



Salmonella exploits suicidal behavior of epithelial cells

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Infection with enteric bacterial pathogens such as *Salmonella* leads to tissue invasion and intracellular replication in the intestinal mucosa. Bacterial invasion is detected by the host innate immune system and triggers a stereotypical, inflammatory response characterized by recruitment of immune cells to the infected tissue. In a remarkable paper, Knodler et al. (2010) propose a novel mechanism by which the intestinal epithelium can clear *Salmonella*-infected cells through a form of proinflammatory cell death and how *Salmonella* in fact may exploit this mechanism.

TAKING ONE FOR THE TEAM: PYROPTIC CELL DEATH OF INFECTED EPITHELIAL CELLS AS A PROINFLAMMATORY SIGNAL

Using a polarized epithelial cell culture model, Knodler et al. (2010) observed that in a fraction of infected cells, *Salmonella enterica* serovar Typhimurium (*S. Typhimurium*) replicated with an astonishing doubling time of only 20 min. Although conventional wisdom holds that intracellular *Salmonella* typically reside in a vacuolar compartment, this population had escaped the membrane bound compartment by unknown mechanisms and was replicating rapidly inside the cytoplasm. Epithelial cells harboring hyper-replicating bacteria were expelled from the monolayer into the luminal space. This process resembled the homeostatic turnover of epithelial cells in the intestinal tract. However, during infection with a pathogen, extrusion of dying, infected cells was accompanied by activation of caspase-1, and secretion of the caspase-1 substrate interleukin (IL)-18, a proinflammatory cytokine (Figure 1). This observation suggests that a proinflammatory programmed (pyroptotic) cell death of epithelial cells may contribute to the induction of inflammatory responses *in vivo*. Indeed, in a murine model of *Salmonella*-induced colitis, Muller et al. (2009) have shown recently that SopE, a translocated effector of the invasion-associated type three secretion system, triggers intestinal inflammation

by activating caspase-1 in intestinal stromal cells, presumably enterocytes. IL-18 signaling downstream of caspase-1 was required for SopE-mediated induction of inflammation. Taken together, these findings support the idea that pyroptotic cell death contributes to the initiation of the inflammatory host response in the gut (Bergsbaken et al., 2009) and suggest that intestinal epithelial cells serve as sentinels for bacterial invasion.

EXPLOITATION OF HOST IMMUNE RESPONSES BY SALMONELLA

The inflammatory response induced by *S. Typhimurium* leads to profound changes in the intestinal tract, turning the gut lumen into a nutritional niche in which *S. Typhimurium* efficiently outcompetes

the endogenous microbiota (Stecher et al., 2007; Winter et al., 2010). Interestingly, Knodler et al. (2010) also observed that *S. Typhimurium* might exploit the pyroptotic cell death of bacteria-laden epithelial cells for its own benefit. *S. Typhimurium* rapidly replicating inside the cytosol of extruded epithelial cells expressed flagella and the invasion-associated type III secretion system, two key virulence factors for invasion of non-phagocytic host cells. Expression of these virulence factors might prime a sub-population of released bacteria for re-entry into other epithelial cells, thereby prolonging the duration of disease. Furthermore, epithelial pyroptosis might aid in reseeding the intestinal lumen, thereby contributing to transmission by the fecal oral route.

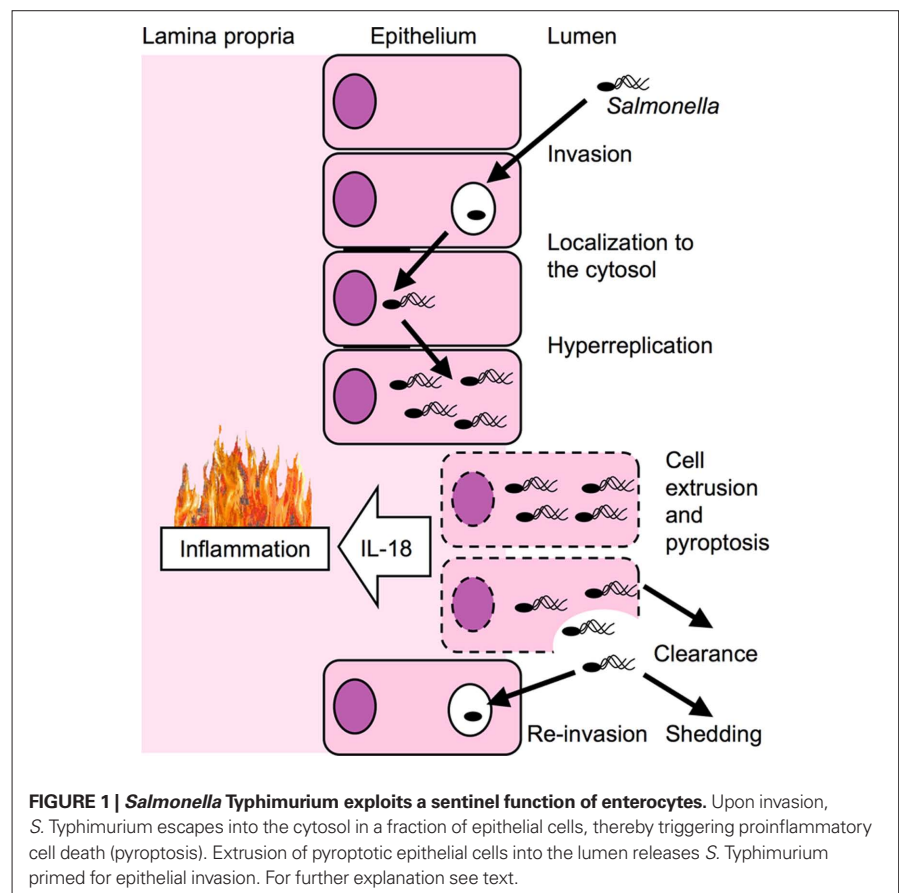


FIGURE 1 | *Salmonella Typhimurium* exploits a sentinel function of enterocytes. Upon invasion, *S. Typhimurium* escapes into the cytosol in a fraction of epithelial cells, thereby triggering proinflammatory cell death (pyroptosis). Extrusion of pyroptotic epithelial cells into the lumen releases *S. Typhimurium* primed for epithelial invasion. For further explanation see text.

This work by Knodler et al. (2010) is pioneering since it sheds light on a new mechanism of host response aimed at clearing invasive pathogens from the intestinal epithelium and initiating intestinal inflammation. At the same time, the experiments suggest that *S. Typhimurium* may take advantage of this pathway to enhance its transmission success.

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