electron microscope (STEM) (*10*). The scattering cross section of an atom for both elastic and inelastic processes varies with atomic number; consequently, a record of the total scattering is just as good a method of forming images as is interference of elastically scattered waves. The problem lies in how to monitor total scattering as a function of position within the specimen. In the STEM, this is achieved by scanning a fine probe of electrons across the specimen. Formation of this electron probe uses the technology developed over the years for HRTEM operation, in that if electromagnetic lenses can produce a highly magnified image of a specimen with a very small spread function, they may also be used to produce a highly de-magnified image of the electron source. If this image is then focused at the specimen, it can be scanned while the total scattering is monitored by a annular detector placed beneath the specimen, with the unscattered electrons passing straight through. This mode of imaging is equally suited to all types of specimens, periodic or not. The gain in contrast is considerable, and the method is limited only by probe size and specimen thickness because the diameter of the probe increases as it passes through the specimen. With STEM, isolated atoms, dimers, and trimers of moderately heavy atoms on a support of lower atomic number can be resolved, as reported by Nellist and Pennycook (*1*). In addition, by correlating directions in the atomic images with images of the support recorded with the unscattered electrons, the exact crystallographic relation between monodispersed species and the supporting medium can be established, information that is crucial to understanding the reactivity of such species, as in heterogeneous supported catalysts.

Although frequently used for the study of surface-supported species, STEM resembles HRTEM in that it is a technique for bulk structural examination. For example, atom clusters can be observed even when they are accommodated within a second phase, as is frequently found when one metal is dispersed within another. If investigation is limited to atoms adsorbed on surfaces, although STEM and even HRTEM (*11*) techniques have been used, the ultimate atomic images have been produced by means of the scanning tunneling microscope (STM). In this method, all resemblance to optical imaging methods has been lost, as the probe used is a mechanical one, but the tunneling current that is recorded as the probe is scanned involves such short-range effects that "contrast" from all but the atom under study can be minimal. If an atomic image is defined merely as a pictorial representation of the atom arrangement, STM images must surely represent the most spectacular achievement of imaging science.

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Signaling Across Membranes: A One and a Two and a ...

Jeff Stock

Receptors on the surfaces of cells transmit information into the cytoplasm to effect appropriate responses to extracellular signals. One kind of receptor—type I—consists of a single hydrophobic, membrane-spanning α helix that links an extracellular sensory domain to an intracellular signaling domain (*1*). But how does the binding of a signaling molecule to the domain of the receptor outside the cell change the catalysis performed by the part of the receptor inside? According to current models, transmembrane signaling is accomplished either by dimerization of the receptors once the signalling molecule binds or by altering the orientation of one monomer with respect to the other within a preexisting dimer. In this issue of *Science*, two genetic studies of the bacterial chemotaxis receptor for aspartate, Tar, seriously question a fundamental assumption made by all of the models (*2*), namely, that a dimer is necessary at all. In fact, the Tar receptor functions quite well with a monomeric intracellular domain.

The sensing and signaling domains of type I receptors are each an independent soluble cassette that can be synthesized and studied alone. Although type I receptors all seem to use a common mechanism for transmembrane signaling, their structures are startlingly different. The x-ray crystallographic structure of the sensory domain of the human growth hormone receptor, hGHR (*3*), is not at all like that of the bacterial receptor Tar (*4*): Whereas the sensing portion of hGHR is composed of two seven-stranded β sandwich domains, the sensory domain of Tar is a bundle of four parallel α helices. The only common feature is that both ligands, hGH and aspartate, bind within single asymmetric binding sites at the interface between sensory-domain monomers. This commonality provides a structural basis for the dimer-interaction mechanisms that have been proposed to explain type I receptor function.

Type I receptors have also been termed catalytic receptors because their signaling domains either are signal-transduction enzymes or are proteins that form complexes with such enzymes. Virtually any signal-transduction enzyme can function as a type I receptor signaling cassette. The signaling domains of type I receptors such as the insulin receptor or hGHR either are protein tyrosine kinases or form complexes with protein tyrosine kinases (*5*), and the signaling domains of bacterial receptors such as Tar either are themselves protein histidine kinases or form complexes with protein histidine kinases (*6*). Other type I receptors

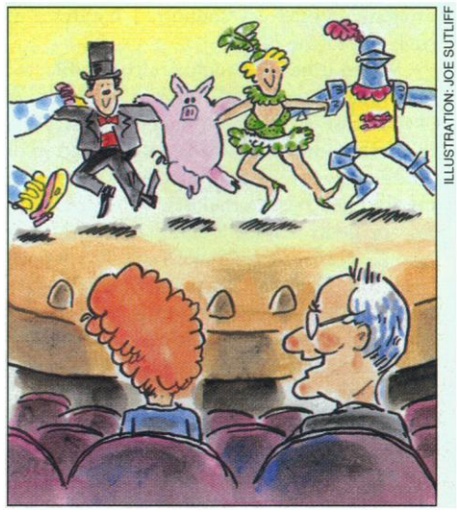

ILLUSTRATION: JOE SUTLIFF

"And she's a marvelous soprano!"

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have signaling domains that are serine-threonine kinases, phosphoprotein phosphatases, or guanylyl cyclases. In several instances, intermolecular interactions between signaling cassettes are critical to activation: Homodimer formation is clearly essential for the activity of the protein kinase that is regulated by Tar (*7*), and phosphorylation of one subunit of the insulin receptor by the other is critical for signaling (*5*).

There seems to be little specificity between sensing and catalytic domains; almost any combination works. Nature herself has produced a huge variety of pairs of signaling and sensing domains, and researchers have added to the collection with the construction of artificial (and functional) chimeras. The sensing domain of Tar fused to the signaling domain of the human insulin receptor yields a chimeric receptor with tyrosine kinase activity regulated by aspartate (*8*). This versatility has supported the notion that type I receptors make use of a simple and extremely robust mechanism for transmembrane signaling. Stimulatory ligands are thought to regulate intersubunit interactions between sensing domains at the outside surface of the membrane to control intersubunit interactions between signaling domains on the other side of the membrane. The simplest case would be a ligand-induced monomer-dimer transition. But, at least for some receptors, this mechanism is clearly an oversimplification; insulin receptors or Tar proteins with intersubunit disulfide cross-links between sensing domains can still be regulated by stimulatory ligands. In these cases, it has been posited that the relative orientation of monomers within a preexisting dimeric structure is responsible for signaling (*1*, *9*).

In molecular biology, the ultimate test for any hypothesis is genetic. The two reports in this issue describe genetic studies of Tar function which demonstrate that heterodimers with one signaling domain deleted can still function normally (*2*). The authors asked the question, "What is the sound of one hand clapping?" by genetically deleting one hand. Amazingly, the result of this Zen-like experiment was not an imponderable silence but loud applause—a robust cellular signal. These findings call for reexamination of the basic assumption that Tar functions as a dimer. In fact, although there is ample evidence that the ligand binding domains can exist as dimers, the isolated signaling domain of Tar appears to be a loosely folded monomer. It is only when Tar monomers associate into a complex with the histidine kinase that the signaling domain assumes its functional form. Moreover, it has been shown that in cells, Tar is localized with the protein kinase and other auxiliary signal-transduction proteins in a complex or a patch that contains hundreds of receptor monomers (*10*).

What are the implications of these results with Tar for other type I receptors? One might argue that Tar is different, and that these results are not generalizable. And it is true that Tar is unique: It has an NH_2-terminal transmembrane extension that is absent in most type I receptors; it is specifically designed to solve a unique problem; and it is bacterial. But every type I receptor has its own unique structural, functional, and phylogenetic features. Nevertheless, all share with one another and with Tar the same set of mechanistic properties common to transmembrane signaling. Moreover, we need not look far for natural type I mammalian receptors that function as heterodimers with one subunit lacking a signaling domain just like the engineered variants of Tar described in this issue. Well-known examples include the nerve growth factor receptor, as well as several interleukin receptors that are closely related to hGHR (*5*).

A receptor signaling complex is a dynamic two-dimensional array of sensory elements that project through connecting transmembrane helices onto a network of signal-transduction components at the opposite side of the membrane. The portions of the receptors in the cytoplasm are ill-defined compared to the ligand binding domains at the surface, but it is known that they participate in complex interactions with a variety of signal-transduction components. Besides being regulated by ligand binding domains from without, receptor signaling networks are also controlled by intracellular feedback and feedforward mechanisms from within. This property gives these systems a plasticity that may in part account for the functions of dramatically altered receptor variants. Perhaps, in light of these considerations, our view of type I receptors as couples waltzing freely in a lipid sea should be supplanted by a new paradigm in which the music and the motions involve a much more complex choreography.

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The World Wide Web as an Instructional Tool

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The Internet was born in December of 1969 (*1*) and has grown phenomenally since (*2*–*4*). Its graphically attractive, user-friendly modality, the World Wide Web (WWW), is younger and growing even more explosively (*5*–*7*). By its nature, the WWW is a tool ideally and uniquely suited for the advancement of education.

The WWW is composed of multiple computer "servers," which can send documents or "pages" to Internet users who navigate from server to server by means of Web-browser software. Web documents can contain text, sound, pictures, or movies, and they can be interactive. Traditional paper-bound tasks—searching large databases or completing questionnaires—can be replaced by WWW-based technology. Harnessing the multimedia and interactive features of the WWW in conjunction with its vast store of information is presently the premier challenge to educators.

There are three ways in which the WWW can be used for educational purposes (*8*). The first relies on the student's (or client's, in WWW terms) ability to access information. This information can be general—for example, the prodigious quantities of information organized at indexing sites such as Alta Vista (*6*) and Yahoo (*7*)—or specific—such as the large quantities of specialized informa-

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