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EDITORIAL

Intestinal Epithelial Interference in Cryptospordium Infection: Type III Interferon Confers Protection Against Protozoan Parasites

Infection with the apicomplexan parasite *Cryptosporidium* species, is the most common cause of water and foodborne diarrheal disease in the United States. Cryptosporidiosis results in severe diarrhea in individuals with a compromised immune system, and is the second leading cause of diarrheal death in young children in developing countries.[1]

Transmitted via the fecal–oral route, *Cryptosporidium* induces extensive intestinal epithelial cell shedding, villus blunting, and crypt hyperplasia after invasion of the small intestinal villous epithelium. Although nitazoxanide is effective in treating intestinal cryptosporidiosis in immunocompetent patients,[2] the lack of additional therapies for immunocompromised individuals and the absence of supportive care often leads to dehydration and death. Under normal circumstances, *Cryptosporidium* is minimally invasive and readily can be cleared by an epithelial-induced immune response.[3] However, much remains unknown regarding the mechanisms by which the epithelium combats this invasive pathogen.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Ferguson et al[4] use a neonatal piglet model to investigate the transcriptional response of intestinal epithelial cells to *Cryptosporidium parvum*, one of the most common species of *Cryptosporidium* reported in human beings. At the peak of infection, microarray analysis of ileal epithelium identified a significant enrichment in interferon (IFN)-stimulated genes, including IFN-stimulated gene 15. Furthermore, the investigators showed that of all IFNs, only expression of type III IFN (IFN-λ) was up-regulated significantly in both the mucosa of infected piglets and in a neonatal suckling mouse model of *C parvum* infection. Administration of neutralizing antibodies against IFN-λ2/3 before infection resulted in a greater epithelial burden and increased shedding of *C parvum* in neonatal mice compared with pups receiving isotype control antibodies.

Concomitant with increased parasite burden, more severe mucosal injury was observed in the absence of an appropriate type III IFN response. To determine if exogenous IFN-λ could limit the severity of *Cryptosporidium* infection, porcine epithelial monolayers were pretreated with recombinant human IFN-λ3 before *C parvum* exposure. One of the key findings of this study was that priming with IFN-λ3 not only inhibited *C parvum* invasion as early as 12 hours after infection, but also limited the maturation of the parasite within 6 hours after infection. This resulted in a significant reduction in overall parasite burden, indicating that activation of type III IFN signaling in the intestinal epithelium initiates a protective response to limit *C parvum* infection. In addition, IFN-λ3 pretreatment prevented increased tight junction–mediated Na^+ flux observed in response to *Cryptosporidium*.

Type I and III IFN signaling previously was thought to be redundant because ligand binding to either receptor results in the activation of an identical signal transduction pathway. However, intestinal epithelial expression of IFNλ receptor has been shown to be critical for an IFN-mediated antiviral response.[5,6] Although the investigators did not exclude a role for type I IFN, these studies provide evidence that type III IFN signaling is a key contributing factor in epithelial defense against *Cryptosporidium* infection.

In addition to initiating an antiviral immune response, a growing body of literature indicates that type III IFN signaling represents a conserved mechanism for controlling pathogen infection at mucosal surfaces. To date, IFNλ has been shown to promote innate antifungal immunity,[7] and regulate host susceptibility to bacterial,[8] and now, protozoal, infection. Although activation of type III IFN and downstream IFN-stimulated genes have been well characterized in relation to their antiviral functions, the current study opens the door to explore the activation of these pathways and their role in antiparasite immunity.

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