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Lambda interferons come to light: dual function cytokines mediating antiviral immunity and damage control
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Lambda interferons (IFNs, type III IFNs or interleukins-28/29) were described fifteen years ago as novel cytokines sharing structural and functional homology with IL-10 and type I IFNs, respectively. IFNs engage a unique receptor complex comprising IFNLR1 and IL10R2, nevertheless they share signaling cascade and many functions with type I IFNs, questioning their possible non-redundant roles and overall biological importance. Here, we review the latest evidence establishing the primacy of IFNs in front line protection at anatomical barriers, mediating antiviral immunity before type I IFNs. We also discuss their emerging role in regulating inflammation and limiting host damage, a major difference to type I IFNs. IFNs come thus to light as dual function cytokines mediating antiviral immunity and damage control.

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Introduction
For a long time, type I interferons (IFNs) have been considered as the primary antiviral defense system, acting in an autocrine and paracrine manner to induce resistance to infection and enhance innate and adaptive immune responses needed for viral clearance [1]. Moreover, they have attracted major interest in oncology and multiple sclerosis as biological response modifiers able to improve therapy [1]. However, although type I IFNs have been approved for diverse indications including genital warts, viral hepatitis, hairy cell leukemia and chronic myelogenous leukemia, their use in the clinic is limited due to the frequent and severe adverse effects (including flu-like disease and depression) they exhibit.

With the completion of the Human Genome Project, it became apparent that another cytokine family, termed lambda IFNs (IFNs), type III IFNs or IL-28 and IL-29, exists and shares structural homology with the interleukin (IL)-10 family and functional homology with type I IFNs [2,3]. Similarly to type I IFNs, IFNs are triggered by infection and induce multiple antiviral responses mediating viral clearance. They also exert pleiotropic effects on the immune system, many of which highly reminiscent to those of type I IFNs. This raised the question whether IFNs and type I IFNs are redundant, and why our organism needs two IFN-based antiviral defense systems to confront infection. Here, we review the latest evidence highlighting the primacy of IFNs in antimicrobial, and in particular antiviral, immunity. We survey their unique and common biology with type I IFNs, their co-operation with type I IFNs in the fine-tuning of antimicrobial immunity and their emerging role in damage control. We also discuss their potential as novel therapeutics that exhibit the beneficial effects, but lack the pro-inflammatory activities causing side effects, of type I IFNs.

IFNλ members, induction mechanisms and expression patterns
There are four IFNλ members in humans, IFNA1/IL-29, IFNA2/IL-28A, IFNA3/IL-28B, IFNA4, and two (IFNA2/IL-28A, IFNA3/IL-28B) in mice [2–4]. Much like type I IFNs, IFNs are only transiently expressed following stimulation by viruses and microbial products. These include all major respiratory (influenza and parainfluenza viruses, rhinoviruses, respiratory syncytial viruses, coronaviruses etc), gastrointestinal (rotaviruses, reoviruses, noroviruses) and hepatotropic (hepatitis B and C) viruses [2,3,5,6], intracellular and extracellular bacteria (Listeria monocytogenes, Streptococcus pneumonia, Haemophilus influenzae, Staphylococcus aureus, Salmonella enterica, Shigella sonnei and Mycobacterium tuberculosis) [7,8,9], and numerous microbial components and synthetic ligands (imidazoquinolines, polynosinic-polycytidylic acid, flagellin, peptidoglycan and CpG oligodeoxynucleotides) [10,11].
Central to IFNα production are pattern-recognition receptors (PRRs) such as toll-like receptor (TLR)3, TLR5, TLR7/8 and TLR9, RIG-I and MDA-5 which trigger a downstream signaling cascade leading to the activation of nuclear factor κB (NF-κB) and interferon regulatory factors (IRFs). Accordingly, IFNα genes have binding sites for NF-κB, IRF1, IRF3 and IRF7 in their promoter regions similarly to type I IFNs [2,3,12]. Although this would suggest co-regulation, this is often not the case; IFNαs exhibit a restricted pattern of expression compared to type I IFNs which are almost ubiquitously expressed. IFNαs are most abundant at barrier surfaces including the respiratory and gastrointestinal tracts, and can be robustly produced by epithelia and epithelial-origin cells including hepatocytes and some immune cells [10,11,13,14]. This goes beyond the ability of all cells to respond to PRR engagement, suggesting the existence of additional cell-specific epigenetic, transcriptional and post-transcriptional regulation of IFNα production. For example, RIG-I-like receptor signaling through mitochondrial antiviral signaling protein (MAVS) in peroxisomes [15], sensing through the cytosolic DNA sensor Ku70 [16], induction of the transcriptional co-activator Med23 [17] or presence of transcriptional repressors such as ZEB1 and BLIMP-1 [18,19] have all been associated with IFNα production. Whether such mechanisms can broadly account for IFNα expression patterns remains to be established.

**Downstream signaling cascades, target cells and functional consequences**

All IFNα members engage a unique heterodimeric receptor complex, the IFNLR, that comprises IFNLR1 (IFNLR1A, IL-28RA), and IL10R2 (IL-10RB). IFNLR1 confers ligand specificity and enables receptor assembly, while IL10R2 is shared with IL-10 family members and is required for signaling. Binding of IFNα to IFNLR1 and IL10R2 occurs at a 1:1 stoichiometry compared to the 2:1:1 ratio between IL-10, IL10R1 and IL10R2 [20*]. IFNLR stimulation leads to the activation of the tyrosine kinases Jak1 and Tyk2, and the transcription factors STAT1 and STAT2 which bind to IRF9, forming the IFN-stimulated gene factor 3 (ISGF3) complex [2,3]. ISGF3 then enters the nucleus and induces the transcription of hundreds of genes, termed IFN-stimulated genes (ISGs), that generally inhibit viral replication and spread, and exhibit broad antimicrobial functions against viral, bacterial and parasitic infections [21]. Notably, this pathway is also shared with type I IFNs, highlighting the very similar antiviral activity these two systems exhibit [22–24]. Thus, it has been difficult to segregate IFNα from type I IFN functional or transcriptional responses, with IFNα-induced genes typically representing a subset of all genes elicited by type I IFNs but exhibiting a delayed peak and longer duration [23–26].

The most striking difference between the two IFN systems is their receptor distribution. The type I IFN receptor is expressed in almost all cell types. On the contrary, the IFNLR1/IL10RB complex is expressed primarily in cells of epithelial origin and few immune cells, mainly neutrophils and subsets of dendritic cells (DCs), conferring selective IFNα responsiveness to them. This has been demonstrated for both mouse [27,**28**,29**] and human neutrophils [29**] and plasmacytoid DC (pDCs) [11,30], as well as human monocyte-derived DC [31,32], and mouse bone marrow-derived or lung-sorted conventional DC (cDC) of the DC2 phenotype [33] (Figure 1). The expression pattern of the receptors largely follows that of their ligands with human and mouse epithelial cells [2,3,13,28**,34], pDCs [10,11,30,35,36], DC1 [37] and DC2 [11,28**,36,38] cells, as well as human monocyte-derived DC [31,32,38,39] and macrophages [34,38,40] expressing high levels of IFNαs upon activation. This points to more specialized roles for IFNαs in localized immune responses at epithelial barrier surfaces conferred by epithelial and immune cells. However, subtler differences also exist. For example, JAK2 phosphorylation is induced only by IFNαs but not type I IFNs [15], while other less well-described pathways may also be important for antiviral functions [41**], indicating the existence of distinct signalling events that remain to be characterized.

**IFNαs in antiviral immunity**

From the very first publications describing the discovery of IFNαs, it became evident that IFNαs exhibit potent antiviral activity [2,3]. Treatment of infected cells in culture or experimental animals with recombinant IFNαs has been effective against a very diverse range of viruses [42–44]. However, endogenous non-redundant roles of IFNαs that are not compensated by type I IFNs have been difficult to establish. Important progress has recently come from the study of gastrointestinal infections where it was shown that cell responsiveness to IFNαs is largely compartmentalized with IFNαs acting on intestinal epithelial cells (expressing high levels of IFNLR1) and having minimal effects on lamina propria cells (expressing low levels), while type I IFNs exhibiting the opposite effects [45,46**]. Accordingly, it was demonstrated that rotavirus — which infects epithelial cells — is solely controlled by IFNαs while reovirus -which replicates in both epithelial and non-epithelial cells and can spread systemically- requires the co-operative action of IFNαs with type I IFNs [45,46**,47]. Similarly, norovirus that grows at the gastrointestinal epithelium but spreads systemically is confronted by both IFN systems [48**]. Interestingly, IFNαs can effectively clear norovirus in antibiotics-treated mice, an effect prohibited by gut commensals [49], adding another level of complexity to the equation.
In the respiratory tract, such compartmentalization is less obvious. Respiratory epithelial cells express receptors for and respond to both types of IFNs, as do certain immune cell populations residing or infiltrating the lung. Moreover, although nose, bronchial and alveolar epithelial cells express high levels of IFNs following infection [34,50], smooth muscle cells, fibroblasts, and DCs can also do so [10,11,51,52]. This suggested a degree of redundancy between the two IFN systems, supported by early work showing increased susceptibility to respiratory viral infections in mice deficient in both IFNLR1 and IFNAR1, but not in mice deficient in only IFNLR1 [23,53,54]. However, more recent studies have uncovered major and unique roles of IFNs in antiviral immunity in the lung. They have revealed that IFNs are induced first, at lower viral burden than type I IFNs, and act to limit initial infection spread [28**]. This is possibly due to the propensity of airway epithelial cells to selectively produce type III IFNs [23,55]. In line with that, it has been reported that IFNs are essential for preventing virus transmission from the upper airways to the lungs, a process that takes place early during infection [56**]. Interestingly, IFNs lack the strong pro-inflammatory effects of type I IFNs and are rather anti-inflammatory and tissue protective. As a result, IFNLR1<sup>−/−</sup> mice exhibit increased viral load, inflammation and host damage following infection [28**], whereas recombinant IFNα2 treatment potently suppresses these outcomes [57]. This is also the case when mice are treated with IFNα2/3 neutralizing antibodies [58]. These data support a model where IFNs confer initial antiviral protection without provoking unnecessary inflammation, while type I IFNs come into play as a second line of defense to enhance antiviral responses at the expense of collateral damage (Figure 2).

This model of IFNα action is consistent with the behavior of IFNs in the gastrointestinal tract and may therefore explain their broader role in antiviral defense. Indeed, in the liver, IFNs are also important in providing protective immunity against HBC and HCV infections as demonstrated by the many IFN gene polymorphisms linked to improved spontaneous or treatment-induced viral clearance, and the effectiveness of IFNα therapy [59]. Interestingly, this is attributed to the ability of human hepatocytes to preferentially generate and respond to IFNs similarly to respiratory epithelial cells [60]. Moreover, in the skin, IFNs are predominantly expressed over type I IFNs and are associated with reduced incidence to infections [61].

**IFNs in antibacterial and antifungal immunity**

In addition to viruses, bacterial and fungal infections can also trigger IFNα production. *L. monocytogenes, S. enterica* and *S. sonnei* as well as several bacterial ligands induce IFNs [7,9*], mainly in a MyD88-dependent manner [9*]. This is functionally important. *In vitro*, IFNs enhanced epithelial barrier integrity, preventing bacterial dissemination [9*]. *In vivo*, in models of *S. aureus* or *Pseudomonas aeruginosa* infection, IFNLR1<sup>−/−</sup> mice exhibited lower
bacterial loads and less pathology, although inflammatory cell infiltration was not affected [62]. Also, intranasal infection of IFNLR1−/− mice with S. aureus led to significantly increased bacterial clearance and, at the same time, decreased proinflammatory cytokines including IL-1β in the airways [63]. Interestingly, in this study IL-1β production appeared to be regulated by proteases released by neutrophils rather than NLRP3 and caspase-1 activation. Moreover, in a model of invasive aspergillosis with Aspergillus fumigatus, IFNLR1−/− mice developed aggravated disease, with higher fungal loads in the lungs and more severe fungal invasion [64**]. This was largely due to IFNα/mediated STAT1 activation in neutrophils, that was shown to protect the host. Further studies are therefore needed to shed light into the wider role of IFNαs in antimicrobial defenses beyond viral infections.

**IFNαs in immune modulation and damage control**

In sharp contrast to type I IFNs, IFNαs and their receptor are not ubiquitously expressed in the immune system. Rather, IFNαs are produced by pDCs [10,11,30,35,36], cDCs (DC1 [37] and DC2 [11,28**,36,38]), and monocyte-derived DC [31,32,38,39] and macrophages [34,38,40], as earlier discussed, while IFNLR1/IL10RB is functional in neutrophils [27*,28**,29**], pDCs [11,30], monocyte-derived DCs [31,32] and DC2 cells [33] but not other leukocytes. IFNαs therefore signal on a restricted set of leukocytes, exerting selective immune modulatory functions which are only now starting to become understood.

A primary emerging activity of IFNαs is the regulation of innate immunity. Contrary to type I IFNs, IFNαs suppress innate pro-inflammatory responses and limit the host damaging effects associated with inflammation. This is largely due to their selective action on neutrophils, preventing their pro-inflammatory activation and functions. Thus, in the context of influenza viral infection, IFNαs restrain the production of TNF, IL-1β and other tissue destructive mediators from neutrophils, while allowing effective antiviral responses to develop [28**]. Although it is unclear whether this is a direct effect, it nevertheless shows that IFNαs are critically involved in keeping inflammation under control and limiting collateral damage. In the context of chronic intestinal inflammation, IFNαs act directly on neutrophils to inhibit the generation of ROS and their degranulation through a process mediated by JAK2 [29**]. IFNαs can also induce additional beneficial effects by accelerating mucosal healing [65*]. Exogenous administration of recombinant IFNαs in experimental animal models with influenza virus infection or colitis has further confirmed their regulatory and anti-inflammatory activity, and has highlighted their therapeutic potential [29**,57]. Moreover, exogenous administration of recombinant IFNαs has shown therapeutic potential in other diseases where IFNαs may not be produced naturally such as collagen-induced...
arthritis [27*] and arterial thrombosis [66**]. In arthritis, the efficacy of IFNA treatment was attributed to the inhibitory effects of IFNλs in neutrophil migration [27*]. In arterial thrombosis, IFNA-mediated protection was due to the suppressive effects of IFNλs on neutrophil-extracellular traps (NETs) formation [66**]. This anti-inflammatory or immune-modulatory behavior of IFNλs is reminiscent of the activity of IL-10 with which IFNλs share sequence homology and the IL10RB subunit for signaling (Figure 3).

Another major activity of IFNλs is the regulation of adaptive immunity. IFNλs signal on DC2 cells [31–33] and pDCs [11,30], of both human and mouse origin, and modulate their function. in vitro, IFNλs enhance the propensity of human monocyte-derived DCs to generate Foxp3+ regulatory T cells [31,32]. in vivo, IFNλs suppress the ability of mouse DC2 cells to induce T helper 2 (Th2) and Th17 differentiation, and enhance Th1 cell development [33]. This is consistent with cell culture studies using mouse DC2 and T cells [33], or human peripheral blood mononuclear cells (PBMC) [67]. Interestingly, a SNP in the IIfnλ3 locus (rs8099917) is linked to higher IFNλ3 production and Th1 skewing following PBMC stimulation with influenza virus [68]. A shift in IFNγ production from NK cells is also observed but this might be indirect as neither NK cells [11,13] nor T cells [11,33] seem to respond to IFNλs. The Th1 skewing effect of IFNλs may be related to their capacity to increase the expression of the Th1 polarizing cytokine IL-12 in a context-dependent manner [33,69]. Noteworthy, cytotoxic T cell responses may also be affected by IFNλs as increased CD8+ T cell responses have been reported in IFNL1R1−/− mice following acute LCMV infection [70].

Interestingly, in T cell-driven diseases in experimental animals IFNλs are therapeutically effective. In allergic asthma, IFNλs potently suppress the activation of Th2 and Th17 responses, and the development of immunopathology [33]. In autoimmune arthritis, they also inhibit the induction of Th17 and γδ T cell responses and they ameliorate disease [27*]. IFNλs therefore appear to be broadly protective, in both acute and chronic inflammatory diseases, mediating immune modulatory actions aiming at restoring immunological balance and limiting direct tissue damage caused by the byproducts of host defense (Figure 4).

Conclusions

Over the last few years IFNλs have come out of the shadow of type I IFNs. They have emerged as a front line defense system mediating antiviral immunity at anatomical barriers such as the gastrointestinal and respiratory tracts. They have also emerged as novel immune regulatory cytokines with a special duty in damage control that act to maintain immunological balance and limit immunopathology. This extends beyond infections as IFNλs limit inflammation and prevent host damage in diverse other diseases including colitis, autoimmune arthritis and allergic asthma.

Central to the unique biology of IFNλs is their selective action on neutrophils, preventing their pro-inflammatory activation, inhibiting ROS production, degranulation and NET formation, and down regulating their migratory capacity. This is in sharp contrast to the pro-inflammatory effects of type I IFNs, which instead activate neutrophils and other leukocytes, and highlights the IL-10-like properties of IFNλs that remain to be further investigated.
This may also explain the improved safety profile IFNαs exhibit in the clinic.

The dual antimicrobial and immune regulatory function of IFNαs makes them particularly attractive for the treatment of infectious diseases or chronic disorders such as asthma and colitis where infections can exacerbate their severity, as IFNαs can selectively up regulate antiviral responses while limiting host damaging inflammation and symptoms. It also advocates for the broader evaluation of IFNαs in the fine-tuning of immunity in diseases which involve neutrophilic inflammation and alterations of the Th1/Th2/Th7 balance. Further studies towards these directions are therefore eagerly awaited.
Conflict of interest statement

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