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Invited critical review

Interferon-γ in foam cell formation and progression of atherosclerosis

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ABSTRACT

Interferon-γ (IFN-γ), the sole member in type II IFN predominantly secreted by macrophages and T cells, is a critical regulator of immune function and provides a robust first line of defense against invading pathogens. Binding of IFN-γ to its receptor complex can activate a variety of downstream signaling pathways, particularly the Janus kinase (JAK)/signal transducer and activator of transcription (STAT), to induce gene transcription within the target cells. This pro-inflammatory mediator is highly expressed in atherosclerotic lesions and promotes foam cell formation, but its effects on the atherogenesis are complex, with both pro- and anti-atherogenic properties. IFN-γ also contributes to the development of myocardial infarction and stroke, the two main atherosclerotic diseases. Inhibition of IFN-γ signaling may prevent the development of atherosclerosis and help treat atherosclerotic diseases. Since IFN-γ may also exert anti-atherogenic effects, the safety and efficacy of anti-IFN-γ treatment still require careful evaluation in the clinical setting. In the current review, we summarize recent progression on regulation and signaling pathways of IFN-γ, and highlight its roles in foam cell formation, atherosclerosis, myocardial infarction as well as stroke. An increased understanding of these processes will help to develop novel IFN-γ-centered therapies for atherosclerotic diseases.

Contents

Abbreviations: IFN-γ, interferon-γ; IFNGR, IFN-γ receptor; VSMC, vascular smooth muscle cell; IL, interleukin; LPS, lipopolysaccharide; TNF-α, tumor necrosis factor-α; STAT, signal transducer and activator of transcription; NF-κB, nuclear factor-κB; TLR, Toll-like receptor; Tyr, tyrosine; Ser, serine; PI3Ks, phosphatidyl inositol-3 kinases; miRNAs, microRNAs; TGF-β, transforming growth factor-β; Blimp-1, B lymphocyte-induced maturation protein-1; Bcl-6, B cell lymphoma-6; NOD2, nucleotide-binding oligomerization domain 2; JAK, Janus kinase; GAS, IFN-γ activation sequences; ERK, extracellular signal-regulated kinase; PKC, protein kinase C; SOCS, suppressor of cytokine signaling; IP-10, inducible protein-10; ox-LDL, oxidized low-density lipoprotein; SRs, scavenger receptors; ACAT1, Acyl coenzyme A:cholesterol acyltransferase 1; ABCA1, ATP-binding cassette transporter A1; apo E, apolipoprotein E; MMP, matrix metalloproteinase.

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1. Introduction

Atherosclerotic diseases such as myocardial infarction and stroke are the major cause of mortality and morbidity in developed countries and their prevalence is increasing in developing countries, and atherosclerosis is the pathological basis of these disorders. Atherosclerosis occurs at susceptible sites in large and medium-sized arteries, and its risk factors predominantly include genetic predisposition, age, stress, physical inactivity, dietary habits, diabetes, infection, smoking, hypercholesterolemia as well as hypertension. The development of atherosclerosis or atherogenesis is multifactorial and complex with involvement of endothelial dysfunction, vascular inflammation, vascular smooth muscle cell (VSMC) proliferation, thrombus formation, infiltration of monocytes and their differentiation into macrophages, and conversion of lesion-resident macrophages into foam cells [1].

Atherosclerosis is a chronic inflammatory disease of the arterial wall with lipid-laden lesions, involving a complex interaction between multiple different cell types and cytokine networks. Macrophages, T cells and, to a lesser extent, mast cells contribute to the inflammatory response. A number of cytokines including interleukin (IL)-1, IL-17, interferon (IFN)-γ and tumor necrosis factor-α (TNF-α) are expressed highly in the lesion regions and display pro- and/or anti-atherogenic actions [2,3]. Among these, IFN-γ is believed to have a critical role in the atherogenesis. The IFN family cytokines are divided into two types. Type I IFNs constitute the largest IFN class and contain IFN-α, -β, -ε, -κ, and -ω, all of which share notable sequence homology and are produced by most cell types. However, IFN-γ is the sole member in type II IFN, which forms a homodimer. It is principally synthesized by monocytes, macrophages, T cells, natural killer (NK) cells, dendritic cells and B-lymphocytes. Although originally defined as an agent with direct antiviral activity, IFN-γ has a multitude of biological functions including regulation of several aspects of the immune responses, stimulation of antigen presentation *via* upregulating class I and class II major histocompatibility complex (MHC) molecules on the surface of macrophages and T cells, promotion of leukocyte–endothelium interactions, stimulation of inflammatory mediator production in target cells, and recruitment of cells to the site of injury through enhancing expression of chemokines and adhesion molecules [4]. In addition to these, IFN-γ affects cellular proliferation, differentiation and apoptosis [5]. Notably, all of these properties potentially influence the process of atherogenesis. In the present review, we summarize the regulation and signaling pathways of IFN-γ, and analyze its roles in foam cell formation and several main atherosclerotic diseases like atherosclerosis, myocardial infarction and stroke.

2. Regulation of IFN-γ expression

The expression of IFN-γ is regulated by multiple factors, including cytokines. Addition of exogenous IL-2 facilitates the secretion and expression of IFN-γ induced by lipopolysaccharide (LPS) in human dendritic cells through phosphorylation of signal transducer and activator of transcription (STAT) 5 [6]. IL-18 also contributes to induction of IFN-γ expression in a transgenic mouse model of human papillomavirus (HPV)-associated epidermal hyperplasia, driven by the expression of the HPV16 E7 oncoprotein from a keratin 14 promoter [7], whereas IL-18-binding protein (IL-18BP), a naturally occurring antagonist of IL-18, remarkably downregulates IFN-γ expression by inhibiting STAT3 in IL-1α-stimulated splenocytes cultured from rats with experimental autoimmune myocarditis [8]. Recent studies from our group have revealed that IL-18 combined with IL-12 promotes its production *via* activation of nuclear factor-κB (NF-κB) in THP-1 macrophage-derived foam cells [9]. On the other hand, IFN-γ secretion by activated NK cells is reduced when these cells are cocultured with IL-27 pretreated autologous monocytes [10]. A significant increase of hepatic IFN-γ levels is found in mice lacking IL-4 when compared with those in wild-type animals, suggesting that IL-4 is also an inhibitor of IFN-γ production [11].

MicroRNAs (miRNAs) are endogenous, single-stranded RNA molecules with 21–23 nucleotides in length, which regulate their target mRNAs by loading them onto the miRNA-induced silencing complex and result in gene silencing by suppressing translation and/or degrading mRNA at the post-transcriptional level. Recently, a variety of studies have focused on the roles of miRNAs in the regulation of IFN-γ expression [12]. MiR-21 dramatically increases the synthesis of IFN-γ in hepatic effector CD8(+) T cells isolated from mice expressing dominant-negative transforming growth factor-β (TGF-β) receptor II [13]. Overexpression of miR-155 also enhances the expression of IFN-γ induced by IL-12 and IL-18 or in response to CD16 stimulation, whereas knockdown or disruption of miR-155 inhibits IFN-γ induction in monokine and/or CD16-stimulated NK cells [14]. These effects are mediated at least in part *via* miR-155's direct effects on the Src homology 2 domain-containing inositol-5-phosphatase 1 (SHIP1), a hematopoietic cell-specific 5′ inositol phosphatase. On the other hand, two groups have reported that miR-29 degrades murine IFN-γ mRNA [15,16]. However, another group found that repression of IFN-γ production by miR-29 in murine helper T cells involves direct targeting of both T-box expressed in T cells (T-bet) and eomesodermin (Eomes), two T-box transcription factors known to induce IFN-γ production [17]. Transfection of T cells with miR-144 precursor induces a significant reduction of IFN-γ levels [18]. Suppression of miR-9 has been shown to elevate the expression of B lymphocyte-induced maturation protein-1 (Blimp-1) and B cell lymphoma-6 (Bcl-6), which subsequently results in diminished secretion of IFN-γ in activated human CD4 + T cells [19]. MiR-122 directly targets nucleotide-binding oligomerization domain 2 (NOD2), thereby leading to activation of NF-κB and subsequent decrease in IFN-γ expression in LPS-stimulated HT-29 cells [20]. In addition, miR-24 and miR-181 negatively regulate IFN-γ expression by binding directly to their target sites in the IFN-γ mRNA 3′ untranslated region (UTR) in activated human CD4 lymphocytes [21]. Thus, identifying the target sites for these two miRs in IFN-γ-3′UTR reveals a novel regulatory mechanism for this crucial cytokine.

In addition to cytokines and miRNAs, other factors can modulate IFN-γ expression. The amount of IFN-γ is remarkably increased in tonsillar mononuclear cells in response to LPS stimulation in patients with IgA nephropathy [22]. Umbelliprenin, a member of the 7-prenyloxycoumarins with potential therapeutic properties such as cytotoxic effects on various cancer cells, markedly promotes the release of IFN-γ in a mouse model of lung cancer [23]. CD4 + T cells from C57BL/6 mice immunized with recombinant Brucella cell-surface protein 31 (rBCSP31) exhibit an increase in IFN-γ production compared