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## Quick guide

# Two-component systems

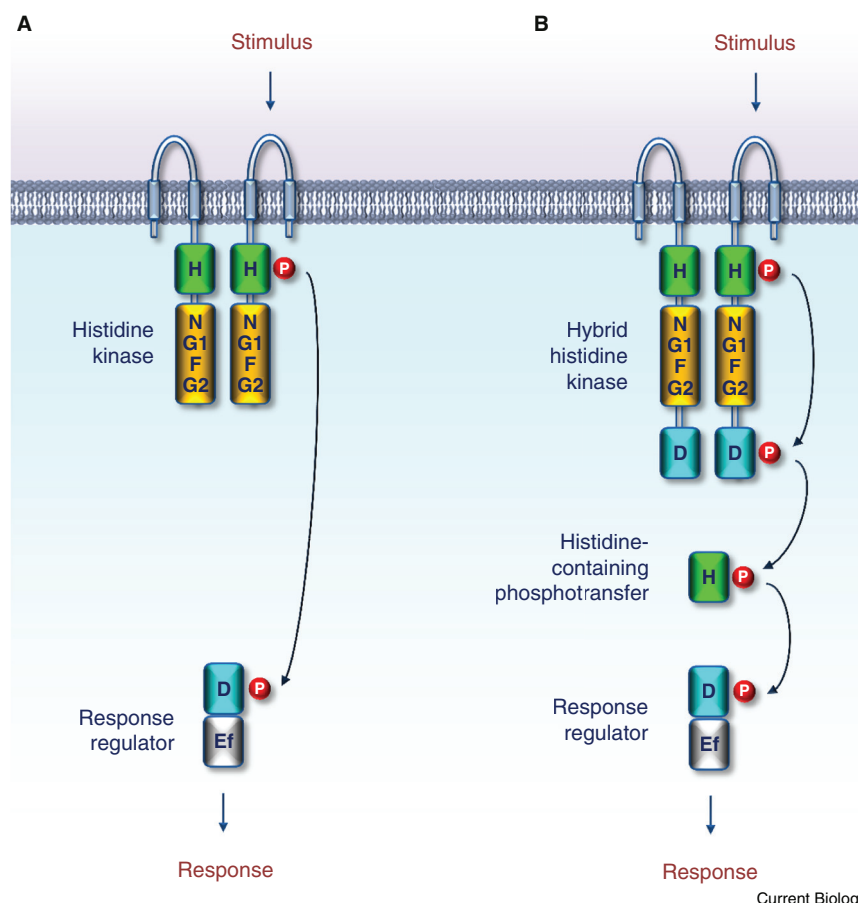
Nicolas Papon<sup>1,\*</sup> and Ann M. Stock<sup>2,\*</sup>

### What are two-component systems?

Two-component systems are cell-signaling circuitries that first came into prominence in the early 80s, notably through their discovery in the model bacterium *Escherichia coli*. They allow organisms to perceive and transduce many different input signals and provide adaptive responses to extracellular and intracellular environmental changes. To date, more than 300,000 two-component systems have been identified in many clades of the tree of life including archaea, bacteria, amoebae, terrestrial plants, algae and fungi, and recent advances support their occurrence in many other microorganisms related to SAR (Stramenopiles, Alveolates, Rhizaria), Apuzosoa, Mesomycetozoa, and Excavata. Interestingly, typical two-component system proteins are absent from animals.

### How do these two-component systems work?

The designation ‘two-component system’ originated from the occurrence of conserved domains in two gene products of several bacterial regulatory systems. Subsequently, the two protein components were shown to communicate by phosphorylation events occurring on two types of amino-acid residues, histidine and aspartate. In prokaryotes, two-component systems are usually composed of a pair of proteins that belong to the histidine kinase and response regulator families and coordinate a single phosphotransfer step (Figure 1). In canonical systems, the histidine kinase, which is structurally dimerized and often transmembrane, acts as a sensor protein that perceives the input signal and autophosphorylates on a conserved histidine residue. The phosphoryl group is then transferred to a conserved aspartate residue of the cognate response regulator, activating it to effect a response,



**Figure 1. Two-component system phosphotransfer schemes.**

(A) A typical phosphotransfer pathway, as is usually found in prokaryotes. The perception of a stimulus by extracytoplasmic domains of the histidine kinase regulates its activities. The histidine kinase autophosphorylates at a conserved histidine residue (H) using ATP bound to the catalytic ATPase domain (containing conserved motifs N, G1, F, and G2). The phosphoryl group (P) is transferred to a conserved aspartate residue (D) located within the cognate response regulator. (B) An example of a multi-step phosphorelay, as often occurs in eukaryotes. The histidine kinase is termed ‘hybrid’ because an additional aspartate-containing domain is fused to the ATPase domain. The phosphorelay involves multiple phosphoryl transfer steps. The first is an intramolecular transfer between the conserved histidine (H) and a conserved aspartate residue (D) located within the carboxy terminus of the sensor histidine kinase. Subsequently, the phosphoryl group is transferred to a histidine-containing phosphotransfer protein and finally to a cognate response regulator. Conserved domains of the two-component proteins are shown in green, gold, and blue. Variable sensor domains of the histidine kinase and effector domains (Ef) of the response regulator, which adapt the systems to a wide range of input stimuli and output responses, are shown in gray.

often transcriptional regulation of specific genes. The signaling schemes observed in eukaryotic two-component systems are usually more complex and involve additional modules, for instance a response-regulator domain fused to the sensor histidine kinase and shuttle proteins termed ‘histidine-containing phosphotransfer’ modules. In this case, these signaling proteins orchestrate a multi-step phosphorelay path. Often, eukaryotic two-component phosphorelays interface

with conventional eukaryotic signaling strategies (such as MAP kinase cascades, cAMP signaling pathways, etc.) that mediate the output response (Figure 1).

### Why are two-component systems important?

The huge diversity of signals that can be perceived and the broad palette of physiological processes regulated by two-component systems testify to the importance of these cellular pathways



in the adaptation of organisms to environmental challenges. Beyond the knowledge acquired from more than three decades of active research on two-component systems, recent advances have provided evidence of the pivotal ecological role of these signaling systems, notably in inter-species communications. This is illustrated for instance by the demonstration that one of the two-component systems in the phytopathogenic bacterium *Xanthomonas* is dedicated to the perception of a host plant hormone (specifically, a cytokinin) to establish the infection.

**How abundant are two-component systems compared to other cell signaling routes?** Although they occur in variable numbers in different bacterial clades, two-component systems are the predominant form of multi-component signaling circuitries in prokaryotes. This is not the case in all of the eukaryotic clades, where two-component systems rank differently among other signaling systems, including for instance serine/threonine and tyrosine kinase pathways. For example, whereas flowering plants commonly display ~10 two-component systems, recent advances in amoebae have provided evidence that the battery of two-component systems in these organisms is predominant and highly diversified. This was illustrated by the recent genome analysis of the ‘blob’ (*Physarum polycephalum*), which appears to have more than 50 two-component systems. In fungi, the number of two-component systems appears to be highly variable, ranging from a single system in the model yeast *Saccharomyces cerevisiae* to more than 20 in some plant pathogenic molds. One interesting observation is that globally, within species belonging to the same phylum, there is a correlation between the number of two-component systems and genome size, as well as with the range of environments in which the organism can develop. This can be illustrated by the fact that, likely as a result of genome-erosion processes, obligate parasitic species display no or few two-component systems compared to phylogenetically related free-living species.

**What types of signals are perceived and what are the processes regulated by these systems?** In bacteria, it is now well documented that two-component systems regulate a large array of fundamental processes. These include adaptation to changes in the environment (osmolarity, light, temperature, oxygen), regulation of developmental pathways and behaviors (sporulation, biofilm formation, competence, chemotaxis), nutrient acquisition and metabolism (nitrogen, glucose, cell wall), virulence, antibiotic resistance, and many others (flagellar assembly, secretion systems). In fungi, these signaling pathways are generally known to be involved in response and adaptation to environmental conditions in connection with the diversity of their lifestyles ranging from saprophytism to pathogenicity. To date, the most striking associations reported between fungal two-component systems and physiological processes include osmotic adaptation, response to oxidative stress, light perception, adaptation to hypoxia, various developmental programs (hyphal growth, asexual spore production, morphogenetic switch, cell wall composition and integrity), virulence, melanin production, regulation of secondary metabolism, and biofilm formation. The two-component systems found in flowering plants are mostly reported to be involved in the perception and transduction of two major hormones, cytokinins and ethylene, but also participate in the regulation of drought and salt stress responses. Knowledge about the role of two-component systems in amoebae remains restricted to the so-called ‘social amoebae’ (dictyostelids) where these pathways control crucial processes during the multicellular developmental program (motility, morphogenesis, osmoregulation, light perception, and spore differentiation).

**Can two-component systems be targeted for therapeutic purposes?** From a phylogenetic perspective, one singularity of these signaling circuitries is that no typical two-component system proteins have yet been found in animals. Given that these signal transduction pathways are often involved in essential processes and virulence in both

prokaryotic and eukaryotic pathogenic microorganisms, two-component systems have been targeted for development of inhibitors of histidine kinases and response regulators as novel antimicrobial drugs.

**What is there still to learn about two-component systems?** To date, these cell signaling systems have been mostly studied in bacteria and plants, and to a lesser extent in fungi and amoebae. Research on two-component systems in these phyla is likely to continue, especially with regard to the roles of two-component regulation in both organismal and environmental microbiomes. In addition, it will be interesting to characterize their functions within clades in which these systems have only recently been identified such as SAR, Apuzosoa, Mesomycetozoa, and Excavata.

#### Where can I find out more?

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