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PASsing a Signal: Low Carbs, Less Protein

PAS kinases combine the sensor functions of PAS (Per-Arnt-Sim) domains with the regulatory phosphorylation activity of protein kinases. Complementary multidisciplinary reports reveal coordinated regulation of sugar storage and protein synthesis by PAS kinase and suggest structural coupling of ligand and kinase binding by the PAS domain.

PAS domains were originally identified [1] in the *Drosophila* **P**eriod clock protein (Per), the vertebrate **A**ryl hydrocarbon receptor nuclear translocator (Arnt), and *Drosophila* **S**ingle-minded (Sim), a protein determining cell fate during development. In diverse multidomain proteins, PAS domains function in sensing and signal transduction [2–9] by as yet poorly understood mechanisms. PAS domains share with the single-domain bacterial blue-light photosensor photoactive yellow protein, a common modular three-dimensional fold encompassing ~125–150 amino acid residues [4, 5]. Most well characterized PAS domains bind small molecule ligands, cofactors, or chromophores, including oxygen-sensing hemes, redox-sensitive flavins, light-activatable *para*-hydroxycinnamic acid, and other small aromatic or conjugated compounds. PAS domains also mediate intra- and intermolecular interactions that can transmit sensor signals into actions or catalysis by other proteins or protein domains. Many PAS domain proteins sense environmental signals or energy and metabolic levels and use this information to appropriately regulate pathways for cell development, chemotaxis, circadian rhythms, homeostasis, and/or metabolism.

Many PAS domain proteins in eubacteria and plants have been found to be protein kinases. In bacteria, sporulation [10] and nitrogen fixation [5, 11, 12] are regulated by phosphorelay two-component histidine kinases controlled by PAS domains. In plants, the light-activated, bilin binding phytochromes are histidine kinases [13], and flavin-mediated, photocycling phototropins are serine/threonine kinases [14]. In contrast, mammalian PAS domain proteins of known function frequently act as transcriptional regulators. However, PAS kinase [15] or PASKIN [16] was recently identified as the first PAS domain-regulated protein kinase in animals.

Two new papers in *Cell* [17] and *Structure* [18], from collaborating laboratories in the Department of Biochemistry at the University of Texas Southwestern Medical Center, provide insights into PAS kinase functions from two different directions. Starting from the whole organism level, Rutter et al., from the McKnight lab, demonstrate mechanisms by which PAS kinase coordinates sugar storage and protein synthesis with carbohydrate availability in budding yeast [17]. Starting from the intramolecular level, Amezcua et al., from the Gardner lab, focus on the three-dimensional structure of a PAS domain from PAS kinase and structural mechanisms for coupling its intermolecular binding to small molecule ligands with its intramolecular interactions to the kinase domain [18].

After determining the NMR structure of the N-terminal PAS domain of human PAS kinase, Amezcua et al. mapped its flexibility and identified separate but nearby binding regions for small molecule ligands and for the kinase domain [18]. These binding and structural analyses by the Gardner lab suggest that the N-terminal PAS domains of PAS kinases may mediate cellular metabolism by coupling intermolecular binding of small molecule ligands that signal the organism's energy status, with intramolecular binding to regulate the kinase domain. The McKnight lab identified five protein targets phosphorylated by PAS kinase: two are enzymes catalyzing the pathway for sugar storage as glycogen, and three are polypeptides involved in the control of protein synthesis [17]. Rutter et al. further demonstrated that yeast knockout strains lacking PAS kinase accumulate excess storage carbohydrates and are temperature sensitive for growth on galactose as the sole carbon source. This phenotype can be genetically suppressed not only by the PAS kinase genes but also by genes encoding another (upstream) enzyme leading to glycogen synthesis and RNA and polypeptide components involved in protein synthesis. Thus, PAS kinase concertedly downregulates both glycogen storage and protein production, when incoming carbohydrate sources are limiting.

By comprehensively addressing many aspects of PAS kinase function, these two papers [17, 18] help to integrate the evolving picture of PAS domain proteins and their roles in helping to regulate the metabolism, growth, and activity of cells in different stages of development and under different types of environmental stress.

Elizabeth D. Getzoff
Department of Molecular Biology and
Department of Immunology and
Skaggs Institute for Chemical Biology
The Scripps Research Institute
La Jolla, California 92037

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