REVIEW ARTICLE

Suppression of interleukin-17 by type I interferons: a contributing factor in virus-induced immunosuppression?

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ABSTRACT. Type I interferons (IFNs) are the first line of defence after various infections, and, as immunomodulatory cytokines, bridge innate and adaptive immunity. IL-17, mainly secreted by specific T cells, has recently been identified regulating neutrophil-mediated inflammation, and has been implicated in the pathogenesis of many acute and chronic inflammatory disorders. This cytokine is considered of critical importance for an effective anti-bacterial and anti-fungal immune response as needed subsequent to many viral infections. Recent studies have demonstrated that type I IFNs potently suppress IL-17 expression and Th17 differentiation *in vitro* and *in vivo*. Therefore, suppression of IL-17, as well as many other well-defined interactions of type I IFNs with the cytokine cascade, may contribute to virus-induced immunosuppression making the host vulnerable to bacterial and fungal attacks.

Keywords: type I interferon, Th17 cells, mononuclear cells, IL-10, viral infection

Viruses are the most abundant and diverse pathogens affecting various species including human beings. Almost all nucleated cells respond to viruses by producing type I interferons (IFN). Interferon-alpha (IFNα) was the first cytokine to be identified and is of great importance in various diseases [1, 2]. In addition to viral dsRNA, foreign DNA, also recognized by an intracellular sensor, triggers type I IFN production [3]. Even certain intracellular bacterial pathogens are able to exert a potent type I IFN response [4]. It has become evident in the last two decades that, in addition to their anti-viral (and anti-cancer) effects, type I IFNs also have several immunomodulatory functions [5]. IFNα controls the expression of many pro-inflammatory cytokines such as IL-8 and IL-18 [6, 7], and induces several anti-inflammatory mediators such as IL-1 receptor antagonist (IL-1Ra), soluble TNF receptor p55, IL-10 and IL-18 binding protein [8-10]. Despite this knowledge, the mechanisms of actions of this important mediator are still not sufficiently understood [5].

$CD4^+$ T cells play an important role in many immune processes. They expand and differentiate into different effector cells termed Th1, Th2, T_{regs}, and Th17, all of which are characterized by production of a certain subset of cytokines [11, 12]. Whereas Th1 cells produce mainly IFN-gamma (IFNγ) and IL-2, Th2 cells produce IL-4, IL-13 and IL-25. Recent identification of the Th17 family of effector T cells represented a major advance in the field [13, 14]. The IL-17 cytokine family is a group of cytokines that includes IL-17A, B, C, D, IL-17E (IL-25) and IL-17F [14]. It is increasingly recognized that, besides T cells, other cells such as NK cells and neutrophils might also be an important source of IL-17. In addition to IL-17A, which is the major cytokine produced by Th 17cells, these cells also release IL-17F, IL-21 and IL-22 [15-17]. It is currently believed that Th17 cells play a major role in host defence against certain pathogens, however, an exaggerated Th17 response may lead to severe inflammatory responses and autoimmune diseases [14, 18]. Therefore, interaction with this Th17 cytokine family could be an important mode of action for type I IFNs.

Secondary bacterial infection can occur after viral infection, and is a common cause of severe disease in humans; however the mechanisms underlying this virus-induced immunosuppression remain poorly understood. In this article, we try to summarize how type I IFNs interact with the cytokine cascade, thereby also regulating critical anti-bacterial/anti-fungal cytokines such as IL-17.

TH17 CELLS AND TH17-RELATED CYTOKINES

Th17 cells are characterized by the synthesis of IL-17A (usually called IL-17), IL-17 F, IL-21, IL-22 and others

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[19]. Members of this cytokine family are believed to be of critical importance for the clearance of extracellular pathogens such as *Klebsiella spp*. or *fungi*, and therefore reflect a major defence against such infections. IL-17A is the main product of Th17 cells, and is therefore considered as "the major player" of this cytokine group. One of the key functions of IL-17 is its strong potency to induce a pro-inflammatory response with the induction of IL-6, IL-1β and TNF-α [20]. In addition, IL-17 induces various chemokines (CXCL1, IL-8, CCL2 and others) and matrix metalloproteinases [21, 22].

The IL-17 receptor (IL-17RA) is expressed at high levels mainly on hematopoietic cells, and at lower levels on many cells such as fibroblasts and epithelial cells [19]. Kuestner and colleagues have identified another receptor, IL-17RC, as receptor for IL-17F [23]. In humans, IL-17RA and IL-17RC may result in heterodimer binding of IL-17A [24]. Similar to the transcription factors regulating Th1 and Th2 responses, a Th17-specific transcription factor has recently been identified as RORγt [25]. Current data support a major role for this orphan nuclear receptor in the differentiation of Th17 cells; however, other transcription factors such as RORα might also be needed to guarantee a high level of IL-17 expression [26]. Furthermore, a "cocktail" of cytokines is needed for induction, amplification and maintenance of Th17 cells which might include IL-6, TGFβ, IL-1β, IL-21 and IL-23 [19]. Whereas there seem to be major differences between mice and men, loss of any one of the above mentioned mediators might impair the development of a strong and robust IL-17 response.

TH17 AND INFECTIONS

Th17 cells have an important role in host defence against specific pathogens [27]. This strong immune response and the potent induction of other pro-inflammatory cytokines by IL-17, lead to tissue inflammation and, in certain situations, to autoimmunity. Th17 cells appear at sites of inflammation, especially at mucosal surfaces, with rapid kinetics. Furthermore, Th17 cells potently induce chemokines, thus bridging innate and adaptive immunity, and subsequently attract other immune cells, limiting infection. IL-17 is currently considered the key cytokine modulating neutrophil homeostasis and neutrophil infiltration [28]. A strong neutrophilic infiltration is mainly a hallmark of bacterial infection but is rarely observed in most viral infections. IL-17 induces differentiation and migration of neutrophils through induction of cytokines and chemokines including granulocyte-colony stimulating factor and CXCL8/IL-8. Various bacterial pathogens such as *Bacteroides spp., Borrelia spp., Citrobacter rodentium, Mycobacterium tuberculosis, Klebsiella spp*., *Candida* and others can induce a strong Th17 response [29, 30].

IL-17R-deficient mice are highly sensitive to intranasal *Klebsiella pneumoniae*, with 100% mortality after 48 h compared with only 40% mortality in controls. This study suggested that impaired IL-17R signalling is an important mechanism by which deficiency of CD4 lymphocytes predisposes to bacterial pneumonia [31]. A sufficient IL-17 response might also be needed in *Mycoplasma pneumoniae* infection, a common complication after upper respiratory tract viral infections. Using an acute respiratory *Mycoplasma pneumoniae* infection murine model, Wu *et al*. found significantly upregulated lung IL-23p19 mRNA in the early phase of infection and increased IL-17 protein levels in bronchoalveolar lavage. *In vivo* blocking of IL-23 led to a significant reduction of IL-17 protein and IL-17/IL-17F mRNA expression, accompanied by a trend toward reduced lung neutrophil recruitment [32]. Tyrosine kinase 2 (Tyk2), a member of the JAK-signal transducer family, is involved in intracellular cytokine signalling, including IL-23. γ/δ T cells in $Tyk2^{-/-}$ mice produce less IL-17 in response to IL-23 than those in $Tyk2^{+/+}$ mice. Accordingly, γ/δ T cells in the peritoneal cavity of $Tyk2^{-/-}$ mice showed impaired IL-17 synthesis after intraperitoneal injection of *Escherichia coli*. Therefore, Tyk2-signaling might be critical for IL-23-induced IL-17 production by immune cells [33]. In view of these studies, IL-17A might be an attractive target in the treatment of septicaemia as this cytokine is part of the "cytokine storm" observed in this disease and potently induces other pro-inflammatory cytokines. In sepsis induced in mice by cecal ligation and puncture, plasma IL-17A levels increase dramatically [34]. Neutralization of IL-17A by antibody treatment improved mortality considerably, and antibody treatment was protective even when administered 12 hours after cecal ligation. The protective effects of IL-17A blockade were accompanied by decreased bacteremia together with significant reductions in plasma levels of proinflammatory cytokines and chemokines [34]. An exciting paper has been recently published by Aujla and colleagues [35]. In this study, both IL-17A and the related cytokine IL-22 were crucial for maintaining local control of the Gram-negative pulmonary pathogen *Klebsiella pneumoniae*. Although both cytokines regulated CXC chemokines and granulocyte colony-stimulating factor production in the lung, only IL-22 increased lung epithelial cell proliferation and increased transepithelial resistance to injury [35]. Therefore, both cytokines might be needed to exert a strong and effective anti-bacterial response at mucosal barriers.

INHIBITION OF TH17 PRODUCTION BY IMMUNE CELLS: A ROLE FOR TYPE I IFNS

IFNα controls IL-17 production in vitro *and* in vivo

We recently presented evidence that IFNα, an important mediator of innate immunity, potently suppresses the synthesis of IL-17 in both peripheral blood mononuclear cells (PBMC) and Th17 cells *(figure 1)*. Furthermore, such an IL-17-suppressive effect was also observed in patients with ulcerative colitis, a common chronic inflammatory disorder of the bowel, when immunomodulatory treatment with pegylated IFNα caused a marked downregulation of IL-17A expression in colonic tissue paralleled by clinical remission. In addition, IFNα also constrained IL-17 responses in mouse cells [36]. Notably, IFNα exerted this IL-17-controlling function both in

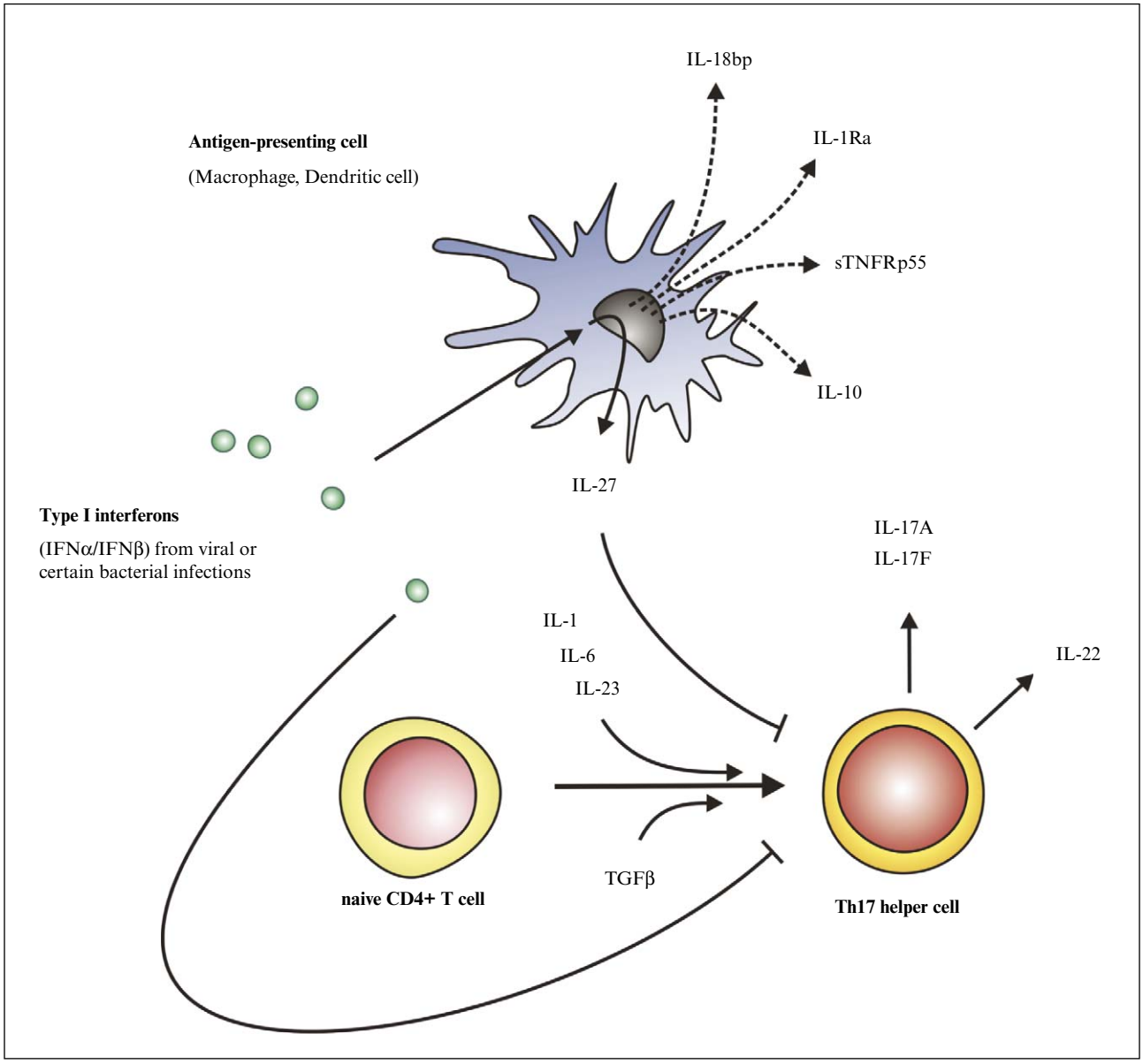

Figure 1

Type I IFNs interact at many stages with the immune system and regulate many immunomodulatory cytokines. Whereas recent data suggest that type I IFNs potently suppress IL-17 and Th17 generation, thereby improving immune-mediated disorders such as allergic encephalomyelitis, earlier data have shown that type I IFNs also suppress immunoregulatory cytokines such as IL-12 and/or IL-23. Overall, type I IFNs have certain anti-inflammatory properties such as suppression of IL-1 or TNF and induction of IL-1 and TNF antagonists. Furthermore, type I IFNs are able to up-regulate anti-inflammatory cytokines such as IL-10 and IL-27. IL-18 binding protein (IL-18bp) is also markedly up-regulated in patients undergoing IFNα therapy. This ability may also contribute to its immunosuppressive potential making the host vulnerable to bacterial and fungal infections subsequent to viral infections.

humans and in mice. IFNα therapy seems to be quite successful in ulcerative colitis, a more Th2-linked disorder where high levels of IL-17 expression have also been demonstrated [37-40]. Our findings suggest that an enhanced IL-17 expression might contribute to the disease pathology observed in ulcerative colitis, a disease where neutrophilic infiltration and crypt abscesses play a major role. Our results are also in accordance with data presented by Meyers *et al.,* who demonstrated that blockade of TLR9 agonist-induced type I IFNs enhanced not only IFNγ but also IL-17 production by PBMC [41]. IFNα-induced suppression of IL-17 could therefore contribute to its anti-inflammatory and disease-modifying properties as discussed later. Suppression of IL-17 might be not only beneficial as discussed, but could also result in an immunosuppressive state. Therefore, whereas IFNα-induced suppression of IL-17 might limit intestinal inflammation, it might also pave the way for an increased susceptibility to bacterial infections.

Type I IFN limits Th17-mediated autoimmune inflammation in mice

Guo *et al.* also presented evidence that type I IFNs affect IL-17-mediated inflammation [42]. Mice with defects in Toll-IL-1-receptor domain-containing adaptor-inducing

IFN-β (TRIF) or the type I IFN receptor develop more severe experimental allergic encephalomyelitis (EAE). The authors found that EAE in $TRIF^{-/-}$ mice was accompanied by dramatically enhanced IL-17 expression in the central nervous system mainly due to infiltrating $CD4^+$ T cells. These results suggest that activation of the TRIF pathway in innate immune cells may limit the development of pro-inflammatory Th17 cells. In further, quite elegant experiments, the authors demonstrated that TRIF-deficient macrophages produced much less IL-27 protein, an anti-inflammatory cytokine, than wild type cells [42]. IL-27 has been recently demonstrated to inhibit both the differentiation of Th17 cells and inflammatory autoimmune diseases [43-45]. In support of a potential role for IFNβ in the control of IL-17 generation, the authors observed a strong induction of IL-27 production by this cytokine [42]. Supernatants from IFN-treated macrophages inhibited the development of Th17 cells *in vitro* and this effect could be reversed by the addition of a neutralizing, anti-IL-27 antibody. Strikingly, and supporting the importance of this IFNβ/IL-17/IL-27 pathway, injection of IL-27 suppressed the severity of the EAE phenotype in IFNAR-deficient mice compared with PBS controls. This study therefore clearly proved that a type I IFN, namely IFNβ, regulated Th17-mediated inflammation and that this effect is mainly mediated by IL-27, supporting a role for this cytokine in limiting Th17-mediated inflammation.

Simian-immunodeficiency virus infection leads to mucosal IL-17 deficiency

Raffatellu and colleagues recently presented evidence that simian immunodeficiency virus (SIV)-induced reduction in mucosal IL-17 could promote bacterial infection with *Salmonella spp.* [46]. In this exciting work, the authors demonstrate that depletion of mucosal Th17 cells in rhesus macaques impairs mucosal barrier function leading to disseminated *Salmonella typhimurium* infection. In these studies, *Salmonella typhimurium* infection led to a strong upregulation of ileal IL-22, IFNγ, IL-26, IL-17 and IL-17-regulated genes such as lipocalin-2, CCL20 and IL-8. After oral SIV infection, mRNA expression of IL-22, IL-17 and IL-17-regulated genes was blunted in the SIV-infected macaques compared to non-infected animals, suggesting that SIV-infected macaques develop a mucosal cytokine deficiency characterized by a severely impaired IL-17 response during *Salmonella typhimurium* infection. At the end of their experiments (8 h after inoculation of loops), SIV-infected macaques had a 330-fold increase in *Salmonella typhimurium* in the mesenteric lymph nodes than SIV-negative macaques, highlighting a major role for IL-17 in the antibacterial defence. To support these findings, the authors treated IL-17-receptor-deficient mice with streptomycin, and inoculated them with *Salmonella typhimurium*, showing that these mice developed disseminated infection. Although the authors cannot define how SIV infection impairs the IL-17 response, a strong, type I IFN response by gut epithelial cells could contribute to such an effect. This work is an excellent example how a viral infection impairs the mucosal immune defence, making animals highly susceptible to a subsequent bacterial infection.

Immunoregulatory and anti-inflammatory effects of type I IFNs

Regulation of various Th17-promoting cytokines by type I IFNs

Type I IFNs inhibit *Staphylococcus aureus* Cowan strain-induction of IL-12 and IFNγ production by mouse splenic leukocytes. In addition, endogenous type I IFNs induced by latent cytomegalovirus inhibit LPS-induced IL-12 production, suggesting that type I IFNs could suppress IL-12-dependent immune responses during viral infections [47]. Byrness and colleagues also found that type I IFN potently inhibits IL-12 production by human monocytes/macrophages by down-regulation of PU.1 binding activity at the upstream Ets site of the IL-12p40 promoter [48]. IFNβ also suppresses IL-12p40 expression in mature DC subsets during respiratory syncytial virus (RSV) infection, while only very high doses of IFNα had an inhibitory effect [49]. The effects of type I IFNs on Th1 responses however, may be very much dependent on the cytokine milieu as demonstrated by Nagai *et al*. [50]. Indeed, the timing of IFNβ exposure determines how IFNβ affects naive Th cell differentiation into Th1 cells. Adding IFNβ during TNFα-induced DC maturation enhances the capacity of DC to promote the generation of IFNγ-secreting Th1 cells, whereas exposure to IFNβ during mature DC-mediated primary stimulation of naive Th cells has the opposite effect, namely inhibiting Th1 cell polarization and promoting the generation of an IL-10-secreting T cell subset. Importantly, we and others have also demonstrated that IFNα is a potent inducer of IL-10 synthesis in both monocytes/macrophages and T cells [10, 51, 52] *(figure 1)*. Induction of this key anti-inflammatory cytokine could also contribute to an immunosuppressive mode of action of type I IFNs. Type I IFNs also regulate transforming growth factor-beta (TGFβ), a key cytokine involved in the generation of Th17 responses. IFNα is able to downregulate TGFβ mRNA expression in murine macrophages [53]. Furthermore, IFNβ suppresses TGFβ in a mouse model of liver fibrosis [54]. The effects of type I IFNs on IL-6 expression are less clear, as studies suggest either enhancing or suppressing effects depending on the chosen experimental setting.

Anti-inflammatory and immunosuppressive effects of type I IFNs

IFNα is able to suppress pro-inflammatory cytokine responses and in some cases acts as an anti-inflammatory agent [55] as it reduces IL-1- and phorbol myristate acetate (PMA)-induced IL-1 synthesis by human leukocytes [56]. We and others have demonstrated that IFNα induces IL-1Ra *in vitro* and *in vivo* [8, 57]. IFNβ has also been demonstrated to induce IL-1Ra, and this effects is even more pronounced compared to IFNα [57, 58]. Several reports show that IFNα may suppress TNFα gene expression and protein synthesis [59, 60]. Two additional mechanisms might contribute to the anti-inflammatory properties of IFNα, as IFNα therapy leads to induction of circulating TNFsRp55, and IFNα suppresses IL-1β-induced TNFα synthesis *in vitro* by PBMC from healthy volunteers. IFNα-induced concen-

trations of TNFsRp55 in patients with chronic hepatitis C were approximately only two-fold less than peak levels achieved in LPS-treated normal volunteers, suggesting that levels could be biologically relevant [9]. IL-8 mRNA expression in PBMC from patients with chronic myelogenous leukemia is downregulated during IFNα therapy and IFNα suppresses LPS- and IL-1-induced IL-8 synthesis in bone marrow stromal cells [6]. These data suggest that the anti-inflammatory activities of type I IFNs may be, at least partially, mediated by suppression of IL-1, TNF and/or IL-8 production and induction of IL-1/TNF antagonists.

At present, the cytokines and cytokine receptors affected by type I IFN include IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, IL-13, IL-17, IL-1Ra, TNFα, TNFR p55 and p75, and IFNγ, any of which may account for the anti-inflammatory actions of IFNα in the treatment of human disease or in the pathophysiology of viral diseases *(figure 1)*. Recently, we showed that IFNα upregulates the physiological antagonist of IL-18, namely IL-18 binding protein (IL-18bp) [7]. In these studies, we were able to demonstrate that during IFN treatment, there is a significant decrease in free circulating IL-18 due to high levels of endogenous IL-18bp. Therefore, the IL-18 cytokine family reflects an additional, important group of mediators being controlled and regulated by type I IFNs.

CONCLUSIONS

Type I IFNs exert one of the first and most rapid cytokine responses to invading pathogens, particularly viruses. This highly effective defence regulates and successfully eliminates most of these infections without the “price” of subsequent superinfections with diverse bacteria/fungi. However, a situation with a strong type I IFN response might impair and regulate other critical immune mediators of an early immune response against invading pathogens. As outlined in this article, such a response might be accompanied by reduced synthesis of IL-17, IL-12 and other cytokines, impairing an anti-bacterial defence. Therefore, type I IFN-induced suppression of these key cytokines of defence may pave the way for secondary bacterial/fungal infections. A better understanding of these early immune/cytokine responses might help to develop new treatment approaches in such situations.

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