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EDITORIAL

Stinging Tight Junctions With WASPs

Extracellular bacterial pathogens can hijack the N-WASP–based machinery to promote actin nucleation and polymerization in their hosts. One well-studied example is the family of attaching and effacing (A/E) bacterial pathogens, which includes the human diarrheagenic enteropathogenic *Escherichia coli* (EPEC) and enterohemorrhagic *E coli*, and the mouse pathogen *Citrobacter rodentium*. These bacteria, which infect the intestinal epithelium, activate a syringe-like machinery, termed the *type III secretion system*, through which they translocate a battery of protein effectors from their own cytoplasm into the infected host. These protein effectors hijack diverse host processes, and are thought to contribute to EPEC pathogenesis. One such effector is *E coli* secreted protein F (EspF), a multifunctional protein that interacts via its proline-rich regions with the Src homology 3 (SH3) domains of N-WASP and another host protein, Sorting nexin-9 (SNX9), which mediates endocytic membrane remodeling.[1,2] In addition, EspF is involved in the disruption of epithelial tight junctions, a process that may contribute to diarrhea. However, the role of these EspF interacting proteins in tight junction breakdown remains largely unknown.

In this issue, Garber et al[3] report the results of experiments designed to test the hypothesis that interactions between EspF and N-WASP/SNX9 are involved in the disruption of tight junctions. To this end, they generated a conditional knockout of the *N-WASP* gene in the mouse intestine. They also used an in vitro model of polarized human intestinal Caco-2 cells whose N-WASP expression was knocked down by short hairpin RNA. First, Garber et al showed that N-WASP expression is involved in maintaining apical junctional complex morphology and intestinal permeability. Calcium-switch experiments showed that N-WASP regulates the tight-junction barrier by modulating junctional protein dynamics. These data, which principally agree with previous in vivo studies in *Drosophila*,[4] suggest that N-WASP may regulate the organization and function of epithelial cell–cell junctions. Subsequently, using the experimental systems described earlier, they have been able to show the significance of N-WASP and SNX9 binding to EspF in the disruption of tight junction barrier functions. Strikingly, they also observed that infection with wild-type *C rodentium* induced a robust A/E phenotype in the wild-type mice, but not in the N-WASP–deficient mice. Together, these findings suggest novel roles for N-WASP in maintaining the tight junctions homeostasis and host colonization by A/E pathogens.

Despite this advance, it is not clear yet how EspF subverts the host junctions. EspF shares common characteristics with another protein effector, mitochondrial-associated protein (Map). For instance, both effectors target host mitochondria and modulate the actin cytoskeleton and tight junctions, raising the possibility that they cooperate in space and time. Map is a potent activator of the Rho guanosine triphosphatase Cdc42. Active Cdc42 is needed for Neural Wiskott-Aldrich syndrome protein (N-WASP) activation. Thus, Map activates Cdc42, which in turn may activate EspF-associated N-WASP. The plasma membrane phosphoinositide phosphatidylinositol(4,5)bisphosphate (PIP_2), which EPEC recruits at infection sites,[5] also has been implicated in N-WASP activation. SNX9 binds PIP_2, dynamin, and N-WASP to couple actin polymerization with endocytic membrane remodeling.[6] Thus, PIP_2, EspF-associated N-WASP and SNX9, and Map-associated Cdc42 may work together in coupling actin remodeling with endocytic dynamics. Because endocytic trafficking is thought to control the localization and activity of junctional proteins, it would be conceivable to consider a working model whereby EspF and Map and their associated modulators cooperate to hijack endocytic platforms that alter the localization and trafficking of junctional proteins in a way that causes tight junctions disruption. Further investigation is needed to validate this hypothesis. Nevertheless, the findings by Garber et al reveal exciting new insights into bacterial pathogenesis, and bacterium-host interactions.

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Conflicts of interest
The author discloses no conflicts.

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