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Insights into Eukaryotic Multistep Phosphorelay Signal Transduction Revealed by the Crystal Structure of Ypd1p from *Saccharomyces cerevisiae*

Hyun Kyu Song, Jae Young Lee, Myong Gyong Lee, Jinho Moon, Kyeongsik Min, Jin Kuk Yang, and Se Won Suh*
Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151-742, Korea

"Two-component" phosphorelay signal transduction systems constitute a potential target for antibacterial and antifungal agents, since they are found exclusively in prokaryotes and lower eukaryotes (yeast, fungi, slime mold, and plants) but not in mammalian organisms. *Saccharomyces cerevisiae* Ypd1p, a key intermediate in the osmosensing multistep phosphorelay signal transduction, catalyzes the phosphoryl group transfer between response regulators. Its 1.8 Å structure, representing the first example of a eukaryotic phosphorelay protein, contains a four-helix bundle as in the HPt domain of *Escherichia coli* ArcB sensor kinase. However, Ypd1p has a 44-residue insertion between the last two helices of the helix bundle. The side chain of His64, the site of phosphorylation, protrudes into the solvent. The structural resemblance between Ypd1p and ArcB HPt domain suggests that both prokaryotes and lower eukaryotes utilize the same basic protein fold for phosphorelay signal transduction. This study sheds light on the best characterized eukaryotic phosphorelay system.