center of the thymus use all of their genes at once to produce all of their possible proteins.

This deluge of protein molecules from a wide range of teacher cells greatly challenges the T cells to produce more and more receptors. With so many teacher cells testing individual T cells—each type bombarding the student cell with a plethora of proteins—it is clear that T cells undergo rigorous training before they begin their ultimate jobs. But the most important part of the training is that T cells must understand not to attack normal human cells and tissues while they search the body for trouble. When T cells are able to identify the difference between "foreign" molecules and "self" molecules, they avoid causing autoimmune diseases.

Antigens and Affinity

A molecule that could trigger an immune response is called an antigen. When the molecules advertised on the surface of a cell are normal, they are called "self-antigens." Self-antigens placed in a special groove on the outside surface of cells tell T cells that this cell has no problems and there is no foreign material inside, such as a virus. Self-antigens signify a normal cell.

It is a T cell's most important function to not harm normal human cells, while actively destroying microbes, cancer, and debris. If T cells don't get self-antigens right, they attack normal human cells, leading to tissue destruction and autoimmune diseases.

The thymus exam system is, in fact, more subtle than just turning a switch on or off or providing a yes or no answer about self-antigens. For simplicity, the training is often described as a simple dichotomy of the cell knowing whether to respond to foreign molecules with a dangerous attack or not respond at all to self-

molecules.

But the process is more complex. To fulfill their multiple functions, T cells must respond to all cells, but in different ways. T cells have to maintain an attraction to all normal human cells to continue communication while not attacking. For example, they must be attracted to neurons enough to engage in back-and-forth conversations about illness but not attracted enough to do damage. Most immune signals that T cells produce are called cytokines, but they also use neurotransmitters to converse with brain cells. When conversing with T cells, neurons use both types of signals as well.

It is not just the ability to recognize self or not-self that is measured by T cell instructors, but even more importantly the ability to measure the intensity of attraction—called affinity—for normal cells that allows graduation. If attraction doesn't exist at all, T cells can't communicate well enough with these cells. If attraction is too strong, problems will arise, such as tissue destruction. The amount of attraction has to be just right—not too weak and not too strong.

After graduation, T cells do their job, wandering through blood, lymph, and various types of tissue searching for molecules in the surface grooves of all cells. Unfortunately, after taking a series of exams in the thymus university to test their ability to make these receptors, most T cells fail. Failure to advance is often not just because they cannot produce a large, accurate range of signals and receptors. Many are rejected because they have a poor rating on their ability to avoid harming human cells during attacks.

Recent studies have shown that some of the rejected cells are rerouted into different pathways to produce regulatory T cells instead of the master regulators (as described earlier in the chapter). Future understanding of the signals used for this selection process could allow alterations of T cells to fight a wide range of diseases.

PRODUCING SIGNALS

The T cell builds the largest repertoire of receptors and signals—more than any other cell—for its myriad functions. It is not known how T cells can build so many varied molecules and then adapt them to changing conditions. But it does involve regulating multiple layers of genetic processes to produce unique proteins and then modifying them. Many of these levels of genetic activity occur in all cells, but T cells have the additional ability to edit sections of their own DNA.

As is well known, DNA code produces a particular RNA strand based on that code. A protein is then constructed from this strand of RNA. Other RNAs that are produced from DNA code don't lead to proteins but instead perform other actions.

Some produce factories that manufacture proteins, some carry amino acids to the factories to build proteins, and others are used as signals against microbes and for other purposes. Forming RNA molecules from the DNA code and then manufacturing proteins involve multiple layers of complexity that are not yet fully understood. People used to think that a gene was a single strand of DNA that produces code for one particular RNA and then a protein. In fact, the DNA code that is gathered for the RNA template can be taken from one "gene" and multiple other regions.

Once produced, the RNA template, called messenger RNA, has sections deleted, and the remaining code is sewn together into one usable messenger RNA strand. Once this messenger RNA molecule is produced, it is then further edited in multiple ways without any obvious direction. This single strand of messenger RNA can be cut and pasted in different ways to produce a large number of different proteins. After this editing of the messenger RNA, signals and tags modulate the actions of all the other types of RNAs. Once proteins are produced, they are also tagged and modified in various ways.

Although these editing and modification steps are used by all cells, T cells are one of only two cells that can also self-edit their own strands of DNA to produce totally new types of receptors and signals with entirely new arrangements of DNA code. By editing their own DNA, T cells can produce receptors to respond to newly evolved viruses and microbes, poisons from the environment, and synthesized chemicals that human bodies have never encountered before.

This DNA editing process is complex and tightly orchestrated, with at least ten completely different steps, using a series of large enzymes in sequence. Sections are cut from three regions of their own genes and are sewn together in different ways to make brand-new receptors.

In addition to receptors, T cells produce a wide range of signal molecules that are transmitted to other cells in a variety of ways. Most often, signals are released into the tissue between cells or in blood vessels, where they travel to their target. Signals can also be wrapped in a small sac and launched to their destination. Another tactic is sending signals via tiny protein-based tubes built between cells. T cells can also communicate by direct physical contact between cells with rapid back-and-forth exchanges of molecules.

The only other human cells able to edit their own DNA are B lymphocytes, which use a similar sequence of enzymes to readjust their own DNA in order to produce antibodies. But B cells need T cells to produce the most effective antibodies.

CONVERSATIONS WITH THE BRAIN

While stationary connections between neurons in brain circuits make up the "wired brain" for direct communication to distant locations, traveling T cells can be seen as a "wireless system" that directly communicates with the brain. Neurons and T cells are always talking and working together to keep the body healthy. They both respond to infections, foreign material, trauma, perceptions, and stress.

It is well known that cells in organs talk with their local neurons and traveling immune cells for many reasons. But it has recently been learned that frequent conversations also involve elaborate long-distance communication between immune cells and brain cells. This can occur via secreted signals in the blood or brain fluid or by stimulating local neurons to signal to distant brain circuits.

One example of this signaling phenomenon with local nerves involves T cells that lie in tissue between local neurons. Signals from T cells traveling in the tissue to nearby neurons trigger actions in distant brain circuits that produce an acupuncture effect in an unexpected organ. (This is further discussed later in this chapter and in section two in relation to chronic pain syndromes.)

In the past, conversations between T cells and brain cells were known to be important for infections in the brain, but little research was available to show exactly how these conversations occur. With more advanced lab equipment, scientists now have the ability to pick up distant small molecular signals, which have been found to be vital for global regulation of cognition in normal conditions, as well as mental changes related to stress, depression, and the "sick feeling" during illness. In the future, discovering more of these relevant signals could enable completely new types of psychiatric treatments by intercepting and modifying these communications.

When all is well, T cell signals tell the brain that conditions are safe for normal activity. The T cells do this with a constant pulse of signals to the brain, which enables normal mental processes. The brain responds with its own signals to let the immune system know that everything is okay.

Upon finding microbes, infections, or trauma, T cells change their messages to the brain to signal that the body is sick and the brain must slow it down to rest and conserve energy while fighting the infection. This conversation triggers the "sick feeling" of lethargy and achiness. When the infection has ended, only T cells have the authority to signal that it is okay to restore normal cognitive functions.

Until recently, the brain was considered to be free of immune cells—it was incorrectly called "immune privileged." With better microscopes, scientists can observe immune cells in the cerebrospinal fluid (CSF) that bathes and protects the entire brain. This fluid was thought to function only as protection for the brain when jostled. But now it is known to be a river of wireless communication, with signals coursing throughout the brain from all regions and all types of cells. Also, it is now known that at most times there are about 500,000 T cells in the CSF along

with smaller numbers of other immune cells.

Into the Brain and Through Other Difficult Terrain

T cell conversations with gatekeeper cells determine what is allowed to cross between the sheltered brain fluid and the busy blood vessels. Other immune cells approved for entry into CSF all have particular jobs in relation to T cells. One type of white blood cell picks up molecular samples of microbes, cancer cells, or debris and presents them to T cells for evaluation. B cells are there to make antibodies when needed to fight infections.

If there are no T cells in the CSF to direct these other cells, inflammation is triggered. Other immune cells don't understand the subtleties of living in the brain as T cells do. So, T cells must actively suppress the actions of all these other cells to keep them from producing dangerous inflammation. Conversations to suppress inflammation occur constantly among T cells and neurons, using both neurotransmitters and cytokine signals.

CSF circulates around the brain, drains along nerves, then joins lymph nodes and blood in the neck. T cells travel through the entire brain fluid, leave the brain, and go to the neck lymph nodes looking for suspicious particles to evaluate. They gain permission from gateway cells over and over as they travel in and out of the CSF and to other parts of the body.

Signals from other cells also help with T cell travel. Local tissue cells and blood vessel cells send supportive and directional signals along the way, both in the brain and throughout the body, to further assist in this difficult journey to the lymph nodes. Using these signals, T cells travel to lymph nodes across a difficult terrain—through dense scaffolding in between cells and often without enough oxygen. T cells also receive permission from capillary cells when they need to leave the blood vessel to get to an infection. Signals even allow them to grab onto the blood vessel lining cells and climb against the flow of blood to get to particular locations.

To pick up invading microbes, cancer cells, and dangerous material, T cells rapidly change their size, shape, and function by altering their internal metabolism, which allows production of powerful armies of killer cells and regulatory cells. Killer cells form potent physical attachments with other cells to rapidly destroy them. They produce regulatory T cells that slow down inflammation after their healing job is done, avoiding damage to tissue. These regulatory cells are similar to the cells inhibiting reactions to food particles, but with other targets and conversations.

T cells also produce memory cells to leave behind. These memory cells stay

indefinitely at the inflammation site to monitor the situation. For years, memory T cells screen for any future recurrence and immediately signal for help if there are problems.

T Cells and Microglia—Vital Partners

There is another reason that scientists did not understand immune function in the brain. Until recent technology emerged, conversations between T cells and microglia, the primary immune cells in the central nervous system, could not be detected. Microglia are now known to be vital partners with T cells for all immune activity affecting the brain.

Microglia travel from bone marrow to the brain during fetus development. Once there, microglia and their offspring remain throughout an adult human's life. Microglia keep up constant conversations with wandering T cells, brain cells, and other immune cells. Chapter eleven presents the complex life of microglia.

Under normal conditions, microglia help to maintain and prune neuron connections. In emergencies, microglia are called to duty as immune cells through signals from T cells. They change their shape and become more aggressive in protecting the brain from infection, cancer cells, or damage from trauma and Alzheimer's disease.

Activity in microglia's belligerent state can increase inflammation in some situations and can actually expand the damage caused by Alzheimer's. Intercepting these natural conversations among T cells, microglia, and other brain cells is now in the vanguard of research into Alzheimer's and other brain diseases.

T Cells and Acupuncture

Communication between T cells and the brain occurs in other ways. Back-and-forth signals are sent between the brain, lymph tissues, and bone marrow using neurons that extend throughout the body. Two major nerve systems, sympathetic and parasympathetic, perform opposite functions in most internal organs, such as increasing or decreasing heart rate, or making the gut muscles active or inactive. T cells have conversations with neurons in both of these systems while in local regions of the body. Signals between neurons and nearby T cells diffuse through tissue back and forth.

This type of conversation between nerves and T cells appears to be part of the mechanism for the effects of acupuncture. Recently, it was found that an acupuncture point in the arm, not near any blood vessels or nerves, triggered an

effect in the brain. Stimulating the acupuncture point with electricity, in fact, activated a T cell at that spot between two nerves. The T cell then sent signals to the nerves that were relayed into the brain, causing effects in distant locations. This type of signaling between nerves and independent traveling cells is discussed in more detail in chapter nine, devoted to neurons, and in chapter fourteen about pain.

A Complex Interplay Between Inflammation and Depression

Other conversations among T cells and the brain reflect a complex interplay between inflammation and depression. When there is no infection, T cells send signals that stimulate normal activity for the brain's memory center, including the production of new neurons. With depression, T cells signal for inflammation and for less production of memory cells. Then, when treatments help alleviate depression, T cells again send signals to trigger production of new memory cells. Much more needs to be learned about these cellular conversations, which could lead to new treatments for depression. This is discussed further in section two, about the brain.

Stress is another human experience at the interface of brain function and inflammation. T cells are essential for dealing with stress in several ways. Both brain and immune cells pick up perceptions of stress. Brief stress related to learning or the unexpected can be helpful in stimulating positive brain activity. However, chronic stress can trigger damaging inflammation through immune responses.

During brief stress associated with normal learning, T cells help stimulate spatial learning and memory with signals. With chronic stress, T cells direct destructive inflammation responses that can decrease memory and contribute to depression. All of this occurs with back-andforth signals among T cells and a variety of brain cells.

KILL OR DO NO HARM—A COMPLEX PROCESS

We know now that a molecule that could trigger an immune response is called an antigen, and when the molecules advertised on the surface of a cell are normal, they are called self-antigens. Self-antigens that are placed in a special surface groove of a cell's membrane tell T cells that this cell has no problems and there is no foreign material inside, such as a virus. Self-antigens signify a normal cell.

The T cell's most important function is to not harm the body while actively

destroying microbes, cancer, and debris. If T cells don't get self-antigens right, they attack normal human cells, which leads to tissue destruction.

Mature T cells scan each cell they meet, looking for specific signs of normalcy and disease. Signs include identification molecules from inside the cell placed on the surface in a special groove, and tags placed by other immune cells to mark internal infections. Identification molecules are placed by each cell to reflect what is occurring inside—normal function, infection with microbe invaders, cancer, or damage.

Two Systems for Evaluation

There are two major systems that T cells use to identify molecules on other cells for evaluation. One system involves special presentation cells that take molecules from abnormal cells and present these particles to T cells. If both the T cell and the presentation cell agree that this is a dangerous particle, the T cell becomes activated and morphs into the fighting variety. For this activation, the presentation cell must not only present the particle but also give a second signal of agreement to the T cell.

The second system occurs with all other cells, except red blood cells, where sample molecules from inside are placed onto their surfaces. T cells evaluate these molecules without the help of presentation cells, but only T cells that are already activated killer cells are able to respond aggressively to these dangerous particles without the additional help of presentation cells.

Daily intake of food presents a special type of foreign material that is evaluated by T cells. In the gut, a constant barrage of food particles that could all potentially be considered foreign could produce deadly immune reactions with every meal. It is necessary for regulatory T cells to be produced strictly for the task of inhibiting such food reactions.

T cells are so expert at this that they can even avoid reactions to synthetic chemicals that have never been seen in nature before. What is difficult about responses to food particles is that these special T cells must be supported by collaborative conversations with gut cells and microbes on a daily basis. Gut lining cells and microbes imbue these T cells with an understanding of necessary nutrients and digestion products, as well as which particular gut microbes are friends.

Vitamins, such as vitamin D3, vitamin A, and folic acid, also serve as important signals in these conversations to remind protective T cells to avoid attacks. The way that gut cells and friendly microbes train T cells on a daily basis is described further in chapter six on gut cells and chapter seventeen about microbes in the

gut.

In Hostile Territory

To chase microbes, killer cells must rapidly reproduce and travel throughout the body in hostile territory, often without oxygen and food. T cells are able to use their internal metabolic cycles in totally new ways that are designed for this difficult trip. Molecules that are normally part of ordinary nutrition and energy pathways inside the cell are turned into signals that stimulate the dramatic transformation into a larger, aggressive cell.

The new metabolism that is necessary for aggressive T cells uses alternative methods of obtaining energy from locations inside the cell other than the usual mitochondria. New substituted foods, such as glutamine, are not part of their usual diet. Burning glutamine instead of sugar increases energy production by two hundred times the normal rate for rapid aggressive behavior. However, using this alternative food is very costly to the cell, with extreme demands placed on internal resources; therefore, the new situation cannot last long.

The conversations for this dramatic alteration into a fearsome belligerent cell occur inside, between several cell compartments. One is the location of metabolic pathways in the cell, and another is the nucleus, where genes trigger production of new materials to build the powerful aggressive cell. A similar type of internal signaling also allows cancer cells to have unusually aggressive properties. Understanding these internal T cell signals could allow new treatments based on stimulating T cell strength while decreasing that of cancer cells.

In the midst of battle, as described earlier, killer T cells form a physical attachment, called the immune synapse, with an unfortunate targeted cell. This connection is quite different from a neuron synapse in structure and function, and it only lasts for a brief time. When T cells touch the target cell, almost instantly membranes of both cells form a temporary interlocking connection resembling interlaced fingers. Within minutes, larger scaffolding molecules make a flat, permanent connection, and the interdigitation recedes.

A large, complex molecular machine—usually used during cell division to orchestrate chromosomes being dragged into place—is pushed and pulled by motors into place near the synapse. This machine then produces a large, syringe-like device that launches packets of toxic granules into the poor victim. This complicated process takes only minutes and has dramatic results.

Protecting Healthy Tissue

Another important T cell tactic protects local tissue cells during battles, somewhat similar to protecting against responses to food particles. The original T cell knew how not to kill normal cells, but the army of cloned killer cells needs help with this.

The original T cell doesn't pass on this subtle knowledge to the rapidly produced army of derivative cells. But when the battle is winding down, T cells produce a new kind of regulatory T cell that watches for danger and instructs killer cells to slow down and avoid attacking normal human cells. These regulatory T cells patrol the action.

Many different signals are used in this protective process to alter the metabolism of the killer cells. If killer cells do attack normal cells, these regulatory T cells actively intervene with signals. This is another area in which future research into signals could enable new ways to treat dangerous infections.

CHAPTER 4

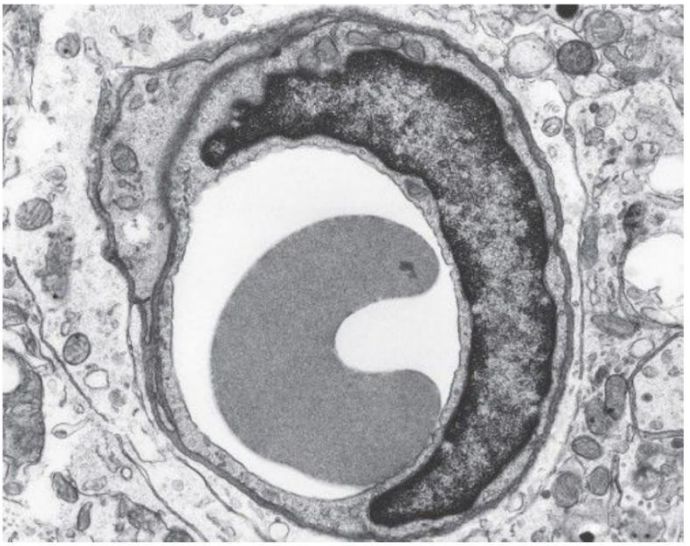
CAPILLARIES—THE "BRAIN CENTERS" OF TISSUE DEVELOPMENT

THE LARGEST ARTERIES AND VEINS carry fast-moving blood to and from the heart. These blood vessels branch out into smaller ones, which connect to the smallest of all blood vessels, the capillaries. In these tiny vessels, blood flow slows to a crawl, with only enough space for individual blood cells to slide through in single file. Here, the blood cells communicate with the capillaries and the nearby tissue cells to enable oxygen and carbon dioxide exchange through diffusion.

Capillaries, composed mostly of a single layer of lining cells, form intricate webs called vascular beds. These webs are embedded into tissue and bone. They extend into every part of the body and almost every crevice. With tens of billions of capillaries tracing through the human body, these vessels make up 90 percent of all blood vessels by area. Using advanced microscopes, researchers have begun to observe the subtle differences in the microenvironments of these vascular beds in each organ. Also, capillaries are unique to each organ.

Perhaps the most important recent discovery is that capillaries do more than funnel blood, oxygen, and nutrients to every corner of the body. Capillary lining cells are now found to be vital "brain centers" of tissue, stimulating, regulating, maintaining, and inhibiting the stem cells that make up each organ. This concept of capillaries directly influencing the growth of various tissue and bones goes back to Aristotle, who first proposed the notion that blood vessels somehow determine how organs and other tissue develop throughout the body.

But it has not been clear how blood vessels and tissues maintain their intricate relationship, or which first triggers production of the other. Until recently, there appeared to be only a few known functions of the lining cells, most importantly protecting blood flow as cells and signals course through every region of the body.



Red blood cell in a capillary, showing the capillary cell's large nucleus. Electron micrograph. *(Dennis Kunkel Microscopy/Science Source)*

There is much we don't yet know about capillaries, but new research is continuously surprising the scientific community. Somehow, capillaries are able to change their own shape for particular situations, such as becoming more tightly bound to adjacent cells, or altering cell properties to allow fluid through. Most of the examples of shape alterations are not well understood. But it is known that in the uterus, progesterone triggers holes in membranes that allow secretions to come out.

It was also recently found that capillaries use large sacs filled with information molecules for communicating with other cells. Launching these sacs can help other cells alter the matrix around blood vessels in unique ways for each tissue. This information helps build the unique capillary niches already observed in liver, bone, lung, and brain.

A CRITICAL BUILDING PARTNER

Scientists are now realizing that capillaries are vital building partners in all phases of tissue growth and also contribute to tissue maintenance. Capillaries send signals to maintain normal metabolism of tissue. They also regulate the growth of all tissue cells, including additional blood vessels when needed. Direction comes from discussions among stem cells, blood cells, tissue cells, and local neurons. When infections occur, capillary signals call for immune-response

help and alert T cells into action. When rebuilding tissue, capillaries communicate with stem cells to avoid production of scars from excess fibers.

The Stem Cell Connection

Adult stem cells have been found in numerous areas throughout the body, including in the brain, liver, heart, gut, teeth, skin, and bones. Small groups of these stem cells appear to reside in a protected place, what's known as a "stem cell niche" of each type of tissue or bone area where they are found. These niches are located next to capillaries, and conversations between them can occur with secreted molecular signals or by direct contact.

Capillaries also can easily send messages into the bloodstream for distant communication with immune cells and bone marrow cells. They somehow understand the precise needs of each diverse organ and either stimulate or inhibit stem-cell activity.

Surprisingly, an unusual type of capillary lining cell is able to transform into a stem cell when necessary. After these capillary cells have turned themselves into tissue stem cells, they then need instruction signals from other original capillary cells to operate.

Capillaries also secrete multiple signals for local tissue cells. Signals inform cells about the shape of the organ they're in and its precise functions. During tissue rebuilding, signals sent in sequence direct production of three-dimensional spatial patterns. Tissue cells are instructed about the concentrations of cells needed for particular locations to form the exact size and contour of the tissues. Tissue cells don't just take direction from capillaries; they also express their organ's needs in two-way conversations among capillaries and stem cells.

Orchestrating the Rebuilding and Maintenance Process

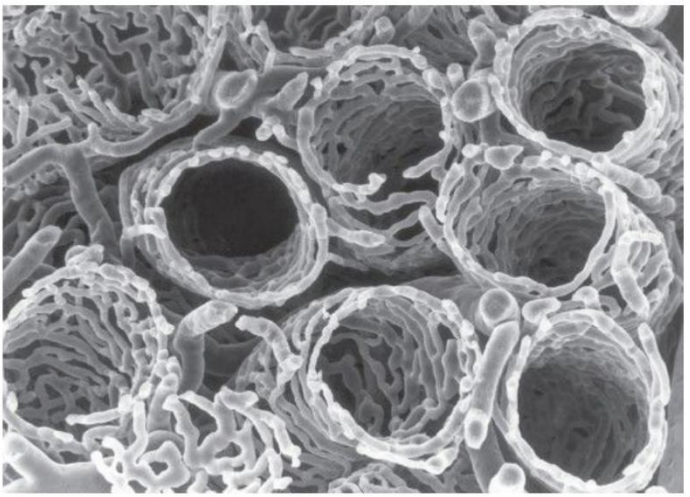
Research shows that discussions among tissue cells and capillaries are needed to grow each organ and to rebuild tissue when damage occurs. Capillary conversations, for example, give specific directions to stem cells for building, maintaining, and rebuilding specific features of every organ. Capillaries determine whether stem cells should be quiet or whether they need stimulation to produce more cells. It's also been recently found that capillaries are distinct in each organ.

Details of capillary conversations in each type of tissue are just now being discovered—in the brain, bone, liver, pancreas, gut, and muscle. For example, capillary signals send travel routes to immune cells, directing them to infected

tissue and determining what goes in and out of the brain with signals to other barrier cells.

These discoveries occurred gradually. First, capillaries were observed helping to construct the pancreas and liver. Capillaries were then found to be vital for the spread of cancers. Further research found that capillaries are vital for normal development of the fetus and for maintenance of adult tissues. All of these discoveries are now known to be based on cellular conversations.

One of the defining characteristics of an organ is the matrix of molecules that sits between its tissue cells. This extracellular scaffolding holds together tissue architectures and produces specific local environments. Capillaries also direct the building of extracellular matrixes around blood vessels with characteristics needed for a specific organ, bone, or other body part.



Unusual rich capillary network of the epididymis. Electron micrograph. *(Don W. Fawcett/Science Source)*

Another type of cell—the pericyte—wraps around the capillary lining cells. Pericytes can contract like muscles and also take part in capillary discussions throughout the body. Pericytes are vital for the tight barrier around blood vessels in the brain, where the capillary lining cells converse with the pericytes about whether to allow immune cells out of blood vessels and into brain tissue. Both capillaries and pericytes operate independently, but in most types of tissue, capillaries integrate all of the conversations and, ultimately, direct local operations. There is more about pericytes in chapter thirteen.

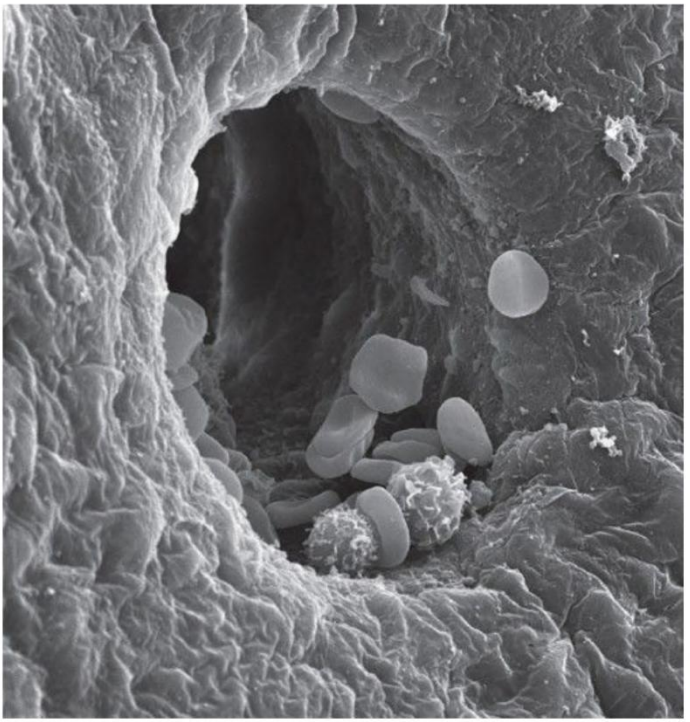
Understanding How Capillaries Affect Individual Organs

The liver is an amazing organ. When it suffers trauma, it can restore up to 70 percent of its tissue, with capillaries orchestrating the rebuilding process. Capillary signals also stimulate the production of new blood vessels to supply nutrients for new liver tissue. Capillaries somehow understand how large the liver should be. They signal for new stem cells to build tissue until it reaches the exact size, and then inhibition starts.

When the liver can't regenerate normally, it forms a type of scar tissue called fibrosis, which takes up the space that would have been normal tissue. Unfortunately, capillaries lead the development of the abnormal type of scar tissue as well. In short, if acute injury occurs in an otherwise healthy liver, capillaries stimulate normal growth. With chronic liver disease from alcohol or metabolic syndrome that causes cell exhaustion from constant rebuilding, capillaries direct other pathways to produce abnormal liver fibrosis.

Capillaries also contribute to lung function and tissue development. In the lungs, capillaries are interwoven with respiratory cells that exchange oxygen and carbon dioxide using microvilli protruding from their surfaces. The capillaries and lung cells must be almost touching for the gases to diffuse properly across them. Capillaries engage in a great amount of discourse, using a wide range of signal molecules related to producing the distinctive membranes that sit between capillaries and air space. They also stimulate the production of new lung cells after lung tissue is removed. Elaborate signaling back and forth produces more stem cells for the development of new tissue.

A somewhat similar situation occurs in the pancreas. Capillaries sit near cells that make insulin and are in constant communication about the body's metabolism through signals in the blood. Capillaries can stimulate regeneration of pancreas cells to help regulate an unbalanced metabolism. Another process turns some of the capillaries into fat cells, and this alters metabolic actions related to fat. These altered cells are similar to stem cells in that they then need direction from normal capillaries.



Specialized sinusoid liver capillary with multiple red blood cells and two white blood cells. Electron micrograph. *(Steve Gschmeissner/Science Source)*

Capillaries that surround cardiac muscles also can help stimulate the heartbeat with signals. When capillaries sense low oxygen, they produce a particular signal. If heart muscle is damaged by low oxygen, capillaries dramatically increase their activity, stimulating repair, as well as stronger muscle contractions to help continue pumping blood.

Calling for Help

When tissue destruction occurs—caused by chemicals, trauma, low oxygen, or radiation—capillaries working with stem cells respond by calling for particular immune cells for each situation. These immune cells, nomadic in nature, might have to travel a great distance from bone marrow on the other side of the body. Also, signals from the capillaries to the bone marrow might first have to stimulate production of diverse cells needed for the specific rebuilding task.

In fact, capillaries direct the entire operation of getting immune cells to help when needed. During the entire transit of helper cells, the capillaries continue to

send messages about the exact site of the problem. They stimulate other local cells along the way to take up the cause and produce factors that help guide the trekkers. These signals allow attachment of traveling cells onto blood vessels to enable movement in a particular direction, even against the flow of blood.

After the traveling blood cells arrive at the precise location, capillaries make sure they are the ones that are needed. When certain, the capillaries send signals to allow the blood cells' exit from the blood vessel into tissues. Normally, to maintain blood vessel boundaries and keep fluid from seeping out of blood into tissue, capillaries are tightly connected to adjacent cells. For these helper immune cells to enter surrounding tissue, signals alter the capillary junctions, creating a path for cells in the blood to go through. With several more barriers between the blood and tissue in the brain, getting through is more complex.

A PARTNER IN BRAIN DEVELOPMENT

Capillaries are directly involved in the production of all brain cells, just as they are in stimulating stem cells in other organs. While production of new neurons in the brain greatly decreases in adult humans, supportive brain cells are produced in great numbers. (These supportive brain cells, called glia, are explained at length in chapters ten through twelve.)

In a developing fetus, billions of neurons are minted in all regions of the brain, and as life progresses, smaller numbers of new neurons are produced in select locations. In adults, these new neurons support memory centers and turnover of smell neurons. A recent study looked at brains of human adults who had died suddenly and found that up to hundreds of new neurons were produced each day in memory centers, even into old age. However, this study also noted that decreasing blood flow in the very old might make these new neurons somewhat less effective.

It is now known that capillaries sitting next to stem cells are part of the vital process of producing new neurons in the brain, as well as outside the brain in local tissues. In the brain, newly minted neurons stimulated with capillary signals migrate to locations where they are incorporated into active brain circuits. An example of locations outside the brain include the lungs, where capillary signals stimulate stem cells that produce local neurons. Another is the umbilical cord, where capillaries produce a signal necessary to produce new neurons.

Capillaries also stimulate production of supportive brain cells (again, each type detailed in subsequent chapters). Brain lining cells—called choroid lining cells—sit at the critical barrier between blood vessels and cerebrospinal fluid. Capillary lining cells use signals to regulate the stem cells that produce these choroid lining

cells, telling the stem cells to either maintain a quiet state or produce more cells for the barrier. These choroid lining cells are discussed in chapter thirteen.

For regeneration of brain tissues after trauma and strokes, capillaries coordinate activity to greatly increase production of signals that nourish the new types of cells needed to clean up and repair damaged brain regions. Signals instruct brain stem cells to travel to particular places for more cell production. Signals include directions for travel and the stimulus to produce more cells. Crosstalk between capillaries and neurons is increased in this situation to regulate growth and energy usage for brain structures.

In the brain and several other organs, capillaries provide three distinct levels of support for producing new cells. In the first level of support, capillaries send signals that alter brain stem cells from a universal type that produces a wide range of cells to a limited type that produces just one particular cell, such as a neuron or lining cell. There are numerous different stem cell types that capillaries stimulate to produce more than a thousand types of neurons and multiple types of supportive brain cells. After signals to produce the limited-edition stem cell, capillaries then provide two additional levels of support.

The second level of support instructs limited-edition stem cells to move to exact locations in order to produce these particular brain cells where they are needed. One example is the production of cells that wrap insulation around axons to determine the speed of electrical signals for neuron circuits. The amount of insulation material—called myelin—is different in each location based on the signal speeds needed for various circuits. Capillaries instruct new limited-edition stem cells to travel to exact locations in the brain to find a particular neuron and produce a supportive brain cell that manufactures the appropriate amount of wrapping on the neuron's axon.

The third level of stimulation from capillary cells comes when the brain is functioning normally. Capillaries send signals that stimulate maintenance of performance to both stem cells and brain cells.

TALKING WITH BONES

Bone in a normal, healthy body is constantly being remodeled. In the process, solid bone architectures are altered and blood cells are produced in the marrow. Bone builds and breaks down structures in a process directed by two distinct types of capillaries. One type stimulates production of new bone cells, and the other stimulates the bone cells to carve out sinusoid cave environments, where the capillaries reside in the bone. Other stem cells in the marrow participate in producing diverse blood cells. Bone marrow produces all types of blood cells for

the entire body, and capillaries are positioned next to the stem cell niche in bone sinuses, where they converse about producing varieties of blood cells.

Capillaries in the bone respond to calls from tissue cells, immune cells, and other capillaries throughout the body seeking particular blood cells to respond to local emergencies. Capillary signals to stem cells can inhibit production when supplies are full and stimulate when more cells are needed. As in the brain, capillaries in bone marrow contribute three levels of instructional support to stem cells when producing the wide variety of blood and immune cells. In the first level, the capillaries initiate the production of more stem cells. The next set of signals limits the stem cell to a particular family of blood cells. The third level triggers specific cells in the lineage or inhibits production of cells that are only rarely needed.

Capillary signals stimulate stem cells for both white and red blood cells. One type of stem cell produces red blood cells and another produces white blood cells (described in chapter two). Stem cells for white blood cells transform into limited types to produce T lymphocytes (described in chapter three) and B lymphocytes. They also produce two lesser-known cells—the natural killer cell, which is similar to T cells but without as many capacities, and a B cell derivative that mass-produces antibodies.

Capillary signals also stimulate another type of white blood cell in the fetus, which travels to the brain. These cells live in the brain throughout adult life as the already mentioned resident immune cells, microglia. Another important cell in the white blood cell lineage is the large mother cell that produces platelets, which are described in the next chapter.

When bone marrow is depleted, perhaps during serious infection, capillaries change gear and send signals to repopulate it. The conversations to repopulate marrow are complex and consist of cascades of multiple signals in sequence. Some signals help avoid stem cell exhaustion, and others produce new stem cells to help. Other signals are global and stimulate production of all cell types at once—lymphocytes and red blood cells. If too many are produced, capillaries send inhibitory factors to shut down production.

CHAPTER 5

PLATELETS—MUCH MORE THAN A PLUG

SCIENTISTS WERE SURPRISED to learn that even lowly platelets without a nucleus—not even considered a real cell—use elaborate communication with many other cells. Until recent discoveries, platelets were thought to be only a fragment of a larger cell with the sole purpose of making clots to stop bleeding and sometimes plugging arteries in the wrong places. By inadvertently clotting heart and brain blood vessels, platelets can contribute to heart attacks and strokes.

Before the discovery of platelet conversations with immune cells, blood vessel cells, and tissue cells, it was hard to even imagine a platelet functioning as a cell. How could platelets manufacture signals and receptors and respond to situations without a nucleus and DNA?

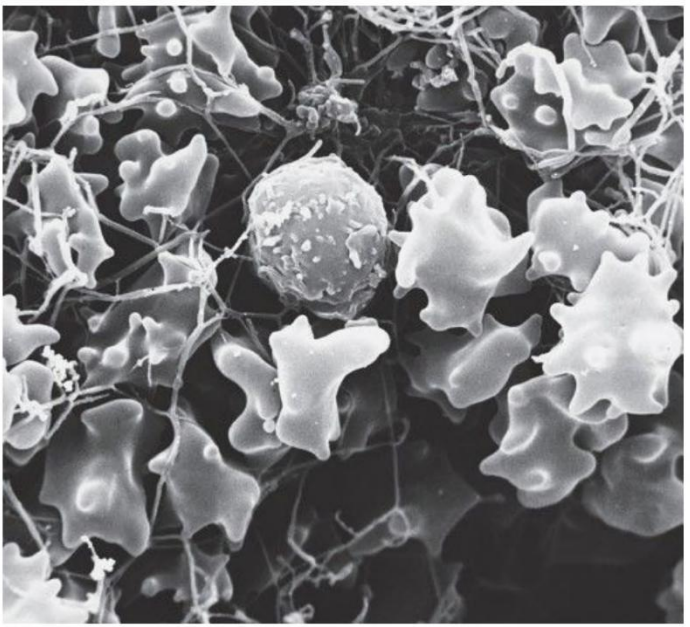
The answer is that they get what they need before they break off from their mother cells, large bone marrow cells called megakaryocytes. These mother cells supply platelets with a large repertoire of messenger RNA molecules, which is coded from their own DNA, as well as protein-production machines called ribosomes. With all of this support, platelets are able to manufacture a full vocabulary of signals and receptors by themselves.

Platelet conversations are as vital and varied as those of most immune cells in their early responses to invaders and injury. Platelet signals are critical when defending against microbes, often being the first cells to encounter microbes in the body. Present throughout the blood in large numbers, platelets find microbes quickly and send messages to immune cells to stimulate defenses. Platelets call for white blood cells and actively participate with immune cells in fighting infections. They assist T cells in directing the B cells to make better antibodies.

As well as signaling to immune cells for defense against invaders and confronting microbes themselves, platelets tackle another difficult problem—blood dynamics. Stopping blood loss is not as simple as it seems. While they halt

bleeding, platelets must also respond to each type of tissue's need for an exact amount of blood flow. Too much or too little blood will damage tissue. If the clotting is too great, it can become generalized throughout all of the blood and can damage multiple bodily regions at the same time. Without enough clotting, tissue will die.

As first responders to damage, platelets must immediately stop bleeding, keep blood flowing appropriately, and, at the same time, defend against microbes. At the moment of an injury, microbes enter tissue through paths of trauma or foreign bodies. Damage to tissue and blood vessels triggers cascades of blood-clotting factors, which instruct platelets to change their shape for clotting. Platelets also send signals to attract immune cells for rebuilding tissue and help mold scaffolding molecules outside cells that form scars. Somehow, they engage in all of these activities simultaneously.



Blood clot with platelets, red blood cells, and fibrin strands. Electron micrograph. *(David M. Phillips/Science Source)*

PLATELETS UP CLOSE

Only mammals have platelets. Other creatures use different blood cells for the same work. As just mentioned, platelets are produced by megakaryocytes in bone marrow. Responding to signals from the liver and kidneys, megakaryocytes grow

twenty times larger just before they produce thousands of platelets, which live for about a week. Mother cells travel from bone marrow and are stored in the spleen for emergencies. They are released by signals from neurons. Wide-ranging conversations keep the necessary supply of platelets, but not too many.

Platelets can change shape rapidly because they are wrinkled, with a large amount of extra membrane tucked into folds. Messages from other cells tell them when to alter their shapes. Inside the platelet, scaffolding molecules respond and produce many long arms, stretching from the platelet's body. Platelets change shape in three stages—multiple new arms and legs, a spreading body, and a thicker center. Motors just below the membranes rapidly increase the membrane surface area without needing to stretch or add new material. Arms then attach to breaks in blood vessels. After that, multiple platelets join their arms together to form a plug.

Platelets produce messages and attack molecules sent via sacs filled with chemicals. Platelets only use these sacs when they have changed from being round to having arms. Sacs contain three kinds of signals, each with multiple varied effects. One type regulates blood flow. A second type attaches and kills microbes. A third remodels clots to help heal the damaged organ. To kill microbes, platelet arms grab them and inject sacs. Platelets have a wide range of receptors to sense each type of microbe, and they have specific toxic chemicals to kill each species.

ALL-OUT WAR—FIGHTING MICROBES

Platelets can sense the type of injury and its exact location, and they move rapidly to the site. Because there are many more platelets than other blood cells, platelets become the most abundant player at the trouble spot while they wait for more powerful T cells and neutrophils to arrive. When platelets sense a microbe, they change shape and release molecules for attack.

To fight microbes, platelets use various techniques. For one difficult bacteria species, platelets release multiple different sacs, some with phosphate energy particles and others with proteins that use these same energy particles to attack the microbe. Bacteria respond to the attack with their own signals that block the platelet secretions and break down platelet proteins. Platelets then secrete enzymes to break down the bacterial attack proteins. This battle of back and forth attacks continues in various forms. There will be much more about bacterial responses in section three on microbes.

Platelet secretions used against microbes can serve multiple purposes at once. One enzyme known to initiate the clotting process has been recently found to also cut pieces of a platelet product into multiple fragments, each designed to target

specific microbe species. Another multipurpose molecule from platelets has varied sections and modules that evolve as microbes change. Distinct regions of the molecule signal to other cells for help and kill microbes of various types. Signals can call for reinforcements as the platelets are directly attacking the microbes.

In the fight against microbes, platelets also use special receptors. Internal receptors can sense how many attack molecules they have left. When needed, signals are sent internally to mobilize messenger RNAs and ribosomes to produce more attack molecules, sometimes increasing production by a factor of a hundred. Receptors also allow platelets to distinguish membranes of human cells from those of microbes by analyzing specific fat molecules sticking out from both cells. In this way, platelet attacks can focus on killing only microbes, not human cells.

The large number of platelet attack molecules is effective against a wide variety of microbes, including bacteria, fungus, protozoa, and many viruses. Recently, platelets were shown to be a critical first line of defense against HIV (human immunodeficiency virus). Platelet factors have been shown to limit strep heart infections. One specific platelet molecule attacks parasites that cause malaria by entering the red blood cells where the microbes have taken over. Research shows that the more platelets in the body, the better the chance against malaria. Platelets are also effective against a variety of fungi. To attack worms, platelets produce hydrogen peroxide and other attack molecules. Platelets can't eat microbes, but they can hold them off till the bigger scavenger cells arrive to consume them.

HELPING IMMUNE CELLS

Perhaps platelets' most important function is helping immune cells. Platelets examine surfaces of immune scavenger cells and identify those that are infected and losing the battle against microbes. Platelets send signals about their findings to attract reinforcements. They help white blood cells by stimulating receptors that bind to microbes, making it easier to eat the microbes.

Platelets have receptors for a wide range of immune signals. They can direct travel anywhere in the body and can respond to very distant calls for help. Once at the site, platelets have a large repertoire of receptors and signals for diverse types of cellular damage. Some platelet signals produce rapid responses from white blood cells. Platelets can use many of the most powerful immune signals to trigger inflammation. After evaluating situations, platelets send sequences of messages, which are altered as the conditions change. With such complexity, sometimes signals go awry and clots are produced in the wrong places.

Platelets increase the ability of white blood cells to eat microbes. When

platelets determine a particular strategy is needed, they signal for specific types of scavenger white blood cells to travel to the location where the battle is raging. Debris-eating scavenger cells then produce enzymes that cut molecules secreted by platelets into smaller pieces. This attack is effective only with the combined effort of both platelet signals and scavenger enzymes. Microbes respond with their own enzymes in attempting to destroy the platelet attack molecules. But these enzymes can inadvertently produce even smaller pieces of platelet molecules that hurt the microbes.

Neutrophils produce traps for microbes called nets. These nets are made of DNA molecules along with proteins. Platelets join in this process by building a fibrous assembly of themselves along with the nets and white blood cells. This amalgam structure recruits and activates more immune cells. Platelet fibers then attach even more widely to microbe molecules in order to kill them. Nets are a critical mechanism for killing multiple bacteria without damaging human tissue.

Platelets help in still other ways. For powerful T cells to respond to situations, they need other cells to present pieces of microbes or particles from cellular damage. Platelets don't present material themselves, but their activity in this regard makes presentations to T cells more specific. For this, platelets connect with microbes and bind them rapidly to the presenting cells.

Platelets also send multiple direct signals that activate T cells, such as when a virus invades a platelet. Via platelet signals, T cells are alerted to attack other infected cells as well. Platelet signals call for the exact types of T cells needed for particular situations. These platelet signals also are essential for vital communication between T cells and B cells in producing the best antibodies.

PLATELETS AND CANCER

Cancer cells have a unique relationship with platelets. As will be discussed in chapter eight, cancer cells enlist support of local tissue cells, immune cells, and blood vessel lining cells. Recently, platelets have been found helping cancers. They can coat cancer cells with fibers normally used for clots, protecting the cancer cells from immune scavenger cells and killer immune cells.

Platelets help build structures for metastatic cancer colonies, and the more platelets at the site, the worse the prognosis. Recent treatments to address this platelet buildup have helped somewhat. Another platelet signal triggers cancer cells to change from passive types of cells with little movement into mobile aggressive cells that enable a cancerous tumor to grow. Without platelet signals, invading cancer cells may revert back to their more passive state, stopping cancer's expansion.

Cancer signals themselves can alter the particular types of clots that are formed to help the cancer's efforts—small clots, widespread dangerous clots, or plugs that damage the lungs. Conversations among platelets and tissue cells help traveling clusters of cancer cells land in distant tissue to start a new colony. Despite the fact that each tissue in the body is different, platelets are able to use signals that are distinct to each type of tissue.

Cancer and platelets interact in other ways as well. Cancer cell signals stimulate conversations of platelets and nearby tissue cells to encourage support for the cancer, since platelets have a preexisting relationship with these local cells. Platelet signals can also enable blood vessels to leak so cancer cells can travel more easily in and out of the vessels.

It is difficult to imagine how a cell without a nucleus can do so much!

CHAPTER 6

CONVERSATIONS IN THE GUT

PERHAPS THE MOST BEWILDERING situation confronted by a single human cell is in the gastrointestinal tract, or the gut, which consists of the stomach, small intestine, and large intestine. The surface area of the gut lining, with all its folds and invaginations, is at least ten times larger than the skin that covers our bodies.

Other than the skin, the gut has the greatest exposure to the outside environment by far. Cells that form the single layer that line the gut have to deal with everything we eat, including synthetic chemicals that have never been seen in nature before. These gut lining cells converse with trillions of microbes to determine which are friendly, which will help digestion, and which must be destroyed.

It's amazing that a single layer of lining cells separates a hundred trillion microbes from tissue below it. Lining cells use a large variety of signals to keep friendly bacterial communities nearby and enemies at a distance. They determine what lymph tissues are needed and monitor the amount of inflammation used against microbes to avoid harm to tissues. They provide the most influential immune centers in the entire body by educating T cells about the special circumstances in the gut. Understanding these gut conversations could contribute significantly to the future science of probiotics. Chapter seventeen, about microbes in the gut, provides more on this topic.

Signaling from the gut lining cells determines the types of immune tissues built just below the lining cells, which can provide protection against particular invasions. Daily signals from gut lining cells provide alerts to T cells to ensure that they don't attack each type of food particle as if it were a foreign invader.

GUT CONVERSATIONS

A delicate balance of signals among lining cells, immune cells, and microbes must be maintained to ensure that microbes digest food to produce vitamins while fighting enemy bacteria. Inflammation must also be monitored to avoid the production of cancerous cells. Friendly microbes can call on lining cells for protection from inflammation. But this protection is a double-edged sword, because it can also be intercepted by cancer cells for their own defense. The ways that cancer benefits from conversations with microbes are discussed in chapter twenty-one.

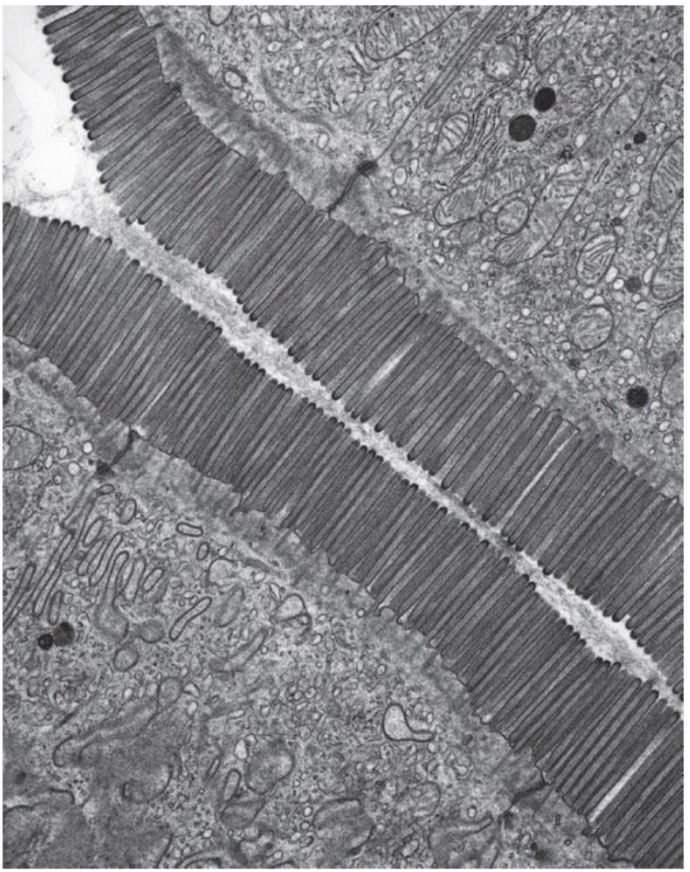
Neurons and neuron support cells participate in gut conversations as well. The semiautonomous gut nervous system has been called the second brain because it has more neurons than any region other than the central brain. The lining cells help neurons function through conversations among immune cells, tissue cells, blood cells, and microbes. Neurons sense environmental changes and alert the lining cells to appropriately alter their signals to immune cells and microbes. They also stimulate muscles to keep the intestines moving.

All along twenty-five feet of stomach, small intestine, and large intestine, there are varied microenvironments where diverse microbes interact with particular single lining cells. Environments also vary across the diameter of the intestinal tube—in locations adjacent to the lining, near the layer of protective mucus, and in the rapidly flowing center of the gut. Gut lining cells choose microbes (which are different in each region) to keep close by. Lining cells call friendly colonies to travel closer to become permanent residents at the edge of the lining. Also, the layer of protective mucus secreted by lining cells produces a distinct protected niche not far from the lining for selected microbes.

The lining surface area is greatly increased by invaginations deep into gut tissue, called crypts, and projections, called villi, that stick out from the surface. Stem cells contained in crypts produce gut lining cells. Lining cells at the tip of the villi stick farthest into the sea of microbes and food particles in the gut lumen, the center of the long continuous hollow tube that makes up our intestines. Mature lining cells at the outermost point of the villi—sticking farthest into the lumen, where there is the most action—have gone through modifications and have attained the most advanced capacities for communication and decision making. They must deal with the incredible complexity in the flow of cells and material through the lumen to its end at the anus.

Like T cells, gut lining cells are gradually educated to produce a large number of receptors and signals for communication as they mature. Climbing from the deep crypts to the high-action villi, lining cells become gradually more able to handle complex interactions in which they absorb material, evaluate situations, and secrete signals in response. These cells are able to move along the surface of the villi without creating holes in the barrier, where material could seep from the

lumen into tissue below. When a mature cell has lived long enough at the top of the villi, it kills itself by programmed suicide—somehow without disrupting the tight barriers between cells. Mature cells live for less than a week and are replaced with other cells traveling up from the crypts that are "learning" along the way.



Two gut lining cells showing microvilli, which greatly extends membrane surface area for absorption of nutrients and secretion of signals into the lumen. Also, organelles can be seen in each cell. Electron micrograph. *(MicroScape/Science Source)*

AN ELABORATE COMMUNICATION NETWORK

In the gut, the single layer of lining cells directs all activity as it sits atop connective tissue, lymph tissue, blood vessels, muscles, and nerves. The lining cells integrate a wide variety of signals from all these tissues and microbes. Signals from friendly bacteria to gut lining cells can stimulate more mucus for protection.

Microbial signals can trigger loosening of tight junctions between cells to allow material through. Signals from microbes are immediately relayed to immune cells to stay in the loop with lining cells. Signals from various cells direct development of immune centers just below the lining cells. Signals can stimulate immune scavenger cells to present microbe molecules to T cells.

To engage in elaborate communications, gut lining cells have a unique shape and structure. They have asymmetrical rectangle shapes and sit on a hard barrier connected to tissue below. They restrict travel from the free-flowing lumen into gut tissue below with a bottom barrier and sides that are tightly joined to neighboring cells. Receptors near the top of the cell have one type of response, and those near the base a different response. Lining cells can alter the leakiness of their junctions and basement membranes, allowing specific cells to travel through between lining cells, just as the capillary cells in blood vessels call for traveling white blood cells and allow them into tissue. Gut lining cells—like capillary cells in blood vessels—decide via back-and-forth signals which cells or particles can pass through the gut.

Stem cells produce various gut lining cells that specialize in diverse functions: master lining cells that direct all the activity, cells that produce hormones, mucus-secreting cells, and protein-producing cells for digestion and fighting microbes. Signals from all of these cells, along with friendly microbes, provide direction for building villi and crypts. Signals control the number and placement of stem cells. They also control the density of blood vessels in the tissue. Signals among all cells help lining cells in the complex process of moving up the villi from the crypts while maintaining the barrier. Nourishing signals protect lining cells from dying prematurely as they travel up the villi.

One type of lining cell manufactures mucus with special cross-linking structures that make the mucous barrier stronger. Signals back and forth between microbes and mucus-producing cells expose breaks in the mucous barrier and these conversations instruct the goblet cells to produce more mucus to repair the discontinuities.

Mucus provides a layer of protective fibers that provides a sheltered space for friendly microbes to live near the lining. With permissive messages from lining cells, specific types of microbes and viruses survive in and around mucus. Surprisingly, in the mucous niche, viruses become friends and protectors of human cells by fighting off invaders. Some microbial colonies that are allowed near the lining make a different highly structured slimy layer, called a biofilm, discussed in chapter fifteen. Secreted signal molecules or those sent in sacs determine which microbes are allowed to touch the gut lining cells. These lining cells engage in constant conversations, even with cells in biofilms.

Hormone-producing lining cells provide the greatest variety of molecules that

kill microbes. Enzymes break open microbe membranes. Particular poisons are produced based on the types of microbes that are present. Also, friendly bacteria send signals to these lining cells asking for toxins to kill threatening species.

WORKING WITH T CELLS TO MAINTAIN IMMUNE BALANCE

Signaling between lining cells and T cells maintains immune balance in the complex gut. In other parts of the body, T cells travel to lymph nodes and various types of tissue, looking for dangerous particles. They become activated when they find microbes, foreign material, or damage. In the gut, T cells sit just below the base of the lining cell and are tolerant toward food and microbes in one situation and hostile in another.

Conversations among gut lining cells and various immune cells educate the local T cells about issues only occurring in the gut. In parts of the human body where microbes are not expected, receptors trigger a strong response. But in the gut, the master lining cells influence immune cells to produce various modified responses, including no response at all or even offering to help specially chosen microbe species.

Most T cells throughout the body are educated in the thymus. Gut environments are so complex that training for gut T cells must occur on-site. Modulation of gut lymph tissues below the lining also creates a class of T cells that travel to the thymus and throughout the entire body, bringing knowledge of the compromises that are made with friendly bacteria in the gut.

The training of the special gut T cells occurs via conversations among all types of gut lining cells, capillary cells, neurons, and friendly microbes. Interactions with lining cells and friendly microbes allow these T cells to learn how to build unique receptors and signals needed to deal with food and digestion. T cells engage in constant inhibition of unwanted responses to food particles. T cells also have a say in the amounts of mucus needed to protect friendly bacteria.

In chapter three, it was noted that without constant inhibitory activity from specially trained T cells and gut lining cells, allergic reactions to food would occur frequently. These T cells must also control reactions from all other immune cells through continuous signaling. For this inhibition, T cells require reinforcing signals from lining cells, blood cells, and even microbes. These messages instruct T cells to control their army of dependent immune cells ready to attack any unusual particle. Many well-known vitamins and food molecules have vital roles in stimulating these special T cells needed to avoid food allergies. Without daily conversations reinforcing this inhibition, we would be allergic to every foreign particle of food each day.

COOPERATION ORCHESTRATED THROUGH SIGNALING

Multiple gut cells work together to decide whether to respond to particles by grabbing and analyzing them. Just below the lining, several types of special immune cells have long "arms" that reach into the gut lumen to sample particles floating by. Their arms stick out between junctions of lining cells far into the middle of the flow to grab particles. Samples can also be transported by master lining cells themselves to the bottom of the cell, where they are presented to T cells beneath the lining barrier. An immune scavenger cell, also right below the lining, sends signals that can loosen junctions between lining cells to enable arms to go through to catch particles up in the lumen. This scavenger cell decides whether to let bacteria travel into the tissue or eat it on the spot.

Gut lining cells also transport signals from immune cells below the barrier back up into the lumen. These molecular signals are also designed to fight dangerous microbes. The molecules first attach to receptors at the bottom of the barrier, which triggers transporters to bring them into the bottom of the lining cell. They are then transported to the top of the lining cell and secreted into the gut lumen. All of this cooperative activity is orchestrated with signals, including maintenance of the barrier and alterations when necessary. When disrupted by metabolic problems and infections, a dysfunctional barrier can contribute to inflammation, diabetes, multiple sclerosis, arthritis, and cancer.

Complex communication among all of the cells determines which particular immune cells are needed to form the specialized intestinal lymph tissues just below the lining. Multiple specific immune cells are called to build the growing cluster of immune cells, which takes a form somewhat similar to a lymph node. Signals from lining cells produce adhesion molecules that enable cells to coalesce in order to form these unique gut lymph tissue structures. Densely populated immune centers become a source of rapid production of specific cells when needed for particular problems.

CHAPTER 7

SIGNALING ACROSS THE SKIN LANDSCAPE

From a cell's point of view, the surface of the skin is a vast, hard, barren landscape spotted with a lattice of proteins and fatty molecules. As the organ most exposed to the external environment, the skin must defend against physical assaults, particularly from toxins and insect bites.

Just beneath the skin's surface, there are deep follicles that regulate hair growth and harbor glands that secrete various molecules, such as salts, enzymes, and fats, as well as peptide molecules to fight microbes. Peptides are short chains of amino acids (longer chains of amino acids form into proteins). The surface of the skin is acidic, with high salt levels and lots of oxygen. Within the follicles, there is little oxygen but a lot of fat. On such an arid surface (compared to the gut and other internal organs), signals are even more important than in other organs to maintain order and avoid infections.

The landscape across the skin varies considerably—fingers, hair, armpits, face, palms. Like the gut, each local environment has particular cellular conversations to determine which microbes are friendly and which are dangerous. Varied amounts of follicles and glands create niches for specific bacteria. Yet wet, dry, and oily settings on the skin are unlike microbe-laden surfaces in the gut. Healthy skin is less than an ideal place for microbes, providing little nutrition and exposing them to ultraviolet light, which can kill or inactivate them. The skin seems so stable that it is difficult to grasp how dynamic it truly is.

SKIN STRUCTURE

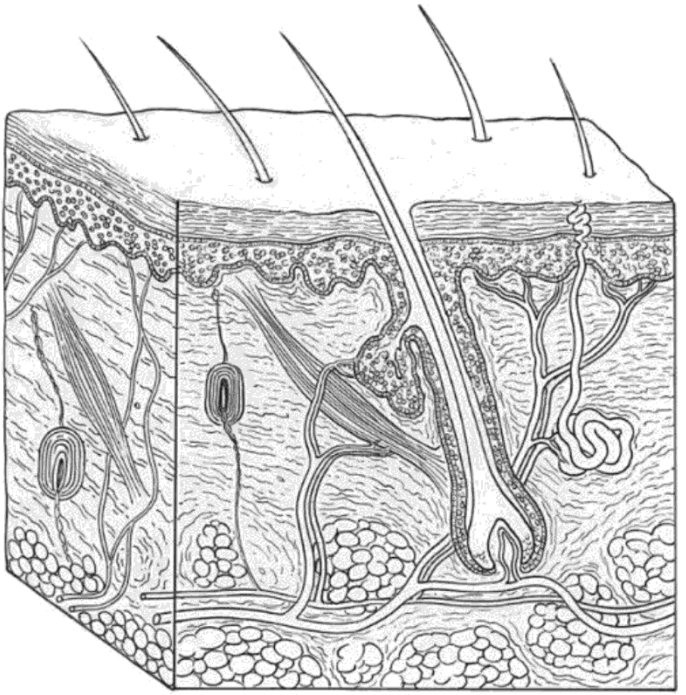
The two main layers of skin are the epidermis, the outermost layer, and the dermis, which is beneath. The dermis is made up of connective tissue, blood and

lymph vessels, sweat and oil glands, and hair follicles. There is also a third deeper layer of skin, called the hypodermis, which is made up of connective tissue and fat cells.

The vast majority of the top layer is made up of master lining cells called keratinocytes. These specialized lining cells, analogous to master lining cells in the gut, migrate from deeper layers to the surface while talking with immune cells, neurons, muscles, connective cells, and varied microbes, including bacteria, fungi, and viruses. Keratinocytes produce keratin, the fibrous protein that forms the structural basis of hair, nails, fur, and feathers and also protects the surface of the skin from damage or stress.

The epidermis also contains pigment cells, resident and traveling immune cells, and supportive cells that surround sensory neurons. At the bottom, capillaries provide oxygen for the cells not near the surface. These blood vessels also provide a channel for signals with other regions and a route for traveling blood cells to enter the topmost skin regions.

Cooperation among all the different kinds of cells maintains normal skin and repairs damaged skin from scrapes, cuts, ultraviolet light, and oxidative reactions. Cellular activity uses considerable energy to secrete complex lipid molecules, maintain tight junctions between cells, and avoid water loss by building a lipid protein coat. (There is much more about lipids in chapter twenty-five on membrane production.)



Anatomical illustration of a section through human skin, showing the epidermis, sweat gland, hair follicle, blood vessels, fat cells, and sebaceous gland. *(Science Source/Science Source/Science Source)*

The superficial epidermis has multiple layers, with a surface that is hard but flexible. It regulates water release and is the major barrier against external toxins, microbes, and infections. The physical barrier includes tight junctions between cells and multiple large scaffolding proteins. A chemical barrier consists of enzymes to break down toxins, fats, acids, and peptide molecules. Toxic particles secreted against multiple intruders must be eliminated after battle.

The thickness of the epidermis is quite variable—three times thicker on the palms and soles of the feet than on the eyelids. In the epidermis, oxygen diffuses from the air to feed the topmost cells. The dermis structure below consists largely of the proteins collagen, for strength, and elastin, for flexibility. Diverse types of extracellular matrix in the dermis serve as signals to immune cells to stimulate varied activities.

The subterranean dermis houses a wide range of immune cells and a large number of connective cells that secrete matrix between cells. There is also the basement membrane that separates the dermis and epidermis. Very recently, a new layer of fluid channels, called the interstitium, has been found below the skin's surface, as well as in connective tissue throughout the body. It was not possible to observe this layer until now because previous research techniques for

observing tissue always eliminated water. It remains to be seen in future research whether these channels are conduits for signals throughout the body.

The very top hard layer of skin is made of more than twenty layers of specialized keratinocytes that have shed their nuclei and are tightly joined together with sticky molecules. These cells produce fatty material for a strong, waterproof barrier that is resistant to infection and trauma. In this outermost layer, there are also large numbers of traveling T cells with diverse skills that converse with keratinocytes.

DYNAMIC CONVERSATIONS

Only recently has it become clear that skin cell conversations are as dynamic as those of gut cells and capillaries. The skin is the largest organ in the body and has the second-largest number of microbes to deal with after the gut. Skin has the most varied environments and is the most exposed. Individual keratinocytes must organize resources to defend against physical assault and deal with a wide range of microbes of all kinds, including fungi and viruses. Like the gut, skin serves as a barrier that is vital for the entire body. Increasingly, as in the gut, immune activity on the skin has been found to have ramifications in other organs throughout the body.

While gut cells talk with microbes about digestion, skin has other issues. Conversations maintain its strong surface to protect against microbial invasions and injuries. Keratinocytes must engage in various healing projects as well. Even on the barren skin, an army of immune cells can be called to rapidly respond. Keratinocytes must determine which bacteria are allowed to stay on the surface in each location along with particular immune cells. As in the gut, multiple conversations must work to inhibit immune attacks on vital friendly microbes and the skin tissue itself. Much of the communication is with friendly microbes that help protect against other, dangerous invaders.

Conversations among lining and connective cells regulate the various matrixes between cells that provide specific functions. These conversations determine the matrix for the topmost barrier where keratinocytes are fixed. Fat cells converse about matrix that provides some cushion below the surface of the skin. Surprisingly, fat cells also send signals to stop particular bacterial infections and can signal to increase the amount of brown fat, which regulates temperature, among other functions.

Via signals, connective cells produce matrix for different situations using various amounts of molecular fibers, ground substance, and extracellular fluid. Ground substance is a thick liquid, composed of large molecules, that uses variable

amounts of amino acids, peptides, proteins, and sugars for different situations. In some situations, ground substance can be so thick that microbes find it hard to navigate through it.

MORE ABOUT KERATINOCYTES

Keratinocytes are born from stem cells deep within the hair follicle, or in between follicles. Like gut lining cells that gradually move up from deep crypts to the top of villi, keratinocytes move through various layers of skin cells to the surface. During this migration, they also undergo gradual maturation with a series of modifications that enable them to build more signals and receptors for complex decision making. Upon arriving at the top, some of the lining cells shed their nuclei to form the tight barrier. Signals from mature keratinocytes direct all activity in all layers and particularly protect nerves, immune cells, friendly microbes, and T cells traveling at the outermost layers of the skin.

Keratinocyte decision making includes responding to harsh conditions such as heat, cold, moisture, toxins, ultraviolet light, bruises, and cuts. Neighboring connective cells stay in close contact with these lining cells via signals. Traveling immune cells live in the skin and communicate constantly with keratinocytes about microbes, infections, and trauma. Neurons provide sensation related to touch and pain and also engage in signaling to the master lining cells about changing conditions.

Talking with Immune Cells and Microbes

Because the skin landscape is relatively desolate, keratinocytes do not build large lymph tissue, as in the gut and other organs. Instead, because of its flat nature, skin must rely on an abundance of individual traveling immune cells on the surface. To organize a large army of individual mobile cells spread over the skin, even more signals are essential than when dealing with the fixed large lymph centers of other tissues.

Keratinocyte signals, in conjunction with neurons and microbes, call for immune cells that produce low levels of chronic inflammation. This serves as protection against more severe infections by keeping active immune cells readily available. Specific immune cells work to repair the minimal damage produced by this low-level inflammation. With stress or injury, more powerful signals are sent that alter the inflammation to cope with greater problems. Keratinocyte signals can also do the opposite and stop recruitment of all traveling immune cells.

The skin also requires many more subtypes of supportive immune cells than anywhere else. Unlike in other organs, multiple subtypes of the immune cells that present material to T cells work in tandem. Some talk to each other, and others signal at different times in sequence while the suspicious particle is evaluated. When producing a particular type of protective inflammation against a fungus, for example, actions from three distinct presentation cells and multiple types of T cells take place for one process.

Microbial conversations among keratinocytes, connective cells, and immune cells have various effects. Some microbes live peacefully on the skin and only become dangerous when there are breaks in the skin, such as with insect bites and traumatic injuries. Microbial signals can gather all the cells to fight particular enemy species. With immune deficiencies, conversations among immune cells and microbes are altered, producing dangerous infections.

Microbial signals have diverse effects. In one situation, a fungus stimulates a neuron that causes pain and itching. Alternatively, fungal signals to neurons can cause painless ulcers. They can signal lining cells to produce various types of inflammation. Microbial signals to T cells can increase or decrease inflammation activity. These signals can directly trigger more T cells that chase specific enemy microbial species. Signals can also inhibit T cells that would otherwise turn against human cells and cause autoimmune disease.

Unlike in the gut, where food attracts particular microbes, there are not a lot of food-attracting microbes on the skin. Still, there are at least a million microbes every square centimeter. Various types of microbes live near glands, neurons, or immune cells. Multiple factors determine which microbes survive—skin pigment, cleaning products, temperature, moisture, and acidity.

The most complex skin region for microbes is deep in hair follicles, somewhat analogous to the crypts in the gut. The follicle is the point of entry for immune cells from the blood. The follicles that dot the skin have the most diverse immune cells and microbes. As in gut crypts, stem cells often live in deep follicles. Multiple layers of keratinocytes protect the follicle and immune cells nearby.

Directors of Communication

Among wide-ranging conversations about health and disease, keratinocytes direct all of the action. Keratinocyte signals to connective cells determine particular matrixes. Keratinocytes monitor conversations among microbes and immune cells. They trigger inflammation and instruct T cell responses. Keratinocytes must constantly temper T cell responses to avoid reactions against friendly microbes and human cells. Even when immune cells support friendly microbes and repel

enemies, keratinocyte signals are the controlling factors. In fact, most immune signals to microbes are relayed through keratinocytes.

Recent research is discovering a wide variety of immune cells stimulated by keratinocyte conversations. These immune cells are produced in bone marrow, lymph tissue, or at a particular site on the skin. Like immune memory cells, keratinocytes maintain their own history of events for future reference. They remember the range of immune cells that are available for them to call for help, and even the location of the problem.

Keratinocytes also don't just sit still when a cancer invasion starts; they behave like local police to repair damage that aberrant cells are creating. When keratinocytes come across abnormal mutated cells that could be cancerous, these master skin lining cells take dynamic action by themselves against these cells. Signals suppress the types of inflammation that can lead to cancer. Keratinocytes have now been observed surrounding invading cancer cells, shepherding them away, and repairing the damage. Because of the extensive use of signals among skin cells, the new science of signaling might have the most rapid impact on skin diseases.

MEMORY T CELLS

Twice the number of T lymphocytes live on the skin as in lymph tissue for other organs. These T cells include multiple varieties, including the largest number of memory cells of any organ in the body and diverse types of active T cells. Active T cells are the first and best defense against microbes. Particular T cells are also called from the thymus to the skin to monitor for cancer and other skin diseases. With a cut, T cells and keratinocytes produce an intense array of signals to avoid immediate severe infections.

After trauma, inflammation, or infection, T cells produce special memory cells that continue to monitor troubled sites. Memories are maintained of all exposures to dangerous microbes, toxins, trauma, and cancer. The same conditions could rapidly flare up at any moment, and these cells are ready. Memory cells retain knowledge of the exact locations on the skin where an infection occurred, the particular microbes involved, and the signals that eliminated them. Skin conditions are constantly changing, and memory cells keep up conversations with microbes that are nearby to determine whether action is needed.

Memory cells have spatial memory that allows them to understand the unique topography and landscape where a battle occurred. For example, fungi are particularly difficult to monitor. Fungus can exist as buds on the surface or as needles deep into tissues. Dangerous subterranean hyphae (the long tubular

branching structures of a fungus) track into underlying skin layers and must be followed and attacked by memory cells.

Perhaps the most unusual feature of skin memory T cells is that they don't need presentation cells that other T cells require to become killer cells. Skin memory cells can rapidly change their mode when necessary by themselves. They can produce molecules to attack microbes directly and can send immune signals to get help. They can rapidly become an army of killer cells. They have the ability to change the entire local environment.

SKIN IMMUNITY AND DISEASE

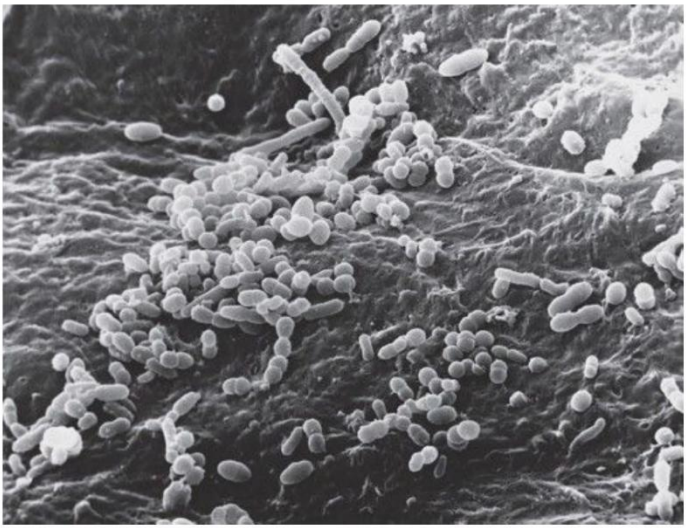
The field of immunology has recently evolved based on the discovery of these wide-ranging conversations among varied cells. Previously, most research delved into the complexities of bone marrow, lymph node communities, and the thymus. While it is difficult for research to follow small signal molecules on the skin that travel among many cells, the modern focus has changed to study conversations among multiple types of cells, including immune cells, microbes, neurons, connective cells, capillaries, and lining cells. On the skin, almost all of the action is based on these signals, especially back-and-forth communication between microbes and keratinocytes.

To fight various skin diseases, such as psoriasis or dermatitis, keratinocytes invite new types of immune cells among hundreds of possible subtypes of T cells and other white blood cells. Only mature keratinocytes have learned to produce large amounts of unique signals specific to the skin's needs. Without these signals, the skin would be overrun with allergic responses to its wide-ranging exposure to microbes.

When keratinocytes die, molecular signals are released that activate particular immune cells, which cause inflammation. Sometimes keratinocytes kill themselves by programmed suicide in order to send signals for inflammation. Planned suicides produce vital signals for emergencies in both the gut and skin. In response, viruses and microbes produce molecules to interfere with planned cell suicide, so signals will not trigger inflammation and harm microbial colonies.

Potentially dangerous microbes most often exist on the skin without producing any problems. They can even be helpful while living peacefully. But then they can suddenly change, which often occurs from communication among multiple other species. Peaceful colonies can suddenly change to produce infections in hair follicles, cellulitis, or even severe blood infections that can go to the bone and heart. Bacteria can rapidly become dangerous "flesh-eating" varieties in a wound, mostly in those with impaired immunity from other diseases.

Bacteria can also be part of chronic infections and even contribute to autoimmune disease.



Bacteria on the surface of the skin. Electron micrograph. *(David M. Phillips/Science Source)*

Recently, signals were identified that incite certain bacteria—often *Streptococcus pyogenes*, which causes sore throat and often lives peacefully on the skin—to become the dangerous flesh-eating type. A specific toxin was found that triggered a local neuron in two ways based on natural conversations among immune cells and neurons. The first signal caused severe pain out of proportion to any signs of disease.

The second exploited the normal neuron signal for wounds with pain but without infection that inhibits immune activity. Instead of using the neuron signal for infection that calls for immune cells, the neuron was manipulated into using signals that inhibit as if there were no infection. This signal stopped neutrophils both from traveling to the site and from sending attack molecules. The result was that the bacteria had no resistance and therefore became flesh-eating microbes.

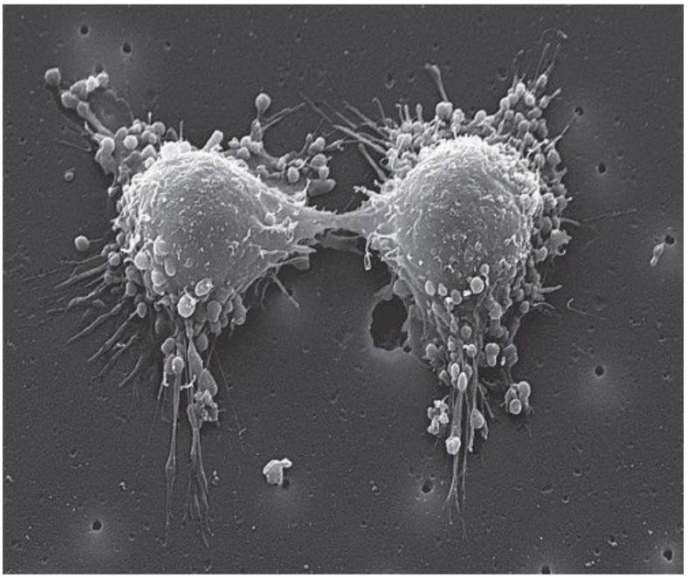
CHAPTER 8

CANCER CELLS—THE ULTIMATE MANIPULATORS

THE MOST ACCEPTABLE current theory holds that cancer starts through a set of random mutations, which produce an abnormal cell with unhinged cellular processes, including runaway duplication. Mutations can be genetic, or from environmental factors (including foods), interactions with microbes, and the disarray that ensues with inflammation.

Mutations can occur in the very pathways that proofread DNA duplication, which leads to a vicious cycle in which even more mutations are produced that break the ordinary limits on reproduction. When cancer begins, a cell slowly accumulates multiple mutations—often over years—usually starting as a cancer cell with as many as a dozen mutations. A cancer cell may have a hundred different mutations, and individuals with the same type of cancer can have large, varied sets of diverse mutations. Only a small percentage of abnormal cells become cancerous. But one abnormal cell is enough to start the entire process of building a cancer.

There are several ways that mutations allow cancer cells to overcome the controls that are designed to stop abnormal cell behavior. All cells have a built-in system called the programmed cell suicide pathway, which eliminates both aberrant cells and severely infected cells. But in cancer, suicide is not triggered, and abnormal cells continue to grow and multiply. In another mechanism, cancer cells alter the tips of chromosomes, called telomeres, that are needed for the cell to reproduce. These normally wear down gradually, with successive division, until eventually cell division stops. Cancer cells stimulate an enzyme that rebuilds the telomeres so the cell can continue to reproduce out of control, even producing as many as five cells in division rather than two.



Cancer cells divide rapidly in a chaotic, uncontrolled manner. Electron micrograph. *(Steve Gschmeissner/Science Source)*

Cancer mutations alter RNA production as well in complex ways that just now are being discovered. RNAs that normally stimulate repair of cell damage are inhibited, which helps the cancer develop. RNAs can also trigger cancer-producing genes. For example, researchers recently found a large system of RNAs that regulate five hundred genes, which are altered to trigger, inhibit, or otherwise affect cancer growth. These genes have 250,000 distinct interactions, with many of them producing cancer.

Cancer cells create their own unique communities using advanced cellular communication. Similar to microbe behavior, cancer cells can act as individuals at one moment and then join comrades to behave as if they were a multicellular creature. Signals to cancer comrades warn about viral attacks. They can signal for the growth of new blood vessels and reroute existing blood vessels for their own benefit. Via signals, cancer cells trick healthy cells around them to produce protein factors for their benefit. The matrix between the cells is altered by the cancer cell signals. Conversations attract microbes to become helpers and inhibit immune attacks. Cancer cells are able to subvert local immune cells to help them rather than attack.

Cancer signals vary extensively. Cancer cells generate ways to make blood vessels become leakier, enabling aggressive travel into other tissue. Signals recruit neurons to help cancer colonies grow. Messages that normally allow neurons to migrate in a fetus also give directions for cancer cell travel in the fetus. Signals

increase production of proteins and energy molecules, enabling cancer cells to survive in altered environments with less food. As T cells rapidly build an army of fighting cells, cancer cells use these same internal signals to alter their own metabolism to rapidly copy themselves as they begin to form a large colony.

CONVERSATIONS WITH LOCAL SUPPORTIVE CELLS

Via signals, cancer cells seduce all sorts of nearby normal cells to join them in their growth agenda. Cancer cells are able to intercept the conversations of local neighboring cells and send their own signals to subvert them to the cancer's cause. Signals entice connective cells to alter scaffolding, making extracellular matrix more helpful to cancer growth and less helpful to ordinary tissue cells. The new environment provides low oxygen and more fluid to stop immune cells from chasing down the invading cancer.

Signals can provide many benefits for cancer to grow in the local environment. Cancer cells induce tissue damage, which blocks medications from getting to the cancer cells. Local structural lining cells cooperate by producing protective linings for the cancer tissue and new blood vessel linings that prohibit immune cells from tracking cancer cells. Immune cells are stimulated to produce factors for cancer growth that are normally used to heal wounds and enlarge ordinary tissue. Local cells that normally help T cells fight cancer do the opposite by sending signals to inhibit T cell aggressive behavior.

More is being learned about how cancer cells and surrounding tissue cells cooperate via signaling. Cancer cells first use a variety of signals to organize the existing cancer cells into a preliminary structure. Then they recruit surrounding connective tissue cells to build the best internal structural configuration for growth of the cancer. This same organizing principle occurs to form metastases in distant tissue. First, the cancer cell signals to organize other cancer cells, then it signals to local neighbor cells to organize further support for the cancer structure and its growth.

One important way cancer cells manipulate local cells via signals is to stimulate them to become stem cells. These stem cells revert into fetal-like cells with unusual properties that support cancer growth. Cancer cells are able to use these same fetal-like capacities as well. As fetal-like stem cells, both cancer cells and local cells are able to transition from being stable cells to cells that are mobile and aggressive. This allows local cells to help cancers proliferate in a variety of unique ways.

In the fetus, two fundamental types of tissue are connective tissue cells and lining cells. Lining cells are passive and structural, and connective tissue cells are

active, mobile, and aggressive. When a cell moves into position in the developing fetus, it transitions from the migrating type to the structural type. It has been found that cancer cells, and their activated neighbors, can use this switch back and forth in both directions to build tissue and metastatic colonies. There is more about this transition later in the section on metastasis.

DISRUPTING THE IMMUNE SYSTEM

Cancer cells are eager for inflammation. Normally, inflammation protects against microbe invasions and helps heal wounds. In the chaos of inflammation, when cells fight microbes and repair damage, there is more opportunity for mutations stimulated by immune attack signals. Maintaining a continual level of inflammation, cancer has been called "a wound that doesn't heal." When inflammation becomes the norm, alterations allow cancer cells to confuse immune cells in multiple ways. Immune cells are fooled into considering cancer cells as part of the healing process and even help "repair" them.

Cancer cells develop a close relationship with immune scavenger cells. Scavenger cells become abundant in cancer tissue, providing a third of the total mass of certain types, such as many solid malignant tumors. Responding to cancer cell signals, scavenger cells don't behave normally and don't listen to T cells that track abnormalities. These scavenger cells also work with cancer stem cells to stimulate new blood vessels, and they are coaxed by cancer cell signals to help produce new metastatic colonies. The more scavenger immune cells found at a cancer site, the worse the prognosis.

Cancer cells benefit from T cells' typical behavior because T cells are ill prepared for the slow, drawn-out fight needed against cancer. T cells normally direct fairly short attacks on abnormal cells or microbe invaders. Once the assault is done, regulatory T cells inhibit inflammation to stop tissue damage. This short-lived aggressive confrontation severely limits the ability of immune cells to eradicate cancer cells, which are complex and long-lived.

Although ultimately not properly prepared to fight cancer, early-warning T cells start an attack and stimulate a delayed response with other cells as well. But the complexity of cancer variations makes these attacks problematic. Abnormal material is ordinarily presented to T cells, and they attack these cells. But inside a cancer, a particular stem cell can suddenly develop a new and different mutation. This cell multiplies and becomes a new subset of cells—a variant cancer within a cancer. It is difficult for T cells to adjust to produce multiple varied responses. To remedy this, the latest cancer treatments design new T cell receptors for particular cancer cell types and place them in T cells for very specific attacks on

particular subsets of cancer cells.

Fighting cancer takes a long time and needs various sequences of immune signals for each stage of cancer development. After more ordinary short attacks, regulatory T cells are triggered that tamp down aggressive behavior; unfortunately, the killer types needed for continued cancer eradication are not the ones that are triggered. Cancer cells help stimulate more of these regulatory cells, which become the most abundant cells and interfere with further attacks on the cancer. Cancer cells also compete directly with T cells and damage them by eating most of the amino acid arginine that T cells need.

Because of ineffectiveness in long-lasting warfare against cancerous growth, T cells have been called "exhausted." But, recently, a small number of long-acting cancer-fighting T cells have been discovered. These act more subtly against the cancer. They are not as aggressive and don't cause tissue damage. New therapies aim to stimulate these rare, longer-acting T cells. But as local cells work to help the cancer by inhibiting T cells, short-term, aggressive T cells are triggered, which interfere with the longer-acting T cells. Effective therapies will have to send signals to avoid triggering new short-acting T cells, while stimulating more of the long-acting variety.

Because of the normal protective pathways in T cells that inhibit aggressive behavior after short attacks, new cancer medications attempt to eliminate the natural brake on T cells' aggressive behavior. In most situations, normal pathways inside T cells, called "checkpoints," inhibit extended attacks that are damaging to human tissues. These "checks" on T cell activity stop unnecessary aggressive behavior. New cancer medications attempt to block these checkpoints, thus releasing more aggressive behavior against the cancer. An entire class of new medications are called checkpoint inhibitors.

THE ROLE OF MITOCHONDRIA IN CANCER PROLIFERATION

The important relationship between mitochondria signals and cancer growth is also becoming clearer. As free-floating, oval-shaped organelles inside cells, mitochondria provide energy and other metabolic functions for all cells, but for cancer, they help in many other specific ways. In fact, altered mitochondria have been found to be vital in producing many of cancer's already mentioned capabilities.

The mutated mitochondria in cancer cells are able to alter their complex metabolism to provide help in various ways. It is in mitochondria that the process of programmed cell death is triggered to eliminate infected or abnormal cells. In cancer cells, mitochondria are altered to avoid this. Cancer cells rely on unusual

sources of food for energy, and altered mitochondria produce new pathways to use these new sources of energy. Mitochondria also alter pathways to deal uniquely with chronic cell stress.

In T cells, mitochondrial metabolic signals supply the necessary fuel for their rapid reproduction, attachment to cancer or infected cells, and production of deadly immune synapses to kill targeted cells. Similar altered signals help cancer's rapid growth and aggressive behavior. Also, mitochondrial signals are involved in the cellular pathways related to the checkpoints on T cells' aggressive behavior already mentioned above. In the future, understanding mitochondrial signals will enable new medications for "checkpoint" inhibition. There is more about mitochondria in chapter twenty-four.

Surprisingly, cancer cells can share their mutated mitochondria by sending them in transport vesicles, called exosomes, to other cancer cells. Another way that cancer cells transfer mitochondria to other cells is by using tunneling nanotubes between cells. (More on signal transfer vesicles and tunneling nanotubes later in this chapter.) Mitochondria that are altered to benefit the cancer cause are basically sent as signals to help strengthen comrades in the cancer community.

ENLISTING THE HELP OF BRAIN CELLS

Support from neurons is a necessity for cancer growth. Signals from neurons inhibit T cell attacks on cancer cells. Cancer cells invade tissues around neurons and travel along the ready-made highway next to nerves. Without neurons, cancer cells don't grow and produce distant colonies. Several neurotransmitters can stimulate cancer growth, while others inhibit it. For example, sympathetic neurons stimulate early cancer development, and parasympathetic signals trigger later development. The more neurons that help, the more dangerous the cancer becomes.

Supportive brain cells, described in the next section, can aid cancer cells in many ways, such as helping them cross multiple barriers that ordinarily keep the brain safe from invasion. Also, these supportive brain cells, along with white blood cells, are fooled into helping to build cancer tissue. Cancer cells that grow from supportive brain cells can connect into wiring circuits of neurons by producing synapses with neurons similar to the types normally found in signaling between neurons. The two basic types of synapses that brain cancer cells co-opt include those that transmit sacs filled with neurotransmitters and those that use a flow of electricity between cells. Both of these are discussed in chapter nine about neurons.

Using electrical synapse connections, brain cancer cells hijack the electrical energy of neurons to produce more cancer growth. At least 10 percent of cells in one type of brain cancer receives electrical signals directly from synapses with neurons. Another 40 percent of the cancer cells are not connected to neurons but are connected by electrical synapses among the cancer cells. Through these cancer-cell-to-cancer-cell synapses, electrical energy first taken from neurons is transmitted throughout the brain cancer community. Therefore, half of the brain cancer cells benefit from signals and electricity from neural circuits to help cancer cells grow and organize. It is not yet understood exactly how this neuronal electricity is used by the cancer cells.

Astrocytes, the most abundant supportive brain cell, can also provide significant support to brain cancer proliferation. Growth factors from astrocytes that normally nourish neurons are diverted to help the cancer grow. With damage in the brain from the cancer, astrocytes rapidly multiply to protect all other cells with a unique type of inflammation, but they inadvertently block T cell entry into the cancer colony. Astrocytes additionally help cancer growth by sending signals to immune cells to increase the chaos of inflammation. Astrocyte conversations are further described in chapter ten.

INTERACTING WITH MICROBES

The life of cancer is complicated by the presence of trillions of microbes and their large number of signals. Microbes can benefit cancer cells but can also attack them. Like skin and gut lining cells, cancer cells must determine which microbes are friendly and converse with them. They must also evade attack from antagonistic species.

Twenty percent of the various types of cancer are known to be helped by microbe infections. A recent study showed that 12 percent of worldwide cancer types were initiated by infections related to microbes. Of trillions of microbes, ten types definitely are known to cause particular types of cancer. These microbes infect large numbers of people, but cancer only appears in a small number of them. Several bacteria are known to produce molecules that initiate cancer. Viruses initiate several cancer types by injecting RNA or DNA into human cells, sometimes placing them permanently in genes.

Thousands of other microbes likely help produce cancer in unknown ways—these cancer types include lung, genital, urinary, colon, rectum, gall bladder, and lymph. Recently, bacteria have been found traveling with metastatic cancer cells. Another recent study found two distinct microbe species interacting in the colon to stimulate cancer. With combined signals, these two species work together to