Pathogens use previously undescribed mechanism to sabotage host immune system

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New research identifies a previously unknown enzymatic mechanism that subverts the early host immune response and promotes pathogenicity by manipulating a common signaling pathway in host cells.

The research, published by Cell Press in the December 14th issue of *Molecular Cell*, may have important implications for the food industry and for development of new antibiotics. In addition, the results lead to intriguing questions about whether mammalian cells can make use of a similar mechanism for potentially permanent and irreversible posttranslational modifications.

Many gram-negative bacterial pathogens have evolved specialized mechanisms for disrupting the ability of host cells to activate innate immune responses that will provide immediate defense against infection. Mitogen-activated protein kinase (MAPK) pathways play key roles in activating host innate immune responses and are frequent targets of pathogenic effectors in both plants and animal systems.

All MAPKs contain a threonine -X-tyrosine motif and require phosphorylation of both threonine and tyrosine for activation. Previous work demonstrated that members of the OspF family, including OspF from Shigella and SpvC from Salmonella, are phosphothreonine lyases that promote pathogenicity by directly targeting and irreversibly inhibiting the activation of MAPKs.

Dr. Feng Shao from the National Institute of Biological Sciences,

Beijing and colleagues used mass spectrometry to examine the mechanism underlying inactivation of MAPKs by the OspF family of effectors. The researchers determined the crystal structure of SpvC and its complex with a phosphopeptide substrate. The enzyme-substrate complex revealed how SpvC docks with activated MAPK by recognizing the phosphotyrosine and then maneuvers the phosphothreonine into the enzyme active site. These data implicated the MAPK p38 as the likely preferred substrate for OspF and SpvC during bacterial infection because it has the required conformational flexibility for this interaction. The researchers went on to identify a previously unknown catalytic mechanism of acid-base mediated "-elimination of phosphoserine/phosphothreonine that irreversibly inactivated the kinase.

“Our data provide biochemical and structural evidence for specific recognition of the dual phosphorylated MAPK substrates by the OspF family of phosphothreonine lyases and explain the enzyme’s differential activities towards different MAPK substrates,” explains Dr. Shao. Further, as phosphorylation of serine and threonine residues is widely used as a regulatory mechanism in mammalian cells, the researchers speculated that phosphoserine or phosphothreonine lyases might exist in eukaryotes and serve as post-translational modification enzymes that irreversible dephosphorylate kinases or other phosphorylated substrates.

Source: Cell Press