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NEUTROPHILS

Interfering with intestinal inflammation

IFNλ is an important regulator of the immune response to infection at mucosal barriers, where it acts on epithelial cells to induce interferon-stimulated genes (ISGs). However, it is unclear what effect IFNλ has on non-epithelial cells. Broggi and colleagues now report that IFNλ can modulate the function of neutrophils, leading to the suppression of intestinal inflammation.

The authors examined the ability of different immune cell subsets that were isolated from mice to respond to IFNλ. Only neutrophils expressed *Ifnlr1* (part of the IFNλ receptor) and responded to IFNλ by upregulating an ISG (*Rsad2*). Furthermore, treating neutrophils with the pro-inflammatory mediators tumour necrosis factor (TNF) or lipopolysaccharide (LPS) upregulated *Ifnlr1* expression. Importantly, these results were recapitulated in human neutrophils, as treatment with IFNλ increased the expression of *RSAD2* and treatment with LPS upregulated *IFNLR1* expression.

> “Treating human and mouse neutrophils with IFNλ suppressed their ability to produce reactive oxygen species”

Neutrophils must be regulated during inflammation, as they release tissue-damaging compounds. Treating human and mouse neutrophils with IFNλ suppressed their ability to produce reactive oxygen species and to degranulate in response to treatment with TNF or LPS. This effect was independent of transcription or translation as neutrophils treated with cycloheximide (to block protein synthesis) or deficient or inhibited in signal transducer and activator of transcription 1 (STAT1) or STAT3 (transcriptional regulators of ISGs) activity were still suppressed by treatment with IFNλ.

Next, using an *in vivo* mouse model of dextran sodium sulfate (DSS)-induced colitis, the authors showed that IFNλR1-deficient mice, irradiated wild-type mice that were repopulated with IFNλR1-deficient leukocytes or mice that were treated with IFNλ-blocking antibodies had more severe disease and higher levels of oxidative stress compared with wild-type mice. In addition, a mouse model with the selective ablation of *Ifnlr1* in neutrophils recapitulated the more severe disease phenotype, which indicates that *in vivo* neutrophils must be responsive to IFNλ to suppress intestinal inflammation. Deletion of *Ifnlr1* from epithelial cells had no effect on DSS-induced colitis, which suggests that the protective effect of IFNλ is independent of IFNλR1 expression in epithelial cells.

Infection with enteric viruses has been previously shown to protect against DSS-induced colitis. Interestingly, wild-type mice, but not IFNλR1-deficient mice, had more severe colitis when treated with antiviral drugs, suggesting that endogenous enteric viruses induce IFNλ expression in the intestine that suppresses inflammation. In support of this, treatment of wild-type, enteric virus-free mice with exogenous IFNλ reduced intestinal inflammation in the DSS-induced model.

In summary, these data indicate that IFNλ may act as an immunomodulatory cytokine by modifying neutrophil responses, either by inducing ISG expression or by translation-independent mechanisms.

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