New insight into an old reaction: Adenylylation regulates cell signaling

April 9 2009

A new study reveals the importance of adenylylation in the regulation of cell signaling from bacteria to higher organisms. The research, published by Cell Press in the April 10th issue of the journal *Molecular Cell*, provides new insight into bacterial pathogenesis and opens intriguing avenues for exploring post-translational modifications in eukaryotic cells.

Immunoglobulin binding protein A (IbpA) is a large fibrillar surface antigen that is produced by the respiratory pathogen Histophilus somni and has been implicated in virulence and host toxicity. One section of IbpA is similar to YopT, a known cytotoxic effector, while a separate domain resembles Bordetella pertussis filamentous hemagglutinin, which mediates attachment to host cells.

A research team led by Dr. Jack E. Dixon from the University of California at San Diego and the Howard Hughes Medical Institute hypothesized that IbpA's filamentous hemagglutinin-like domain likely mediates attachment to host cells, while the YopT-like domain could serve as a cytotoxic effector. Unexpectedly, a systematic examination of IbpA's function revealed that the filamentation induced by c-AMP (Fic) domain, and not the YopT-homologous region, represented a virulence determinant in IbpA.

"Although Fic domains are found in proteins from bacteria to humans, their activity has remained unknown until recently, when Yarbrough et al. (Science, 2009, v. 323, p. 269) reported a Fic domain containing

protein that catalyzed an adenosine monophosphate (AMP) modification on threonine residues of Rho GTPases," explains Dr. Dixon. Rho GTPases regulate multiple key signaling pathways in mammalian cells.

The researchers went on to show that the Fic domain of IbpA catalyzed a unique, reversible adenylylation event that used ATP to add an AMP to a specific, conserved tyrosine residue in Rho GTPases, thereby inactivating them and inducing cytotoxicity.

Further, the only known human protein with a Fic motif, Huntingtin yeast-interacting protein E (HYPE), was also capable of adding AMP to RhoA, Rac, and Cdc42. Further studies are needed to better understand the significance of the interaction between HYPE, which is ubiquitously expressed in mammalian cells, and Rho GTPases. It also remains to be seen if HYPE might have targets for adenylylation beyond Rho GTPases.

Taken together, these results support an evolutionarily conserved enzymatic activity for the Fic domains of H. somni and human HYPE. "These findings identify a new class of enzymes that mediate bacterial pathogenesis and suggest that addition of AMP may be an underappreciated post-translational modification that can regulate key signaling events in higher organisms," concludes Dr. Dixon.

Source: Cell Press (news : web)