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EDITORIAL

Desmosome Disruption by Enteropathogenic *E coli*

Attaching and effacing (A/E) pathogens, which include the well-studied enteropathogenic *Escherichia coli* (EPEC), cause malabsorption and diarrhea. These bacteria colonize the gut by first attaching to intestinal epithelial cells (IECs) and subsequently effacing the apical microvilli via virulence effectors injected through the bacterial type III secretion system (T3SS). On the basis of a growing body of studies detailing the molecular mechanism of cytoskeletal hijacking by bacteria, these virulence effectors are believed to be integral to pathogen-host attachment, entry, and functional perturbation. For example, *E coli*–secreted protein H (EspH) was reported to modulate host cell actin cytoskeleton via recruitment of neural Wiskott–Aldrich syndrome protein to EPEC attachment sites[1] and inhibiting Rho guanosine triphosphatase (GTPase) signaling through its interaction with Rho guanine exchange factors (GEFs).[2] However, no association has been made between EspH and the disruption of intestinal epithelial barrier integrity, which is a major contributor to diarrhea. Furthermore, despite the recent implication of A/E pathogens in inducing tight junction reorganization,[3] their potential impact on other junction-related structures, such as desmosomes, has not been determined.

In this issue, Roxas et al[4] investigated the impact of EPEC on desmosome disruption in the intestinal epithelia. They examined the contribution of EspH and Rho GTPase signaling to the loss of intestinal epithelial integrity. By using an in vitro model of human IECs (Caco-2 Brush Border-expressing cells), Roxas et al[4] detected a rapid loss of desmosomal junction proteins, desmoglein-2 (DSG2) and desmocollin-2, 3 hours after EPEC infection. Transepithelial resistance assays showed that EPEC infection compromised the IEC barrier integrity. In contrast to the wild-type EPEC, infection by a T3SS-deficient strain did not alter the expression or localization of desmosomal proteins. Thus, the investigators analyzed a number of EPEC mutants that lacked individual components of T3SS machinery, and identified that EspH was responsible for the observed phenotypes of desmosome disruption and barrier impairment. Because it is known that EspH interacts with p115-RhoGEF to inhibit RhoA activity,[2] Roxas et al[4] showed that EspH-mutant EPEC strains incapable of binding to RhoGEF also failed to disrupt the desmosomal junctions. Interestingly, treating EPEC-infected cells with a RhoA activator restored the expression as well as the localization of DSG2 to cell junctions, collectively suggesting that EspH might act on desmosomal junctions through perturbing RhoGEF. By infecting mice with EPEC, the investigators provided in vivo evidence that the wild-type but not EspH-deficient EPEC strains elicited a mislocalization of DSG2 and a disruption of the lateral epithelial membranes shown by electron microscopy. Overall, these data nicely led to a model that EPEC effector protein EspH acts on host RhoGEF to induce rapid desmosomal perturbation that consequently may impair epithelial junctions and barrier integrity.

Tight junction disruption has been studied extensively as the prominent target of pathogens for compromising barrier function. The study by Roxas et al[4] extended our understanding of this process by shedding light on the perturbation of a non–tight junction structure, the desmosome, by A/E pathogens. Notably, their data suggested that desmosomal perturbation might precede tight junction disruptions because the tight junctions appeared normal in the infected cells where desmosomes already were altered. Indeed, loss of DSG2 and desmocollin-2 has been reported in the ileum of Crohn's disease patients, where a reduction of the tight junction protein claudin-1 also was observed.[5] Silencing or stabilizing DSG2 in Caco2 cells affected the expression of claudin-1,[5] suggesting a potentially causative relationship between desmosome and tight junction perturbations. Whether and how tight junction perturbation is consequential to the loss of desmosomal proteins should be examined further in the future.

Several gastrointestinal pathogens exploit the host Rho GTPase machinery in spatiotemporal manners. *Salmonella enterica* activate host Rho GTPases through the bacterial RhoGEFs and GTPase activating-proteins to gain entry into the cytoplasm and initiate invasion. After invasion, bacterial factors inhibit Rho GTPases.[6] For EPEC, EspH appears to selectively inactivate the host (eukaryotic) cell RhoGEFs, but not the bacterial RhoGEFs.[7] EspH therefore may both activate and inhibit the Rho GTPase machinery, at different times, for reasons including, but not limited to, promoting bacterial survival. Exactly how RhoA inactivation leads to desmosome disruption was not explored here, but is an important question for future study. Two other Rho GTPases, Cdc42 and Rac, have been shown to activate p38 mitogen-activated protein kinase (MAPK),[8] which also is able to trigger or induce desmosome disruption.[9] Whether EspH-mediated Rho inhibition perturbed desmosomes through a similar pathway can be explored further. As shown by this study, pathogenic hijacking of key cellular machineries remains an area ripe for investigation.

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