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EDITORIAL

# Interferon-γ: Promising therapeutic target in atherosclerosis

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## Abstract

Atherosclerosis is a chronic inflammatory disorder of the vasculature and is the primary cause of cardiovascular disease (CVD). CVD is currently the world's leading cause of death and the numbers are predicted to rise further because of a global increase in risk factors such as diabetes and obesity. Current therapies such as statins have had a major impact in reducing mortality from CVD. However, there is a marked residual CVD risk in patients on statin therapy. It is therefore important to understand the molecular basis of this disease in detail and to develop alternative novel therapeutics. Interferon-γ (IFN-γ) is a pro-inflammatory cytokine that is often regarded as a master regulator of atherosclerosis development. IFN-γ is able to influence several key steps during atherosclerosis development, including pro-inflammatory gene expression, the recruitment of monocytes from the blood to the activated arterial endothelium and plaque stability. This central role of IFN-γ makes it a promising therapeutic target. The purpose of this editorial is to describe the key role IFN-γ plays during atherosclerosis development, as well as discuss potential strategies to target it therapeutically.

**Key words:** Atherosclerosis; Interferon-γ; Inflammation; Neutralization; MicroRNA



**Core tip:** Atherosclerosis is an inflammatory disorder of the vasculature and studies in mouse model systems have highlighted the beneficial effects of counteracting inflammation in limiting the progression of this disease. Due to its key role in inflammation and atherosclerosis development, interferon-γ (IFN-γ) is seen as a promising therapeutic target. In this editorial we discuss the role of IFN-γ in atherosclerosis together with potential therapeutic approaches against this cytokine and its key downstream targets.

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## INTRODUCTION

Atherosclerosis is the underlying cause of cardiovascular disease (CVD) such as myocardial infarction (MI) and

stroke. The World Health Organisation estimated that there were 17.5 million deaths from a CVD-related event in 2012, equating to approximately 1 in 3 global deaths[1]. The number of global deaths related to CVD has been predicted to increase due to rises in the incidences of obesity and diabetes and the acquisition of a westernised diet in developing countries. The disease is a major healthcare and economic burden and therefore there is a need to understand the disease in more detail and to develop new therapeutic approaches.

## ATHEROSCLEROSIS DEVELOPMENT

Atherosclerosis is a chronic, inflammatory disease characterized by the formation of foam cells in initial atherosclerotic lesions which then progress into advanced plaques. Low-density lipoprotein (LDL) can become trapped in the intima of medium and large arteries and modified to oxidized LDL (OxLDL). The presence of OxLDL triggers an inflammatory response in the neighbouring endothelial cells (ECs), causing the release of a variety of pro-inflammatory cytokines and chemokines, and expression of adhesion molecules on the cell surface (activation of ECs). These factors include macrophage chemoattractant protein-1 (MCP-1), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) as well as P- and E-selectins[2,3]. Such pro-inflammatory molecules guide circulating monocytes in the blood stream to the OxLDL accumulation in the intima of arterial walls and aid the progression of atherosclerosis development[4-6]. Once in the intima the monocytes become exposed to macrophage colony-stimulating factor, triggering their differentiation into macrophages as well as inducing scavenger receptor (SR) expression on their surface[2,7]. Macrophages are then able to uptake OxLDL by SR-mediated endocytosis, macropinocytosis or phagocytosis and develop into foam cells, causing the appearance of the initial lesions and fatty streaks in arteries, which can then progress into mature plaques[8,9].

Mature atherosclerotic plaques are made up of vascular smooth muscle cells (VSMCs) and extracellular matrix (ECM), as well as accumulated OxLDL, cholesterol and apoptotic cells, which form a lipid-rich necrotic core[10]. During plaque progression VSMCs proliferate and migrate towards the LDL accumulation and form a fibrous cap, which is tightly controlled and influenced by the nearby macrophages, ECs and T-cells[2,11]. As the fibrous cap continues to develop it forms a stable lesion by covering the large lipid-rich necrotic core, therefore the balance of ECM production and degradation can affect the stability of the lesion[2]. If the plaque ruptures it triggers a thrombotic reaction and in turn platelet aggregation, which can quickly impede or obstruct blood flow through the artery[7]. Depending on the location of the rupture it can potentially cause a MI or stroke. Therefore acute CVD events may be manageable by affecting plaque stability and preventing them from rupturing[7,12]. Amongst the cytokines involved in the development of atherosclerosis, interferon-γ (IFN-γ) is potentially a master regulator and will therefore be addressed in more detail.

## IFN-γ

IFN-γ is a key pro-inflammatory cytokine in atherosclerosis development as it is capable of inducing the expression of approximately a quarter of genes expressed in macrophages[3]. Immune cells present in the atherosclerotic lesions, including T-lymphocytes, natural killer T-cells, macrophages and other antigen presenting cells, secrete IFN-γ at pronounced levels[13,14]. Stimulation of many signaling pathways that regulate the immune and inflammatory responses can be induced by IFN-γ. The major signaling pathway that IFN-γ signals through is the Janus kinase (JAK)-Signal Transducers and Activators of Transcription (STAT) pathway[3].

### *JAK-STAT pathway*

The IFN-γ cell surface receptor complex (IFN-γR) is made up of two subunit pairs (IFN-γR1:IFN-γR) which dimerize upon binding of the cytokine[13]. Bound to each subunit are two JAKs 1 and 2, which become activated by phosphorylation of tyrosine residues in the N-terminus in a mainly JAK2-dependent process[15]. Once activated, the JAKs phosphorylate the tails of the IFN-γR which triggers the recruitment of STAT1 monomers from the cytoplasm that then interact with the receptor *via* their src-homology 2 domains[16]. The recruited STAT1 monomers are then phosphorylated by the JAKs at tyrosine 701 and dissociate from the receptor complex to form STAT1:STAT1 homodimers[3]. The dimer is then able to translocate into the nucleus and stimulate the transcription of IFN-γ target genes, such as MCP-1 and ICAM-1, by binding to γ-activated sequence (GAS) elements in their promoters[13,15]. Furthermore, extracellular signal-regulated kinase (ERK) and other kinases are capable of phosphorylating the homodimer at serine 727 for maximal activity[17].

## ROLE OF IFN-γ IN ATHEROSCLEROSIS DEVELOPMENT

Therapeutically targeting IFN-γ in order to reduce the incidence of CVD represents a promising avenue due to its pro-inflammatory functions during atherosclerotic plaque formation, including the recruitment of immune cells to the site of OxLDL accumulation, foam cell formation, and plaque development and stability. A 2-fold increase in the size of atherosclerotic lesions has been reported in the Apolipoprotein E (ApoE) deficient mouse model that was injected with recombinant IFN-γ every day, even with a 15% reduction in plasma cholesterol levels[18]. Furthermore, ApoE deficient mice which also lacked IFN-γR showed a reduction in atherosclerosis development, as well as a 60% decrease in lipid

build up in the lesions when fed on a western diet[19]. Deficiency of STAT1 in mouse model systems is also associated with reduced atherosclerosis development and foam cell formation, highlighting the key role of the JAK-STAT1 pathway in IFN-γ signaling during plaque progression[20,21].

### *Recruitment of immune cells*

IFN-γ is a key recruiter of immune cells in the development of atherosclerosis and therefore important in the growth of lesions[22]. IFN-γ has been shown to be localized in atherosclerotic lesions and mice models lacking either IFN-γ or its receptor have been reported to have a reduced cellular content in their lesions[19,23,24]. The expression of key pro-atherogenic chemokines and their receptors, such as MCP-1 that has been detected in atherosclerotic lesions by immunohistochemistry and *in situ* hybridization, can be induced by IFN-γ[25,26]. Mouse models which were deficient for either MCP-1 or its receptor showed a reduced cellular content in lesions, as well as a reduction in the size of the lesions without changes in circulating lipid or lipoprotein levels[25]. IFN-γ can also influence the recruitment of immune cells by inducing the expression of adhesion molecules, such as ICAM-1 and VCAM-1, in ECs during the early stages of atherosclerosis development[27,28].

### *Foam cell formation*

Cholesterol uptake and efflux is carefully balanced during homeostasis of this sterol in healthy cells. The formation of foam cells can be regarded as a pathological imbalance in favour of reduced cholesterol efflux and increased uptake of OxLDL[7,29]. The expression levels of a number of key genes involved in cholesterol metabolism are regulated by IFN-γ, including ApoE, ATP-binding cassette transporter A1 (ABCA1) and acetyl-CoA acetyltransferase 1 (ACAT1)[22]. *In vitro* studies that have incubated macrophage-derived foam cells with IFN-γ have shown a reduction in cholesterol efflux *via* increasing the expression of ACAT1 and attenuating the expression of ABCA1, resulting in increased accumulation of intracellular cholesteryl esters which promote the formation of foam cells[30]. Furthermore, the expression of several key SRs in foam cell development, including SR-A and SR that binds phosphatidylserine and oxidized lipids (SR-SPOX; also known as CXCL16), have been shown to be increased in human THP-1 and primary macrophages stimulated with IFN-γ, resulting in an increased uptake of OxLDL[31-33]. Therefore IFN-γ is capable of altering cholesterol homeostasis towards lower cholesterol efflux and higher retention of OxLDL in macrophages and contributes to foam cell formation.

### *Plaque progression and stability*

IFN-γ can influence a variety of processes involved in the development of the early atherosclerotic lesions into mature plaques as well as their stability. Part of plaque development involves the migration of VSMCs and the formation of the fibrous cap. IFN-γ induces the expression of integrins on the surface of VSMCs which are capable of binding to fibronectin in ECM, triggering the VSMCs to differentiate from their inactive to their proliferative phenotype allowing migration towards the lesion to form the fibrous cap[34]. The stability of atherosclerotic plaques relies on the balance of ECM production and degradation which can also be affected by IFN-γ[2,22]. Foam cell apoptosis is also promoted by IFN-γ and causes them to expel their contents into the intima, contributing to the lipid-rich necrotic core and ECM degradation[35,36]. The balance can be tipped further towards ECM degradation by IFN-γ-mediated inhibition of the expression of several collagen genes, thereby suppressing matrix synthesis by VSMCs and resulting in reduced plaque stability and increased risk of a rupture[7]. ECM degradation can also be triggered by matrix metalloproteinases (MMPs) which are found in atherosclerotic plaques and are often localized to the shoulder regions where a rupture is more likely to occur[37]. MMPs are released by macrophages and VSMCs and their expression can be induced by IFN-γ stimulation[38].

## THERAPEUTICALLY TARGETING IFN-γ

Due to the high prevalence of CVD there are a variety of therapeutics designed to reduce various aspects of atherosclerosis development, including decreasing serum cholesterol levels and altering the expression of genes that are involved in cholesterol metabolism or the inflammatory response[3,39]. Statins, the most widely used and successful cholesterol lowering therapy class of drugs, are primarily designed to inhibit the enzyme 3-hydroxy-3-methylglutaryl-CoA reductase (HMG CoA reductase)[3]. HMG CoA reductase catalyses the rate limiting step in cholesterol biosynthesis, thereby lowering the levels of circulating LDL[40]. However there is a marked residual risk of CVD in patients on statin therapy, with a significant proportion unable to attain their target LDL levels even when receiving the highest recommended dosage, stressing the importance of developing new therapeutics[2,41].

One new potential therapeutic target is IFN-γ due to its key roles in atherosclerosis development. There are currently two strategies that have been developed that either target IFN-γ directly (IFN-γ neutralization) or inhibit its signaling pathways. Statins and agonists of nuclear receptors also attenuate IFN-γ actions in part by modulating its signal transduction pathways[42-44]. In human macrophages, IFN-γ-induced phosphorylation of STAT1 on serine 727 can be blocked using adenosine[45]. Work by Lee *et al*[46] has shown that stimulation of the adenosine A3 receptor with a novel agonist, thio-CL-IB-MECA, resulted in attenuated IFN-γ-induced STAT1-dependent gene expression. Furthermore a naturally occurring phenol in plant extract, resveratrol, is capable of preventing STAT1 phosphorylation at tyrosine 701

or serine 727 as well as JAK2 activation in human macrophages *in vitro*[47]. These compounds represent promising avenues for therapies targeted at the downstream signaling events in the JAK-STAT pathway in order to reduce the pro-inflammatory effects of IFN-γ. Other therapies target IFN-γ *via* alternative signaling pathways, for example, ACS14 (a hydrogen sulphide releasing aspirin) is capable of attenuating the expression of IFN-γ-stimulated CX3 chemokine receptor 1 (CX3CR1) *via* a peroxisome proliferator-activated receptor-γ-dependent mechanism[48]. Hydrogen sulphide has previously been shown to exert anti-atherogenic effects and its use in ACS14 has been shown to reduce atherosclerosis development in ApoE mice models[48,49].

IFN-γ neutralization involves the use of a soluble IFN-γR (sIFN-γR) which acts as decoy receptor to prevent the activation of IFN-γR and in turn the phosphorylation of STAT1 in the JAK-STAT pathway, in effect "neutralizing" the IFN-γ. The approach was first developed by Koga *et al*[50], and demonstrated in ApoE mice which were fed a high fat diet for 8 wk and given two intramuscular injections of a plasmid encoding sIFN-γR at weeks 4 and 6. Compared to the control mice, those that received the sIFN-γR injections had dramatically reduced atherosclerotic lesion size as well as greater plaque stability. This increase in plaque stability was found to be due to an increase in the number of VSMCs in the fibrous cap in addition to greater collagen deposition. Additionally, there was also a decrease in the amount of lipid accumulation and number of macrophages in the necrotic core, which further improved plaque stability and reduced the risk of rupture. Furthermore, neutralizing antibodies have been used for other cytokines such as IL-1β and show great therapeutic promise[51,52], therefore similar strategies could potentially be developed to use antibodies to achieve IFN-γ neutralization.

Although targeting IFN-γ in atherosclerosis development may result in reduced lesion size and improved plaque stability, there are potential drawbacks that need to be assessed before IFN-γ targeting can be recommended therapeutically. The major concern involves the systemic inhibition of IFN-γ due to the major role it performs in the immune response[53]. Sustained universal inhibition of IFN-γ may increase an individual's risk of acquiring intracellular infections and tumour development[53]. On the other hand it may benefit those high-risk patients who are unable to achieve target LDL plasma levels using currently available therapeutics. A possible solution to overcome universal inhibition would be to try and develop a drug delivery system, for example using nanoparticles, that would allow IFN-γ-targeted therapeutics to be delivered to a specific location rather than system wide[53,54].

Another possible solution would be to target further downstream targets of the IFN-γ signaling pathways, either alone or in combination with therapies that target IFN-γ directly. IFN-γ is known to induce the expression of several microRNAs (miRNAs) in addition to having its own expression regulated by miRNAs[55]. miRNAs are short non-coding single-stranded RNAs approximately 19-25 nucleotides in length that are evolutionary conserved in eukaryotic organisms[56]. Evidence is continuously accumulating that indicates that miRNAs are capable of regulating gene expression by inhibiting translation or inducing targeted mRNA degradation[57]. miRNAs have also been found to regulate a number of key steps during atherosclerosis development, including the inflammatory response triggered by IFN-γ[58-60]. One miRNA that is thought to play a key role in atherosclerosis development is miR-155. Evidence for the role of miR-155 in the inflammatory response was found by O'Connell *et al*[61]. miR-155 was the only miRNA out of 200 tested that was considerably up-regulated in primary murine macrophages after being treated with pro-inflammatory stimulants. Additional evidence for the involvement of miR-155 in the inflammatory response comes from studies which have shown its levels to be up-regulated in macrophages in atherosclerotic lesions as well as having an association with increased pro-inflammatory cytokine expression, potentially due to its ability to repress the expression of the Suppressor of Cytokine signaling 1 (*SOCS1*) gene[62-64]. However the specific role miR-155 plays during atherosclerosis is still being debated, with a number of studies reporting miR-155 to exert pro-atherogenic effects in ApoE deficient mouse models[65,66]. Targeting miRNAs, which are either regulated by IFN-γ and are known to be involved in atherosclerosis development or regulate the expression of IFN-γ, may provide an excellent therapeutic avenue that allows specific arterial targeted treatment to reduce atherosclerosis development and improve plaque stability without potential consequences from systemic IFN-γ inhibition.

## CONCLUSION

Due to the central role of IFN-γ during atherosclerosis development and plaque stability, along with the expected rise in global rates of CVD-related events, this cytokine represents a promising therapeutic target. Targeting either IFN-γ directly or its signaling pathways in both *in vitro* and *in vivo* studies has shown that directed therapies have the potential of reducing atherosclerosis development. However the potential side effects of long term IFN-γ inhibition still needs to be assessed.

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