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Cell Communications: The Inside Story by John D. Scott and Tony Pawson

Before reading this article, review pages 445-455 in Lehninger Principles of Biochemistry, 3e.

Cell signaling has become one of the most exciting and productive areas of biochemical research. Signals carried by a wide variety of extracellular ligands (such as growth factors, hormones, and neurotransmitters) trigger changes in the metabolic activities of a cell by acting through specific receptors in the plasma membrane. Many signal transductions occur via a series of protein-protein interactions that begin with the binding of the extracellular ligand to an external domain of a specific transmembrane receptor in the plasma membrane. For one large class of ligands (platelet-derived growth factor, PDGF, is one example), ligand binding induces clustering of two or more receptor molecules, whose interaction with each other initiates signal transduction. The intracellular domain of the receptor is an enzyme, protein tyrosine kinase, which catalyzes reciprocal phosphorylation of Tyr residues in the intracellular domains of the paired receptor molecules. As described in this article, phosphotyrosine residues of these receptor tryosine kinases (RTKs) become the point of nucleation for a multiprotein complex. Scaffolding proteins that bind both a phosphotyrosine residue on the RTK and a specific region of another protein serve as adaptors, holding the complex together, like a Lego block between two others. The SH2 (sarc homology 2) domain of these scaffold proteins (Grb2, for example) binds phosphotyrosine; other domains of the protein have specific regions for interfacing with other proteins in the signaling pathway.

This article describes the role of these multiprotein complexes and their scaffolding proteins in carrying signals of various kinds into the cell, triggering a change in metabolism or gene expression. Genetic defects in any of the proteins of the multiprotein complex can interfere with proper signaling through the associated receptor. In many cases, the defective signaling leads to serious disease, including cancer. The proteins of these complexes have therefore become attractive targets for drug action.

FURTHER READING

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QUESTIONS

1. Why is it essential for receptors of the RTK type to form dimers before they become active in signaling?

2. What is an SH2 domain, and what is its function in signaling? What other domains are commonly found in scaffold proteins? What does each of these domains bind to?

3. A number of scaffold proteins have SH2 domains, but each binds to a different signaling partner. How is this specificity achieved?

4. What are the advantages to a cell in using scaffold proteins in signal transduction?

5. What is the role of protein tyrosine phosphatases in signaling through RTK receptors? What effect would an inhibitor of protein tyrosine phosphatase have on insulin signaling?

The tiny cells in our bodies harbor amazing internal communication networks. Understanding how those circuits are organized could help scientists develop new therapies for many serious disorders

Cell Communication:
The Inside Story

by John D. Scott and Tony Pawson

MESSENGER-EMITTING CELL

RECIPIENT CELL

MESSENGER MOLECULES

SIGNALING PATHWAYS

RECEPTOR

SIGNAL TRANSMISSION in a cell begins when messenger molecules, such as hormones, dock with receptor molecules on the cell surface. This docking induces the cell to relay the messenger's command down specific signaling pathways to molecules that respond to the order. In this case, the response includes activation of a gene, followed by production and secretion of the protein it encodes. How is such precise signaling accomplished? Until recently, answers were scarce.

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As anyone familiar with the party game "telephone" knows, when people try to pass a message from one individual to another in a line, they usually garble the words beyond recognition. It might seem surprising, then, that mere molecules inside our cells constantly enact their own version of telephone without distorting the relayed information in the least.

Actually, no one could survive without such precise signaling in cells. The body functions properly only because cells communicate with one another constantly. Pancreatic cells, for instance, release insulin to tell muscle cells to take up sugar from the blood for energy. Cells of the immune system instruct their cousins to attack invaders, and cells of the nervous system rapidly fire messages to and from the brain. Those messages elicit the right responses only because they are transmitted accurately far into a recipient cell and to the exact molecules able to carry out the directives.

But how do circuits within cells achieve this high-fidelity transmission? For a long time, biologists had only rudimenta-

ry explanations. In the past 15 years, though, they have made great progress in unlocking the code that cells use for their internal communications. The ongoing advances are suggesting radically new strategies for attacking diseases that are caused or exacerbated by faulty signaling in cells—among them cancer, diabetes and disorders of the immune system.

Refining the Question

The earliest insights into information transfer in cells emerged in the late 1950s, when Edwin G. Krebs and Edmond H. Fischer of the University of Washington and the late Earl W. Sutherland, Jr., of Vanderbilt University identified the first known signal-relaying molecules in the cytoplasm (the material between the nucleus and a cell's outer membrane). All three received Nobel Prizes for their discoveries.
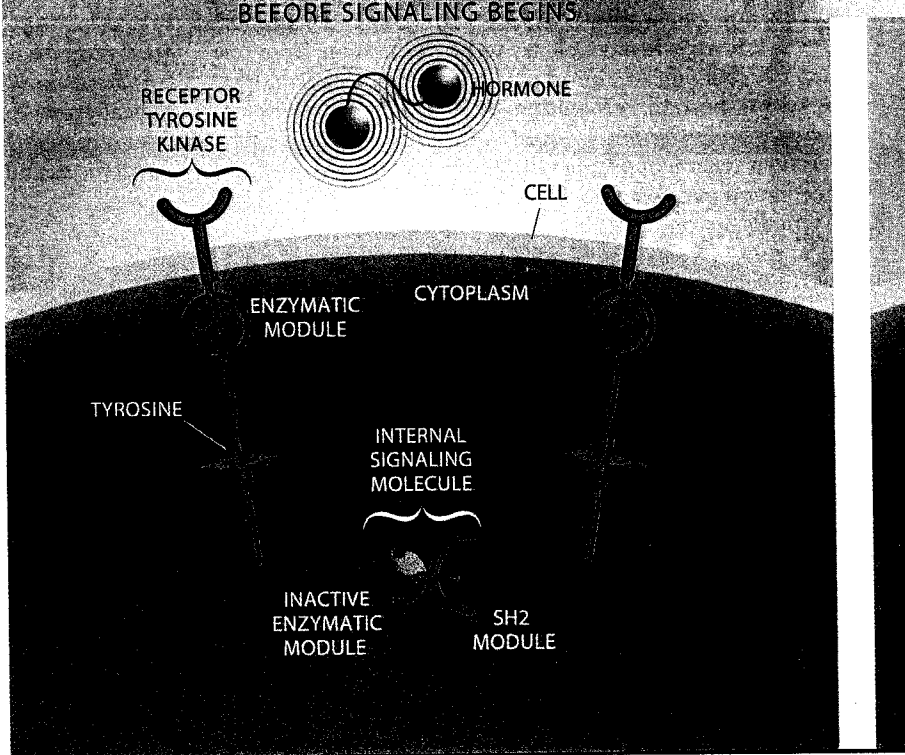
By the early 1980s researchers had gathered many details of how signal transmission occurs. For instance, it usually begins after a messenger responsible for carrying information

SECRETED
PROTEIN

DNA
IN
NUCLEUS

ACTIVATED
GENE
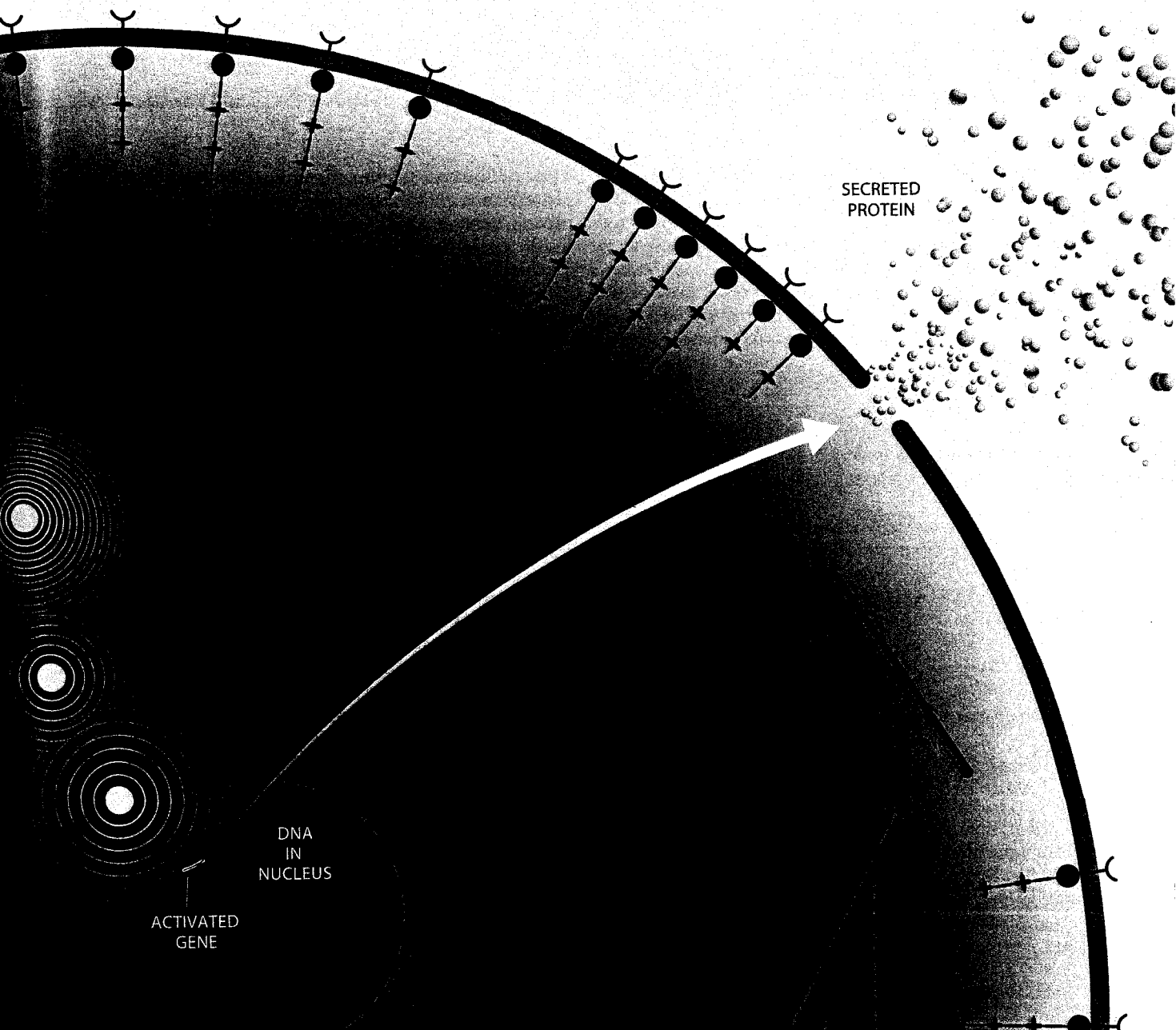
The Role of Modules in Signaling

The molecules that form signaling circuits in cells are often modular—built from components that carry out distinct tasks. This discovery emerged in part from studies of molecules known as receptor tyrosine kinases (*pogo-stick shape in first panel*). When a hormone docks with those molecules at the surface of a cell (*second panel*), the receptors pair up and add phosphates to tyrosine, an amino acid, on each other's cytoplasmic tails. Then so-called SH2 modules in certain proteins hook onto the altered tyrosines (*last panel*). This linkage enables "talkative," enzymatic modules in the proteins to pick up the messenger's order and pass it along.

BEFORE SIGNALING BEGINS

RECEPTOR TYROSINE KINASE — HORMONE — CELL — ENZYMATIC MODULE — CYTOPLASM — TYROSINE — INTERNAL SIGNALING MOLECULE — INACTIVE ENZYMATIC MODULE — SH2 MODULE

between cells (often a hormone) docks temporarily, in lock-and-key fashion, with a specific receptor on a recipient cell. Such receptors, the functional equivalent of antennae, are able to relay a messenger's command into a cell because they are physically connected to the cytoplasm. The typical receptor is a protein, a folded chain of amino acids. It includes at least three domains: an external docking region for a hormone or other messenger, a component that spans the cell's outer membrane, and a "tail" that extends a distance into the cytoplasm. When a messenger binds to the external site, this linkage induces a change in the shape of the cytoplasmic tail, thereby facilitating the tail's interaction with one or more information-relaying molecules in the cytoplasm. These interactions in turn initiate cascades of further intracellular signaling.

Yet no one had a good explaination for how communiqués reached their destinations without being diverted along the way. At that time, cells were viewed as balloonlike bags filled with a soupy cytoplasm containing floating proteins and organelles (membrane-bound compartments, such as the nucleus and mitochondria). It was hard to see how, in such an unstructured milieu, any given internal messenger molecule could consistently and quickly find exactly the right tag team needed to convey a directive to the laborers deep within the cell that could execute the order.

On the Importance of Lego Blocks

Today's fuller understanding grew in part from efforts to identify the first cytoplasmic proteins that are contacted by activated (messenger-bound) receptors in a large and important family: the receptor tyrosine kinases. These vital receptors transmit the commands of many hormones that regulate cellular replication, specialization or metabolism. They are
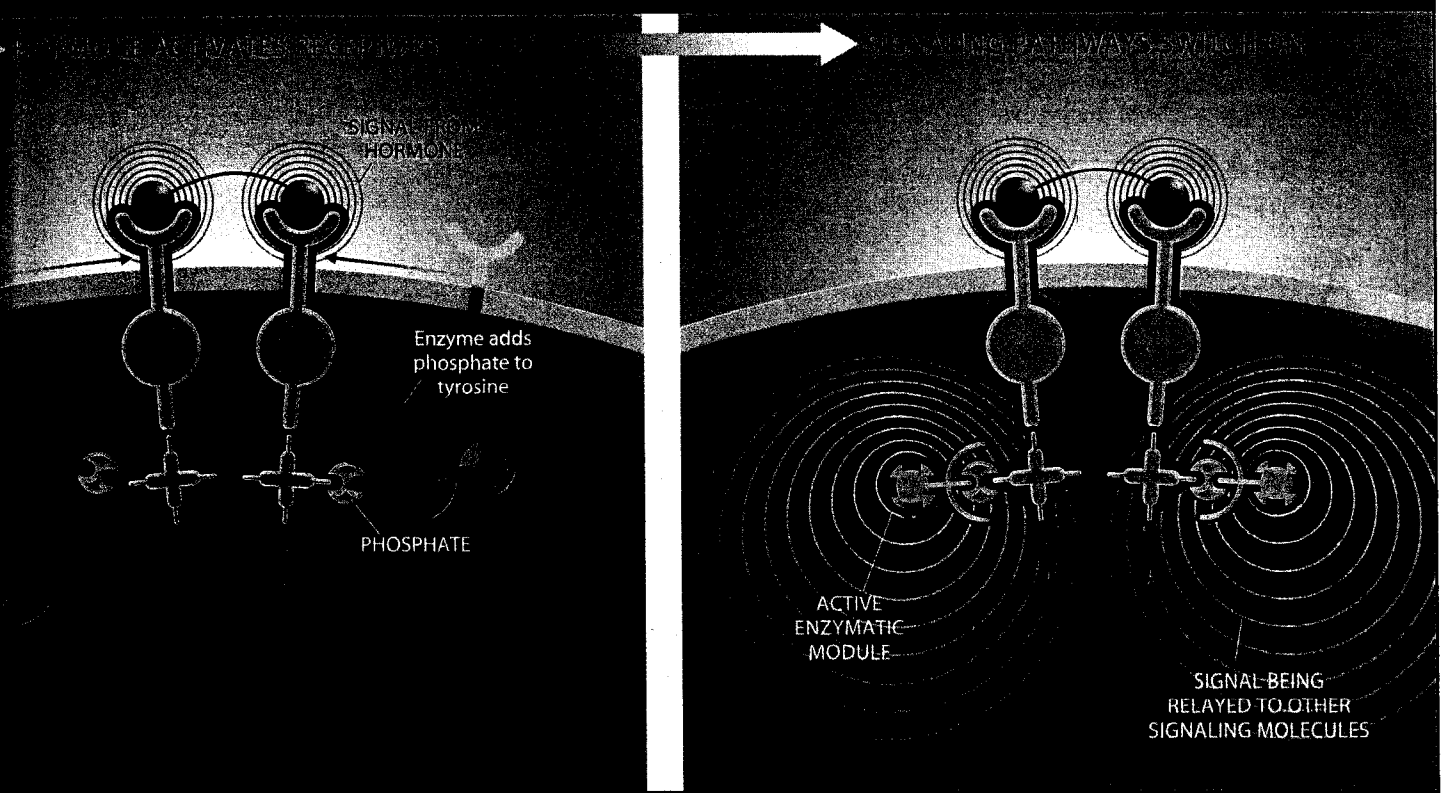
so named because they are kinases—enzymes that add phosphate groups to ("phosphorylate") selected amino acids in a protein chain. And, as Tony R. Hunter of the Salk Institute for Biological Studies in La Jolla, Calif., demonstrated, they specifically put phosphates onto the amino acid tyrosine.

In the 1980s work by Joseph Schlessinger of New York University and others indicated that the binding of hormones to receptor tyrosine kinases at the cell surface causes the individual receptor molecules to cluster into pairs and to attach phosphates to the tyrosines on each other's cytoplasmic tails. In trying to figure out what happens next, one of us (Pawson) and his colleagues found that the altered receptors interact directly with proteins that contain a module they called an SH2 domain. The term "domain" or "module" refers to a relatively short sequence of about 100 amino acids that adopts a defined three-dimensional structure within a protein.

At the time, prevailing wisdom held that messages were transmitted within cells primarily through enzymatic reactions, in which one molecule alters a second without tightly binding to it and without itself being altered. Surprisingly, though, the phosphorylated receptors did not necessarily alter the chemistry of the SH2-containing proteins. Instead many simply induced the SH2 domains to latch onto the phosphate-decorated tyrosines, as if the SH2 domains and the tyrosines were Lego blocks being snapped together.

By the mid-1990s groups led by Pawson, Hidesaburo Hanafusa of the Rockefeller University and others had revealed that many of the proteins involved in internal communications consist of strings of modules, some of which serve primarily to connect one protein to another. At times, whole proteins in signaling pathways contain nothing but linker modules.

But how did those nonenzymatic modules contribute to swift and specific communication in cells? One answer is that

Cell Communication: The Inside Story

RECEPTOR ACTIVATES RECEIVERS

SIGNAL FROM
HORMONE

Enzyme adds
phosphate to
tyrosine

PHOSPHATE

SIGNALING PATHWAYS SWITCH ON

ACTIVE
ENZYMATIC
MODULE

SIGNAL BEING
RELAYED TO OTHER
SIGNALING MOLECULES

they help enzymatic domains transmit information efficiently. When a protein that bears a linker also includes an enzymatic module, attachment of the linker region to another protein can position the enzymatic module where it most needs to be. For example, the act of binding can simultaneously bring the enzymatic region close to factors that switch it on and into immediate contact with the enzyme's intended target. In the case of certain SH2-containing proteins, the linker module may originally be folded around the enzymatic domain in a way that blocks the enzyme's activity. When the SH2 domain unfurls to engage an activated receptor, the move liberates the enzyme to work on its target.

Even when a full protein is formed from nothing but protein-binding modules, it can function as an indispensable adapter, akin to a power strip plugged into a single socket. One module in the adapter plugs into a developing signaling complex, and the other modules allow still more proteins to join the network. An important benefit of these molecular adapters is that they enable cells to make use of enzymes that otherwise might not fit into a particular signaling circuit.

Nonenzymatic modules can support communication in other ways, too. Certain molecules in signaling pathways feature a protein-binding module and a DNA-binding module

that meshes with, or "recognizes," a specific sequence of DNA nucleotides in a gene. (Nucleotides are the building blocks of genes, which specify the amino acid sequences of proteins.) James E. Darnell, Jr., of Rockefeller showed that when one of these proteins attaches, through its linker module, to an activated receptor kinase, the interaction spurs the bound protein to detach, move to the nucleus and bind to a

SH2 DOMAIN

POSITIVELY
CHARGED
POCKET

PHOSPHATE

SEGMENT
OF
RECEPTOR
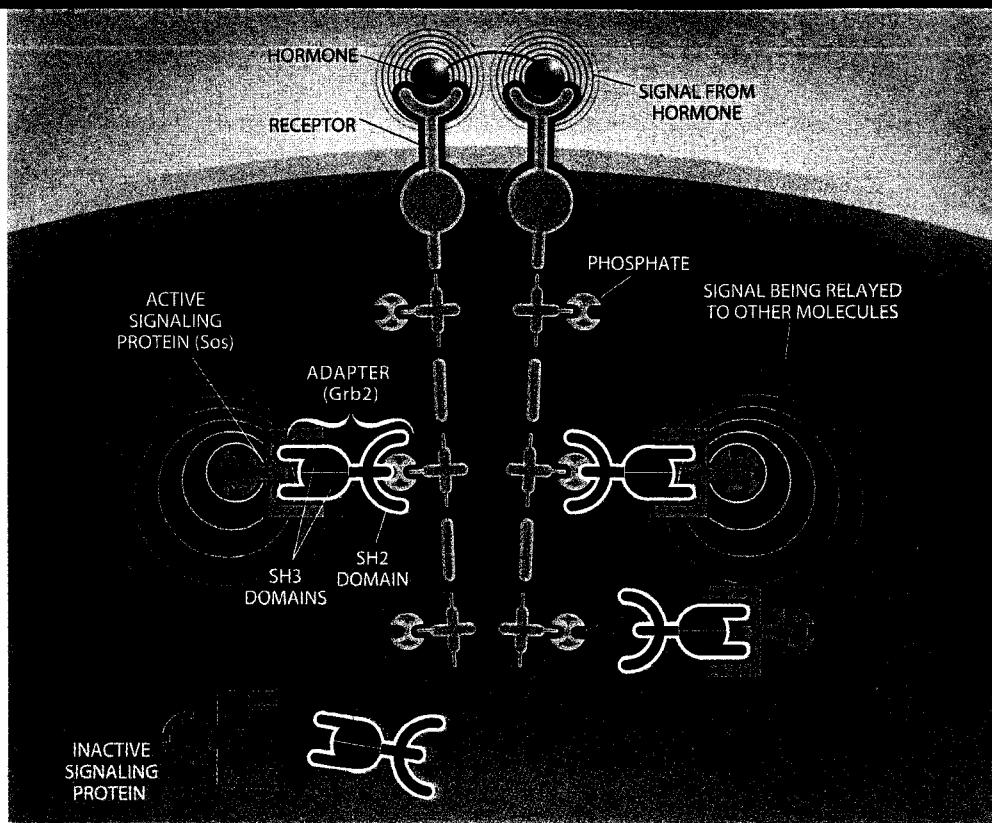
HYDROPHOBIC
CLEFT

TYROSINE

SH2 DOMAIN (*globular structure*) in a signaling molecule is bound to a segment of a receptor (*stick model*). The two fit together in part because a positively charged pocket in SH2 is attracted to a negatively charged phosphate that has been added to the amino acid tyrosine in the receptor. Also, the nearby amino acids in the receptor fit snugly into a hydrophobic (water-hating) groove on SH2. All SH2 domains can bind to phosphate-bearing tyrosines, but they differ in their binding partners because they vary in their ability to lock onto the amino acids that lie next to tyrosine in a protein.
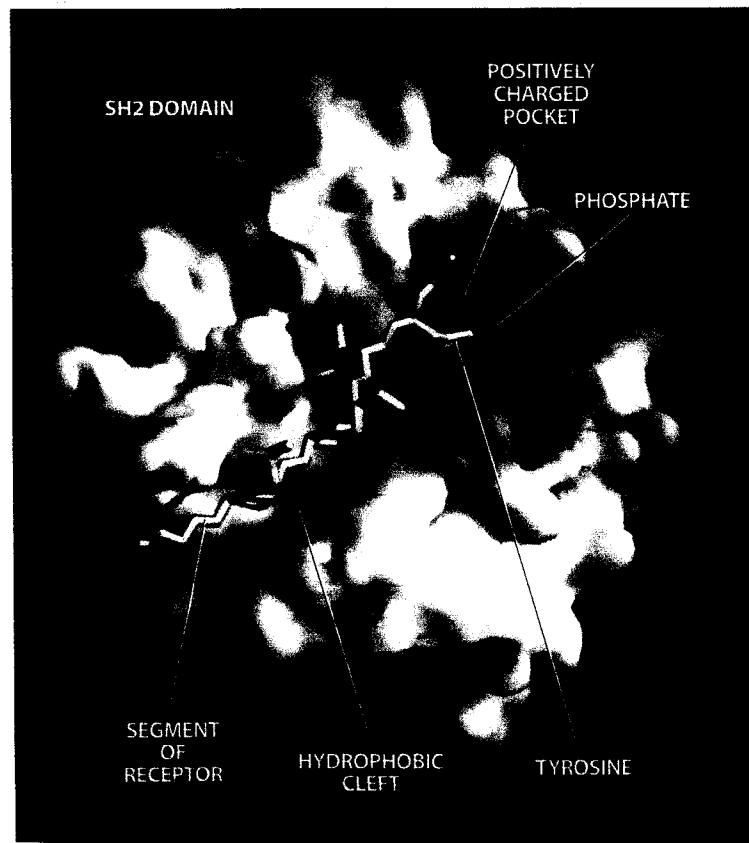
The Advantages of Adapters

Adapter molecules, which consist entirely of linker modules such as SH2 and SH3, turn out to be important players in many signaling pathways. They enable cells to make use of proteins that would otherwise be unable to hook into a given communication circuit. Here, for instance, the adapter protein Grb2 (*red*) draws an enzymatic protein—Sos—into a pathway headed by a receptor that itself has no means of interlocking with Sos.

(Figure labels: HORMONE; RECEPTOR; SIGNAL FROM HORMONE; PHOSPHATE; SIGNAL BEING RELAYED TO OTHER MOLECULES; ACTIVE SIGNALING PROTEIN (Sos); ADAPTER (Grb2); SH3 DOMAINS; SH2 DOMAIN; INACTIVE SIGNALING PROTEIN)

particular gene, thus inducing the synthesis of a protein. In this instance, the only enzyme in the signaling chain is the receptor itself; everything that happens after the receptor becomes activated occurs through proteins' recognition of other proteins or DNA.

As these various discoveries were being made, work in other areas demonstrated that the cytoplasm is not really amorphous after all. It is packed densely with organelles and proteins. Together such findings indicate that high-fidelity signaling within cells depends profoundly on the Lego-like interlocking of selected proteins through dedicated linker modules and adapter proteins. These complexes assure that enzymes or DNA-binding modules and their targets are brought together promptly and in the correct sequence as soon as a receptor at the cell surface is activated.

Fail-Safe Features Aid Specificity

Studies of receptor tyrosine kinases and of SH2 domains have also helped clarify how cells guarantee that only the right proteins combine to form any chosen signaling pathway. Soon after SH2 domains were identified, investigators realized that these modules are present in well over 100 separate proteins. What prevented different activated receptors from attracting the same SH2-containing proteins and thereby producing identical effects in cells? For the body to operate properly, it is crucial that diverse hormones and receptors produce distinct effects on cells. To achieve such specificity, receptors must engage somewhat different communication pathways.

The answer turns out to be quite simple. Every SH2 domain includes a region that fits snugly over a phosphate-bearing tyrosine (a phosphotyrosine). But each also includes a second region, which differs from one SH2 domain to another.

That second region—as Lewis C. Cantley of Harvard University revealed—recognizes a particular sequence of three or so amino acids next to the phosphotyrosine. Hence, all SH2 domains can bind to phosphorylated tyrosine, but these modules vary in their preference for the adjacent amino acids in a receptor. The amino acids around the tyrosine thereby serve as a code to specify which version of the SH2 domain can attach to a given phosphotyrosine-bearing receptor. Because each SH2 domain is itself attached to a different enzymatic domain or linker module, this code also dictates which pathways will be activated downstream of the receptor. Other kinds of linker modules operate analogously.

A pathway activated by a protein called platelet-derived growth factor illustrates the principles we have described. This factor is often released after a blood vessel is injured. Its attachment to a unique receptor tyrosine kinase on a smooth muscle cell in the blood vessel wall causes such receptors to cluster and become phosphorylated on tyrosine. This change draws to the receptor a protein called Grb2, which consists of a specific SH2 domain flanked on either side by another linker domain, SH3. Grb2 is a classic adapter; it has no enzymatic power at all, but its SH3 domains (which like to bind to the amino acid proline) hook an enzyme-containing protein called Sos to the receptor. There Sos activates a membrane-associated protein known as Ras, which triggers a series of enzymatic events. These reactions ultimately stimulate proteins in the nucleus to activate genes that cause the cells to divide, an action that promotes wound healing.

The signaling networks headed by receptor tyrosine kinases seem to rely on relatively small adapter proteins. Analyses of communication circuits in nerve cells (neurons) of the brain show that some proteins in neuronal pathways have an incredibly large number of linker domains. These proteins are

often called scaffolding molecules, as they permanently hold groups of signaling proteins together in one place. The existence of such scaffolds means that certain signaling networks are hardwired into cells. That hardwiring can enhance the speed and accuracy of information transfer.

Scaffolds Abound

One well-studied scaffolding protein goes by the name PSD-95. It operates primarily in neurons involved in learning. In nerve tissue, signals pass from one neuron to another at contact points called synapses. The first neuron releases a chemical messenger—a neurotransmitter—into a narrow cleft between the cells. Receptors on the second cell grab the neurotransmitter and then cause ion channels in the membrane to open. This influx of ions activates enzymes that are needed to propagate an electrical impulse. Once generated,

the impulse travels down the axon, a long projection, to the axon's abundant tiny branches, inducing them to release more neurotransmitter. For the impulse to be produced, many components of the signaling system must jump into action virtually simultaneously.

Among the multiple linker modules in PSD-95 are three so-called PDZ domains. One binds to the cytoplasmic tail of the receptor for the neurotransmitter glutamate. A second grabs onto a membrane-spanning ion channel (which controls the inflow of potassium), and a third clasps proteins in the cytoplasm (as does an additional module in the scaffold). PSD-95 thus yokes together several signaling components at once, enabling them to coordinate their activities. The eye of a fruit fly also relies on a PDZ-containing scaffolding protein—InaD—for the efficient relay of visual information from the eye to the brain [see illustration on next page].

Yet another preformed signaling complex has been found

Getting a Line on Human Diseases

A surprising number of human disorders involve aberrant signaling in cells. Cancer, marked by uncontrolled cell proliferation and migration, is a prime example. At its root, cancer results from genetic mutations. Certain of those mutations work their mischief by leading to the overactivity of proteins in signal-relaying pathways within cells—notably, in pathways that normally induce the cells to divide in response to external commands. The affected proteins cause cells to behave as if other cells were constantly telling them to reproduce even when no such orders were sent.

Signal blockers are already in use against breast cancer, and more are under development. For instance, recent clinical trials suggest that a drug able to halt excessive "talk" by an enzyme called Abelson tyrosine kinase might help treat particular forms of leukemia.

Overzealous signaling is similarly destructive in an inherited syndrome known as X-linked lymphoproliferative (XLP) disease. In XLP patients, the normally benign Epstein-Barr virus sparks a deadly runaway response by "killer" T cells of the immune system.

Two years ago investigators found the reason for that lethal overreaction. People with XLP turn out to be missing a small protein termed SAP, which consists of a single SH2 domain (related to the SH2 domains mentioned in the main article). When killer T cells detect that other cells have become infected by the Epstein-Barr

virus, they switch on an internal signaling cascade that enables them to attack the infected ones. Usually SAP keeps the attack under control—by sheathing interactive sites on some of the signaling components and thus breaking the signaling chain. But without SAP, XLP patients lack an important inhibitor of T cell hyperactivity.

"BLACK DEATH" epidemic of the 14th century was caused by *Yersinia pestis*. That bacterium makes use of signaling pathways in host cells to promote its own spread.

Disease can also arise when intracellular signaling systems that should be busy are too quiet, as happens in various disorders involving inadequate immune responses. Insufficient signaling occurs as well in type 2 (maturity-onset) diabetes. Muscle and fat cells of the body take up sugar from the blood only after being told to do so by insulin sent from the pancreas. If insulin receptors on those cells fail to deliver insulin's message to relay molecules inside,

diabetes (abnormally high blood sugar levels) can result. Oral medications designed to increase the activity either of the insulin receptor or of later players in the signaling cascade could potentially replace therapeutic insulin injections for some diabetics. One such compound, which stimulates the insulin receptor, has been tested successfully in mice.

Bacteria and viruses are experts at exploiting the signaling systems of human cells to spread and reproduce. This capacity is especially evident in such bacteria as *Yersinia pestis*, which caused the "black death" plague of the 14th century, and in disease-causing strains of *Escherichia coli*. The microbes inject their own proteins into human cells. Some of these proteins alter signaling pathways in ways that can both promote the association of the bacteria with a host's cells and disarm the cells' antibacterial defenses.
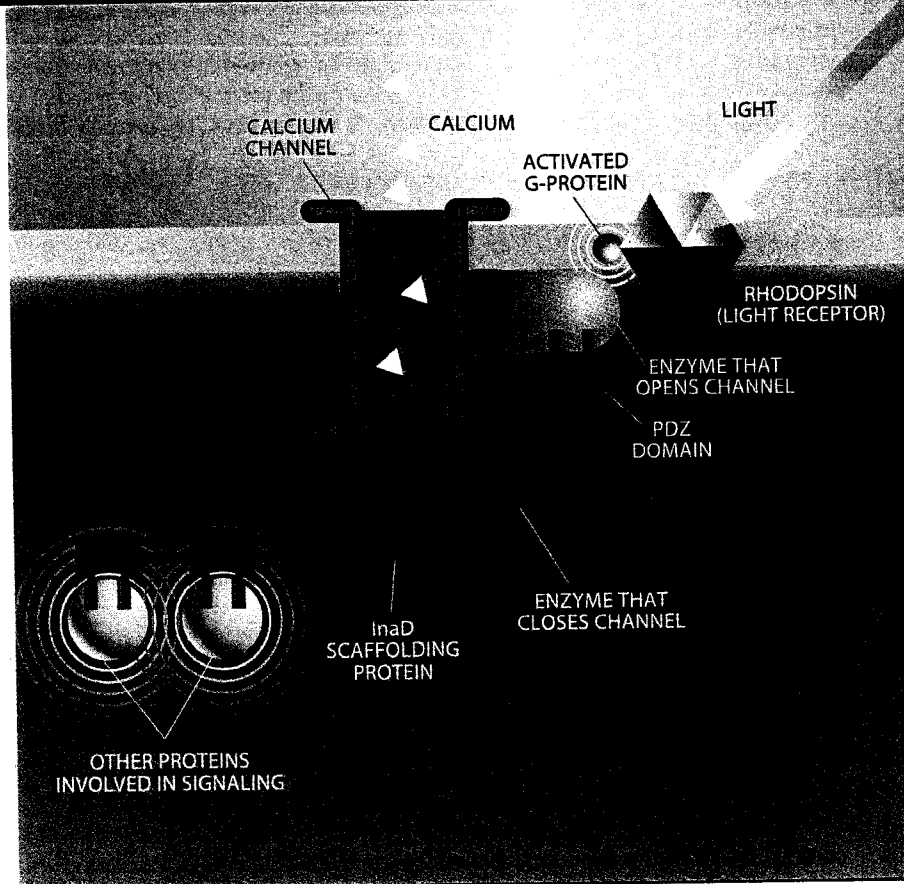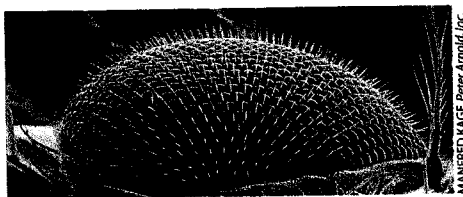
Viruses, for their part, often gain entry into human cells by attaching to receptors that head signaling circuits; then they may modify a cell's internal communication networks to enhance their own replication and release. The human immunodeficiency virus (HIV), the cause of AIDS, is one of many viruses that act in these nefarious ways.

As the links between signaling abnormalities and disease become clearer, therapies that repair or compensate for those disruptions should become increasingly commonplace. —T.P. and J.D.S.

Scaffolds Speed Signal Transmission

Scaffolding proteins, which hold onto several other proteins, can ensure that multiple signaling molecules act almost simultaneously. One, InaD (*diagram*), operates in cells of the fruit-fly eye—a compound structure containing many smaller eyes (*photograph*)—and participates in sending visual messages to the brain. Three of the scaffold's five "PDZ" linker domains separately grasp an ion channel, an enzyme that opens the channel when light hits a nearby light receptor (rhodopsin) and an enzyme that closes the channel promptly thereafter. Two more PDZ domains help to relay information by holding other signaling molecules in place.

CALCIUM CHANNEL — CALCIUM — LIGHT — ACTIVATED G-PROTEIN — RHODOPSIN (LIGHT RECEPTOR) — ENZYME THAT OPENS CHANNEL — PDZ DOMAIN — ENZYME THAT CLOSES CHANNEL — InaD SCAFFOLDING PROTEIN — OTHER PROTEINS INVOLVED IN SIGNALING

only recently, in mammalian neurons. The core is a scaffolding protein named yotiao. As one of us (Scott) and his colleagues have shown, this molecule grasps a dual-purpose, membrane-spanning protein that is both a glutamate receptor and an ion channel. It also clasps a kinase that adds phosphate to, and thereby opens, the ion channel when the receptor is activated by glutamate. And it anchors a phosphatase, an enzyme that removes phosphates from proteins. The bound phosphatase closes the ion channel whenever glutamate is absent from the receptor. This elegant arrangement ensures that ions flow through the channel only when glutamate is docked with the receptor.

Kinases and phosphatases control most activities in cells. If one kinase activates a protein, some phosphatase will be charged with inactivating that protein, or vice versa. Yet human cells manufacture hundreds of different kinases and phosphatases. Scaffolding proteins, it appears, are a common strategy for preventing the wrong kinases and phosphatases from acting on a target; they facilitate the proper reactions by holding selected kinases and phosphatases near the precise proteins they are supposed to regulate.

Many Payoffs

From an evolutionary perspective, the advent of a modular signaling system would be very useful to cells. By mixing and matching existing modules, a cell can generate many molecules and combinations of molecules and can build an array of interconnected pathways without having to invent a huge repertoire of building blocks. What is more, when a new module does arise, its combination with existing modules can in-

TWO SCAFFOLDING PROTEINS are highlighted in the larger nerve cell (neuron) in this micrograph. One, yotiao (*green*), tethers signal-relaying enzymes next to an ion channel involved in signal transmission. The other, PSD-95 (*red*), clusters a receptor and a different ion channel at selected synapses, the contact points between neurons. The blue in both neurons marks the location of a specific signaling enzyme.

FLOW OF MESSAGE in a skin cell was made visible by coloring two components of a signaling pathway: a scaffolding protein (*green*) and one of two enzymes tethered to that scaffold (*blue*). Actin, a structured element in cells, is red. The top cell is quiet. Soon after an external messenger activated a signaling pathway in the bottom cell, the scaffolding protein moved its bound enzymes to their targets deeper in the cell. That movement is revealed by the yellow hue, which derives from the overlap of the colored signaling components with actin (to which the enzymes' targets were bound). The blue mass at the center reflects extra copies of the colored enzyme.

crease versatility tremendously—just as adding a new area code to a city turns already assigned phone numbers into entirely new ones for added customers.

For cell biologists, merely chipping away at the mystery of how cells carry out their myriad tasks is often reward enough for their efforts. But the new findings have a significance far beyond intellectual satisfaction.

The much publicized Human Genome Project will soon reveal the nucleotide sequence of every gene in the human body. To translate that information into improved understanding of human diseases, those of us who study the functioning of cells will have to discern the biological roles of any newly discovered genes. That is, we will need to find out what the corresponding proteins do and what happens when they are overproduced, underproduced or made incorrectly.

We already know the amino acid sequences and the functions of many modules in signaling proteins. Hence, we have something of a key for determining whether the nucleotide sequence of a previously unknown gene codes for a signaling protein and, if it does, which molecules the protein interacts with. When we have enough of those interactions plotted, we may be able to draw a wiring diagram of every cell type in the body. Even with only a partial diagram, we may uncover ways to "rewire" cells when something goes wrong— halting aberrant signals or rerouting them to targets of our own choosing [see box on page 37]. We might, for instance, funnel proliferative commands in cancer cells into pathways that instruct the cells to kill themselves instead of dividing.
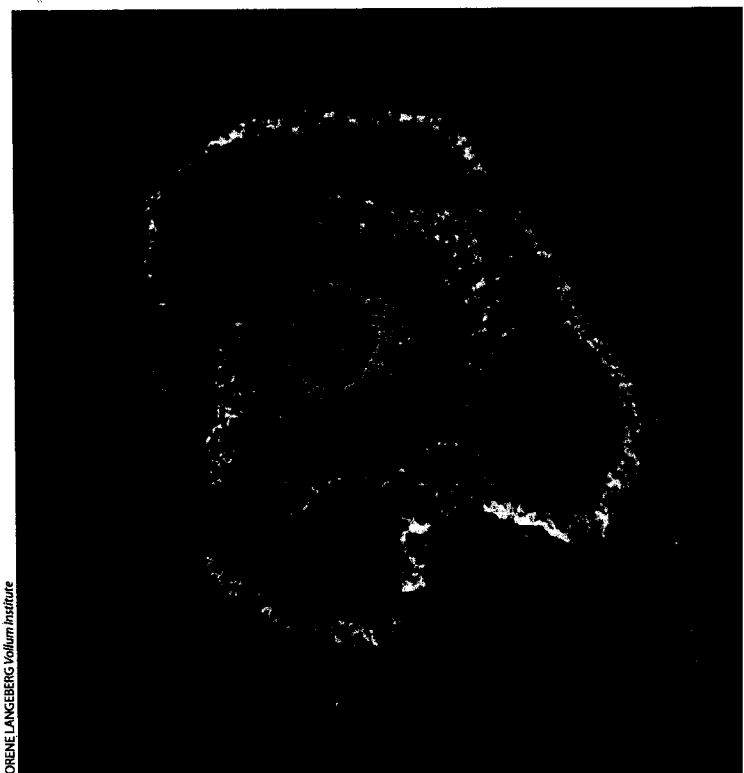
By learning the language that cells use to speak to one another and to their internal "workers," we will be able to listen in on their conversations and, ideally, find ways to intervene when the communications go awry and cause disease. We may yet reduce "body language" to a precise science. ∎

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