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The Paradox of Type III Interferons: A Delicate Balance Between Protection and Pathology in Colitis Development and Gut Tissue Repair

Jena KK, Mambu J, Boehmer D, et al. Type III interferons induce pyroptosis in gut epithelial cells and impair mucosal repair. Cell 2024; 187:7533–7550.

Tissue damage and repair are fundamental aspects of intestinal inflammation, requiring tightly regulated sensing of environmental or endogenous threats to maintain homeostasis. Although type III interferons (interferon gamma [IFN-λ]) have been shown to limit inflammation by restraining neutrophil-driven tissue damage, their role in epithelial repair remains controversial in inflammatory bowel disease (IBD).

In the featured study, Jena et al (Cell 2024; 187:7533–7550) investigated how IFN-λ influences tissue repair after damage to the intestinal mucosa. Although IFN-λ is critical for antiviral defense and dampening the tissue-damaging functions of neutrophils, the authors highlight that IFN-λ signaling paradoxically impairs epithelial healing. They demonstrated that IFN-λ, but not type I or II IFNs, induce pyroptosis in gut epithelial cells after damage to the intestinal mucosa, thereby compromising mucosal regeneration, a relevant mechanism in IBD.

Using epithelial-specific *Ifnlr1* or *Ifnl2/3* knockout mice, the authors showed that type III IFN signaling delays recovery of experimental colitis or radiation-induced epithelial damage, as indicated by impaired re-epithelialization, reduced colon length, and delayed weight gain. Bulk and single-cell RNA sequencing following sublethal partial body irradiation revealed that IFN-λ dampened intestinal stem cell expansion, leading to accumulation of immature progenitors (transit amplifying progenitors) associated with suppression of proliferative and regenerative transcriptional programs (cell migration, extracellular remodeling, wound healing), while enriching IFN-signaling–related antiviral and antibacterial pathways.

Notably, the authors identified pyroptosis, a highly inflammatory form of cell death characterized by membrane rupture and inflammation, mediated by upregulation of Z-DNA-binding protein 1 (ZBP1), as a key pathomechanism of impaired IFN-λ–driven epithelial repair. Z-nucleic acids formed after intestinal injury are sensed by ZBP1, triggering the formation of a multiprotein complex that activates caspase-8 and cleaves gasdermin C (GSDMC), leading to pyroptosis but not necroptosis. Using sophisticated *in vitro* and *in vivo* knockout models (eg, *VilCre Gsdmc1-4*$^{fl/fl}$, *Zbp1*$^{-/-}$ mice), the authors demonstrated that IFN-λ–mediated ZBP1 activation suppresses intestinal stem cell–driven epithelial regeneration. Importantly, pharmacological inhibition of RIPK1, a key regulator of cell death, rescued IFN-λ–induced cell death in intestinal organoids, whereas caspase-8 inhibition reduced pyroptosis and promoted epithelial repair in mice.

From a clinical perspective, the authors showed that the IFN-λ/ZBP1/Casp-8/GSDMC axis is upregulated in patients with active IBD. Overall, these findings provide critical insights into the dual role of IFN-λ, balancing both protective and detrimental effects in colitis development and tissue repair. Targeting the IFN-λ pathway may offer novel therapeutic strategies to mitigate tissue damage in IBD. Future research should further elucidate the relevance of the IFN-λ/ZBP1/Casp-8/GSDMC axis in human intestinal inflammation and explore targeted interventions to counteract its deleterious effects, while preserving protective antiviral functions of IFN-λ.

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Conflicts of interest
The author discloses no conflicts.