Interferons as Essential Modulators of Atherosclerosis

Marieke C.S. Boshuizen, Menno P.J. de Winther

Abstract—Interferons (IFNs) are key regulators of both innate and adaptive immune responses. The family of IFN cytokines can be divided into 3 main subtypes of which type I and type II IFNs are most well-defined. IFNs are known to be important mediators in atherosclerosis. Evidence from both in vitro and in vivo studies shows that the IFNs are generally proatherosclerotic. However, their role in atherosclerosis is complex, with distinct roles for these cytokines throughout different stages of the disease. In this review, we will discuss the current knowledge on the role of type I and type II IFNs in atherosclerosis development, specifically focusing on their role in endothelial activation, cell recruitment, foam cell formation, and regulation of apoptosis. Furthermore, we will discuss whether IFNs could be considered as new molecular targets for therapeutic intervention in atherosclerosis. (Arterioscler Thromb Vasc Biol. 2015;35:1579-1588. DOI: 10.1161/ATVBAHA.115.305464.)

Key Words: apoptosis • atherosclerosis • cytokines • foam cells • interferons

Since their discovery in 1957, interferons (IFNs) have been studied extensively, and it is now well known that IFNs are essential regulators of innate and adaptive immunity. Isaac and Lindenmann initially described these proteins to inhibit viral replication. However, today, many more functions are attributed to IFNs, as over time they were also found to exhibit important immunomodulatory functions and to affect tumor growth and cell survival. The IFNs constitute a family of cytokines, which are divided into 3 main subtypes; type I, II, and III IFNs. They can be distinguished by their respective receptors, inducing stimuli and cellular source. Of the type I IFNs (T1 IFNs), IFN-α and IFN-β are considered to be most important. Both cytokines are predominantly produced in response to viral infections by most cell types, with the plasmacytoid dendritic cells (pDCs) being the main source. In addition, they were shown to have antibacterial, antiproliferative, and antitumor activity. The only type II IFN (T2 IFN), IFN-γ, is among others secreted by lymphocytes, activated macrophages, natural killer cells, endothelial cells, and vascular smooth muscle cells (VSMCs), not only in response to viral encounters but throughout a broad repertoire of immune responses. The type III IFNs were only recently discovered and consists of 3 IFN-λ isotypes with a biological activity similar to the T1 IFNs. They can be secreted by virtually any cell type, whereas its receptor is mostly confined to the epithelium.6

IFN Signaling

IFN-γ signals via a heterodimeric cell–surface receptor consisting of 2 different subunits; IFN-γ receptor (IFNGR)-1 and IFNGR2. After binding of IFN-γ, the receptor subunits heterodimerize, resulting in activation of Janus kinases 1 and 2, which phosphorylate their downstream substrate, signal transducer and activator of transcription (STAT)-1. STAT1 homodimerizes and binds to γ-activated sequences, resulting in subsequent transcription (Figure 1).7,8

The T1 IFNs are structurally unrelated to IFN-γ and bind a different heterodimeric cell–surface receptor that is also composed of 2 different subunits, IFN-α/β receptor (IFNAR)-1 and IFNAR2. After T1 IFN binding, both subunits heterodimerize with a subsequent activation of Jak1 and Tyk2 kinases, thereby phosphorylating STATs as well. This mostly induces STAT1–STAT2 heterodimers that require assembly with IFN-regulatory factor-9 for their function. The resulting complex, termed IFN-stimulated gene factor-3, binds to IFN-stimulated response elements to initiate transcription of IFN-stimulated genes.9 However, T1 IFNs can also activate other STAT family members in various cell types, which can lead to the assembly of many heterodimer and homodimer pairs, resulting in context and cell type–specific cellular responses after IFNAR activation (Figure 1).9,10

Both T1 and T2 IFNs are often secreted in parallel during the same immune response, and data suggest that cross talk between type I and II IFN signaling is needed for an optimal response. It is known that T1 and T2 pathways are linked at several levels. IFN-γ, for instance, can also induce the IFN-stimulated gene factor-3 complex, thereby stimulating the transcription of T1 IFN–related genes.11 Conversely, T1 IFNs can stimulate STAT1 homodimerization, which drives IFN-γ gene transcription patterns.10 Furthermore, low continuous T1 IFN levels prime cells for a strong immune response to both T1 and T2 IFNs.12 It has also been shown that IFNAR1

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can interact with IFNGR2, thereby inducing the expression and activation of STAT1, which provides a basis for IFN-γ-stimulated STAT1 homodimerization, leading to a robust IFN-γ response.13,14

**IFNs in General Inflammation**

The IFNs are essential regulators of immune function. On viral or bacterial infection, the proinflammatory cytokine IFN-γ is secreted by T helper-1 (Th1) cells. IFN-γ can subsequently activate macrophages, resulting in the secretion of proinflammatory mediators, such as interleukin-12 and interleukin-18, to enhance microbicidal actions. Under the influence of IFN-γ, antigen presentation is enhanced by upregulating both major histocompatibility complex class I and class II expression on activated macrophages and the induction of major histocompatibility complex class II expression on mature DCs. This results in a second wave of T-cell activation, thereby linking innate with adaptive immunity.5,15,16

The T1 IFNs were first recognized to be released during viral infections, as their induction can inhibit viral replication and upregulate major histocompatibility complex class I antigen expression on virus-infected cells, thereby inducing the adaptive T-cell response.17 Nowadays, it is known that T1 IFNs also contribute to the antibacterial immune response as macrophages and DCs produce T1 IFNs in response to Toll-like receptor 4 triggering.18 Endogenous proinflammatory mediators, such as tumor necrosis factor (TNF), may also induce the production of T1 IFNs. The resulting T1 IFN autocrine feedback loop then further sustains the inflammatory response.19 Similar to IFN-γ, T1 IFNs can upregulate the expression of major histocompatibility complex class I and class II and costimulatory molecules on DCs and so can initiate T-cell responses.20,21 These diverse examples illustrate that the IFNs are essential for a robust immune response. However, many more immunomodulatory actions can be attributed to the IFNs. A concise overview of these actions is displayed in Table 1. However, it should be noted that not all IFN-induced immunomodulatory actions are described here as details are beyond the scope of this review and are already extensively reviewed elsewhere.5,22,23

**IFNs in Atherosclerosis**

Atherosclerosis is a complex and multifactorial disease in which macrophages, T cells, and VSMCs are important cellular components of the atherosclerotic lesion. Macrophages are abundant in the atherosclerotic lesion and are activated on IFN stimulation. IFN-γ, for instance, is known to polarize macrophages toward a proinflammatory M1 phenotype. Macrophages are major contributors of the atherosclerotic inflammatory response by the secretion of many inflammatory mediators, including cytokines and chemokines. Activated macrophages can also secrete IFNs, resulting in leukocyte attraction to the lesion. The other way around, several studies have shown that the IFNs are also important regulators of macrophage attraction toward the atherosclerotic plaque, as blocking IFN and its signaling led to a decreased macrophage accumulation.24–28

About T cells, many studies have been performed to show their link with atherosclerosis via the induction of IFN-γ. Th1 cells are the main producers of IFN-γ, for instance, on activation by plaque antigens.15 IFN-γ secretion leads to a further skewed Th1 response as it polarizes T cells toward this Th1 phenotype. The Th1 bias promotes atherosclerosis in both
humans and mice. Furthermore, Th1 cytokines are prevalent in both human and murine atherosclerotic lesions. Studies in mice with a deficiency of IFN-γ, IFNGR1, or the Th1 differentiating factor T-bet resulted in diminished atherogenesis, indicating the importance of this Th1 response.

VSMCs are crucial for plaque stability as they contribute to a fibrous cap surrounding the proinflammatory destabilizing the necrotic core. VSMC proliferation is therefore considered beneficial during atherosclerosis progression. IFN-γ is known to have profound effects on their proliferation. Both antiproliferative and proproliferative actions have been attributed to IFN-γ, but the net effect is that IFN-γ inhibits proliferation that has been demonstrated both in vitro and in vivo. IFN-γ also induces collagen I and III production in VSMCs, thereby increasing plaque vulnerability. In addition, IFN-γ was shown to inhibit arterial stenosis after vascular injury in rats by reducing intimal thickening, which is mediated via VSMC proliferation. Similar observations were made for IFN-β as treatment of human VSMCs with this cytokine reduced their proliferation, whereas blocking IFNAR1 stimulated VSMC growth. Furthermore, it was shown that VSMCs can produce IFN-γ and IFN-β, which might serve as an autocrine feedback loop to regulate VSMC growth.

A plethora of cytokines, including IFNs, has been shown to be important atherogenic regulators. Already in 1989, Hansson et al observed IFN-γ and IFN-γ–producing T cells to be abundant in human atherosclerotic plaques. The T1 IFN–producing pDCs have also been found in plaques, with a specific localization in its rupture-prone areas. Overall, the role of IFN-γ in atherosclerosis has been investigated thoroughly, whereas research on the role of T1 IFNs in atherosclerosis development has only recently started. Table 2 summarizes important murine atherosclerotic studies on the T1 and T2 IFNs. In this review, we will further highlight their function in endothelial activation, cell recruitment to the atherosclerotic plaque, foam cell formation, and regulation of apoptosis.

**IFNs in Endothelial Activation and Cell Recruitment**

An early step in atherogenesis is endothelial dysfunction, resulting in increased permeability to circulating low-density lipoproteins (LDL) and recruitment of leukocytes. IFN-γ is known to induce the expression of endothelial cell adhesion molecules, such as vascular cell adhesion molecule-1 and intercellular adhesion molecule-1, which are early markers of atherogenesis and are crucial for leukocyte recruitment to the plaque. Their expression can be further intensified by cross talk between IFN-γ and lipopolysaccharide signaling. High-fat diet–induced monocyte and T-cell recruitment to the microvasculature endothelium was decreased in IFN-γ−/− mice. In atherosclerosis, IFN-γ’s role in leukocyte recruitment could be confirmed, as IFN-γ treatment of ApoE−/− mice resulted in an increased amount of lesional T cells.
versa, a reduced cellular density was observed in lesions from both ApoE+/−IFN-γ−/− and IFN-γ−/− bone marrow–transplanted LDLR−/− mice, indicating less cell recruitment on IFN-γ deficiency. Interestingly, sex-specific effects were observed in IFN-γ−/−ApoE−/− double knockout mice, as this deficiency resulted among others in a decreased lesional

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<td>Injection soluble mutant of IFN-γR (every 2 wk)</td>
<td>ApoE−/−HFD advanced atherosclerosis</td>
<td>Lesion growth ↓</td>
<td>Koga et al26</td>
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BMT indicates bone marrow transplantation; HCD, high-cholesterol diet; HFD, high-fat diet; IFN, interferon; KO, knockout; NC, normal chow; ODNs, oligonucleotides; pDC, plasmacytoid dendritic cell; SCID, severe combined immunodeficiency; and VSMC, vascular smooth muscle cell.
T cell number in male mice only. IFN-γ is also known to induce the expression of several chemokines, such as CXCL9, CXCL10, and CCL2, thereby further promoting cell recruitment toward the atherosclerotic plaque. Altogether, IFN-γ can thus promote leukocyte recruitment to atherosclerotic lesions (Figure 2).

An in vivo stimulatory effect of T1 IFNs in early endothelial cell dysfunction has also been documented. In systemic lupus erythematosus (SLE), chronic exposure to T1 IFNs is present, which can promote and sustain chronic endothelial dysfunction, eventually leading to atherosclerosis. Indeed, patients with SLE show a significant increased incidence of atherosclerosis and cardiovascular events when compared with healthy individuals. The T1 IFN IFN-β is frequently used as a treatment of patients with relapsing remitting multiple sclerosis where it surprisingly has opposite effects on cerebral endothelial activation when compared with the peripheral endothelium. About cell recruitment to the plaque, a recent in vivo study showed that T1 IFNs increased cell recruitment to atherosclerotic lesions in a CCL5-dependent manner. Moreover, IFN-β treatment of LDLR−/− mice increased macrophage lesion area, whereas deleting myeloid IFNAR1 in LDLR−/− mice prevented macrophage accumulation in the lesion. Consistent with these findings, depletion of pDCs in ApoE−/− mice reduced macrophage accumulation. However, it has also been observed that depletion of pDCs results in increased plaque formation because of increased T-cell accumulation. Overall, these data indicate that T1 IFNs promote cell recruitment to the plaque and can thereby promote atherosclerosis (Figure 2).

**IFNs in Foam Cell Formation**

Macrophage foam cell formation in the arterial wall is an early hallmark of atherosclerotic plaque formation. A contributory

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**Figure 2.** Schematic overview of T1 and T2 interferon (IFN) effects on macrophages in atherosclerosis. (1) Activation of the endothelium induces the expression of leukocyte adhesion molecules and the secretion of chemokines, resulting in the recruitment of leukocytes to the vessel wall. (2) In the arterial wall, monocytes differentiate into macrophages. Activated macrophages secrete among others T1 and T2 IFNs, enhancing leukocyte recruitment and macrophage activation. (3) Regulation of scavenger receptors and cholesterol efflux transporters by T1 and T2 IFNs in the presence of modified lipoproteins, resulting in (4) foam cell formation. (5) Apoptosis can occur in macrophage and lipid rich areas in the plaque. T1 and T2 IFNs regulate death receptor expression. (6) This can result in apoptosis of macrophages leading to necrotic core formation. Vascular smooth muscle cells (VSMCs) and T cells are also important sources and targets for the interferons. IFNγ is produced mainly by T helper 1 cells, which can act on VSMCs to regulate their proliferation. VSMCs also produce IFNγ themselves, which results in macrophage activation. Furthermore, they secrete T1 and T2 IFNs and chemokines to attract more leukocytes to the lesion site. Details are given in the text. Green indicates stimulation, and red indicates inhibition. ABCA1 indicates ATP-binding cassette A1; FasL, Fas ligand; ICAM-1, intercellular adhesion molecule-1; IFNGR, IFNγ receptor; SR-A, scavenger receptor-A; SR-PSOX, scavenger receptor for phosphatidylserine and oxidized low-density lipoprotein; TRAIL, tumor necrosis factor–related apoptosis–inducing ligand; and VCAM-1, vascular cell adhesion molecule-1.
role for IFN-γ in foam cell formation is well established; however, the results are conflicting. A first study in 1992 described an inhibiting role for IFN-γ in the foam cell formation of human monocyte-derived macrophages, accompanied by a decreased gene expression of the uptake receptor scavenger receptor-A. An IFN-γ-mediated decrease in CD36 gene expression in human monocyte-derived macrophages was subsequently found in vitro. Decreased CD36 expression was also observed after STAT1 deficiency in the human THP1 cell line and in mouse peritoneal macrophages both in vitro and in vivo, resulting in decreased macrophage foam cell formation. Furthermore, IFN-γ suppresses LDL oxidation, which makes LDL less attractive for macrophage uptake. These examples thus suggest an inhibiting role for IFN-γ in foam cell formation (Figure 2).

In contrast to these data, IFN-γ increases scavenger receptor for phosphatidylserine and oxidized LDL, another scavenger receptor involved in the uptake of oxidized LDL. Moreover, acetylated LDL–loaded murine peritoneal macrophages stimulated with IFN-γ showed a decreased cholesterol efflux. This was accompanied by a decreased expression of ABCA1. In addition, IFN-γ is known to decrease expression of cholesterol 27-hydroxylase in macrophages, which normally stimulates cholesterol efflux via ABCA1. Furthermore, IFN-γ receptor blockade in ApoE−/− mice on a high-fat diet decreased lipid accumulation in the atherosclerotic plaques as analyzed by oil-red-O staining. On the contrary, it was recently observed that IFN-γ decreases lipid uptake in THP1 cells via effects on macropinocytosis. Overall, it is now common thought that IFN-γ disrupts lipid handling of macrophages with a net effect of promoting foam cell formation. However, these effects are mainly based on in vitro studies, and therefore, further in vivo investigations are required (Figure 2).

Studies on the effects of T1 IFNs on foam cell formation are minimal and are to date inconclusive. In a recent study by Goossens et al. it was observed that T1 IFNs promote atherosclerosis. However, no effect on short-term oxLDL uptake by murine bone marrow–derived macrophages was observed after priming with IFN-β. In contrast to this study, IFN-α priming of THP1 cells showed increased oxLDL uptake, accompanied by increased scavenger receptor-A gene expression. Furthermore, peripheral blood mononuclear cells from patients with SLE showed to have increased scavenger receptor-A expression, which was positively correlated with T1 IFN signaling activity. A similar phenomenon seems to play a role in peripheral blood mononuclear cells from patients with HIV, as their PBMCs possess a T1 IFN profile with an increase in lipid uptake, accompanied by increased SR-A expression. Recently, it was described that altering the structure of heparin sulfate on myeloid cells of LDLR−/− mice results in exacerbation of foam cell formation, which was linked to an increased T1 IFN signaling. A growing body of evidence thus supports a role for the T1 IFNs in promoting foam cell formation (Figure 2).

**IFNs in Apoptosis**

Apoptosis is a common phenomenon in macrophage-rich areas of atherosclerotic lesions. Defective clearance of apoptotic cells, or efferocytosis, results in the formation of an inflammatory necrotic core, which makes plaques prone to rupture. Both T1 and T2 IFNs are implicated in the regulation of apoptosis. Their antiproliferative effects have been well described in the oncology field, where the IFNs were the first human proteins to be effective as cancer treatment. Unfortunately, the exact mechanism of their antitumor activity is not fully understood yet. In fact, the direct role of IFN-γ in apoptosis induction is confusing since both proapoptotic and antiapoptotic roles for IFN-γ have been described. Depending on the levels of IFNGR on myeloid or T cells present, the cell will die after IFN-γ stimulation. This phenomenon is attributed to STAT1, as high levels of the IFNGR will rapidly activate STAT1, with a resulting activation of IFN-regulatory factor-1. High levels of IFN-regulatory factor-1 on its turn induce apoptosis by activating caspase-1. Low levels of IFNGR have the opposite effect, as low induction of IFN-regulatory factor-1 is not enough to induce apoptosis and proliferation is induced. IFN-γ also induces the mRNA expression of TNF-α receptor-1 and caspase-8 in THP1 macrophages. In human VSMCs, IFN-γ induced the expression of Fas and TNF-related apoptosis–inducing ligand. Apoptosis of cultured rat smooth muscle cells by IFN-γ is also partially mediated via the production of nitric oxide. This might indicate that apoptosis in the atherosclerotic plaque is the result of the present immune response, in which IFN-γ is indispensable. Overall, these studies show that IFN-γ has proapoptotic effects using different apoptotic mechanisms (Figure 2).

In infections, T1 IFNs sensitize cells for pathogen-induced cell death. In vitro analysis of IFN-β–stimulated THP1 monocytes indeed demonstrated a proapoptotic effect for IFN-β, by increased expression of TNF-related apoptosis–inducing ligand, Fas, and Fas ligand. Patients with SLE, whose monocytes possess a T1 IFN signature, show increased apoptosis of several leukocyte subtypes. In addition, monocyte-derived macrophages from patients with multiple sclerosis who were treated with IFN-β showed more apoptotic cell death when compared with the cells before start of the treatment. In atherosclerosis, the T1 IFNs are also involved in apoptosis; genetic myeloid deletion of IFNAR1 showed a prominent reduction in necrotic core formation when compared with IFNAR1 wild-type mice. This is in line with an observed decrease in apoptosis of monocytes derived from IFNAR1−/− mice. In human atheromas, the secretion of IFN-α enhanced TNF-related apoptosis–inducing ligand surface expression of CD4+ T cells. In vitro coculture of those plaque-derived CD4+ T cells with human primary VSMCs resulted in death of the VSMCs, which would make plaques more vulnerable. Altogether, these data show that T1 IFNs have a proapoptotic role, also in atherosclerosis. A common apoptotic mechanism for both T1 IFNs and IFN-γ may be their overlapping STAT1 pathway as STAT1 plays a critical role in apoptosis of peritoneal macrophages in vitro and in an advanced atherosclerosis model using STAT1−/− bone marrow–transplanted LDLR−/− mice (Figure 2).
Therapeutic Potential

Therapeutic strategies to reduce atherosclerosis have thus far mainly focused on lipid lowering, mostly by use of statins. In addition, several anti-inflammatory approaches have shown potential in reducing atherosclerosis in experimental settings. Ongoing clinical trials now have to prove the relevance of blocking inflammatory mediators in atherosclerosis treatment. As our knowledge on the mechanisms and functions of the T1 and T2 IFNs grows, targeting them might give us the opportunity to dampen atherogenesis progression. IFN-γ has already been targeted in several human diseases, for instance in Crohn disease, with early signs of clinical efficacy. However, actual clinical applications of anti-IFN-γ treatment still seem to fail, probably because blockade of IFN-γ or IFNγR is associated with high rates of infection, particularly of mycobacteria. This susceptibility has also been proven in IFN-γ or IFNγR-deficient humans, which predisposes them to severe infections. About the T1 IFNs, several clinical trials are currently being performed to study the effect of IFN-α inhibition in SLE at different levels of IFNAR signaling or by targeting the pDCs. So to date, these treatments seem promising with no serious adverse effects. However, a potential limitation of these studies might be the increased susceptibility to viral infections or even the possible induction of tumor growth. This can be minimized when the blockade is directed against pDCs as the IFN response in all other cells remains intact. Targeting IFNAR blocks all T1 IFN production, thereby increasing the risk of adverse effects. On the contrary, T1 IFN blockade could still be useful in the control of persistent viral infections in which an unwanted sustained T1 IFN signaling is present, as has been shown in murine lymphocytic choriomeningitis virus infections.

Broad inhibition of either T1 or T2 IFNs in atherosclerotic disease may thus be associated with unwanted risks, and long-term inhibition will therefore not be favorable in treatment of the disease. However, short-term intervention might still have the potential to reduce atherosclerosis progression. The IFNs could for instance be targeted after myocardial infarction or stroke, when the risk of recurrent events is drastically increased. Closely monitored treatment of patients is then critical, outweighing the possible adverse effects of infection. In both atherosclerosis development and myocardial infarction, myeloid cells are critically involved. Myeloid cells might therefore be an important target to influence disease progression. The use of nanoparticles may aid in a cell-specific treatment delivery, as recent studies have shown the value of this upcoming treatment strategy. Future treatment of atherosclerosis may thus involve the cell-specific modulation of IFNs as a short-term therapeutic intervention. However, more preclinical intervention studies are necessary to better understand the value of such approaches for treatment of disease.

Concluding Remarks

Although initially being discovered as antiviral cytokines, we now know many more functions can be attributed to the IFNs as they have been studied at a large extent during the past few decades. It is now recognized that both T1 and T2 IFNs play a central promoting role in the pathogenesis of atherosclerosis, however, their role in this disease is extremely complex as both families of IFNs act at different stages throughout disease progression. During the early phases of atherosclerosis, starting with endothelial activation and leukocyte recruitment, expression of adhesion molecules and chemokines is upregulated by IFN-γ to stimulate cell recruitment to the plaque. T1 IFNs are known to do this mainly in a CCL5-dependent manner. About foam cell formation, conflicting results on the role of IFN-γ are observed. Nevertheless, it is generally thought that IFN-γ disrupts lipid handling of macrophages with a balance toward foam cell promoting effects. Data on T1 IFNs and foam cell formation are minimal, but again, it seems that T1 IFNs promote foam cell formation. In the late phases of atherosclerosis, when apoptosis and necrotic core formation come into play, both IFN families seem to be proapoptotic and could therefore stimulate atherosclerosis progression. Advances in our knowledge on the IFNs make them potential new molecular targets in the cell-specific short-term treatment of atherosclerosis.

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Disclosures

None.

References


Interferons as Modulators of Atherosclerosis


**Significance**

The interferons have been studied extensively during the past few decades. These studies have demonstrated that T1 and T2 interferons not only have important immunomodulatory functions but also play a central promoting role in the pathogenesis of atherosclerosis. Evidence from both in vitro and in vivo studies shows that interferons are generally proatherosclerotic. However, their role in this disease is extremely complex as both families of interferons act at different stages and to differing extents throughout disease progression. In this review, the current knowledge on interferons in atherosclerosis is discussed. As our understanding herein has increased, we now suggest that the interferons may act as possible new molecular targets in the cell-specific and short-term treatment of this disease.
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