Introduction

Cardiovascular diseases (CVDs) are the leading cause of death worldwide (Hess et al., 2017; Lozano et al., 2012; Wang et al., 2016). Atherosclerosis, the main underlying causal factor of CVDs, is a chronic inflammatory disease driven by lipid accumulation in the arterial intima where modified low-density lipoprotein (mLDL) deposition provokes the recruitment of blood-derived immune cells and triggers inflammatory cascades (Rafieian-Kopaei et al., 2014; Tabas et al., 2007). Pro-atherogenic lipids are taken up mainly by smooth muscle cells (SMCs) and monocytes/macrophages, which subsequently secrete pro-inflammatory cytokines and chemokines (den Brok et al., 2018; Owsiany et al., 2019). In lipid-laden macrophage-derived foam cells, endoplasmic reticulum stress-associated apoptosis can be induced by high cholesterol, mLDL-triggered pattern recognition receptor (PRR) signaling, and increased inflammatory cytokines in the plaques (Seimon and Tabas, 2009). As such, atherosclerotic lesion development is characterized by the recruitment of monocytes and macrophages, accumulating pro-apoptotic foam cells and SMCs, infiltrating leukocytes, plaque-stabilizing collagen deposition, and phagocytes responding to engulfed cellular debris (Hansson, 2005; Moore and Tabas, 2011; Williams et al., 2019). As the activation hierarchy progresses to a chronic process, the spatiotemporal homeostasis between inflammation and disease-suppressing resolution pathways is disrupted. Unresolved inflammation, together with subsequently impaired ferroptosis, leads to cell necrosis, microvessel formation, fibrous cap thinning, and destabilization of the advanced atherosclerotic plaques (Kojima et al., 2017; Rafieian-Kopaei et al., 2014). Various cell types with high heterogeneity are involved in this pathogenic process. Notably important are differentially activated monocytes and macrophages, dendritic cells, neutrophils, T and B lymphocytes, and endothelial cells (Kojima et al., 2017; Ketelhuth and Hansson, 2016; Stöger et al., 2012).

The unstable advanced plaques are prone to rupture, increasing the risk of thrombosis and consequent ischemic heart diseases and stroke. Traditional pharmacological strategies for atherosclerosis prevention and treatment focus mainly on reducing plasma low-density lipoprotein (LDL) levels. Given the success of cholesterol-lowering therapy, mainly by statins for secondary prevention of CVDs, new therapeutic approaches usually develop on top of the widespread statin treatment. However, emerging evidence from both clinical and experimental studies reinforced the beneficial effect of dampening inflammation in atherothrombosis where the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study, applying anti-IL-1β antibody therapy, exhibited a significantly reduction of the risk of recurrent cardiovascular events, independent of...
lipid-levels (Bäck and Hansson, 2015; Hansson, 2005; Libby et al., 2009; Ridker et al., 2017, 2018; Zhang and Reilly, 2018).

IFNs are a group of cytokines named by their characteristics of viral interference (Isaacs et al., 1957; Pestka, 2007). IFNs can be classified into three families (type-I, -II, and -III) according to the protein structure and the receptors they signal through. Type-I IFNs are important immune modulator altering both innate and adaptive immunity (González-Navajas et al., 2012; Kopitar-Jerala, 2017; Trinchieri, 2010). Accumulating evidence from both human and murine studies supports their role in atherogenesis and linked clinical manifestations. Experimental data show that systemic or intraplaque type-I IFNs deteriorate atherogenesis by activating endothelium and immune cells, promoting foam cell formation, altering progenitor cell function, and enhancing pro-inflammatory leukocyte recruitment to arteries. Further, individuals suffering from autoimmune diseases with elevated type-I IFN signatures, such as systemic lupus erythematosus (SLE), are predisposed to accelerated atherosclerosis leading to increased risk of CVDs and cardiovascular (CV)-associated mortality. The syndromic con-currences of interferonopathy and cardiovascular manifestations may result from shared pathogenic processes (Ganguly, 2018).

In this review, we focus on the role of type-I IFNs in atherogenesis and discuss the potential opportunities to dampen inflammation for prevention and therapeutic intervention of atherosclerosis. In particular, we specify the effect of type-I IFNs on various atherogenic cell types (Table 1, provided at the end of the review), highlight their involvement in accelerated atherosclerosis in patients with IFN-associated autoimmune diseases, and discuss how anti-type-I IFN treatments could serve as multi-target therapy in disease.

**IFN families and type-I IFNs**

IFNs have been known for their antiviral activity for decades. Studies have broadened the range of their biological roles in metabolic rewiring, viral and nonviral infections, cancer, and autoimmunity (Ganguly, 2018; Ivashkiv, 2018; Schroder et al., 2004). In contrast, type-I and -III IFNs include various subtypes with some protein sequence homology (15–19% amino acid identity), and part of the antiviral activities of these two families.
can be compensated by either one (Crotta et al., 2013; Sheppard et al., 2003). While the three IFN families share some similar properties and signaling cascades (Raza et al., 2014; Waddell et al., 2010), how different cell types regulate the expression and decipher distinct IFN signals is not completely clear and has been shown to be pathogen dependent (Cheng et al., 2019; Lazear et al., 2019; Mesev et al., 2019; Singhania et al., 2019). In this review, we will focus on type-I IFNs. An overview of the three types of IFNs has been extensively reviewed elsewhere (Borden et al., 2007; González-Navajas et al., 2012; Kim et al., 2016; Lazear et al., 2019; Mesev et al., 2019; Wack et al., 2015).

In humans, type-I IFNs consist of 13 IFN-α isoforms (14 in mice), IFN-β, IFN-ε, IFN-κ, IFN-δ, and IFN-ω, which all signal through IFNAR (Kopitar-Jerala, 2017; Ng et al., 2016). As IFN-α and IFN-β are the most characterized and the most predominantly expressed type-I IFNs, we mainly discuss these two subtypes in this review. Most nucleated cells in the body are able to produce type-I IFNs in response to viral pathogens and the bacterial cell wall component LPS. This process is driven by activation of PRRs that induce cGAMP synthase (cGAS), stimulator of IFN genes (STING), retinoic acid-inducible gene 1 (RIG-1), MDA5, and IPS-1, which subsequently provoke nuclear translocation of IFN regulatory factor 3 (IRF3) and IRF7 (Fig. 1; Honda et al., 2006; Kawai and Akira, 2010; Kawai et al., 2005; Li and Chen, 2018; Zhao et al., 2015). Innate immune cells, including monocytes and plasmacytoid dendritic cells (pDCs), can secrete type-I IFNs by triggering TLR3, TLR4, and TLR7–9, which activate TRIF, MyD88, IRF1, 3, 5, 7, and 9, and myeloid-specific IRFs (Blasius and Beutler, 2010; Borden, 2019; Li et al., 2018a; Muskaridin and Niewold, 2018). In addition, TNF induces IFN-β expression by activating NFκB (Fig. 1). The most important STAT is the STAT1 showing up-regulated ISGs were also identified in mouse plaques, cytokine production and IFN-responsive genes are actually suppressed in mLDL-treated or cholesterol-laden peritoneal macrophages (Table 1). Consistently, lipid-probe based analysis suggests that intimal nonfoamy macrophages, rather than foamy cells, exhibit more pro-inflammatory characters in the murine atherosclerotic lesions (Table 1; Kim et al., 2018).

In addition to clusters of cells exhibiting pro-inflammatory NFκB signaling signatures (M1-like) or expressing genes associated with type 2 cytokine activation (M2-like), macrophages showing up-regulated ISGs were also identified in mouse plaques, suggesting a type-I IFN responsive subset (Table 1; Kim et al., 2018; Lin et al., 2019). This IFN-associated subpopulation was enriched in progressing lesions compared with the regressing ones (Lin et al., 2019), implying the involvement of local type-I IFN signaling in the complex cytokine crosstalk during atherosclerosis development. Of note, type-I IFN-stimulated macrophages can exert both pro- and anti-inflammatory phenotypes (Cheng et al., 2019). Type-I IFNs have been shown to suppress both mouse and human macrophages’ inflammatory cytokine production and inflammasome activity through anti-inflammatory cytokine induction, such as IL-10, epigenetic regulation affecting chromatin accessibility, and metabolic rewiring, for instance, oxysterol 25-hydroxycholesterol production (Table 1 and Fig. 3; Ahmed et al., 2018; Cheng et al., 2019; Guarda et al., 2011; Reboldi et al., 2014). By contrast, upon type-I IFN stimulation, human peripheral monocyte-derived macrophages (MDMs) restore their inflammatory function silenced by TNF-induced LPS tolerance through reprogramming the accessibility of NFκB–associated chromatin regions (Table 1; Park et al., 2017). These in vitro data corroborate the observation

Type-I IFN–associated cells in atherogenesis

Monocytes and macrophages

Plaque-residing monocytes and macrophages are highly heterogeneous populations with different functions during atherosclerosis development. Accumulated lipids in the arterial intima are mainly taken up by these cells. Type-I IFN treatment facilitates lipid uptake in both human and mouse monocytes/macrophages through up-regulation of scavenger receptors class A, leading to increased foam cell formation (Table 1, Fig. 2, and Fig. 3; Ahmed et al., 2018; Boshuizen et al., 2016; Li et al., 2011a; Pulliam et al., 2014). Elevated scavenger receptors class A expression can also be found in human peripheral blood mononuclear cells (PBMCs) from subjects with elevated IFN signatures, such as SLE patients and HIV-infected individuals (Table 1 and Fig. 3; Li et al., 2011a; Pulliam et al., 2014). While SLE and HIV infection are associated with accelerated atherogenesis (Kearns et al., 2017; McMahon and Skaggs, 2014), these findings hint on a causal link between type-I IFN–accelerated foam cell formation and the increased CVD risk. Consistently, mice receiving IFN-β treatment showed increased atherosclerotic macrophage area and larger plaque size (Table 1; Goossens et al., 2010).

Another role of monocytes and macrophages in atherosclerosis is their pro- and anti-inflammatory function. Single-cell transcriptomic studies deconvoluted the complex spectrum of blood-derived monocytes and macrophages in the murine plaque where distinct subpopulations were distinguished. A Ly6C+ monocyte subset expressing high Ifnα and Il12b and low anti-inflammatory Il10 mRNA was identified by single-cell RNA sequencing (scRNA-seq) of murine atherosclerotic plaques (Table 1 and Fig. 3; Winkels et al., 2018). Whereas some monocyte and macrophage subsets might serve as a source of type-I IFNs in the murine plaques, cytokine production and IFN-responsive genes are actually suppressed in mLDL-treated or cholesterol-laden peritoneal macrophages (Table 1; Jongstra-Bilen et al., 2017; Qin et al., 2017; Spann et al., 2012). Consistently, lipid-probe based analysis suggests that intimal nonfoamy macrophages, rather than foamy cells, exhibit more pro-inflammatory characters in the murine atherosclerotic lesions (Table 1; Kim et al., 2018).
that isolated myeloid dendritic cells (mDCs) and macrophages from IFN-α-treated human plaque tissue ex vivo show markedly enhanced LPS-triggered TNF secretion as well as other pro-atherogenic cytokines such as IL-12, IL-23, and MMP-9 production (Table 1, Fig. 2, and Fig. 3; Niessner et al., 2007).

Neutrophils
Neutrophils are infiltrating leukocytes present in both mouse and human plaques (van Dijk et al., 2016; van Leeuwen et al., 2008; Zernecke et al., 2008). During human atherosclerosis development, their number significantly increases in the vulnerable lesions (van Dijk et al., 2016). Particularly, neutrophil distribution positively correlates with lipid core size, macrophage numbers, and micro-vessels and negatively with collagen content and SMC numbers in human plaques (Ionita et al., 2010; Maracle et al., 2018). In murine atherosclerosis models, intraplaque neutrophils distribute mainly in the shoulder regions (Rotzius et al., 2010) and accumulate in the early high-fat diet period; then the number gradually reduces over time (Drechsler et al., 2010; Rotzius et al., 2010; van Leeuwen et al., 2008). In advanced murine atherosclerotic lesions, neutrophils correlate with necrosis, plaque size, and vulnerability, and inversely correlate with SMCs and fibrous cap thickness, while no correlation was found to the collagen content, macrophage, and EC activation, which is in contrast to human data (Maracle et al., 2018; Silvestre-Roig et al., 2019).

Neutrophil recruitment to the arterial wall has been shown to be driven by CCL5 in mice (Drechsler et al., 2010), which is induced in type-I IFN–stimulated macrophages and ECs (Table 1, Fig. 2, and Fig. 3; Goossens et al., 2010; Nakano et al., 2012). While the function of neutrophils in atherosclerosis is not completely clear (Drechsler et al., 2010), over recent years, emerging evidence has revealed the contributory role of neutrophils in atherogenesis and plaque instability (Teixeira and Tam, 2018). As a phagocytic granulocyte, neutrophils are capable of discharging granule proteins, proteases, and reactive oxygen species (ROS) and producing neutrophil extracellular traps (NETs; Döring et al., 2017). NETs consist of web-like
chromatin with cytosolic and granule proteins that can trap pathogenic microbes and have been shown to be involved in many (chronic) inflammatory diseases (Papayannopoulos, 2018), including rheumatoid arthritis (RA), vasculitis, and SLE. The presence of NET structures has been shown in atherosclerotic plaques and arterial thrombi in humans and mice, especially in cholesterol-rich or erosion-prone areas (Fig. 2; Franck et al., 2018; Quillard et al., 2015; Warnatsch et al., 2015). Consistently, cholesterol crystals can induce NET formation (NETosis) in vitro (Warnatsch et al., 2015). Studies proposing the mechanistic relation of NETs and atherosclerosis show the ability to induce endothelial cytotoxicity, cause high-density lipoprotein (HDL) oxidative modifications, promote macrophage accumulation and cytokine release, activate T helper (Th) 17 cells, and trigger type-I IFN production from pDCs (Table 1, Fig. 2, and Fig. 3; Döring et al., 2012; Knight et al., 2014; Smith et al., 2014; Villanueva et al., 2011; Warnatsch et al., 2015). Of note, several studies suggest an imbalance between NETosis and NET degradation in autoimmune diseases, which may in part account for the increased CVD risk in these patients (Carmona-Rivera et al., 2015; Kessenbrock et al., 2009; Khandpur et al., 2013). While a recent study shows inhibiting NETosis via Pad4 deficiency in Ldlr-/- mice does not impede atherogenesis but prevents EC injury and thrombus formation (Franck et al., 2018), applying myeloid-specific Pad4-deficient
model on Apoe−/− mice exerts reduced atherosclerosis burden (Liu et al., 2018). Similarly, inhibiting NETosis by pan-protein-arginine deiminase (PAD)–inhibitor chloramidine treatment before starting the high-fat diet feeding decreased atherosclerosis and mitigated Ifnar expression in Apoe−/− mice, suggesting an initiating role of NETs in atherogenesis. Furthermore, the atheroprotective effects of chloramidine could not be reproduced in Apoe−/− Ifnar1−/− mice, indicating a causal role of type-I IFN signaling in NET-driven atherogenesis (Knight et al., 2014).

Low-density granulocytes (LDGs), an immature, pro-inflammatory subtype of neutrophils identified in SLE individuals, display increased expression of IFNA and are associated with IFN signature enrichment in these patients (Denny et al., 2010; Kegerreis et al., 2019). Further, LDGs are capable of inducing an IFN signature in ECs, thus disrupting their differentiation from the progenitors (Table 1 and Fig. 2; Denny et al., 2010). In addition to affecting endothelial maturation directly, LDGs are also capable of inducing mitochondrial ROS and NETs upon stimulation (Table 1; Kaplan, 2011; Lood et al., 2016; Villanueva et al., 2011), leading to increased plaque vulnerability. Several studies have shown that LDG NETs are the main inducer of type-I IFN secretion in pDCs via TLR9 signaling in SLE patients (Table 1; Garcia-Romo et al., 2011; Lande et al., 2011; Villanueva et al., 2011). Moreover, after adjustment for traditional risk factors, noncalcified plaque burden in SLE patients is directly associated with LDG levels (Carlucci et al., 2018). In addition to this particular neutrophil subset LDG, atherosclerotic mouse models applying myeloid-specific deletion of Ifnar1, which mainly affects neutrophils and monocytes/macrophages, revealed smaller lesions, reduced neutrophil and macrophage recruitment, and less necrosis (Fig. 3; Goossens et al., 2010). Of note, while the plasma CCL5 was increased in mice treated with IFN-β, these animals did not show a difference in neutrophil area in the plaque when compared with the untreated controls (Table 1 and Fig. 3; Goossens et al., 2010). These data reinforce the concept of positive feedback between NET formation and type-I IFNs in neutrophils and other cell types during atherosclerosis progression.

**Eosinophils**

Though the direct role of eosinophils in atherogenesis remains unclear, clinical studies reveal that absolute eosinophil count, intraplaque eosinophil markers, and eosinophil-specific chemokines are associated with increased risk of CVDs (Haley et al., 2000; Kitano et al., 2017; Lee et al., 2001; Niccoli et al., 2010; Tanaka et al., 2012). While EG2+ eosinophils are considered to be unclear, clinical studies reveal that absolute eosinophil count, cell types during atherosclerosis progression.

**pDCs and mDCs**

pDCs are known to have the ability to rapidly produce massive amounts of type-I IFNs and are present in both murine and human atherosclerotic lesions as well as intact aorta (Chistiakov et al., 2014; Cole et al., 2018; Döring et al., 2012; Yun et al., 2016). Single-cell data revealed an increased amount of pDCs in aortas from Apoe−/− mice fed a high-fat diet compared with mice fed normal chow (Cole et al., 2018). In human plaques, CD123+ pDCs localize closely to T cells and mDCs in the unstable shoulder region (Chistiakov et al., 2014; Niessner et al., 2006, 2007) and accumulate during atherogenesis (Fig. 2; Li et al., 2017).

The role of pDCs in atherosclerosis is still a subject of discussion. Both whole human plaque tissue and isolated pDCs respond to TLR9 agonists with increased IFN-α transcription and secretion, amplifying pro-inflammatory responses by mDCs and cytolytic T cells (Table 1 and Fig. 2; Niessner et al., 2006, 2007; Yun et al., 2016). Also, sorted mouse pDCs treated with oxLDL show an enhanced capacity to phagocytose and to stimulate antigen-specific T cell responses without altering IFN-α/β secretion (Döring et al., 2012). However, pDC-selective deletion in different atherosclerosis murine models showed conflicting results. Some studies found that antibody-mediated cell ablation or inducible pDC depletion in Ldr−/− mouse deteriorated atherogenesis, suggesting an atheroprotective role of pDCs. This observation was specifically linked to the pDCs’ ability of tuning T cell activation and proliferation in murine models (Table 1; Daissormont et al., 2011; Yun et al., 2016). On the contrary, studies applying similar techniques showed a more favorable phenotype in pDC-depleted Apoe−/− mice with reduced lesion size, more stable plaques, and a reduction in IFN-α serum levels, supporting the pro-atherogenic role for pDCs in murine atherosclerosis (Table 1; Döring et al., 2012; Macritchie et al., 2012).

Of note, without CpG stimulation, IFN-α protein levels in the intact aorta or atherosclerotic plaques in mice are low or undetectable (Macritchie et al., 2012; Yun et al., 2016). This implies that without interferonergic stimuli, the effect of IFN-α-mediated atherogenesis might be minor or localized to restricted regions in these murine model settings. On the other side, NETs have been demonstrated to be present in human plaques and may serve as stimuli triggering pDC type-I IFN production via TLR signaling, which subsequently primes neutrophils for NET formation (Fig. 2). This positive feedback between NETs and type-I IFNs produced by pDCs might be the causal factor exacerbating atherosclerosis in autoimmune diseases with elevated IFN signatures. Moreover, mice stimulated with type A CpGs showed an advanced atherosclerotic plaque phenotype in a pDC-dependent manner (Döring et al., 2012), implying a central role of pDCs in autoimmune-associated atherogenesis. Taken together, the responsiveness of pDCs to TLR7/TLR9 activation and type-I IFN induction corroborates the link between accelerated atherosclerosis and chronic inflammation, and thus serves as additional pathogenic mechanism for increased cardiovascular events in interferonopathies.

**ECs**

EC dysfunction is an important player in the initiation of atherosclerosis, where the permeation and accumulation of lipoprotein particles take place at the arterial lesion-prone areas (Davignon et al., 2018).
and Ganz, 2004; Gimbrone and García-Cardena, 2016). During plaque progression, ECs activated by oxLDL produce chemokines that attract circulating monocytes into the arterial intima. Inflammatory factors expressed by recruited immune cells further increase plaque instability by modulating EC phenotype and extracellular matrix (Gimbrone and García-Cardena, 2016).

Type-I IFN–treated HUVECs produce more adhesion molecules and chemokines, such as VCAM1 and MCP1 (Fig. 2), possibly through the suppression of NO3 (encoding, endothelial nitric oxide synthase) expression and insulin-mediated NO production (Table 1, Fig. 2, and Fig. 3; Buie et al., 2017; Jia et al., 2018). Though the effect on ICAM1 is not clear, studies showed that more human neutrophils attach to the type-I IFN–treated HUVECs (Table 1 and Fig. 2; Buie et al., 2017; Giorelli et al., 2002; Jia et al., 2018; Kobayashi et al., 2008; Shen et al., 1997). However, some studies revealed conflicting results. In vitro IFNα2b exposure of human aortic ECs (HAEC) was shown not to alter the proliferation, tubule formation, or NO production while IFN-signature genes were induced (Table 1; Reynolds et al., 2014). Also, both IFN-α and IFN-β, but not IFN-γ, show a protective effect on growth factor deprivation–induced apoptosis of HAECs in vitro (Table 1; Sano et al., 2012).

In murine atherosclerosis models, IFN-β enhances leukocyte arrest via EC-macrophage CCL5–CCR5 interaction, thus promoting plaque destabilization (Fig. 2; Goossens et al., 2010). The reciprocal interaction between type-I IFNs and other inflammatory mediators exacerbates this process. TNF triggers IFN-β production via TNFR2-IRF1–dependent signaling in ECs (Fig. 1). The secreted IFN-β serves as an autocrine signal triggering HUVECs to generate chemotactic factors, such as VCAM1, that promote monocyte recruitment (Table 1, Fig. 1, and Fig. 2; Venkatesh et al., 2013). IFN-α exposure was shown to disrupt the endothelium, and impair endothelial vasorelaxation and endothelial progenitor cell (EPC) function, resulting in accelerated thrombosis and platelet activation in lupus-prone and non–lupus-prone mice (Table 1 and Fig. 3; Diao et al., 2016; Thacker et al., 2012). In line with this, lupus-prone mice showed impaired function and increased type-I IFN signatures in the EPC compartments already without additional IFN-α application (Thacker et al., 2010, 2012). Co-roaborating the in vitro and animal data, type-I IFN signatures or high serum IFN-α are associated with impaired EPC and EC function, reduced flow-mediated dilation, and elevated endothelial activation markers, such as sVCAM1 and endothelial microparticles, in individuals with autoimmune diseases including SLE, antiphospholipid syndrome (APS), and RA (Table 1, Fig. 2, and Fig. 3; Denny et al., 2007; Somers et al., 2012; Genn et al., 2017; Lee et al., 2007; Rodríguez-Carrio et al., 2014; Tdén et al., 2017). Many of the characteristics of EPC dysfunction in these patients could be overcome by neutralization of type-I IFNs or their receptor ex vivo (Table 1 and Fig. 3; Denny et al., 2007; Genn et al., 2017). Comparable results were found in animal models. Iiunr1 deficiency in lupus-prone mice exhibit an improved EPC function and endothelial vasorelaxation whereas Apeoi–/–Iiunr1–/– mice fed with high-fat diet showed a more preferable atherosclerosis phenotype (Table 1 and Fig. 3; Thacker et al., 2012).

T lymphocytes

T lymphocytes are adaptive immune cells present in both human and murine atherosclerotic plaques (Witztum and Lichtman, 2014). During plaque development, accumulated innate immune cells activate their pro-inflammatory response, exerting deleterious effects. The majority of plaque-residing T cells are CD4+, whereas the remaining are mainly CD8+ (Jonasson et al., 1986). Among the CD4+ T cell subsets, the role of Th1 and Th2 cells in atherosclerosis are still debated, while Th1 and regulatory T (T reg) cells are considered to be pro- and anti-atherogenic, respectively. Details of different subsets and functions are reviewed elsewhere (Ketelhuth and Hansson, 2016; Lahoute et al., 2011). Of note, T cell subset differentiation is not irreversible, as some T cells can acquire different properties under certain (chronic) inflammatory conditions (Geginat et al., 2014; Sakaguchi et al., 2013).

Many animal studies have verified the T reg to Th1 cell plasticity driven by atherosclerotic and hypercholesterolemic environments, in which T reg cells lost the immunosuppressive characteristics and acquired a pro-inflammatory phenotype (Tabas and Lichtman, 2017). Interestingly, the instability of T reg cells can also be found in many autoimmune diseases, implying a possible shared pathophysiology driving both atherosclerosis and autoimmunity (Dominguez-Villar and Hafler, 2018). Plasma from SLE patients with type-I IFN activity impaired T reg cell activation and function in vitro (Golding et al., 2010). Moreover, limited T reg cell generation and increased IFN-γ+ T cell proliferation were observed in activated SLE PBMCs (Table 1; Golding et al., 2010). Consistent with this observation, in a murine colitis model, Trex1 deficiency induced type-I IFN expression and attenuated T reg cell activation and proliferation while promoting Foxp3low/neg T cell expansion and pro-inflammatory function (Table 1; Srivastava et al., 2014a). IFN-α/β directly inhibits both human and murine T reg cell proliferation in vitro, while the murine Ifnar1-deficient counterpart is unaffected. This type-I IFN signaling–mediated inhibition of T reg cells can be observed in murine lymphocytic choriomeningitis virus infection and tumor models (Gangap拉la et al., 2018; Srivastava et al., 2014b). However, studies also showed IFNAR signaling to be important for T reg cells exerting their immunomodulation function as IFNAR deficient T reg cells failed to dampen the effector T cell activation in a mouse model of inflammation (Metdji et al., 2015). These studies suggest that type-I IFNs can alter the pro-versus anti-inflammatory balance of T cell subsets.

Besides the effect of phenotype switching on T reg cells, IFN-α may directly modulate human CD4+ T cells’ cytotoxic function by increasing the expression of TNF-related apoptosis-inducing ligand (TRAIL) on the T cell surface (Table 1 and Fig. 2; Kayagaki et al., 1999; Niessner et al., 2006). Further, experiments applying human plaque-derived or peripheral blood-isolated CD4+ T cells to coronary SMC monolayers showed TRAIL-dependent apoptosis of SMCs, which could be amplified by IFN-α pretreatment of CD4+ T cells (Fig. 2 and Fig. 3). Of note, IFN-α alone did not induce SMC apoptosis in this study (Niessner et al., 2006).

As mentioned in a previous section, IFN-α–producing pDCs colocalize with T cells in human atherosclerotic plaques (Fig. 2; Niessner et al., 2006). The pro-atherogenic effect of type-I IFNs might be through paracrine signaling and exacerbate in autoimmune patients with elevated systemic IFN levels.
**B lymphocytes**

B cell subsets affect the atherosclerotic process through both cellular and humoral immunity functions. While whole blood gene expression profiles imply an association between B cells and coronary heart diseases (Huan et al., 2013), the functional characteristics of B cell subtypes, the antibody targets, and different immunoglobulin classes in atherosclerosis are still elusive (Tsiantoulas et al., 2014). Two major subfamilies of B cells, B1 and B2 cells, process distinct machineries in plaque formation (Domeier et al., 2018; Tsiantoulas et al., 2015). In general, B1 cells are considered to be atheroprotective, as they can secrete natural IgM against oxidation-specific epitopes, thus limiting EC dysfunction and immune cell activation (Fig. 2; Tsiantoulas et al., 2014). B2 subsets, the majority of B cells in the body, show proatherogenic properties in some animal models, though the underlying mechanism remains under debate (Srikakulapu and McNamara, 2017; Tsiantoulas et al., 2015).

Atherosclerotic plaques contain apoptotic and necrotic cell debris, endogenous nucleic acids, and oxidized lipid species, which all can serve as a source of modified self-antigen and TLR ligands (Miller et al., 2011) triggering autoantibody production and adaptive immune responses. Murine atherosclerosis studies have also revealed an increase of anti-double-stranded DNA (dsDNA) antibody titers in high-fat diet–fed ApoE−/− mice (Table 1 and Fig. 2; Döring et al., 2012), again suggesting a shared pathophysiological continuum between autoimmunity and atherosclerosis. Detailed information on the role of B cells and immunoglobulins in atherogenesis is reviewed elsewhere (Sage et al., 2019; Tsiantoulas et al., 2015).

Besides the production of various antibodies, stimulated and early transitional stage B cells can secret type-I IFNs, which are important for B cell development and which might contribute to the pathogenesis of some autoimmune diseases (Table 1; Bénard et al., 2018; Green et al., 2009; Hamilton et al., 2017; Ward et al., 2016). This type-I IFN–IFNAR autocrine loop promotes autoreactive B cell development in the germinal center and strengthens follicular B cells’ ability to produce antibodies in a T cell–independent manner (Table 1; Domeier et al., 2018; Swanson et al., 2010). On the other hand, self-reactive anti-dsDNA IgE is associated with SLE disease activity and potentiates IFN-α production in human pDCs in vitro through promoting phagocytosis of DNA and TLR9 signaling (Table 1 and Fig. 2; Henault et al., 2016). As both IgE and pDCs are present in human atherosclerotic plaques (Wang et al., 2011), the aforementioned mechanisms might exacerbate atherogenesis and plaque instability, especially in individuals with systemically elevated type-I IFN levels or signaling signatures. Since B cells are capable of producing and responding to type-I IFNs, the complex nature of B cells in atherosclerosis and how type-I IFNs shape this process appear to be valuable subjects for further investigation.

**Clinical implications and cardiovascular manifestations**

While type-I IFN administration in murine models exacerbates atherosclerosis, the effects of type-I IFNs in humans, both direct and indirect to the plaque-residing cells, could result in clinical manifestation, especially in individuals with elevated IFN signatures. Therapeutic IFN treatment has been applied in cancer and chronic viral infection patients. In addition to the antivirus and antitumor effects, several clinical studies observed treatment-associated hypocholesterolemia, together with a decreased level of HDL, in these patients (Robertson and Ghazal, 2016). Further, the use of pegylated IFN and ribavirin as an anti-hepatitis C virus therapy is associated with risk factors of atherosclerosis such as insulin resistance (Brandman et al., 2012).

Compared with atheroma-free carotid wall samples, human atherosclerotic plaques show higher IFNA expression, and the level is even higher in inflamed and thrombosed lesions (Table 1 and Fig. 3; Niessner et al., 2006). Similarly, elevated IFN levels and/or its signatures are also observed in some autoimmune diseases, such as RA and SLE. The association between antiviral IFN-α therapy and the presence of autoantibodies indicated the casual role of type-I IFNs in systemic autoimmune pathogenesis (Fabris et al., 1992; Gota and Calabrese, 2003; Movrogiannis et al., 2001; Mayet et al., 1989). Many clinical and epidemiological studies showed the concordance of accelerated atherosclerosis or increased risk of cardiovascular events in these interferonopathy-associated autoimmune diseases (Parker and Bruce, 2013; Pereira et al., 2009). A significant increase in aortic wall inflammation with mild to moderate disease activity is observed in SLE patients (Carucci et al., 2018). In addition, type-I IFN–regulated proteins, such as IFITM1 and RFKRA, are increased in platelets isolated from SLE patients, and are associated with previous CV events including myocardial infarction and venous and arterial thrombosis (Table 1; Lood et al., 2010). Similarly, increased platelet activation was also observed in lupus-prone or normal mice receiving Ifna-expressing virus and reduced in Ifnar−/− mice (Table 1 and Fig. 3; Thacker et al., 2012). Gene expression differential analysis of PBMC or blood leukocytes from SLE patients also revealed a strong enrichment of IFN signaling signatures (Baechler et al., 2003; Bennett et al., 2003; Carucci et al., 2018).

Of note, type-I IFNs play distinct roles in different autoimmune diseases. The response to type-I IFNs and the signature gene expression are usually lower in mononuclear cells from untreated multiple sclerosis (MS) patients compared with healthy controls (Feng et al., 2002). Opposite SLE and RA, many symptoms of MS benefit from recombinant IFN-β as a disease-modifying treatment (Roder and Feng, 2013). MS patients receiving IFN-β usually show a decrease in total cholesterol and an increase in triglyceride plasma level (Fig. 3; Morra et al., 2004; Robertson and Ghazal, 2016; Sena et al., 2000; Uher et al., 2017), similar to the effect of type-I IFN therapies in individuals with cancers or viral infections. In line with this, IFN-β treatment is associated with increased CV risk factors including lower HDL level and higher diastolic blood pressure (Sternberg et al., 2014). However, the increased prevalence of cardiovascular events such as myocardial infarction in MS patients cannot be fully explained by traditional risk factors, and its correlation with disease-modifying treatments was not clear (Marrie et al., 2019). Notably, applying type-I IFNs in murine atherosclerosis models showed increased or unchanged plasma cholesterol or triglyceride levels (Goossens et al., 2010; Levy et al., 2003).

Similarly, traditional risk factors for cardiovascular events including age, gender, smoking, hypertension, and dyslipidemia have been correlated with but cannot fully explain the exacerbated atherogenesis in SLE and RA patients (Bruce et al., 2003; Castañeda et al., 2015; Esdaille et al., 2001). While the serum type-I IFN activity is independently associated with biomarkers of atherosclerosis development in lupus patients (Somers et al., 2012), some studies...
reported that preventive therapies for traditional risk factors, such as hypercholesterolemia and hypertension, failed to significantly reduce the incidence of CVDs in lupus patients (Petri et al., 2011; Schanberg et al., 2012; Tselios et al., 2016; Wigren et al., 2015). Notably, increased subclinical atherosclerosis prevalence is observed in individuals with primary (i.e., antineutrophil cytoplasmic antibody–associated vasculitis) or secondary (i.e., associated with SLE or RA) vasculitis (Argyropoulou et al., 2018; Chironi et al., 2007; Guillaume and Dörner, 2007). Whether vasculitis and atherosclerosis share common pathogenic mechanisms and whether IFNs play a causal role in this disease continuum warrants further investigation.

Although the role for type-I IFN in the pathogenesis and instability of atherosclerosis is supported by studies in both human and mouse models (Table 1; Goossens et al., 2010; Levy et al., 2003; Niessner et al., 2006), there is no statistically significant association between the risk of coronary artery events and IFN-α production–correlated single nucleotide polymorphisms (Nelson et al., 2015). Alternatively, mutations in some components of the IFN regulation and signaling, such as IRF8 and JAK2, are associated with the increased risk of cardiovascular events in different populations (Jaiswal et al., 2017; Leonard et al., 2013).

Anti-IFN/IFNAR signaling therapies

Immunomodulating therapies that dampen IFN signatures have been applied in many autoimmune diseases. Whereas the relation between immunosuppressive steroids and atherosclerosis remains controversial (Wu et al., 2016), hydroxychloroquine (HCQ), an alkalinizing lysosomatropic drug for SLE treatment, has been tested to be atheroprotective and is effective in dampening disease activity and mortality, reducing required steroids dosages, and preventing organ damage accrual and thromboembolic events (Fig. 3; Fasano et al., 2017; Ponticelli and Moroni, 2017; Yang et al., 2019). Mechanistically, the atheroprotective effects of HCQ may be due to interfering with IFN-α and TNF production by TLR7/TLR9–activated pDCs in SLE individuals (Table 1 and Fig. 3; Sacre et al., 2012). In addition to immune cell modulation and the prevention of EC dysfunction, HCQ offers beneficial effects on other traditional CV risk factors, such as dyslipidemia and diabetes (Floris et al., 2018), which are also shown to be associated with systemic type-I IFNs. Similarly, chloroquine, a closely related anti-malarial compound that may also be used in SLE treatment, is shown to be able to inhibit NETosis and the subsequent HDL oxidation in human neutrophils and LDGs from patients in vitro (Smith et al., 2014).

Inhibitors directly targeting downstream pathways of IFN signaling, such as JAK–STAT pathways and IRFs, have been proposed as a potential treatment strategy in CVD (Schwartz et al., 2017; Szlag et al., 2016). RA patients receiving tofacitinib, one of the first-generation JAK inhibitors, showed an increase in plasma total cholesterol, LDL, and HDL without changes in atherogenic index (Kang et al., 2018). In agreement with this observation, in vitro experiments and in vivo animal models revealed that tofacitinib up-regulated ABCA1 expression, promoted anti-inflammatory macrophage polarization, improved EC function, and attenuated atherosclerosis (Table 1 and Fig. 3; De Vries et al., 2019; Furumoto et al., 2017; Pérez-Baos et al., 2017; Wang et al., 2017). However, recently the Oral Surveillance study revealed a statistically significant and clinically relevant increase in pulmonary embolism and an increased mortality in patients older than 50 yr with an increased CV risk when treated with a tofacitinib dose of 10 mg twice daily (Fig. 3; FDA, 2019; Pfizer, 2019). In this respect, more selective JAKI inhibitors may demonstrate a more favorable safety profile. Another anti-IFN approach is to inhibit type-I IFNs and IFNAR signaling directly. Blocking IFNAR on mice has been shown to be cardioprotective in MI (King et al., 2017) and could stimulate mouse arteriogenesis without affecting atherosclerosis burden after 4-wk treatment (Table 1 and Fig. 3; Teunissen et al., 2015). The potential beneficial effects of inhibiting type-I IFNs and their signaling have been applied to clinical trials. Anifrolumab, a fully human IgG1 monoclonal antibody blocking IFNAR signaling, decreased disease activity, reduced NETosis, dampened chemokine serum level elevation, and improved cholesterol efflux capacity in SLE patients (Fig. 3; Casey et al., 2018; Furie et al., 2017; White et al., 2018). Further, sifalimumab, an anti–IFN-α monoclonal antibody, also yielded promising results in SLE patients (Khamashta et al., 2016), though the effect on atherosclerosis and cardiovascular outcome has not been investigated yet.

Given the positive outcomes of these anti-IFN and/or immunomodulating medicines dampening IFN signaling, it is of great interest to further investigate their effects on atherogenesis in autoimmune diseases, from premature, subclinical atherosclerosis to severe CV comorbidities.

Concluding remarks

Dyslipidemia and inflammation are central in the development of atherosclerosis. In addition to the great breakthrough of lipid-lowering therapy, there has been progress in understanding the role of inflammation that leads to plaque development and clinical complications. The causal role of chronic inflammation accelerating atherosclerosis in several systemic autoimmune diseases is well established. Studies applying elegant single-cell profiling approaches and functional studies have advanced our understanding on how type-I IFNs and the IFNAR signaling are regulated in different cell types involved in the pathogenesis, and helped to guide therapy development. As a pleiotropic cytokine modulating pro- and anti-inflammatory phenotypes in various cell types, the putative role of type-I IFNs in atherogenesis and autoimmunity has been verified, though still much remains to be investigated about the complex crosstalk of IFN signaling in the immune system and metabolism (Fig. 3). Future studies should continue to investigate the delicate homeostasis between IFNs’ antitumor and anti-pathogen effects and the pro-inflammatory and systemic lipid-altering effects.

We envision that type-I IFNs and their signaling pathways will be shared therapeutic targets in both atherosclerosis and rheumatic diseases. However, because type-I IFNs mediate important immune responses against infections and cancers, there is reason for caution for applying long-term anti-IFN therapy for CVD prevention. Advanced understanding of the genetic and epigenetic regulation and the biological underpinnings of IFN signaling in cardiovascular and autoimmune diseases might enable us to intervene in these diseases via fine-tuned modulation of type-I IFN signaling using targeted pharmacological technologies, which might serve as a promising and safe treatment strategy for atherosclerosis in patients with autoimmune diseases, and might be generalizable to the nonautoimmune population as well.
| Cell/tissue | Type-I IFN production/induction | Responses to type-I IFNs | Human sample | Murine model | Reference |
|-------------|---------------------------------|--------------------------|--------------|-------------|-----------|
| Aortic tissue | Increased SiglecH and Ifna expression in the aortic tissue and elevated IFN-α in the serum in mice with HFD | Aorta, HFD vs. ND for 12 wk | Apoe<sup>−/−</sup> (in vivo) aorta, HFD vs. | Döring et al., 2012 |
| B cell | Increased type-I IFN expression/secretion in B cell stimulated by Mtb (in vivo and in vitro) | Reduced type-I IFN production in Ifnar1<sup>−/−</sup> B cells | Ifnar1<sup>−/−</sup>, Sting<sup>−/−</sup>, WT pulmonary tissue, pleural fluid, and spleen | Bénard et al., 2018 |
| B cell | Ifnar1<sup>−/−</sup> mice showed reduced auto-Ab production | | Ifnar1<sup>−/−</sup>, WT BM chimera | Domeier et al., 2018 |
| B cell | Increased anti-dsDNA Ab serum levels in symptomatic vs. asymptomatic carotid artery stenosis patients | | Carotid artery stenosis patients | Döring et al., 2012 |
| B cell | Elevated anti-dsDNA Ab in IFN-α/CpG-treated/HFD-fed mice and dampened by pDC depletion by PDCA1 Ab in Apoe<sup>−/−</sup> mice or in Cramp<sup>−/−</sup> mice (Ldr<sup>−/−</sup>) | | Apoe<sup>−/−</sup> (in vivo), HFD vs. ND, Ldr<sup>−/−</sup> Cramp<sup>−/−</sup> vs. Cramp<sup>−/−</sup>, ± IFN-α/CpG treatment | Döring et al., 2012 |
| B cell | Reduced anti-dsDNA Ab in tofacitinib treated mice | | MRL/lpr mice ± tofacitinib | Furumoto et al., 2017 |
| B cell | Ifnb1<sup>−/−</sup> B cells showed suboptimal responses toward TLR7 stimulation | Reduced cytokine production in Ifnar1<sup>−/−</sup> B cell upon TLR stimulation, exogenous type-I IFNs strengthen the responses | Ifnar1<sup>−/−</sup>, Ifnb1<sup>−/−</sup>, WT spleen | Green et al., 2009 |
| B cell | Transitional B cell subsets express type-I IFNs | Endogenous IFN-β promotes survival and development of transitional (autoreactive) B cells | Ifnb1<sup>−/−</sup>, Rag2<sup>−/−</sup>, WT | Hamilton et al., 2017 |
| B cell | Autoantibodies against neutrophil antimicrobial peptides is associated with serum IFN-α in SLE patients | | SLE patients | Lande et al., 2011 |
| B cell | Reduced Ab production as a response to poly(I:C) in Ifnar1<sup>−/−</sup> B cells | | Ifnar1<sup>−/−</sup>, WT | Swanson et al., 2010 |
| B cell | B cells from SLE patients produce IFN-α | | | Ward et al., 2016 |
| EC | SLE serum induced more ISGs compared with HC, IFN-α suppressed NO production and increases CCL2 and VCAM-1 expression and neutrophil migration | HUVEC, SLE patients vs. HC sera | | Buie et al., 2017 |
| EC | Interrupted CD31 staining (EC damage) in vasculature of mice expressing IFN-α | In vivo Ifno5 expressing model (plasmid transduced, 3 wk) vs. WT | | Diao et al., 2016 |
| EC | IFN-β1a induces membrane-bound ICAM protein expression | HUVEC | | Giorelli et al., 2002 |
| EC | IFN-β but not IFN-α inhibits HUVEC proliferation and survival, both type-I IFNs reduce HUVEC NO production | HUVEC | | Jia et al., 2018 |
| Cell/tissue Type-I IFN production/induction | Responses to type-I IFNs | Human sample | Murine model | Reference |
|-------------------------------------------|--------------------------|--------------|--------------|-----------|
| EC                                        | ICAM-1, VCAM-1 and eosinophil adhesion was significantly augmented by IFN-β in the presence of TNF-α but not in its absence | HUVEC | | Kobayashi et al., 2008 |
| EC                                        | Type-I IFNs induce CCL5, CX3CL1 production via JAK signaling | HUVEC, HPAEC, HAEC, HLMVEC | | Nakano et al., 2012 |
| EC                                        | IFNα2b does not affect HAEC proliferation and NO production | HAEC | | Reynolds et al., 2014 |
| EC                                        | Type-I IFNs inhibit the growth factor deprivation- or oxidative cytotoxicity-induced cell death | HAEC | | Sano et al., 2012 |
| EC                                        | Type-I IFNs alone did not affect the expression of E-selectin, P-selectin, VCAM-1, and ICAM-1 | HUVEC | | Shen et al., 1997 |
| EC/TNFRI, TNFR2 signaling TNFR1, TNFR2 signaling induce IRF1 expression and IFN-β production in MHEC | IFN-β increased VCAM-1, CXCR3 chemokines (Cxc9, Cxcl10) expression in MHEC supporting monocyte recruitment | Ifnar1−/−, WT MHEC with/without IFN-β treatment | | Venkatesh et al., 2013 |
| EC/EPC SLE serum/IFN-α prevents monolayer formation and maturation from EPC and induces apoptosis, SLE EPC restores a normal phenotype with IFNA(R) blockade | SLE patient serum, EPC | | Denny et al., 2007 |
| EC/EPC Improved endothelium-dependent vasorelaxation, EPC differentiation in tofacitinib treated mice | MRL/lpr mice ± tofacitinib, aorta | | Furumoto et al., 2017 |
| EC/EPC IFN-α suppresses EPC differentiation | Murine bone marrow and spleen EPC | | Thacker et al., 2010 |
| EC/EPC Loss of type-I IFN signaling improves EPC number and EC function in lupus-prone mice while additional IFN-α worsens EC function and EPC differentiation | IFNαβR−/− or IFNαβR+/− and lupus-prone vs. normal mice, ± ifna-expressing virus, ApoE−/− IfNαβR−/− mice WD for 10 wk | | Thacker et al., 2012 |
| Eosinophil oxLDL up-regulates IFN-α and IFN-β (CD36 dependent), reduce IL-4/IL13 expression | BM-derived eosinophils (in vitro), ± anti-CD36 Mab, ± Cd36 siRNA | | Qin et al., 2017 |
| EPC Increased IFN signature of PBMC and reduced differentiation capacity of EPC in APS patients or EPC treated with APS sera, which could be rescued by anti-IFNAR Ab | APS/SLE patients vs. HC PBMC | | Grenn et al., 2017 |
| mDC Pro-IL-1β synthesis and IL-1β maturation are unaffected by type-I IFNs | WT BMDC ± type-I IFNs | | Guarda et al., 2011 |
| Cell/tissue | Type-I IFN production/induction | Responses to type-I IFNs | Human sample | Murine model | Reference |
|------------|---------------------------------|--------------------------|--------------|-------------|-----------|
| mDC        | IFN-α increases TNF expression upon LPS stimulation | MoDC (in vitro) | Niessner et al., 2007 |
| mDC        | Combining IFN-α with LPS amplifies TNF expression while IFN-α alone does not affect TNF expression (JAK/STAT, NF-κB dependent) but increases TLR4 expression | MoDC (in vitro) | Niessner et al., 2007 |
| Monocyte   | Tofacitinib and JAK1 inhibitor increase IL6 and reduce CXCL10, TNF production in monocyte stimulated with LPS+IFNy | HC monocyte ± tofacitinib/JAK1 inhibitor/JAK3 inhibitor | De Vries et al., 2019 |
| Monocyte   | Reduced recruitment to peritoneal cavity in WT mice upon poly(I:C) followed by TLR4 intraperitoneal injection, but the reduction is reduced in Ifnar1−/− mice | IFnar1−/−, WT mice ± poly(I:C) followed by alum intraperitoneal injection | Guarda et al., 2011 |
| Monocyte   | In vitro IFN-β priming or IFN-β treatment in MS patients suppresses IL-1β production in monocyte upon LPS/Alum stimulation | treated MS vs. HC monocyte ± IFN-β, LPS, Alum | Guarda et al., 2011 |
| Monocyte   | Increased oxLDL uptake in SLE patient monocyte | SLE patients vs. HC | Li et al., 2011a |
| Monocyte   | IFN-α increases TNF expression upon LPS stimulation | THP1 (in vitro) | Niessner et al., 2007 |
| Monocyte   | Increased lipid content and LDL uptake via upregulation of SR-A in HIV patients or HC with IFN-α treatment (correlates with MX1, CXCL10 expression) | HIV patients vs. HC, ± IFN-α | Pulliam et al., 2014 |
| Monocyte   | Ifna1high Ly-6C− monocyte subsets identified | Apoe−/− (in vivo) plaque | Fig. 3 in Winkels et al., 2018 |
| Monocyte/ Mφ | Increased CCL5-dependent leukocyte arrest in the carotid arteries upon IFN-β treatment | Apoe−/− (in vivo) plaque, ± IFN-β 1 d, ± Met-Rantes, HFD 3 wk | Goossens et al., 2010 |
| Mφ         | IFN-α treatment altered gene expression enriched in metabolism pathways, such as lipid metabolism | MDM (in vitro) ± IFN-α | Ahmed et al., 2018 |
| Mφ         | Mtb-treated B cell–conditioned media induce expression of Cox2, Nos2, PDL-1 in WT BMMs which is abrogated in Ifnar−/− BMMs | Ifnar1−/−, WT BMM | Bénard et al., 2018 |
| Mφ         | Increased foam cell formation via upregulation of SR-A with IFN-β treatment | BMM (in vitro), PM (Ldlr−/−, HFD 10 wk, in vivo) | Boshuizen et al., 2016 |
| Cell/tissue | Type-I IFN production/induction | Responses to type-I IFNs | Human sample | Murine model | Reference |
|------------|---------------------------------|--------------------------|--------------|-------------|-----------|
| Mφ         | TNF is restricted by IFN-γ priming but potentiated by IFN-β priming, the effect of timing is gene- and stimulus-specific | WT BMM ± tofacitinib/JAK1 inhibitor/JAK3 inhibitor | Cheng et al., 2019 |
| Mφ         | Tofacitinib and JAK1 inhibitor reduce IL6, CXCL10, TNF production and pro-inflammatory gene expression in BMM stimulated with LPS+IFN-γ | De Vries et al., 2019 |
| Mφ         | Increased IFNAR1/STAT1-dependent CCR2, CCR5, CCL5 expression, EC adhesion upon IFN-α/β treatment | Goossens et al., 2010 |
| Mφ         | Increased CCR5, CCL5 expression/secretion upon IFN-α/β treatment | Goossens et al., 2010 |
| Mφ         | IFN-β suppresses pro-IL-1β synthesis and IL-1β maturation via IL10 and STAT3 signaling, and suppresses NLRP3 inflammasome activation via STAT1 | Guarda et al., 2011 |
| Mφ         | oxLDL loading suppresses Ifnb1 expression | PM | Jongstra-Bilen et al., 2017 |
| Mφ         | Macrophage cluster with upregulated ISGs is identified | Ldlr−/− (in vivo) plaque | Kim et al., 2018 |
| Mφ         | Increased oxLDL uptake, foam cell formation via upregulation of SR-A with IFN-α treatment (could be blocked by anti-IFN-α Ab, B18R or anti-SRA Ab) | Li et al., 2011a |
| Mφ         | IFN signature high macrophage subset enriched in progressing plaque | Ldlr−/− (in vivo) plaque | Lin et al., 2019 |
| Mφ         | IFN-α abrogates TNF-mediated tolerance, increases Ifnb1 expression. Similar ATAC-seq profile resembling IFN-α in vitro could be found in SLE monocytes | MDM (in vitro), SLE monocytes | Park et al., 2017 |
| Mφ         | Tofacitinib restore IFN-γ-inhibited ABCA1 protein expression and IFN-γ-increased lipid accumulation | THP-1 ± tofacitinib ± IFN-γ ± HFD rabbit serum or oxLDL | Pérez-Baos et al., 2017 |
| Mφ         | oxLDL down-regulates IFN-α and IFN-β | PM (in vitro) | Qin et al., 2017 |
| Mφ         | IFN stimulated gene Ch25h−/− macrophages produce more IL-1β | Ch25h−/−, WT BMM | Reboldi et al., 2014 |
| Mφ         | HFD suppresses Ifi1, Ifnb1 in Ldlr−/− | PM (Ldlr−/−, HFD vs. NHD 12 wk) | Table S1 B in Spann et al., 2012 |
| Cell/tissue | Type-I IFN production/induction | Responses to type-I IFNs | Human sample | Murine model | Reference |
|------------|--------------------------------|-------------------------|--------------|-------------|-----------|
| Mφ         | Tofacitinib treatment supresses pro-inflammatory gene expression and increases ABCA1 and anti-inflammatory gene expression reducing foam cell formation | WT ± tofacitinib, PM, + oxLDL | Wang et al., 2017 |
| Mφ         | Tofacitinib treatment reduces pro-inflammatory and increase anti-inflammatory PM cell number, gene expression (in vivo) | Apoe<−/−> mice ± tofacitinib, atherogenic diet, PM | Wang et al., 2017 |
| Neutrophil | Increased type-I IFN production in LDGs | SLE patients | Denny et al., 2010 |
| Neutrophil | Decreased NET formation in tofacitinib treated bone marrow–derived neutrophils | MRL/pr mice ± tofacitinib | Furumoto et al., 2017 |
| Neutrophil | Increased NET formation in SLE neutrophils could promote type-I IFN induction from pDCs | Increased IFN signaling pathway in neutrophil from SLE patients or treated with SLE serum | Garcia-Romo et al., 2011 |
| Neutrophil | IFN-α treatment/SLE serum induce TLR7 expression | HC ± IFN-α | Garcia-Romo et al., 2011 |
| Neutrophil | Reduced recruitment to peritoneal cavity in WT mice upon poly(I:C) followed by TLR4 intraperitoneal injection, but the reduction is ablated in ifnar1<−/−> mice | Ifnar1<−/−>, WT mice ± poly(I:C) followed by alum intraperitoneal injection | Guarda et al., 2011 |
| Neutrophil | Increased NET formation in SLE neutrophils/SLE serum, immune complexes, or monomeric Ig could promote type-I IFN production from pDCs | SLE patients vs. HC | Lande et al., 2011 |
| Neutrophil | Increased NET formation, mtROS in LDGs could promote type-I IFN induction in vivo | SLE/CGD patients | Lood et al., 2016 |
| Neutrophil | Increased NETosis in SLE neutrophils which could promote IFN-α induction from pDCs, and induce apoptosis in ECs partially via NET | SLE patients vs. HC neutrophil/LDG ± Mnase, Gen2.2, HUVEC | Villanueva et al., 2011 |
| PBMC       | upregulated SRA expression in their PBMC (positively correlates with ISGs: MX1, OAS1) | SLE patients vs. HC | Li et al., 2011a |
| PBMC/monocyte | NET-derived 8-OHdG+ DNA is a potent inducer of IFNβ1 in PBMC and THP-1 | PBMC, THP1 | Lood et al., 2016 |
| pDC        | Exacerbated atherosclerosis with unaltered IFN-α serum levels in pDC-depleted mice (by 120G8 mAb administration) | Ldlr<−/−> (in vivo) plaque, ± 120G8, HFD + carotid artery bilateral placement of semiconstrictive collars | Daissormont et al., 2011 |
| Cell/tissue | Type-I IFN production/induction | Responses to type-I IFNs | Human sample | Murine model | Reference |
|------------|---------------------------------|--------------------------|--------------|-------------|-----------|
| pDC        | Increased pDC mRNA signatures/L37 and BDCA2 staining in the advanced plaques | Early vs. advanced carotid artery specimens |             |             | Döring et al., 2012 |
| pDC        | Decreased plaque sizes, anti-dsDNA Ab titers, and IFN-α serum levels in pDC-depleted mice (by anti-PDCA1 Ab injection) | Apoe−/− (in vivo) plaque, ± anti-PDCA1, HFD |             |             | Döring et al., 2012 |
| pDC        | Cramp/DNA complexes and high-anti-dsDNA Ab-titer serum induce pDC-dependent IFN-α production | Apoe−/− (in vivo) Cramp/DNA complexes injection three times/wk for 4 wk, ± anti-PDCA1 |             |             | Döring et al., 2012 |
| pDC        | Increased IFN-α production upon treatment with serum containing high anti-dsDNA Ab titers | isolated pDC (in vitro) |             |             | Döring et al., 2012 |
| pDC        | Anti-dsDNA IgE trigger pDC IFN-α production | HC PBMC, SLE sera |             |             | Henault et al., 2016 |
| pDC        | Decreased plaque sizes (reduced macrophage area, increased collagen) in pDC-depleted mice, but serum and plaque IFN-α was undetectable | Apoe−/− (in vivo) plaque, ± anti-PDCA1, HFD |             |             | Macritchie et al., 2012 |
| pDC        | Expressing IFN-α in the plaque | Plaque (IHC staining) |             |             | Niessner et al., 2006 |
| pDC        | pDC from hydroxychloroguine-treated SLE patients showed decreased IFN-α production upon TLR7/9 stimulation | SLE vs. HC pDC ± TLR7/9 ligands |             |             | Sacre et al., 2012 |
| pDC        | Upon TLR9 in vivo/in vitro challenge, isolated, in vivo expended aortic pDC secret IFN-α, native aortic pDC expressed PDC-TREM and Ifnb1 | WT aorta, Ldlr−/−, Humanized mice (in vivo) plaque, WD for 10 wk |             |             | Yun et al., 2016 |
| Plaque     | Upregulated IFN signaling pathways in ruptured plaques | Ruptured vs. stable carotid endarterectomy specimens |             |             | Goossens et al., 2010 |
| Plaque     | Increased plaque size in IFN-α treated mice | Ldlr−/−, HFD ± IFN-α treatment for 5 wk |             |             | Levy et al., 2003 |
| Plaque     | Increased IFNA expression is associated with instability without treatment, TLR9 ligands trigger IFN-α production in the plaque | Plaque |             |             | Niessner et al., 2006 |
| Plaque     | TLR9 ligands trigger IFN-α secretion | IFN-α increases LPS-triggered TNF secretion | Plaque |             | Niessner et al., 2007 |
| Plaque     | CpG treatment increases IFN-α+ cells and secreted IFN-α | Combining IFN-α with LPS amplifies TNF, IL12, IL23, MMP9 expression while IFN-α alone does not affect the expression | Plaque (IHC staining) |             | Niessner et al., 2007 |
| Cell/tissue       | Type-I IFN production/induction | Responses to type-I IFNs | Human sample | Murine model | Reference                  |
|------------------|---------------------------------|--------------------------|--------------|--------------|----------------------------|
| Plaque           | No changes in plaque sizes,     |                          | Ldlr<sup>−/−</sup> or Apoe<sup>−/−</sup> ± anti-IFNAR1 Ab for 4 wk, HFD for 10 wk | Teunissen et al., 2015 |
| Plaque (DCs)     | pDC and mDC are present in the  |                          | Human plaque |              | Niessner et al., 2007      |
| Plaque (Mφ)      | Increased macrophage area in     |                          | Apoe<sup>−/−</sup> (in vivo) plaque, ± IFN-α two times per wk for 4 wk, HFD | Döiring et al., 2012 |
| Plaque (Mφ)      | Reduced macrophage area in      |                          | Ldlr<sup>−/−</sup> (in vivo) plaque, ± IFN-β for 3 wk, HFD for 6 wk | Goossens et al., 2010 |
| Plaque (Mφ)      | Increased macrophage area,      |                          | Myeloid Ifnar<sup>−/−</sup>/− vs. WT BMT to Ldlr<sup>−/−</sup>, HFD 11 wk | Goossens et al., 2010 |
| Plaque (Mφ)      | Reduced neutrophil area in      |                          | Ldlr<sup>−/−</sup> ± anti-IFNAR1 Ab for 4 wk, HFD for 10 wk | Teunissen et al., 2015 |
| Plaque (Mφ)      | Tofacitinib treatment reduces   |                          | Apoe<sup>−/−</sup> mice ± tofacitinib, atherogenic diet | Wang et al., 2017 |
| Plaque (necrosis)| Reduced necrotic area in plaque  |                          | Ldlr<sup>−/−</sup> (in vivo) plaque, ± IFN-β for 3 wk, myeloid Ifnar<sup>−/−</sup>/− vs. WT BMT to Ldlr<sup>−/−</sup> | Goossens et al., 2010 |
| Plaque (neutrophil)| NET detected in the vicinity of |                          | Clodronate-containing liposome injection-induced monocyte-depleted Lysm<sup>EGFP</sup>/EGFP Apoe<sup>−/−</sup>, HFD | Döiring et al., 2012 |
| Plaque (neutrophil)| Increased Cramp mRNA and CRAMP  |                          | Apoe<sup>−/−</sup> (in vivo) aorta, HFD vs. ND for 12 wk | Döiring et al., 2012 |
| Plaque (neutrophil)| Reduced neutrophil area in      |                          | Myeloid Ifnar<sup>−/−</sup>/− vs. WT BMT to Ldlr<sup>−/−</sup>, ± IFN-β, HFD for 11 wk | Goossens et al., 2010 |
| Plaque (neutrophil)| Increased Ifna expression,      |                          | Apoe<sup>−/−</sup> (in vivo) plaque, ± Cl<sup>−</sup>-amidine for 11 wk | Knight et al., 2014 |
| Plaque (pDC)     | Unchanged Ifna expression after |                          | Ldlr<sup>−/−</sup> (in vivo) plaque, WD for 7 wk | Yun et al., 2016 |
| Platelet         | Increased protein expression of  |                          | SLE patients (platelet) | Lood et al., 2010 |
| Platelet         | Reduced time of clotting,       |                          | IFNaβ<sup>−/−</sup> or IFNaβR<sup>−/−</sup> and lupus-prone vs. normal mice, ± Ifna-expressing virus, Apoe<sup>−/−</sup> IFNaβR<sup>−/−</sup> mice WD for 10 wk | Thacker et al., 2012 |
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Chen et al. Journal of Experimental Medicine
Type-I interferons in atherosclerosis
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