Bacterial glycosyltransferases that inhibit innate immunity

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Many Gram-negative bacterial pathogens use a syringe-like apparatus called a type III secretion system to inject virulence factors into host cells. Some of these effectors are enzymes that modify host proteins to subvert their normal functions. NleB is a glycosyltransferase that modifies host proteins with N-acetyl-D-glucosamine to inhibit antibacterial and inflammatory host responses. NleB is conserved among the attaching/effacing pathogens enterohemorrhagic *E. coli* (EHEC), enteropathogenic *E. coli* (EPEC), and *Citrobacter rodentium*. *Salmonella enterica* strains encode up to three NleB orthologs named SseK1, SseK2, and SseK3. However, there are conflicting reports regarding the activities and host protein targets among the NleB/SseK orthologs. We performed in vitro glycosylation assays and cell culture experiments to compare the activities and substrate specificities of these effectors. SseK1, SseK3, EHEC NleB1, EPEC NleB1, and C. rodentium NleB blocked TNF-mediated NF-κB pathway activation, whereas SseK2 and NleB2 did not. C. rodentium NleB, EHEC NleB1, and SseK1 glycosylated host glyceraldehyde 3- phosphate dehydrogenase (GAPDH). C. rodentium NleB, EHEC NleB1, EPEC NleB1,and SseK2 glycosylated the Fas-associated death domain protein (FADD). SseK3 and NleB2 were not active against either substrate. EHEC NleB1 glycosylates two GAPDH arginine residues, R197 and R200. These two residues are essential for GAPDHmediated activation of tumor necrosis factor (TNF) Receptor-Associated Factor 2 (TRAF2) ubiquitination. These results provide evidence that members of this highly conserved family of bacterial virulence effectors target different host protein substrates and exhibit distinct cellular modes of action to suppress host responses.

Biography

Philip R Hardwidge is a Professor at Kansas State University. His laboratory is interested in understanding, treating, and preventing diarrheal disease caused by bacterial pathogens. His research team has discovered several mechanisms by which bacterial proteins subvert the host innate immune system to promote bacterial colonization and transmission. He is directing his knowledge of these proteins and their mammalian targets to innovative studies of metabolic syndromes, autoimmune disorders, and cancer. He is also developing proteomic techniques to identify vaccine targets in other organisms.

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