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"Type III Interferons Promote Rotavirus-induced Diarrhea"

by
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ABSTRACT

Rotavirus (RV) infection is the leading cause of severe diarrhea in children under five years old, and results in approximately half a million deaths each year. A variety of viral and host factors have been shown to influence the severity of RV-caused disease. Type I and type III interferons (IFNs) are produced in the intestine during RV infection and their combined action is required for the efficient control of RV replication and extra-intestinal spread. However, the impact of IFNs on RV-caused diarrheal disease have not been investigated. To assess effects of IFNs on viral diarrhea, we used mice deficient in type I IFN, type III IFN, and type I/III IFN signaling and a murine model of RV infection, in which suckling mice are infected with rhesus RV (RRV).

Unexpectedly, we found that suckling mice lacking type III IFN (IFN-λ) signaling were more resistant to RRV-induced diarrhea, even though their intestines harbored significantly more virus compared to wild type (WT) mice. Moreover, inhibition of IFN-λ activities attenuated RRV-associated diarrhea, despite increased viral titers. In addition, administration of recombinant IFN-λ to suckling mice infected with a sub-diarrhea dose of RRV triggered diarrhea, whereas viral titers were reduced. These observations uncoupled the positive correlation between the intestinal RRV load and the severity of diarrhea and revealed an unanticipated role for IFN-λ as an important regulator of RRV-induced diarrheal disease. Using mice lacking type III IFN receptor in specific compartments, we identified IFN-λ signaling in intestinal epithelial cells (IECs) as the major drive promoting RRV-induced diarrhea. We used an unbiased RNA-seq approach to identify pathways affected by IFN-λ during the development of diarrhea, and may therefore affect diarrheal disease. These potential pathways were further validated and investigated by a variety of immunological and cell-biological assays. Experiments revealed that IFN-λ stimulates RRV-triggered IEC apoptosis, accelerates intestinal epithelial turnover and alters paracellular permeability. Overall our results suggest that IFN-λ activates a network of interdependent events within the small intestine, which are aimed to achieve the optimal antiviral protection with the minimal collateral damage to the host.