S8-1

Two-Component Signal Transduction by Phosphate and Vancomycin in Bacteria

Barry L. Wanner

Dept. of Biological Sciences, Purdue University, West Lafayette, IN, USA 47907-2054
(E-mail: blwanner@purdue.edu)

This talk will be comprised of two parts. The first will concern two-component signaling systems for phosphate acquisition and vancomycin resistance which the speaker's group has studied for many years. All cells are decorated with an array of cell surface sensory proteins that serve as antennae to detect environmental (extracellular) signals and to communicate with cytosolic effector proteins that in turn mediate responses. Nearly all bacteria (mycoplasma are exceptions) use two-component regulatory systems for many of these signaling processes. These systems are typically comprised of a signaling histidine kinase (HK; also called a sensor kinase) that is usually membrane-associated and a cytoplasmic response regulator (RR) that is usually a transcription factor (an activator or repressor). Similar two-component systems (TCS) control genes for nutrient acquisition, virulence, antibiotic resistance, and numerous other pathways in bacteria.

The *E. coli* phosphate (Pho) regulon is controlled by the PhoR(HK)/PhoB(RR) TCS. PhoB is activated (phosphorylated) by PhoR in response to inorganic phosphate (P_i) limitation. Phospho-PhoB then acts as a transcription factor for many genes, including *phoA*, the gene for bacterial alkaline phosphatase (Bap). However, under certain conditions, PhoB is activated by the non-partner kinases CreC or EnvZ (SK Kim, MR Wilmes-Riesenberg, and BL Wanner. *Molec. Microb.* 22:135-147, 1996). A systematic study has been done to test whether other kinases can also activate PhoB and whether activation of PhoB by these non-partner kinases is due to non-specific (cross talk) interactions (resulting from biochemical cross reactivities) or due to specific (cross regulation) interactions that are important for coordinating metabolic processes, e. g., pathways of carbon, energy, and phosphate metabolism. Recent results will be presented.

The VanS(HK)/VanR(RR) TCS regulates expression of genes for vancomycin resistance in vancomycin-resistant enterococci (VRE). VRE have become clinically problematic human pathogens with high mortality and incidence increasing alarmingly over the past decade. Clinical isolates of VRE have been divided into three types based on the level of resistance (Type A and B, high level resistance; VanC, low or moderate level resistance), inducible versus constitutive resistance (Type A and B, inducible; VanC, constitutive), and inducibility by both vancomycin and teicoplanin (Type A) or inducibility by vancomycin only (Type B). To characterize VRE signal transducing proteins, we have previously studied VanSa and VanRa *in vitro* and *in vivo* using an *Escherichia coli* model system. (SL Fisher, SK Kim, BL Wanner, & CT

Walsh. (1996) *Biochemistry* 35, 4732; A Haldimann, SL Fisher, LL Daniels, CT Walsh, & BL Wanner (1997) *J. Bacteriol.* 179, 5903.) An update on this work will be given.

The second part of this talk will concern the International *E. coli* Alliance (IECA), which has been promoting an *E. coli* systems biology initiative. The speaker has played a leading role in IECA since its inception two years ago (C Holden. Cell Biology: Alliance Launched to Model *E. coli*. *Science* 297 (5586):1459-1460, 2002). The speaker will give provide an update on progress of the *E. coli* Project Initiative.