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IFN- λ ‘guts’ neutrophil-mediated inflammation

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Abstract

Interferon- λ (IFN- λ) curbs neutrophil-mediated intestinal inflammation by diminishing the production of reactive oxygen species and subsequent oxidative stress. This regulatory process is unique to IFN- λ and is independent of interferon-induced transcription and translation programs.

A hallmark of inflammation is the infiltration of neutrophils into the site of infection in response to inflammatory cytokines and chemokines released by infected cells. Neutrophil-mediated restriction of pathogens is conferred by phagocytosis, the production of reactive oxygen species (ROS) and the release of cytotoxic antimicrobial molecules¹. In this issue of *Nature Immunology*, Broggi *et al.* show that the antiviral cytokine IFN- λ (a type III interferon composed of IFN- λ 1, IFN- λ 2, IFN- λ 3 and IFN- λ 4) regulates the effector function of neutrophils by diminishing ROS production and degranulation and thereby reducing oxidative stress and tissue damage during intestinal inflammation². Surprisingly, this regulatory mechanism is unique to IFN- λ , is not mediated by type I interferons (IFN- α and IFN- β) and is independent of canonical interferon-induced antiviral transcription and translation programs.

The rapid initiation of an immune response after pathogen encounter is crucial for the outcome of infection and survival of the host. However, because excessive inflammation can lead to immunopathology, the magnitude and duration of inflammatory responses need to be tightly controlled. The expression and secretion of type I interferons is a hallmark of activation of the innate immune system that functions to contain viral spread and is induced within minutes after sensing of a viral pathogen by an infected cell. In response to secreted type I interferons, cells initiate the expression of hundreds of interferon-inducible antiviral factors that control viral spread through various mechanisms that include targeting of viral entry, replication and egress³. As expression of the IFNAR1 and IFNAR2 subunits of the type I interferon receptor IFNAR is ubiquitous, almost every cell can respond to secreted type I interferons. In contrast, the type III interferon family^{4,5} is restricted in its function, as only a limited number of cell subsets have been shown to express its receptor and thus respond to IFN- λ . The heterodimeric IFN- λ receptor IFNLR, which consists of the subunits IFNLR1 and IL-10R2, is limited almost exclusively to hepatocytes and epithelial cells of mucosal surfaces⁶. Hence, the IFN- λ class of interferons have become a major focus of research investigating host–pathogen interactions for hepatotropic viruses and viral pathogenesis at the epithelial barrier of the lungs and the gastrointestinal tract⁷.

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Initially, cell-intrinsic antiviral programs induced by type I or type III interferons were thought to be highly redundant despite their usage of distinct receptors. That conclusion was based on a shared Jak–STAT signaling pathway downstream of the receptors for type I and type III interferons and the induction of similar interferon-stimulated genes (ISGs) after treatment of cells with either type I interferons or type III interferons. Subsequent work, however, has challenged that proposal of redundancy, as differences in the signaling pathways activated downstream of the receptors, as well as distinct kinetics of interferon-induced antiviral programs, have been identified^{8,9}. Due to the abundant expression of the receptor for type III interferons on epithelial cells, most studies have focused on the cell-intrinsic antiviral effects mediated by IFN- λ at the epithelium. In contrast, little is known about the role of IFN- λ in immune-cell activation and the regulation of cellular effector functions.

Activation of the innate immune response following infection at the epithelium leads to rapid recruitment of neutrophils from the bloodstream¹. These innate immune cells act as first responders to control infection by multiple mechanisms, including phagocytosis, degranulation and the production of ROS. Activated neutrophils also release chemokines, which leads to the recruitment of monocytes and other immune cells to sites of infection. While neutrophil functions provide a first line of defense until adaptive immunity is established, an over-exuberant neutrophil response can lead to extensive tissue damage and therefore must be tightly regulated.

Important for the regulation of inflammation, the interferon response must be ‘fine-tuned’ to induce optimal antiviral function while curtailing pathology at the same time. Published studies have indicated that IFN- λ provides a better balance of robust antiviral protection with diminished inflammation and tissue damage than IFN- α ^{10,11}. IFN- λ has been shown to directly inhibit the migration of neutrophils and their production of the cytokine IL-1 β , which diminishes neutrophil function and leads to alleviation of inflammatory arthritis¹². Additionally, this regulatory role for IFN- λ in neutrophils has been extended to infection of the respiratory epithelium with influenza virus¹¹. While such studies have demonstrated the relevance of IFN- λ in regulating neutrophil function, whether these mechanisms affect the control of intestinal inflammation by neutrophils has remained unknown.

Here, Broggi *et al.* demonstrate that neutrophils derived from the blood, bone marrow and peritoneal cavity all express *Ifnlr1*. These neutrophils respond to treatment with IFN- λ by phosphorylating STAT1 and STAT3 and inducing ISGs similarly to their response to type I interferons². In contrast to the activation of the ISG response, the production of ROS following neutrophil stimulation is significantly reduced with additional IFN- λ treatment but not with additional IFN- β treatment. Intriguingly, other neutrophil effector functions, such as phagocytosis and cytokine production, are unaltered by treatment with IFN- λ or IFN- β following stimulation. Surprisingly, this unique IFN- λ -mediated suppression of ROS occurs independently of transcription and translation. Together these results suggest that IFN- λ and IFN- β have differential capacities for regulating specific neutrophil effector functions, even though the ISG response is induced similarly. While the signaling pathways downstream of IFNLR and IFNAR are considered to be largely redundant, differences do exist, such as the recruitment of Jak2 to IFNLR but not to IFNAR¹³. The authors reveal that

these differences in the neutrophil response are due to phosphorylation of Jak2, which inhibits phosphorylation and activation of the kinase AKT and thereby prevents assembly of the NADPH oxidase complex NOX2 and ROS production² (Fig. 1).

Broggi *et al.* next investigate the contribution of neutrophils and their regulation by IFN- λ in a mouse model of dextran sulfate sodium (DSS)-induced colitis², as neutrophils are known to be key regulators of inflammation during colitis and other human intestinal inflammatory diseases. The authors find that IFN- λ signaling contributes to protection against DSS-induced colitis, because mice treated with IFN- λ neutralizing antibodies and *Ifnlr1*^{-/-} mice have more weight loss and disease and shorter colon length after DSS treatment than their wild-type counterparts. Studies of bone-marrow chimeras, as well as specific deletion of *Ifnlr1* in intestinal epithelial cells and neutrophils, reveal that IFN- λ signaling in neutrophils specifically controls inflammation and disease during DSS-induced colitis. To determine the source of IFN- λ in this model, the authors assess the involvement of enteric viruses, as they have been shown to have a similar protective role in DSS-induced colitis. Treatment of wild-type mice with antiviral agents diminishes the expression of IFN- λ in the intestine and leads to an increase in pathology after DSS administration. This enhancement of DSS-induced disease by antiviral agents is abolished by the addition of recombinant IFN- λ , which indicates that IFN- λ produced in response to enteric viruses is important for controlling DSS-induced disease. Interestingly, IFN- β can diminish the weight loss but not the pathology associated with treatment with DSS and antiviral agents. These findings demonstrate that treatment with IFN- λ provides significantly greater protection against DSS-induced disease than does treatment with type I interferons and provides protection distinct from that afforded by type I interferons. This IFN- λ -mediated reduction in disease is probably due to a mechanism that precedes interferon-induced *de novo* protein synthesis.

In summary, Broggi *et al.* identify a unique, novel role for IFN- λ in the regulation of neutrophil function and intestinal inflammation that involves stimulation by enteric viruses². Unlike type I interferons, the unique ability of IFN- λ to dampen neutrophil functions highlights IFN- λ as a therapeutic molecule for intestinal inflammation. In a broader sense, the general ability of neutrophils to respond to IFN- λ outside the intestinal environment underscores the potential for IFN- λ to function as an ideal antiviral therapeutic agent—that is, one that will effectively restrict the virus while minimizing the tissue pathology promoted by infiltrating neutrophils. The potential broad implications of IFN- λ are supported by the observation of a unique role for IFN- λ in controlling infection with influenza virus while limiting tissue pathology at least in part in a neutrophil-dependent manner¹¹. However, whether IFN- λ signaling in neutrophils in the lungs leads to a similar non-translational regulation of neutrophil function remains unknown. Additionally, these findings raise the interesting possibility that IFN- λ might regulate the cytotoxic functions of other immune cells in a non-translational manner, as most studies so far have assessed only the induction of antiviral responses in immune-cell subsets by IFN- λ .

Through this study, Broggi *et al.* reveal a new role for IFN- λ , which regulates neutrophil function by diminishing ROS production via Jak2 in a transcription- or translation-independent manner². Further studies are needed to determine if the effects of IFN- λ on neutrophils could affect the outcome of viral infection and inflammatory disease in humans.

More importantly, this study highlights yet another critical non-redundant role for type III interferons in immunity.

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Figure 1.

IFN-λ produced in response to enteric viruses regulates intestinal inflammation via diminishing neutrophil function. Enteric viruses constantly trigger the production of interferons. Type I interferons (represented here by IFN-β) and type III interferons (IFN-λ) signal through their respective receptors to induce phosphorylation of STAT1 and STAT2, their translocation to the nucleus and the upregulation of ISGs. This enteric-virus-dependent IFN-λ also signals specifically in neutrophils in a Jak2-dependent fashion to inhibit activation of AKT, which blunts the generation of ROS and limits the damage caused in a mouse model of DSS-induced colitis. RAC-GTP, p67^{phox}, p40^{phox}, p47^{phox} and p22^{phox} are components of the NOX2 complex. *Ifn*, interferon-encoding gene; Tyk2, tyrosine kinase; IRF9, interferon-regulatory factor 9; ISRE, interferon-stimulated response element.