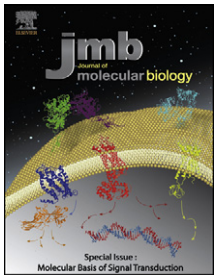
Review



Molecular Mechanisms of Two-Component Signal Transduction

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Abstract

Two-component systems (TCS) comprising sensor histidine kinases and response regulator proteins are among the most important players in bacterial and archaeal signal transduction and also occur in reduced numbers in some eukaryotic organisms. Given their importance to cellular survival, virulence, and cellular development, these systems are among the most scrutinized bacterial proteins. In the recent years, a flurry of bioinformatics, genetic, biochemical, and structural studies have provided detailed insights into many molecular mechanisms that underlie the detection of signals and the generation of the appropriate response by TCS. Importantly, it has become clear that there is significant diversity in the mechanisms employed by individual systems. This review discusses the current knowledge on common themes and divergences from the paradigm of TCS signaling. An emphasis is on the information gained by a flurry of recent structural and bioinformatics studies.

Introduction

The proteins comprising the bacterial two-component system (TCS) are the sensor histidine kinase (HK) and the response regulator (RR; Fig. 1a). These two factors are among the most abundant proteins in the sequence databases, owing to a wide distribution across the bacterial and archaeal kingdom and to significant amplification within bacterial and archaeal genomes [1,2]. Furthermore, TCS are also found in some eukaryotic organisms but are notably absent from genomes of the animal kingdom. Three decades' worth of genetic and molecular microbiology studies on these systems have elucidated the individual roles and importance for cellular survival for many of these systems in diverse bacteria. Full structural characterization of these proteins in contrast has initially lagged despite some early individual successes. However, in the past decade, increased structural and bioinformatics efforts have closed the gap between our functional and mechanistic understanding of these system, in part due to a significant number of structurally characterized TCS protein domains.

In the prototypical TCS, the HK and RR serve to connect the detection of an environmental or cellular signal with an appropriate cellular response. Communication between the proteins occurs via phosphoryl group transfer from a histidine of the HK to an aspartate of the RR. Some HK also function as phosphatase for their respective RR under non-inducing conditions [3]. Owing to the diversities of input signals and the cellular responses, significant variety exists in input and output domains (Fig. 1). In contrast, the structures of the catalytic and regulatory domains of the two proteins are largely conserved; nonetheless, recent studies have revealed diversity on the detailed molecular mechanisms by which these proteins phosphorylate and communicate.

In this review, we divide the signal transduction cascade into four main focus areas: (1) signal

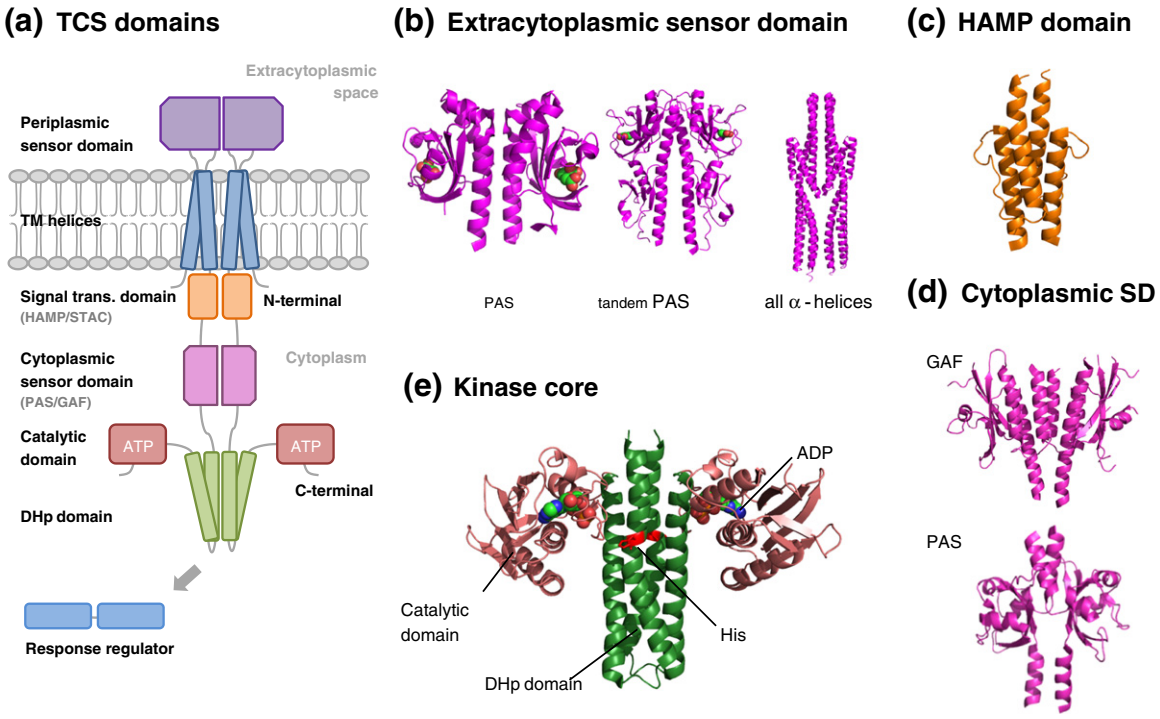

Fig. 1. Domain architecture of the typical TCS. (a) Schematic view of a prototypical membrane-bound sensor HK, featuring domains for signal recognition, transmission, and catalysis. (b) Variable extracytoplasmic SD. The most common extracytoplasmic SD are PAS and α-helical domains. The citrate-bound periplasmic PAS domain of CitA (PDB ID: 2J80), the SD of KinD (PDB ID: 4JGO) with tandem PAS domains, and the α-helical extracytoplasmic SD of TorS (PDB ID: 3O1H) are illustrated on the left, middle, and right, respectively. Ligands are shown in green and red spheres. Only the N-terminal PAS domain of KinD is responsible for ligand binding. (c) Signal transduction occurs via the cytoplasmic HAMP domain. The HAMP domain of Af1503 (PDB ID: 2L7H) is shown as a representative. (d) The cytoplasmic SD are responsible for intracellular signals detection and transmission. GAF (PDB ID: 4G3K) and PAS (PDB ID: 4I5S) domains are shown. (E) The conserved kinase core consists of the DHp and C-terminal ATP-binding catalytic domain. The core of the kinase HK853 is illustrated (PDB ID: 3DGE). The individual dimeric structure of DHp is illustrated in green and the CA domains in red. Location of ADP and phosphorylatable histidine is shown.

detection, (2) kinase activation, (3) phosphotransfer, and (4) response generation. Numerous, excellent review articles in the recent years have focused on individual aspects of the signal cascade, and we refer the reader to these articles for some additional details and reference to specific studies that could not all be featured in a broad review [4–8].

Signal Detection and Transmission

Signal detection and transmission to the catalytic core of the kinase is mediated by modular and variable domains typically at the N terminus of the HK [4,7,8]. We note that the catalytic core of the kinase has sometimes been referred to as transmitter domain. In this article, we refer to transmission as the ligand-dependent conformational changes that ultimately lead to the stimulation of kinase activity. Since the prototypical HK is a transmembrane protein, signal detection and transmission domains are localized to all three compartments of the cell, that is, the extracytoplasmic space, the membrane, and the cytoplasm (Fig. 1). Experimental structures have been elucidated for a variety of domains, and molecular insights about signal detection and transmission have been gained from these structures (Fig. 1b). The remarkable diversity of signals, both chemical and physical, that are detected by HK is evident from a few examples.

For instance, the *Bacillus subtilis* DesK kinase responds to temperature changes by detecting membrane fluidity through its transmembrane domains [9]. Light-sensing PER-ARNT-SIM (PAS) and c**G**MP-specific phosphodiesterases, **a**denylyl cyclases and **F**hlA (GAF) domains have been identified to utilize flavin mononucleotide or Biliverdin cofactors [10–13]. Small ligand nutrients such as amino acids and carboxylic acids are detected directly by a wide variety of domains in the extracytoplasmic space, for instance, by the PAS domains of CitA (citrate ligand) [14] and the tandem PAS domain of KinD (pyruvate ligand) [15] or the all α-helical domain of NarX (nitrate ligand) [16]. The *Salmonella typhimurium* PhoQ HK utilizes a PAS domain to detect small antimicrobial