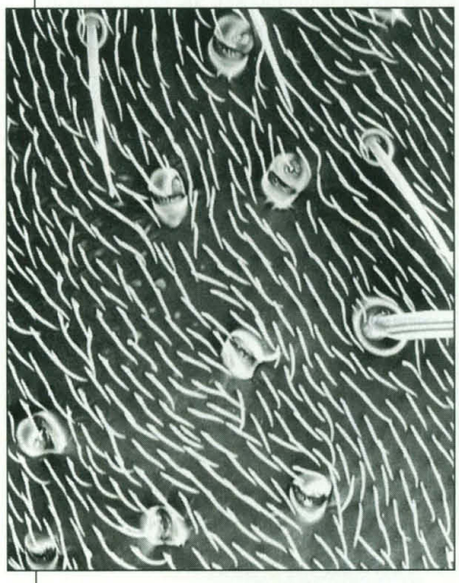
The Science of Signal Transduction

At first glance, it may not be obvious what the four Reviews presented in this special issue of *Science* have in common. But that is just the point. "Signal transduction" is the common term used to define a diverse topic that encompasses a large body of knowledge about the biochemical mechanisms that regulate cellular physiology. The fast-paced progress occurring in this field comes from model systems that range from bacteria to humans and is essential to our understanding of the control of virtually all biological processes. Therefore, we have chosen to highlight several areas in which substantial new information has become available and that span some of the range of model systems and biological contexts in which cellular signaling mechanisms are currently being explored. These Reviews exemplify both the diversity of disciplines in which studies of signal transduction have particular relevance and the rapid increase in the complexity of the information that is becoming available. These same properties have led *Science* to undertake the creation of a new resource for information on signal transduction in an exclusively electronic format on the World Wide Web (see box on the following page). That product will become available in the summer of 1999 but, in the meantime, the Reviews printed in this issue should whet the appetite for what is to come.



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Take, for example, the Review by Cashmore *et al.* (p. 760) of cryptochromes, receptor proteins that allow cells to respond to blue light. A fascinating story has unfolded as the function of these proteins in plants and, more recently, fruit flies and mammals has been explored. Cryptochromes are required for the responsiveness of plant growth to blue light. These same proteins also appear to function in the entrainment of circadian rhythms not only in plants but in fruit flies and mammals. Interestingly though, the cryptochromes of flies and mammals appear not to be evolutionary descendants of the plant genes. Rather, both sets of photoreceptors appear to have evolved from the photolyases, flavoproteins that mediate light-dependent repair of DNA damage. The signaling mechanisms activated by these receptors are still unknown, but nuclear localization of cryptochromes and their ability to bind DNA suggest that they may regulate transcription.

The nuclear receptors are proteins that directly couple the sensing of ligands to regulation of gene expression. After binding their ligands, these receptors are translocated to the nucleus where they bind to DNA and act with coactivators to modulate gene transcription. A number of such nuclear receptors have been identified and called orphans, because their ligand partners (not to mention their biological functions) were unknown. Kliewer *et al.* (p. 757) review emerging physiological and medically relevant roles for five orphan receptors and their potential ligands. The peroxisome proliferator-activated receptors (PPARs) interact with drugs that are commonly used to reduce the amount of triglycerides in the human bloodstream and thus decrease the likelihood of heart disease. Their endogenous ligands may be intermediates of fatty acid metabolism, thus en-

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abling the PPARs to monitor intracellular rates of lipid metabolism. Similarly, liver X receptors (LXRs) are sensitive to oxysterols and thus may contribute to the maintenance of proper intracellular and extracellular concentrations of cholesterol. Another nuclear hormone receptor, the pregnane X receptor (PXR), controls the synthesis of an enzyme that participates in the metabolism of many drugs used in humans. The endogenous ligand or ligands for the PXR are not known, but the receptor might serve as a general sensor of endogenous steroid hormones. Unlike other nuclear receptors, the constitutive androstane receptor, which binds metabolites of testosterone, appears to be inactivated (rather than activated) by ligand binding. Finally, the farnesoid X receptor appears to be a receptor for bile acids and may also help control cholesterol homeostasis.

During development, a limited number of signaling pathways specify many different cell fates. The intricate interactions within and between signaling pathways that allow such developmental control are the subject of intense investigation. One prominent example is signaling through the receptor protein called Notch. Indeed, there are few embryonic tissues that are not influenced by Notch signaling. Artavanis-Tsakonas *et al.* (p. 770) summarize current understanding of how signaling through the Notch receptor controls cellular differentiation, proliferation, and apoptosis. Though most extensively examined in the fruit fly, Notch has critical developmental functions in other invertebrates and also in mammals. The Notch ligand Delta is a transmembrane protein and may even function when both ligand and receptor are present on the same cell. But the extracellular portion of Delta can also be cleaved and can function as a soluble ligand for Notch. Proteolytic cleavage may also allow the Notch receptor to carry signals directly to the nucleus like the nuclear receptors do. The authors weigh the evidence for a role of the cleaved intracellular portion of Notch in the control of transcription in the nucleus. The developmental fate of adjacent cells can be determined in a complex manner by small differences in the relative expression of Notch, its ligand, or antagonistic factors, or through interactions of the Notch system with other signaling pathways.

Like embryonic cells that need to sense small differences in gradients of stimuli to which they are exposed, migrating cells orient their movement in response to gradients of attractants. Intriguingly, such signaling from a gradient can be independent of the absolute concentration of the attractant signal. To accomplish this, cells need to sense tiny differences in the concentration of a stimulus between one end of the cell and another, or they must sequentially sample the concentration of stimulus as they move through the gradient. Parent and Devreotes (p. 765) summarize new insights into how this is accomplished by mechanisms that are apparently conserved between yeast, the social amoeba *Dictyostelium discoideum*, and mammalian leukocytes. Although the G protein–coupled receptors that mediate signaling are evenly distributed across the cell surface, localized activation in the region exposed to the highest concentration of chemoattractant is revealed in movies of live cells. In the model favored by the authors, a global inhibitory signal is determined by the overall concentration of chemoattractant, whereas a localized increase in the fraction of occupied receptors at one side of the cell determines the direction of the response.

There is no doubt that the more we know about signal transduction, the more we realize has yet to be discovered. With the advent of the Signal Transduction Knowledge Environment, *Science* hopes to make information on signal transduction more accessible despite the complexity and diversity that have become hallmarks of the field.

–L. BRYAN RAY

Signal Science on the Web

No matter what the biological topic—be it regulation of synaptic signals that underlie learning and memory, the cellular defense mechanisms that constitute the immune system, control of the cell division cycle and its disregulation in cancer cells, or even the mechanism of action of many commonly prescribed pharmaceuticals—real understanding requires knowledge of the signal transduction "language" by which cells communicate and respond to external and internal cues. Such biochemical signaling pathways that regulate cell function are the essence of the science now frequently known as signal transduction.

The explosive growth of the signal transduction field in recent years has resulted in the definition of many biochemical pathways that are used over and over again in various cell types to allow refined control of processes ranging from fertilization to cell death. Unfortunately, the over-abundance of pathways and their components, and the ever-increasing evidence that the term "pathways" is itself a misnomer because most such paths are interconnected in an elaborate signaling network, makes staying abreast of new developments in the field a daunting task. This is particularly true for those whose primary interest may not be the signaling mechanisms per se but who nevertheless need to understand or manipulate the signaling processes that control a particular biological event. For these reasons, *Science* has teamed up with HighWire Press of the Stanford University libraries, with support from the Pew Charitable Trusts, to produce a new resource for scientists that will provide the world's most comprehensive, easily accessible, and integrated source for authoritative information on signal transduction.

In the summer of 1999, we will launch a new, exclusively electronic publication on the World Wide Web. At *Science*'s Signal Transduction Knowledge Environment, you can get oriented with a map of signaling pathways that is actually an interface to an extensive database of information on components of signaling pathways and their relations, supplied by leading authorities in the field. Full text of the literature from top journals will be accessible through the map or through searches of the "Virtual Journal" of signal transduction. We will also publish original Reviews and Perspectives on signal transduction topics of particularly broad interest. Also unique to the site will be protocols for methods commonly used to study cell signaling. Users will be able to join in moderated discussions of timely, controversial topics led by influential protagonists. All this and more, plus weekly highlights to keep you aware of what's hot in the signaling literature, will be available soon from your computer desktop. If you'd like to be notified of future developments as we approach the launch, sign up now at www.stke.org. **–L. B. R.**