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Molecular mechanisms of the anti-inflammatory functions of interferons

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Abstract

Interferons are pleiotropic cytokines with important proinflammatory functions required in defence against infections with bacteria, viruses and multicellular parasites. In recent years, fundamental functions of interferons in other processes such as cancer immunosurveillance, immune homeostasis and immunosuppression have been established. In addition, anti-inflammatory roles of interferons are well-documented in several inflammatory disease models in the mouse, most importantly in experimental autoimmune encephalomyelitis that resembles multiple sclerosis in humans. While the beneficial effects of interferons in such disease models are known, the molecular mechanisms remain poorly understood. Only recently a few molecular principles for the anti-inflammatory properties of interferons at the cellular level have been revealed. They include the ability of interferons to reduce the expression of the receptors for the inflammation-related cytokines IL-1 and IL-4, or to increase the expression of the potent anti-inflammatory genes *tristetraprolin* and *Twist*. However, the individual contribution of these anti-inflammatory responses to the overall beneficial effects of interferons in inflammatory diseases is still an open question. Also, the reason for the apparently limited number of tissues that are susceptible to the anti-inflammatory functions of interferons remains enigmatic. This review summarizes the present knowledge of the anti-inflammatory effects of interferons, and describes the currently known molecular mechanisms that may help explain the benefits of interferon signalling in several inflammatory diseases.

Keywords

Interferon; Inflammation; Cytokine

Introduction

Interferon (IFN) was originally described 50 years ago as a soluble secreted molecule that interfered with viral replication (Isaacs and Lindenmann, 1957). Over the years a whole family of IFN proteins has been discovered. Currently, IFNs are classified into type I and type II IFNs (Pestka et al., 2004). Type I IFNs comprise multiple alpha IFNs (IFN- α), and single IFN- β , - ϵ , - κ , - ξ and - ω subtypes, all encoded by different genes. Type II IFN consists of a single IFN- γ gene. Recently, lambda IFNs (IFN- λ) have been described that functionally resemble type I IFNs, however they represent a novel class of cytokines (Kotenko et al., 2003). Type I IFNs are produced by most cells in response to viruses, bacteria or their products. In addition, some cells produce, by a still unresolved mechanism, constitutively low amounts of these cytokines in the absence of any detectable stimulus (Karaghiosoff et al., 2003; Sato et al., 2000). The expression of the type II IFN- γ is much

more restricted and the main sources of this cytokine are activated Th1, NKT cells and NK cells, and to a lesser extent antigen presenting cells (Frucht et al., 2001; Schroder et al., 2004; Young, 2006). IFNs exert their biological function primarily through the activation of the Jak/Stat signal transduction pathway (Shuai and Liu, 2003). Binding of type I IFNs to their receptor (composed of the IFNAR1 and IFNAR2 subunits) activates the receptor-associated tyrosine kinases Jak1 and Tyk2 causing phosphorylation of the receptor and, subsequently, recruitment and phosphorylation of the Stat transcription factors (Pestka et al., 2004; Schindler and Brutsaert, 1999). Stat1 and Stat2 are essential for type I IFN responses whereas the still largely elusive role of Stat3 phosphorylation has only recently begun to emerge (Durbin et al., 1996; Ho and Ivashkiv, 2006; Meraz et al., 1996). After translocation to the nucleus Stat complexes bind to distinct enhancer elements and activate transcription of the type I IFN-responsive genes. Herein, the ISGF3 complex consisting of a Stat1:Stat2 heterodimer and the DNA-binding subunit IRF9, which binds to ISRE elements, plays a more important role than the Stat1:Stat1 homodimer that binds to GAS elements. Type II IFN signalling is initiated by binding of IFN- γ to its receptor consisting of the IFNGR1 and IFNGR2 subunits. The receptor-associated Jak1 and Jak2 tyrosine kinases are activated and phosphorylate the receptor, thereby generating a docking site for the SH2 domain of Stat1. After phosphorylation by Jaks Stat1:Stat1 dimers translocate to the nucleus and activate transcription by binding to the GAS elements of IFN- γ responsive genes. For full responses to both type I and type II IFNs the transactivation domain of Stat1 needs to be phosphorylated on serine 727 (Kovarik et al., 2001; Pilz et al., 2003; Varinou et al., 2003; Wen et al., 1995). It should be noted that although the majority of the IFN-responsive genes are induced by IFNs a considerable number of genes is down-regulated (Gil et al., 2001; Ramana et al., 2001).

Both type I and type II IFNs are primarily proinflammatory cytokines that activate immune responses by various mechanisms. Type I IFNs are the principle factors inducing the antiviral state. In addition, they promote cytokine and chemokine production, NK cell activation, maturation of DCs, and antibody isotype switching (Biron, 2001; Bogdan, 2000; Garcia-Sastre and Biron, 2006). IFN- γ is fundamental in both innate responses, by increasing macrophage antimicrobial activity, expression of MHC molecules, antigen presentation or cytokine production, and adaptive responses by promoting Th1 development (Boehm et al., 1997; Pestka et al., 2004).

IFN production is linked to several pathological conditions ranging from adverse effects of IFNs on the host during microbial infections to various autoimmune diseases (Baccala et al., 2005; Decker et al., 2005). The strongest evidence for the detrimental role of IFNs comes from studies with genetically modified mice that show that elevated IFN signalling, achieved either by removing a negative regulator (e.g. SOCS1) or through forced tissue-specific IFN expression, caused serious, sometimes lethal disorders (Akwa et al., 1998; Alexander et al., 1999; Fenner et al., 2006; Wang et al., 2004).

Despite their well-documented role as proinflammatory cytokines IFNs possess also important anti-inflammatory properties that have been exploited in a number of animal studies. The first studies suggesting that IFNs might suppress inflammation were carried out in 1973 by Koltai and Meos (1973). They observed that partially purified type I IFNs were able to reduce carrageenin-induced footpad swelling. This notion was later supported by the finding that IFN suppresses LPS-induced footpad swelling (Heremans et al., 1987). Furthermore, it was shown that systemic administration of type I IFN prevents mortality of LPS-treated mice, and suppresses demyelinating experimental autoimmune encephalomyelitis (EAE), an animal model for multiple sclerosis (Tzung et al., 1992; Yu et al., 1996). Similarly, the delivery of IFN- β and IFN- γ genes to the organism proved beneficial to mice suffering from EAE and collagen-induced arthritis, respectively (Furlan et

al., 2001; Triantaphyllopoulos et al., 1999). Most compelling evidence for the anti-inflammatory capabilities of both types of IFNs provided experiments with genotargeted mice. Animals lacking the gene for IFN- β or IFN- γ are much more susceptible to EAE (Krakowski and Owens, 1996; Teige et al., 2003; Willenborg et al., 1996). In mice lacking IFN- γ or IFN- γ receptor genes the course of collagen-induced arthritis was strongly exacerbated (Guedez et al., 2001; Manoury-Schwartz et al., 1997; Vermeire et al., 1997). Furthermore, mice deficient in the type I IFN receptor develop more severe experimental colitis (Katakura et al., 2005). Thus, there is a considerable amount of data demonstrating that under particular conditions and/or in specific tissues IFNs act to down-regulate inflammation. However, the molecular mechanisms that would explain why in certain situations the anti-inflammatory properties of IFNs prevail remain largely elusive. Consequently and somehow surprisingly, after more than 10 years of the successful use of IFN- β in therapy of multiple sclerosis the beneficial effects of this cytokine on the disease progress are still not understood. Here, we will describe the inflammatory processes that have been found to be negatively regulated by IFNs, and review recent progress in unravelling the molecular principles of the anti-inflammatory roles of IFNs therein.

Inhibition of inflammatory signalling by interferons

Many cytokines that are released during inflammatory reactions can further increase inflammation either locally, by enhancing the activation of immune cells residing at the site of inflammation, or globally, by acting on responsive cells throughout the organism. Such cytokines activate signal transduction cascades that result in increased inflammation state of the target cells. Very recent studies, mostly from Ivashkiv's laboratory, indicate that in several cases IFNs can significantly interfere with the intracellular inflammatory signalling pathways. The Ivashkiv lab has focused on the effects of IFNs on signalling by IL-1 and events leading to production of TNF- α , hereby addressing the most potent proinflammatory cytokines known. The work by Hu and colleagues shows that IFN- γ suppresses the expression of the IL-1 receptor in macrophages making the cells refractory to IL-1 (Hu et al., 2005). The detailed mechanism of the down-regulation of IL-1R by IFN- γ is not clear. However, the fact that for the suppression of IL-1R expression the transcription factor Stat1 was needed suggests that IFN- γ induces the expression of genes involved in IL-1R transcription, IL-1R mRNA decay, or IL-1R protein stability or processing. The inhibition of IL-1R expression by pre-treatment with IFN- γ resulted in an almost complete block of IL-1-elicited signalling. Similar effects on IL-1 responses were achieved also by pre-treatment of macrophages with type I IFNs. These findings demonstrate that IFNs can counteract the very often destructive impact of IL-1 in inflamed tissues, and thereby contribute to homeostasis. In a different study from the same laboratory type I IFNs were found to inhibit the transcriptional activity of NF- κ B on the TNF- α promoter (Sharif et al., 2006). The mechanism of this inhibition is rather complex and includes the up-regulation of the Twist proteins. Twist proteins are transcriptional repressors that bind to the E-boxes in gene promoters, such as the TNF- α promoter, and inhibit transcription (Sosic et al., 2003). Sharif and colleagues showed that type I IFNs increase the amount of Twist proteins in cells and, consequently, the pre-treatment of macrophages with type I IFNs reduces the capability of immunoglobulin complexes or LPS to stimulate the NF- κ B-mediated expression of TNF- α . The up-regulation of Twist by IFNs was indirect and required the IFN-induced expression of the receptor tyrosine kinase Axl. Another signalling pathway that is antagonized by IFNs is the IL-4-evoked cascade that causes B cells to produce IgE antibodies. Both IFN- α and IFN- γ were found to decrease the IL-4 receptor gene expression (So et al., 2000). The primary mechanism of the reduced IL-4 receptor gene expression is an accelerated rate of the IL-4 receptor mRNA decay.

An interesting mechanism for the immunosuppressive role of type I IFNs was recently described by Ho and Ivashkiv (2006) who propose that the type I IFN-activated Stat3 sequesters Stat1 from the Stat1:Stat1 homodimers thereby reducing the amount of Stat1:Stat1 homodimers bound to the target promoters. As mentioned above, type I IFNs cause tyrosine phosphorylation of several Stat transcription factors. While the importance of Stat1 and Stat2 activation for the type I IFN responses is well established, the role of Stat3 activation therein was elusive. In their paper, Ho and Ivashkiv show that IFN- α -activated Stat3 inhibited, in a dose-dependent manner, the transcription of genes that are regulated by Stat1:Stat1 homodimers while the transcription of the ISGF3 (Stat1:Stat2:IRF9) target genes remained unaffected. This finding implicates that the ratio of Stat1 and Stat3 expression or activation will have a decisive effect on the magnitude of the IFN- α -induced Stat1-dependent transcription. Since the relative amounts of Stat1 and Stat3 expression and activation vary between cell types and are not constant during inflammation, the inhibitory effect of Stat3 will strongly depend on the phase of inflammation and the type of affected tissue.

Inhibition of inflammatory cytokine production by interferons

Cytokines that play a crucial role in induction, amplification and dissemination of inflammatory reactions are released upon activation of cells by external cues. In the previous section the ability of IFNs to counteract signal transduction pathways leading to activation of cells and, consequently, to production of cytokines was discussed. Recently, IFNs were found to suppress cytokine production in cells that are otherwise normally activated. Studies from our laboratory show that both types of IFNs induce the expression of the RNA-destabilizing factor tristetraprolin (TTP) (Sauer et al., 2006). TTP binds to the AU rich elements in the 3' UTR of several cytokine mRNAs including TNF- α mRNA. Binding of TTP to its target mRNA initiates the recruitment of mRNA decay enzymes resulting first in removal of the polyadenylated tail and, subsequently, in a complete mRNA degradation (Blackshear, 2002; Carrick et al., 2004). TTP-deficient mice display chronic inflammatory syndromes such as inflammatory polyarthritis and cachexia that are caused by elevated TNF- α levels (Carballo et al., 1998; Taylor et al., 1996). TTP is induced under various inflammatory conditions, and as such it is part of a negative feedback loop that is essential for immune homeostasis. We have demonstrated that both types of IFNs can, in a Stat1-dependent way, induce TTP provided the stress-regulated p38 MAPK is activated simultaneously. Stat1 is recruited to the TTP promoter regardless of p38 MAPK activation, but it requires p38 MAPK to become transcriptionally active. In LPS-treated macrophages both p38 MAPK and, due to LPS-induced IFN- β production, Stat1 are activated resulting in maximal TTP expression. Consequently, TTP limits the production of TNF- α under these conditions. Recently, we and our colleague R. DeMartin have observed that in human endothelial cells IFN- α can stimulate TTP transcription even without simultaneous p38 MAPK activation, suggesting that in these cells type I IFNs may directly elicit the TTP-dependent anti-inflammatory responses (R. DeMartin, personal communication).

IFN-mediated attenuation of pathological inflammation in disease models

Despite the well-documented beneficial effects of IFNs on the course of several inflammatory model diseases only few and still incomplete mechanistic explanations are available.

IFNs and Stat1 are implicated in the regulation of bone remodelling mainly through influencing the osteoblast/osteoclast homeostasis which is often disbalanced during inflammation. On the one hand, Stat1 decreases osteoblast formation by sequestering the osteoblast differentiation transcription factor Runx2 in the cytoplasm (Kim et al., 2003).

Consequently, Stat1-deficient mice display increased bone mass. The inhibition of Runx2 by Stat1 was independent of Stat1 tyrosine phosphorylation ruling out a direct involvement of IFNs in osteoblast differentiation. However, the intracellular levels of Stat1 that are known to depend on type I IFN signalling, are likely to determine the extent of Runx2 inhibition (Karaghiosoff et al., 2000). On the other hand, IFNs negatively regulate the generation of osteoclasts, the cells responsible for bone erosion. IFN- β that is induced in osteoclast precursor cells by the osteoclast differentiation factor RANKL inhibits in a negative feedback loop the generation of mature osteoclasts (Takayanagi et al., 2002). Similarly, IFN- γ produced by resting CD4T cells attenuates osteoclast differentiation from monocytic cells (Shinoda et al., 2003). In good agreement with these data is the study by Treschow and colleagues who showed that osteoclast formation is enhanced during collagen-induced arthritis in IFN- β -deficient mice (Treschow et al., 2005). Thus, IFNs, particularly IFN- β , clearly have the capability to ameliorate the pathological bone loss that frequently accompanies inflammation although the detailed mechanism is still elusive.

Type I IFNs are beneficial in experimental dextran sulphate sodium-induced (DSS-induced) colitis, a model for colonic inflammation. Mice deficient in the type I IFN receptor are hypersensitive to DSS-induced colitis suggesting that type I IFNs play a role in intestinal homeostasis (Katakura et al., 2005). The molecular principles of the IFN-mediated protection of intestinal inflammation is not known, though it likely includes inhibition of the release of proinflammatory cytokines.

Most recently, a very unique function of IFN- γ in protection of oligodendrocytes against demyelination was presented by Lin and colleagues (Lin et al., 2007). The authors used a transgenic animal model allowing temporal regulation of IFN- γ delivery to the central nervous system during EAE. IFN- γ prevented the development of the standard EAE symptoms such as axonal damage, demyelination and oligodendrocyte loss. The cytoprotection was caused by the IFN- γ -mediated induction of ER stress via activation of the pancreatic ER kinase (PERK). ER stress and PERK activation result in phosphorylation of the α subunit of the eukaryotic translation initiation factor 2 (eIF2 α). eIF2 α phosphorylation imposes a strong reduction in translation that was previously associated with increased resistance to stress (Harding et al., 2003). The role of IFN- γ in demyelinating diseases such as multiple sclerosis is controversial since both beneficial and deleterious effects were described. Lin and colleagues suggest that the timing of IFN- γ administration is critical with most significant protection being achieved during the onset of the disease.

Conclusion and perspectives

The original notion that IFNs are proinflammatory cytokines is becoming increasingly challenged since the development of disease models in gene-targeted mice provided clear evidence that under certain conditions IFNs possess anti-inflammatory properties. The current understanding of the immunosuppressive functions of IFNs suffers from the lack of a connection between the anti-inflammatory functions of IFNs at the cellular level (i.e. *in vitro*) and the aggravation of certain diseases in animals deficient in IFN signalling. Consequently, we still cannot answer many important questions. To name some of them: (1) What is the contribution of the IFN- γ -mediated inhibition of IL-1 receptor expression to the protective effects of IFN- γ in the EAE disease model? or (2) Can the beneficial effect of IFN- β in experimental colitis be explained by the IFN-induced expression of the anti-inflammatory gene TTP? Animals with tissue specific genetic modifications (e.g. TTP deletion in the intestines or central nervous system) are currently being developed, and their analysis will provide at least some of the missing information. Answers to these questions will not only expand our knowledge about IFN biology but they are also likely to improve current protocols for the use of IFNs in the therapy of human diseases such as multiple

sclerosis. With more animal disease models becoming available, the range of diseases in which administration of IFNs is indicated may grow even further. In addition, the identification of the yet un-known effector genes downstream of the anti-inflammatory IFN signalling will reveal new targets for pharmacological intervention. The next steps that will take us closer to these goals will also have to address the tissue specific differences in IFN signalling. This issue, which is unfortunately still not sufficiently appreciated, may help to solve the mystery of the beneficial role of IFNs predominantly in inflammation of the central nervous system rather than other tissues. The ambiguity of IFN functions suggests that the role of IFNs in homeostasis of the immune responses, immune cell proliferation and tissue remodelling may be bigger than previously anticipated.

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