License to kill: IFN-λ regulates antifungal activity of neutrophils

Daniel Schnepf and Peter Staeheli

Interferon-λ mediates antifungal immunity by stimulating neutrophils to generate reactive oxygen species.

Epithelial cells of the respiratory and intestinal tract form a vast mucosal surface that is constantly exposed to viruses, microbes, and fungi present in the environment. The host defense mechanisms that protect the mucosa are still not fully understood. In recent years, we learned that type III interferon (IFN-λ) acts primarily on epithelial cells and protects the mucosa against invading viruses (1, 2). Whether IFN-λ can act on immune cells and whether it may also inhibit the growth of nonviral pathogens were unclear until very recently. In the October issue of Science Immunology, Espinosa et al. (3) demonstrate that IFN-λ triggers enhanced production of reactive oxygen species (ROS) by neutrophils to prevent invasive pulmonary aspergillosis. Using Aspergillus fumigatus (Af) infection as a model, the authors have uncovered the sequence of events that drive innate immune responses to Af. They found that in response to Af infection, CCR2+ inflammatory monocytes produce an initial burst of type I IFN that primes other cells to secrete IFN-λ, which in turn acts on neutrophils that drive robust antifungal immune responses.

The authors had previously shown that in addition to neutrophils, CCR2+ monocytes are also essential in pulmonary defense against Af (4). Therefore, they hypothesized that neutrophil activity might be regulated by as yet undefined factors secreted by CCR2+ monocytes. Using an unbiased systems biology approach, the authors uncovered that neutrophil dysfunction in CCR2-depleted mice was linked to an impaired production of IFNs. Kinetic analysis in wild-type mice showed that all three IFN classes were up-regulated upon Af infection, although with remarkably different kinetics. Type I IFN was up-regulated quickly but only transiently. In contrast, IFN-λ and IFN-γ levels increased steadily during the first 48 hours after infection. Using mice strains that lack receptors for type I or type III IFNs, the authors made two key findings. First, the initial burst of IFN-α observed in infected mice was essential to prime cells for efficient production of IFN-λ. Second, mutant mice lacking functional IFN-λ receptors were highly susceptible to pulmonary challenge with Af. Fungal growth in the lungs of these mice occurred unhindered and correlated with a reduced ability of neutrophils to produce ROS. The conclusion was that IFN-λ can mediate antifungal innate immunity via ROS in the respiratory tract. This finding was truly unexpected because IFN-λ has to date been linked exclusively to antiviral but not antifungal host defense.

Little is known about the nature of cells that produce IFNs in response to fungal infections. The authors set out to identify the responsible cell types in the lungs of Af-infected mice. Their analysis showed that CCR2+ monocytes were a rich source of IFN-γ, whereas IFN-λ was produced by still poorly defined CCR2− CD45+ and CD45− cells. To define the IFN-λ-responsive cells during infection, the authors carried out bone marrow transfer experiments. Robust antifungal immunity required that hematopoietic cells express functional IFN-λ receptors were highly expressed in neutrophils. Thus, IFN-λ and STAT1 expression were substantially impaired in their ability to produce ROS. Together, these results confirm that IFN-λ acts directly on neutrophils and regulates their activity in the context of fungal infections.

The work of Espinosa et al. shows that in neutrophils, signaling via the IFN-λ receptor/STAT1 pathway is essential for optimal production of ROS and, in turn, antifungal defense. Intriguingly, two other recent reports (5, 6) also described effects of IFN-λ on neutrophils but concluded that IFN-λ suppresses rather than activates neutrophil activity. In the latter studies, intestinal inflammation was induced by chemical stimuli, whereas inflammation in the current study resulted from pulmonary aspergillosis. Thus, it appears as though IFN-λ can mediate both activation and suppression of neutrophils, depending on the nature of the inflammatory trigger and possibly the organ affected. It is plausible that chemically induced inflammation, accompanied by tissue damage, might generate a different cytokine milieu compared with that of aspergillosis-triggered inflammation. Thus, IFN-λ can either boost or dampen ROS production by neutrophils depending on which insult has triggered tissue inflammation.

IFN-λ receptor and STAT1 expression in pulmonary neutrophils were both required for proper ROS generation in the lungs and for proper control of the Af infection. These findings indicate that classical IFN-λ signaling was at work and that STAT1-mediated gene expression enabled neutrophils to enhance ROS production and mediate antifungal immunity (Fig. 1). In contrast, Broggi et al. (6) reported that IFN-λ limits intestinal inflammation by diminishing ROS production of neutrophils in the absence of IFN-induced...
gene transcription and de novo protein synthesis. In the bowel disease model used by Broggi et al., IFN-λ appeared to negatively regulate ROS production via a nonconventional signaling pathway in which Janus kinase 2 (JAK2)–mediated signaling played a key role. According to these authors, receptor engagement by IFN-λ triggered phosphorylation of JAK2, which in turn inhibited phosphorylation of AKT, negatively regulating ROS production via the AKT pathway (Fig. 1). It thus appears as though the IFN-λ signaling pathway in neutrophils can serve as a switch that, depending on the context, can mediate either activation or suppression of neutrophils. In this context it should be noted that Fuchs et al. (8) recently questioned the functional importance of the classical JAK1/TYK2 (tyrosine kinase 2)–dependent IFN-λ signaling pathway by showing that TYK2 is apparently dispensable for antiviral activity of IFN-λ in human cells. Accumulating evidence indicates that signaling through the IFN-λ receptor is more complex than previously appreciated and may involve mitogen-activated protein kinases (9). Additional studies are required to clarify the roles of the different IFN-λ signaling pathways in infectious and noninfectious disease models.

Another interesting question concerns the observed nonredundancy of the IFN-α/β and IFN-λ systems in the Af infection model. Because neutrophils express receptors for both IFN types (5–7), it remains unclear why one IFN subtype cannot stand in for the other. Nonredundancy may be explained by the different IFN induction kinetics in the lungs of Af–infected mice. Nevertheless, it would be interesting to know whether type I IFN can influence ROS production of neutrophils independently of IFN-λ and whether a neutrophil-specific deletion of the type I IFN receptor might also affect Af resistance.

This study by Espinosa et al. (3) revealed an unexpected role of IFN-λ in antifungal immunity and demonstrates that IFN-λ can confer protection against invasive aspergillosis by boosting ROS generation of neutrophils. Additional studies are needed to determine whether the observed stimulatory effect of IFN-λ on neutrophils can also affect the outcome of infections with viruses or pathogenic bacteria. This study has established that IFN-λ can shape innate immunity in unexpected ways, highlighting once again that IFN-λ plays a critical nonredundant role in pathogen defense.

Fig. 1. Orchestrated interactions of distinct cell types result in IFN-λ–mediated activation of neutrophils and antifungal immunity. CCR2+ inflammatory monocytes produce an initial burst of type I IFN upon Af infection. Type I IFN then primes CCR2+ CD45+ and CD45– cells to secrete IFN-λ during pulmonary aspergillosis. IFN-λ, in turn, acts on neutrophils to initiate STAT1-dependent production of ROS that mediates robust antifungal immunity (red pathway). In the context of infection, IFN-λ resolves inflammation via suppression of neutrophil infiltration and IL-1β production. J. Exp. Med. 212, 845–853 (2015).

REFERENCES
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