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The Two-Component Pathway Comes to Eukaryotes

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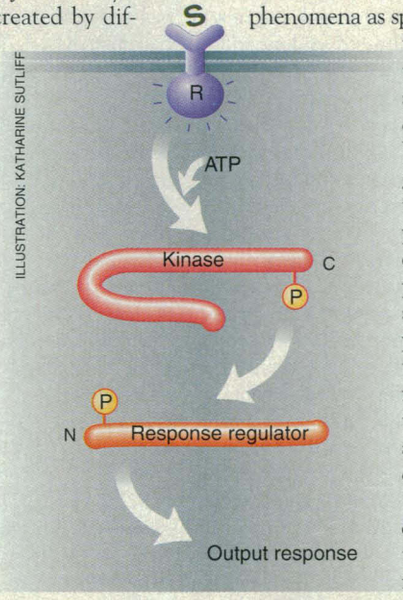
Two simplifying principles of biology are what might be called "the principle of redundancy" and "the principle of diversity." Mother Nature follows the principle of redundancy by selecting a simple mechanism or module as a building block for a complex system and then using that module over and over again in other systems. The principle of diversity utilizes the concept that there are many ways of achieving the same goal, for example, creating a living organism or generating motility. Just as very different chemicals can be created by different permutations of protons, neutrons, and electrons, so can different biological species be constructed from similar receptors, enzyme pathways, and membranes.

These principles are admirably illustrated in this issue of *Science* in which two papers report that a signal transduction system, the "two-component" pathway, known to be widespread in bacteria, also occurs in eukaryotes (*1*, *2*). This pathway, as understood from bacterial systems, is shown in the figure: The stimulus (S)—which can be a nutrient that activates a chemotaxis pathway, a condition such as osmotic pressure, or low nitrogen concentrations—binds to its receptor (R), inducing a conformational change. This change causes the receptor to interact with a kinase and, consequently, the kinase autophosphorylates on a histidine residue near its carboxyl-terminal end. That phosphate is then transferred to a carboxyl side chain of aspartate in the amino-terminal end of the response regulator. The response regulator binds to an output protein, such as a flagellar motor or a transcription factor.



The two-component pathway.

The response regulator is a molecule whose concentration controls an output response. It was originally postulated to explain memory during chemotaxis in bacteria (*3*) and has now been found to operate in mammalian cells as well (*4*). That the response regulator is a part of a two-component phosphorylation cascade (the kinase being the first component) was initially described for the nitrogen fixation pathway (*5*, *6*), then found also in chemotaxis (*7*), and now shown to operate in such varied phenomena as sporulation, virulence, and transformation competence (*8*). Phosphorylation cascades are also common in eukaryotes, but in eukaryotes they generally employ serine, threonine, and tyrosine phosphorylations (*9*). In contrast, bacterial phosphorylation cascades usually use an internal phosphotransfer reaction of the kinase to phosphorylate a histidine, and the response regulators are phosphorylated on a carboxyl group (*7*, *8*, *10*, *11*). Indeed the sequences around the histidine (~100 amino acid residues) and around the carboxyl residue (a three-dimensional array of carboxyl groups) are characteristic and occur in the proteins of each cascade (*8*, *12*).

These characteristic sequence similarities led Chang and co-workers from the Meyerowitz group to identify the ethylene response system in plants (which controls growth and ripening) and Ota and Varshavsky to identify the *SLN1* system in yeast (also critical for growth) as two-component systems. Indeed, the most important technique in making these discoveries was computerized sequence comparison, now a pervasive tool in biological sciences. The number of gene sequences now accumulated in the data banks ensures that the identification of a new gene sequence can in many cases immediately lead to an assignment of function by analogy. In this week's *Science*, the sequences of new genes in a plant and yeast led to the deduction of the identity of the pathways.

The eukaryotic two-component systems have elaborated upon the most common bacterial mechanism in that both the kinase domain and the response regulator domain are parts of the primary structures of the *ETR1* gene product of the ethylene system (*1*) and the SLN1 protein of the yeast growth response (*2*). Both ETR1 and SLN1 have characteristic hydrophobic transmembrane sequences, and so it appears that they are receptors in which the two-component system has been built into the carboxyl-terminal cytoplasmic domain. Bacteria had begun this consolidation process: In the chemotaxis and nitrogen fixation systems, the kinases are separate proteins, activated or deactivated by a receptor with no covalent ties to the kinase. But in osmolarity regulation, for example, the kinase is a domain of the receptor protein primary structure, a part of the receptor itself. And in a few bacterial systems all three functions—receptor, kinase, and response regulator—are combined in one polypeptide. The new reports expand our horizons. It now seems possible that all of the prokaryotic permutations may be found in eukaryotes.

The principle of redundancy leads to similar transduction schemes in markedly different organisms, and the principle of diversity suggests that the new schemes are tailored to the needs of the organism in which they reside. Illuminating the details will be tasks for the future. For instance, in bacteria the response regulators generally have labile carboxyl phosphates due to the presence of phosphatases, and it will be interesting to see whether this specific feature is retained in the eukaryotic two-component pathways. The findings that such diverse systems as plants and bacteria share similar pathways should not be considered denigrating to eukaryotes (even humans) nor uplifting to bacteria. Rather, they are further unifying examples of the general principles of redundancy and diversity.

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