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Rupture, invasion and inflammatory destruction of the intestinal barrier by *Shigella*, making sense of prokaryote-eukaryote cross-talks

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The pathogenesis of bacillary dysentery can be studied at different levels of integration of the cellular components that constitute the colonic mucosal barrier. Interaction of *Shigella flexneri* with individual epithelial cells shows a series of events in which the bacterium, upon contact with the cell surface, releases Ipa proteins (i.e. invasions) through a specialized, activable, type III secretory apparatus (i.e. Mxi/Spa). Via a complex signalling process that involves both the cascade of signals elicited by the three GTPases of the Rho family (Cdc42, Rac and Rho) and pp60^{c-src}, these invasions cause major rearrangement of the subcortical cytoskeletal network, thereby allowing bacterial entry by a macropinocytic event. Invasion by the bacterium turns the epithelial cell to a strongly pro-inflammatory cell, due to activation of NFκB. Then the bacterium lyses its phagocytic vacuole and initiates intracytoplasmic movement, due to polar nucleation and assembly of actin filaments caused by a bacterial surface protein, IcsA. The cytoskeletal-associated protein N-WASP and Arp2/3 to play an essential role in initiation of actin polymerisation. This allows very efficient colonization of the host cell cytoplasm and passage to adjacent cells via protrusions, which are engulfed by a cadherin-dependent process. However, when invasive *Shigella* are deposited on the apical side of polarized monolayers of human colonic cells, they are unable to invade, indicating that bacteria need to reach the subepithelial area to invade the epithelium. In this system, it has been shown that transepithelial signalling caused by apical bacteria induces adherence and transmigration of basal polymorphonuclear leucocytes (PMN), thus disrupting the monolayer's permeability and facilitating bacterial invasion. LPS accounts for a large part of this transepithelial signalling to PMN. Such process could account for invasion in intestinal crypts. Finally, models of infection, such as the rabbit ligated intestinal loop, show that initial bacterial entry occurs essentially via M cells of the follicular associated epithelium. It then causes apoptosis of macrophages located in the follicular dome, inducing release of IL-1β, which in turn initiates inflammation, leading to destabilization of the epithelial structure as modelled above.



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