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Mini-review

Anti-inflammatory properties of Type I interferons

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Dedicated to Prof. Erik De Clercq on the occasion of reaching the status of Emeritus-Professor at the Katholieke Universiteit Leuven in September 2006.

Abstract

The notion that Type I interferons (interferon-α and -β) possess anti-inflammatory potential is supported by data from clinical application in multiple sclerosis, by studies on cultured immune-competent cells and by investigation of experimental diseases in whole animals. These observations deserve the attention of virologists for their potential role in the pathogenesis and clinical management of virus infections.

Keywords: Interferon; Inflammation

Contents

1. Introduction—historical perspective

When, half a century ago, virologists discovered interferon as an endogenous antiviral substance, it soon became evident that the biological role of interferon was not confined to defence against virus infection. For one thing, infection with microbes other than viruses appeared to induce interferon production, and interferon proved to be able to protect experimental animals against infection by non-viral agents. Moreover, in vitro studies documented a variety of biological activities of interferon, including ability to inhibit division of certain tumour cell lines, to activate cytolytic potential of NK cells or T lymphocytes and

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to enhance MHC molecule expression. Together these properties made interferon become recognized as a key component of innate immunity.

Activation of innate immunity manifests itself in many ways, a prominent one being inflammation. Acute inflammation is defined as a combination of: (i) vascular changes, mainly vasodilation, increased vascular permeability, changes in endothelial adherence properties and sometimes intravascular blood clotting followed by disruption of blood vessels and bleeding; (ii) transudation of fluid causing oedematous swelling; (iii) exudation and active diapedesis of leukocytes from the vessels causing cellular infiltration and induration of the inflamed tissue. In chronic inflammation, characteristic for persistent low-grade exposure to inflammatory agents, intermittent vascular changes and oedema are usually less pronounced, but cellular infiltrates may develop into extensive granulomas and initiate fibrous scar tissue which cause destruction and deformation of organs such as bone, cartilage, kidney, lung, etc. Localized or organ-specific inflammation is mostly accompanied by metabolic and haematopoietic changes resulting in altered levels of circulating leukocytes, hypertrophy and changes in architecture of lymphoid organs and altered levels of certain proteins (acute-phase reactants) in plasma.

Given the early recognition of a key role for interferon in innate immunity and the common knowledge that inflammation is a prominent manifestation of innate immunity, it is somewhat surprising to see that, except for a few reports, exploration of a role of interferon in a-specific inflammation was not initiated until in the mid 1980s. Instead, the early focus for exploration of non-antiviral effects was on anti-tumour cell effects and on regulation of B and T cell immunity, activities that were perceived as offering perspective for overall boosting of immune defence against cancer. At the time, inflammation researchers were addressing granulocyte rather than lymphocyte biology and, as a community, they had little interaction with interferon workers. With the discovery and/or characterization of many other cytokines (IL-1, TNF, IL-6) and chemokines, non-antiviral actions of interferons gradually came to be seen as a sector of the cytokine network that controls responses of innate as well as acquired immunity.

In the 1970s our laboratory, then headed by Peter De Somer, pioneered the production of IFN-β from cultivated human skin fibroblasts (Van Damme and Billiau, 1981), an enterprise that led to the first clinical trials of this interferon. Fever reactions and skin inflammation (De Somer et al., 1977) elicited by the interferon injections in the patients made us become interested in the role of interferon in inflammation, a line of investigation that would lead us to the isolation and characterization of novel inflammatory mediators that are co-induced with interferon or that interact with interferons. Just to name a few: the IFN-β-inducing cytokine interleukin-1 (Van Damme et al., 1985), the IFN-β companion cytokine and strong pyrogen IL-6 (Van Damme et al., 1987), the chemokines granulocyte-chemotactic protein-1 (GCP-1), now IL-8 (Van Damme et al., 1989), GCP-2 (Proost et al., 1993) and the monocyte-chemotactic proteins MCP-2 and -3 (Van Damme et al., 1992). Our laboratory's involvement with inflammation was completed by investigation of the matrix metalloproteases (MMPs) and their interaction with cytokines and chemokines (Opdenakker et al., 2003).

Here I will review old and more recent work on the role of Type I interferons in inflammation. As to Type II interferon (IFN-γ), I refer the reader to earlier reviews on its role in inflammatory reactions, such as in local and systemic reactions towards lipopolysaccharide (Billiau and Vandekerckhove, 1991) and the acute systemic inflammation accompanying experimental autoimmune diseases that make use of Freund's adjuvant (Matthys et al., 2000).

2. Evidence from experimental animal models of inflammation

2.1. Footpad swelling tests in mice

In a very early study (1973), Koltai and Mecs (1973) used the carrageenin footpad swelling reaction to study the inflammatory or anti-inflammatory influence of interferon and interferon inducers (poly-rI:rC, mycophage-derived double-stranded RNA and Semliki Forest virus). Their observations indicated that interferon (semi-purified mouse IFN-α/β 10^5 units i.v. 1 h before carrageenin challenge) exerted a significant but modest anti-inflammatory effect (24% reduction in footpad swelling). The inducers also inhibited the response, but the degree of inhibition was not well correlated with levels of circulating interferon, leading the authors to suggest that their effects were due to other induced mediators.

In a similar study using LPS instead of carrageenin, the footpad response was found to be suppressed during the acute phase of infection with lactic dehydrogenase virus or following a bolus intravenous injection of Newcastle disease virus (Heremans et al., 1987a). Both these viruses are potent inducers of systemic IFN-α/β in mice. That interferon was instrumental in bringing about suppression was evident from the demonstration that it could partially be undone by prior administration of neutralizing antibodies directed against mouse IFN-α/β. The inflammatory response could also be inhibited by giving the mice a series of intraperitoneal injections of interferon starting shortly before LPS challenge (Heremans et al., 1987b). The degree of inhibition was dose-dependent requiring at least 20.000–30.000 units/mouse given daily on days 0–3 relative to LPS injection. Inhibition was observed not only with natural IFN-α/β or recombinant IFN-α1, but remarkably also with recombinant IFN-γ.

2.2. Neuroprotection

Veldhuis et al. (2003a) showed that systemic administration of IFN-β protects rats against inflammatory brain damage due to experimentally induced transient ischemia. Protection was evident from diminished infiltration of neutrophils and reduced disruption of the blood–brain barrier (BBB).

Similar IFN-β treatment also provided complete protection against neutrophil infiltration and BBB disruption following a local injection of recombinant rat IL-8 (Veldhuis et al., 2003b). ICAM-1 was overexpressed in the IL-8-injected brain region,

but this upregulation was not reduced in IFN-treated animals, leading the authors to dismiss effects on ICAM-1 expression as the explanation for the protective action of IFN-β. The other possible mechanism considered by these workers was inhibition of MMP-9 (gelatinase B) production or release. Zymography showed the presence of MMP-9 in the injected brain region. Significantly, depleting the animals in neutrophils before IL-8 injection as well as treatment with IFN-β prevented both disruption of the BBB and appearance of MMP-9. The model proposed is that neutrophils need autocrine MMP-9 in order to be able to disrupt and transgress the BBB. Local injection of IL-8 is considered to be a stimulant and IFN-β an inhibitor of MMP-9 secretion by neutrophils.

2.3. Protection against collagen-induced arthritis

A protective effect of IFN-β in collagen-induced arthritis in DBA/1 mice was shown in a study in which the mice received a single injection of syngeneic fibroblasts carrying a retrovirus expressing murine IFN-β (Triantaphyllopoulos et al., 1999). Protection was accompanied by a lower total anticollagen IgG levels, lower anticollagen IgG2a but higher IgG1 levels. In vitro, IFN-β inhibited collagen-induced IFN-γ secretion from lymph node cells, and reduced the levels of TNF-α and IL-12 produced by lipopolysaccharide/IFN-γ-treated bone marrow-derived macrophages (Triantaphyllopoulos et al., 1999).

Similarly, treatment with daily injections of IFN-β was found to protect mice against collagen-induced arthritis, as evident from macroscopic, histopathological and biochemical parameters (van Holten et al., 2004). Of particular relevance was the reduction in the number of osteoclasts, suggesting that IFN-β can inhibit osteoclastogenesis. Immunohistochemical examination of inflamed joint tissue revealed a ca. 50% reduced expression of TNF-α and IL-6, and IL-18 and IL-1β expression also tended to be lower. IL-10 expression, conversely, was more than doubled. The protective effect of Type I interferon in collagen-induced arthritis is echoed by a similar effect of Type II interferon in the same model.

2.4. Experimental auto-immune encephalomyelitis

In rats, both the active and the adoptively transferred form of EAE were reported to be inhibited by systemic administration, during the induction phase of the experimental procedure, of natural, highly purified Type I interferon (Abreu, 1982; Hertz and Degheni, 1985; Abreu et al., 1983). A similar protective effect was reported for EAE induced in SJL/J mice (Billiau et al., 1988; Yu et al., 1996). In addition, infection of mice with lactic dehydrogenase virus, known to act as a strong inducer of transient interferon production, had a similar protective effect in this murine model (Billiau et al., 1988; Inada and Mims, 1986).

2.5. Delayed-type hypersensitivity and transplant reactions

As early as 1973 De Maeyer et al. reported an inhibitory effect of passively administered or actively induced IFN-α/β on the inflammatory response elicited in presensitized mice by the T cell-dependent antigens, sheep red blood cells and Newcastle disease virus (De Maeyer et al., 1975; De Maeyer, 1976; Gresser et al., 1979). The same authors also found that treatment with high doses of IFN-α/β prolonged survival of skin grafts done across the MHC barrier in mice. While some workers could confirm these observations (Hirsch et al., 1974), others working with smaller doses of interferon found the opposite effect (Skurkovich et al., 1973). As discussed by De Maeyer and De Maeyer-Guignard (1982), low levels of systemic interferon might enhance, while high levels might inhibit graft rejection.

3. Clinical studies

3.1. Virus infections

Generally accepted use of Type I interferon to treat virus infections in man is limited to the use of IFN-α in patients with chronic hepatitis B or C. Currently the combination of pegylated interferon and ribavirin is the recommended treatment for persistent HCV infection accompanied by liver inflammation and incipient fibrosis. Sustained viral responses can be achieved in 40 to 80% of cases (for review, see Ward and Kugelmas, 2005). Pegylated IFN-α is also the treatment of choice, reportedly superior to lamivudine, for chronic HBV infection (Lau et al., 2005). Viral responses are accompanied by variable degrees of improvement in liver function and reduction in inflammatory changes in the liver. In the case of HCV-associated chronic liver disease, evidence is accumulating that application of interferon-based treatment schedules also result in a delay in the development of HCV-associated hepatocellular carcinoma (Camma et al., 2001; Azzaroli et al., 2004; Soga et al., 2005; Omata et al., 2005).

Beneficial effects on liver histology and function probably result in part from the direct effect of interferon on viral replicative activity. However, anti-inflammatory and immunomodulatory activities of interferon might also contribute, respectively, by providing direct tissue protection and/or more adequate viral antigen-specific immune responses. Carotenuto et al. (2005) hypothesized that interferon boosts the antiviral response by modifying the function of intrahepatic antigen-presenting cells. In order to separate this effect from the consequences of direct antiviral effects, they examined changes in intrahepatic APC and T cells during interferon treatment in patients whose viral load had already been reduced by treatment with lamivudine. During therapy, expression of CD14 on Kupffer cells in liver biopsies increased and, simultaneously, serum levels of soluble CD14 also increased. These effects were considered as an indication that IFN-α promotes differentiation of myeloid dendritic cells, an effect also reported to occur in in vitro systems. At the same time T cell infiltration in the portal spaces was reduced, mainly due to a drastic decrease in the number of $CD8^+$ T cells. The authors noted that T cell infiltration in the liver generally concerns non-antigen-specific bystander cells and depends on the presence of increased levels of matrix metalloproteases. Hence, they speculated that the depletion of $CD8^+$ T cells during IFN-α

therapy is an effect independent from that on hepatic APC and may be due to a reduction in the release of matrix-degrading metalloproteases. Other studies, however, indicate that increased intrahepatic $CD8^+$ lymphocyte counts are important for the viral response to IFN-α (Tang et al., 2005).

3.2. Multiple sclerosis

Long-term IFN-β treatment of patients with relapsing-remitting MS is now generally recognized to reduce the frequency of relapses as documented by gadolinium-enhancing MRI. This would by far be the strongest supportive evidence for the anti-inflammatory and/or immunosuppressive potential of interferon, if it were not that the mechanism by which the treatment protects the integrity of the blood–brain barrier remains unclear. Monitoring of immunological markers in MS patients before and in the course of treatment with IFN-β has shed some light on which mechanisms may be involved.

Calabresi et al. reported increased levels of soluble VCAM-1 soon after initiation of IFN-β therapy (Calabresi et al., 1997b). From in vitro studies (vide infra), the authors propose that treatment with IFN-β induces conversion of membrane-bound into soluble VCAM-1. Concomitantly with increased sVCAM-1 levels, expression of the VCAM-1 counter-receptor VLA-4 on lymphocytes decreased (Calabresi et al., 1997a); in vitro treatment of lymphocytes with IFN-β did not reproduce this effect, though treatment with VCAM-1 did reduce VLA-4 expression. The authors proposed that, following IFN-β treatment in patients, the increase in soluble VCAM-1 causes downregulation of VLA-4, the net effect being inhibition of adhesive interactions between lymphocytes and brain endothelial cells. These in vivo studies demonstrate that the in vitro actions of IFN-β on the biology of VCAM-1 do take place in vivo. However, whether or not they are indeed modulating inflammation and accompanying tissue damage remains to be proved.

Evidence that IFN-β affects the course of MS by inhibiting production and/or activity of proteases comes mainly from studies on MMP-9. Blood monocytes (Gveric et al., 2001) as well as monocyte-derived dendritic cells (Kouwenhoven et al., 2002) of MS patients reportedly express higher than normal levels of MMP-9. Also, serum levels of the enzyme are increased (Waubant et al., 1999; Liuzzi et al., 2002; Dubois et al., 2003). In several independent studies treatment with IFN-β was associated with a decrease in serum MMP-9 and/or an increase in the level of TIMP-1 (Trojano et al., 1999; Waubant et al., 2001; Giannelli et al., 2002; Waubant et al., 2003; Yushchenko et al., 2003; Karabudak et al., 2004; Avolio et al., 2005). Expression of the enzyme by leukocytes was similarly affected (Galboiz et al., 2001; Gilli et al., 2004). Together these observations led the authors to postulate that IFN-β exerts its beneficial influence by shifting the balance between proteases and their inhibitors.

An unresolved question is, at what stage of lesion development protease activity intervenes. Is it essential for leukocytes to be able to infiltrate the CNS? Does it play a role in disrupting the BBB with all its consequences? Does it play a role by degrading myelin?

4. Cellular and molecular mechanisms

4.1. Dendritic cells

Type I interferons play an important role in dendritic cell biology, leading some authors to consider them as potential adjuvants for dendritic cell-based vaccines (Santini et al., 2002). Dendritic cells generated in vitro from peripheral blood monocytes in the presence of Type I interferons have properties different from those of dendritic cells generated by the classical combination of GM-CSF plus IL-4 (Santini et al., 2000). In the presence of IFN-β, maturation of dendritic cells progresses more rapidly. The resulting cells are generally more potent in exerting antigen-presenting activity, e.g. when used in mixed leukocyte reactions or as APC primed with specific antigens. Their cytokine secretion profile is also distinct in that IL-12 production may be low, while IL-15 (Santini et al., 2000) and IL-6 (Detournay et al., 2005) production levels are high. IL-6 was shown to be instrumental in enhancing MLR by acting antagonistically on $CD4^+CD25^+$ suppressor cells (Detournay et al., 2005). Murine dendritic cells derived in vitro from bone marrow cells, or isolated from the spleen express Type I interferons, suggesting that an autocrine positive feed-back loop is operational during dendritic cell maturation (Montoya et al., 2002).

Santodonato et al. (2003) used priming with EBV antigens to compare the functional activities of dendritic cells induced with GM-CSF plus either IL-4 or IFN-α. Dendritic cells generated in the presence of IFN-α triggered a stronger cellular expansion and conveyed higher levels of cytotoxicity on $CD8^+$ T lymphocytes for EBV antigen-carrying cells. Similar observations were reported by Carbonneil et al. (2003) who showed that dendritic cells generated in the presence of IFN-α expressed higher levels of MHC class I molecules and produced similar or higher levels of IL-12 following CD40 ligation or stimulation with superantigen. The cells expressed low levels of CD4, CXCR4 and DC-SIGN. HIV antigen-pulsed cells were able to activate CD8 T cells from HIV-negative donors to produce IFN-γ and to mount cytotoxic activity against target cells expressing HIV antigens.

Type I interferon was also found to inhibit secretion of MMP-9 by dendritic cells (vide infra) (Bartholomé et al., 2001). The in vivo significance of these various findings remains to be defined. Possibly, dendritic cells with the phenotype and functional properties of those generated in vitro in the presence of Type I interferons form a distinct subpopulation occurring transiently in vivo during the acute phase of virus infections. If so, they could represent an important player in making the link between innate and acquired immunity to the virus.

Antigen presentation is not the sole prerogative of dendritic cells. In the central nervous system astrocytes express MHC Class II molecules in a tightly controlled fashion, whereby IFN-γ is a strong inducer. In an astrocytoma cell line Type I interferons were described to inhibit MHC Class II molecule induction by IFN-γ (Ransohoff et al., 1991; Devajyothi et al., 1993).

4.2. Cell adhesion and cell adhesion molecules

Corsini et al. (1997) reported that long-term (6 month) but not short-term (48 h), IFN-β treatment of MS patients is associated with decreased adhesion of their PBMC to cultured human umbilical vein endothelial cells in vitro. Both types of exposure resulted in increased serum levels of soluble VCAM-1. Treatment of cultured endothelial cells with IFN-β failed to affect VCAM-1 or ICAM-1 expression, while antagonizing IFN-γ -induced overexpression of HLA-DR antigen. However, subsequent studies indicated that in vitro exposure to IFN-β does inhibit basal expression of ICAM-1 in cultures of human umbilical vein endothelial cells or human brain-derived microvascular endothelial cells (BMEC) (Defazio et al., 2001). Overexpression of ICAM-1 in cultured BMEC following exposure to TNF-α was also reported to be counteracted by IFN-β (Trojano et al., 2000; Defazio et al., 2000).

The report that treatment of patients with IFN-β induces increased levels of soluble ICAM-1 (Corsini et al., 1997) was subsequently confirmed (Trojano et al., 2000) and echoed by an in vitro study (Calabresi et al., 2001) showing that co-culture of BMEC with IFN-β-conditioned T cells induced VCAM expression on the cell membrane, rapidly followed by shedding of soluble VCAM. Overexpression was mediated in part through activation of the TNF receptor as it could be abrogated by addition of soluble TNF receptor. Soluble adhesion molecules may interfere with adhesion of leukocytes to the residual membrane-bound adhesion molecules.

Together these observations seem to indicate that Type I interferon produced within inflammatory foci inhibits expression of the adhesion molecules on the surface of endothelial cells while stimulating release of the soluble form into the cellular environment. This may lead to reduced adhesion of leukocytes to endothelial lining of blood vessels and hence to attenuation of the inflammatory reaction. These mechanisms have been invoked to explain the protective action of IFN-β against relapsing remitting MS (Corsini et al., 1997; Defazio et al., 2001; Trojano et al., 2000; Calabresi et al., 2001).

4.3. Inhibition of matrix metalloprotease-9 (MMP-9)

Increased extracellular proteolysis is a key element in the pathogenesis of inflammation. Unbalanced production of proteases and their inhibitors accounts not only for structural tissue damage (demyelination, cytolysis, desintegration of basement membranes,. . .) but also facilitates leukocyte infiltration, generates auto-antigens and regulates the activity of cytokines and chemokines (for review, see Cuzner and Opdenakker, 1999). Amongst extracellular proteases, MMP-9 has particularly well been studied (Opdenakker et al., 2003).

Stuve et al. (1997) found that IFN-β antagonizes chemokines (RANTES, MIP-1α and MCP-1) as stimulants of migration of peripheral blood mononuclear cells across a fibronectin matrix; IFN-β abrogated chemokine-induced elevation of MMP-9 mRNA level and MMP-9 secretion. Inhibition of MMP-9 production was also seen in human peripheral blood mononuclear cells and human umbilical vein endothelial cells stimulated by PECAM-1 (platelet endothelial cell adhesion molecule-1) ligation (Nelissen et al., 2002). A similar study employing dendritic cells generated in vitro by incubation of human blood monocytes in GM-CSF plus IL-4 (Bartholomé et al., 2001) deserves special mention as it showed inhibition of not only MMP-9 secretion but also demonstrated a net inhibitory effect of IFN-β on the total protease load, i.e. the balance between MMP-9 and its inhibitor TIMP-1.

In reverse, MMP-9 can hit back at IFN-β by causing it proteolytic degradation and abolishing its activity (Nelissen et al., 2003), an effect that may impact on the effectiveness of therapy with IFN-β in MS.

4.4. T lymphocytes

In human lymphocyte stimulation assays, IFN-β was reported to inhibit cellular proliferation and to modify both expression of membrane receptors and cytokine secretion (Noronha et al., 1993; Rep et al., 1996). Upregulation of CD40L was not affected, but induction of CD25 on stimulated T- and B-lymphocytes was blocked. Secretion of IFN-γ, TNF-α and IL-13 was inhibited, whereas IL-4 secretion was unaffected. Secretion of IL-2 increased about two-fold and that of IL-10 nearly four-fold. In additional studies, IFN-β rapidly upregulated CD95 expression on both primed and unprimed T cells and augmented the release of sCD95 in culture supernatant fluids (Rep et al., 1999). In MS patients treated with IFN-β, the IL-10 serum level increased transiently, and a similar change was seen when their monocytes were cultured. Treatment also resulted in an initial rise in the mean percentage of CD95pos T cells and in a gradual increase in the mean level of soluble CD95 in plasma (Rep et al., 1999).

IFN-β-mediated inhibition of IFN-γ production by stimulated lymphocytes was confirmed in a study employing murine preimmunized lymph node cells and bovine collagen as the antigen (Triantaphyllopoulos et al., 1999).

4.5. Mononuclear phagocytes

Activated mononuclear phagocytes produce many cytokines, amongst them TNF-α which is generally considered a most important pro-inflammatory factor. Activation of MPC results from stimulation by foreign agents combined with endogenous macrophage-activating factors, the most important of which is IFN-γ, alias Type II interferon. Not unexpectedly, Type II interferon was shown to enhance TNF-α production by activated MPCs (Nedwin et al., 1985; Svedersky et al., 1985). Though Type I interferon was first believed to possess similar potentiating effect on TNF-α production (Wallach, 1986), a later study (Abu-khabar et al., 1992) demonstrated that IFN-α and IFN-β rather inhibit TNF-α production by mitogen-activated human PBMC. A similar inhibitory effect was seen with LPS as inducer of IL-1 and IL-1 receptor antagonist in whole human blood in vitro (Huang et al., 1995). Also in a study on the effects of IFN-β in collagen-induced arthritis in mice, IFN-β was found to reduce the levels of TNF-α and IL-

12 produced in vitro by lipopolysaccharide/IFN-γ-stimulated bone marrow-derived macrophages (Triantaphyllopoulos et al., 1999).

Phagocytosis of apoptotic cells, in particular apoptotic T cells, is important for control of inflammation. Significantly, mononuclear phagocytes engaged in this process, rather than being activated, are downregulated in terms of cytokine production (Magnus et al., 2001). In a system consisting of rat microglia ingesting apoptotic encephalitogenic T lymphocytes, IFN-β was found to enhance phagocytic activity without affecting this downregulation of cytokine production (Chan et al., 2003).

4.6. Myelosuppression

Suppression of haematopoiesis is a common finding in most clinical studies with Type I interferon (Wong et al., 1996; Schmid et al., 2005; Peck-Radosavljevic et al., 2002). This suppression concerns erythropoiesis as well as leukopoiesis and thrombopoiesis. Acute inflammation is mostly associated with a myelopoietic burst responsible for increased blood leukocyte counts and contributing to infiltration of local inflammatory sites with leukocytes. By its myelosuppressive effect, any interferon produced during inflammatory reactions, might therefore mitigate both this systemic response as well as leukocyte infiltration at local inflammatory sites. As to Type I interferon, no information supporting this proposal seems to be available. However, in the case of IFN-γ, studies in mice have shown that endogenous IFN-γ is a powerful downregulator of myelopoiesis elicited by inflammatory stimuli, such that ablation of IFN-γ by administration of neutralizing antibody or by gene knock-out results in more severe inflammatory reactions (Matthys et al., 2000).

5. Discussion

From the data reviewed here (see summary in Table 1), it appears that Type I interferons exert several cellular effects that may endow them with overall anti-inflammatory activity. Many of the observations supporting this conclusion were done in the context of the need to provide an explanation for the now generally recognized beneficial effect of IFN-β therapy in RRMS. However, in a few in vivo animal models for inflammatory reactions or diseases with a strong inflammatory component, Type I interferon was confirmed to provide at least partial protection. Finally, evidence is available to suggest that, also in chronic viral hepatitis, part of the beneficial effect of Type I interferon therapy may well be accounted for by an anti-inflammatory effect.

Leukocyte traffic within lymphoid organs and between such organs and inflamed tissues is the foremost important feature of acute inflammation. It serves the purpose of immediate early defence against local insults, typical for innate immunity, but it is also essential for adequate development of later adaptive immunity. For instance, whether any adaptive response assumes a Th1 or Th2 character depends largely on the assortment of leukocytes and their cytokines and chemokines participating in the preceding acute inflammation. Given the observation that IFN-β has the potential to regulate recruitment as well as secretory activity of leukocytes during inflammation, it follows that IFN-β may also participate in the regulation of adaptive immune responses. This may be part of the explanation for observations in mice or rats that treatment with IFN-α/β can modify the course of experimental diseases with complex pathogenesis such as EAE, CIA, or skin graft acceptance.

So, it is an interesting thought that while Type I interferons evolved to become signals for activation of intracellular

Table 1
Summary of anti-inflammatory effects of Type I interferons (for references, see text)

Type I IFN administration in animal models	
Skin reactivity	Reduced reaction to LPS or carrageenan
Brain damage - Blood-brain barrier rupture	Reduced response to ischemic insult; reduced response to chemokine injection
Collagen-induced arthritis	Protection
Experimental autoimmune encephalomyelitis	Protection
DTH - allotransplant rejection	Protection
Cells exposed to Type I IFN	
Dendritic Cells	Faster differentiation; altered phenotype; stronger antigen presentation
Cell adhesion molecules	Basal and induced expression inhibited
Leukocyte transmigration	Chemokine-induced transmigration inhibited
Matrix metalloproteases	Elevation of MMP-9 mRNA level and MMP-9 secretion inhibited
Mononuclear phagocytes & activated lymphocytes	Production of most monokines and lymphokines suppressed; lymphoproliferation inhibited
Patients treated with Type I IFN	
Haematopoiesis	Mild myelosuppression
Inflamed Liver	$CD8^+$ lymphocyte infiltration reduced; CD14 expression on Kupffer cells increased
MS patients	Levels of soluble VCAM-1 increased; VLA-4 expression on lymphocytes decreased; serum MMP-9 decreased; TIMP-1 level increased

antiviral mechanisms, evolutionary pressure may at the same time have moulded signals for several inflammatory mechanisms to respond negatively to interferon. Interferon's natural task during acute virus infection may therefore consist not only in inhibiting virus replication but also in mitigating inflammation. If this would indeed be the case, one would be allowed to think (perhaps a bit wishfully) that interferon is a suitable anti-inflammatory agent to be used in severe acute virus infections, superior to steroids or NSAIDs. Clinical tests done in the 1980s have shown that Type I interferons were of very little value in 'common' acute virus infections. However, severe acute infections caused by 'unusual' viruses such as the SARS coronavirus, seem to owe their life-threatening severity to excessive inflammatory reactions, as has been documented by massive production of certain cytokines (Huang et al., 2005) and chemokines (Law et al., 2005). Remarkably, this so-called cytokine storm appeared to be accompanied with only low-level production of IFN-β. Interferon therapy, thanks to a combined direct antiviral and a 'natural' anti-inflammatory potential, might represent a prototype approach for management of such infections.

Will the anti-inflammatory activities of Type I interferons continue to stir the interest of clinical investigators? If so, the spectrum of diseases amenable to interferon therapy may still expand. Moreover, as underlying mechanisms will be further elucidated, investigators may more easily find agents that have anti-inflammatory actions similar to those of interferon, and that may replace Type I interferons in the treatment for MS or other chronic inflammatory illnesses. Clearly, there is a need for further and more thorough investigation. Further in-depth characterization of cellular effects, such as those reviewed here, will be extremely important to make this possible. But perhaps more important will be the expansion and refinement of experimental animal models, so they may be employed to more strongly underpin the anti-inflammatory potential of Type I interferons and to evaluate their clinical potential.

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