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The Role of IL-10 in Atherosclerosis

Xinbing Han¹ and William A. Boisvert²

¹*Department of Medicine, Beth Israel Deaconess Medical Center,
Harvard Medical School, Boston, MA,*

²*Center for Cardiovascular Research, John A. Burns School of Medicine,
University of Hawaii, Honolulu, HI,
USA*

1. Introduction

Cardiovascular diseases, including coronary artery disease (CAD), ischemic gangrene, abdominal aortic aneurysms, and many cases of heart failure and stroke currently account for the most number of deaths in the Western world (Hansson et al., 2006). The root cause of these diseases is atherosclerosis, which is widely accepted these days to be a chronic inflammatory disease in addition to the more recognized disorder of lipid metabolism. Although it was established long ago that high levels of low-density lipoprotein (LDL) cholesterol is a major risk factor for atherosclerosis, more recently both innate and adaptive immune systems have been accepted as major participants in the initiation and progression of atherosclerosis. Besides monocytes/macrophages, T cells and dendritic cells (DCs) can be detected within atherosclerotic lesions and have been implicated in the pathogenesis of atherosclerosis (Hansson and Libby, 2006) (Weber et al., 2008). Atherosclerotic lesion progression has been shown to depend on ongoing, chronic inflammation in the artery wall. Following hyperlipidemia, a rapid influx of circulating monocytes into the atherosclerosis-prone areas of the arterial intima occurs. These recruited inflammatory monocytes differentiate into macrophages and take up modified atherogenic cholesteryl ester (CE)-rich lipoproteins in the intima of the vessel wall (Lusis, 2000) (Ross, 1999) (Wang and Tall, 2003). The accumulation of cholesterol-loaded macrophages in the arterial wall called "foam cells" is a key feature of early atherosclerotic lesions (Brown and Goldstein, 1983).

Upon lipid uptake within the artery wall, macrophage foam cells activate a compensatory pathway for cholesterol efflux, mediated by the ATP-binding cassette (ABC) transporters ABCA1 and ABCG1 (Wang et al., 2007). During systemic hypercholesterolemia, however, this homeostatic mechanism is overwhelmed, leading to the accumulation of foam cells and the initiation of fatty streak lesions. The importance of these transporters is illustrated by the fact that a combined deficiency of ABCA1 and ABCG1 accelerates foam cell accumulation and atherosclerotic development in mice (Yvan-Charvet et al., 2007). Cholesterol loading of macrophages also stimulates the production of inflammatory mediators, which recruit other cell types and contribute to the development of a complex lesion (Hansson et al., 2002). Thus, processes that interfere with the intracellular cholesterol balance would be expected to exacerbate lesion formation.

Cholesterol is an essential structural component in the cell membrane and a precursor for steroid hormone and bile acid synthesis in metabolic pathways. Thus, cholesterol homeostasis needs to be strictly regulated. The intracellular cholesterol concentration is tightly controlled by feedback mechanisms that operate at both transcriptional and posttranscriptional levels (Brown and Goldstein, 1997). For example, the liver X receptor (LXR), belonging to the family of nuclear hormone receptors, contributes to cholesterol homeostasis by activating the transcription of genes involved in the response to cholesterol excess, including ABCA1 and ABCG1 (Beaven and Tontonoz, 2006). These transporters promote cellular cholesterol efflux to high-density lipoprotein (HDL) and its associated apolipoprotein (apo)-A1, a crucial step in the initiation of reverse cholesterol transport (RCT) to the liver for excretion (Tall et al., 2008). Other ways in which lipid-loaded and activated macrophage foam cells can significantly contribute to the maintenance and progression of atherogenesis is by producing nitric oxide, reactive oxygen species, inflammatory lipids, growth factors, and pro-inflammatory cytokines such as interleukin (IL) -1, IL-6, interferon (IFN)- γ and tumor necrosis factor (TNF)- α (Hansson, 2001). Taken together, alterations in both lipid metabolism and the immune responses in macrophages play a significant role in promoting the development of atherosclerotic lesions. Knowledge of the mechanisms that regulate these responses could therefore be of considerable value with respect to the development of new approaches to prevention and treatment.

As a prototypic anti-inflammatory cytokine, IL-10 is made primarily by the macrophages and T lymphocytes of the Th2 subtype. Its major functions include inhibition of macrophage activation as well as inhibition of MMP, pro-inflammatory cytokines and cyclooxygenase-2 expression. IL-10 induces the proliferation of mast cells, B and T lymphocytes, and enhances T cell response to IL-2. Although it is clearly documented that IL-10 is expressed in the atherosclerotic plaque (de Vries, 1995) (de Waal Malefyt et al., 1991) (Gerard et al., 1993) it is not fully understood how IL-10 influences the atherogenic process. This chapter will highlight the current knowledge about the role of IL-10 in the initiation and progression of atherosclerosis. Inasmuch as macrophages play a critical role in the pathogenesis of atherosclerosis, the review will focus largely on how IL-10 stimulates and regulates the activities of macrophages that are important in the development of atherosclerosis.

2. Anti-atherogenic properties of IL-10

IL-10 exerts its atheroprotective effect on plaque progression, rupture, or thrombosis throughout the different stages of atherosclerosis by influencing the local inflammatory process within the atherosclerotic lesion. As an anti-inflammatory cytokine IL-10's atheroprotective effects are exerted mainly by inhibiting various cell processes including the production of inflammatory mediators, matrix metalloproteinases (MMPs) and tissue factor (TF) production, and apoptosis. IL-10 is produced predominantly by macrophages within the local atherosclerotic lesion where it could play a significant role in the modulation of the local inflammatory response for both macrophages and T cells.

2.1 Influence on macrophage function

Macrophages play a central role during all stages of atherosclerosis (Moore and Tabas, 2011). Early *in vivo* studies using immunochemistry and PCR have indicated that macrophages in atherosclerotic lesion are the main source of IL-10 production in advanced atherosclerotic plaques (Mallat et al., 1999b). IL-10 plays an essential role in down-modulating adaptive and

innate immune responses, partly by inhibiting the activation of human monocytes and monocyte-derived dendritic cells (Woszczek et al., 2008).

Atherogenesis is initiated with the recruitment of inflammatory cells to the intima. Following inflammatory activation, the recruited monocytes are differentiated into macrophages which take up modified LDL particles such as oxidized LDL (oxLDL), through scavenger receptors, thereby promoting cholesterol loading and foam cell formation in the plaque's core. Lipid-laden macrophages produce multiple pro-inflammatory mediators, reactive oxygen species (ROS), and TF pro-coagulant that promote local inflammation and promote thrombotic complications. The paradigm that macrophages play a critical and definitive role in human atherosclerosis has been evidenced by a large number of publications from various studies of experimental atherosclerosis. The morphological observation that macrophages are abundantly distributed from early stage lesion in fatty streak to the late stage within fibrous plaques indicates; macrophage-derived foam cells are absolutely critical for development of atheromas (Libby et al., 2011) (Little et al., 2011).

The mechanisms by which IL-10 may protect against atherogenesis can be categorized, albeit artificially, into 4 aspects of macrophage function: 1. anti-inflammatory properties 2. inhibition of MMPs and TF 3. anti-apoptotic feature 4. modulation of lipid metabolism.

2.1.1 Anti-inflammatory properties of IL-10

Atherosclerosis is a chronic inflammatory condition of the arterial wall characterized by progressive accumulation of lipids, cells (macrophages, T lymphocytes, and smooth muscle cells), and extracellular matrix (Ross, 1999) (Libby et al., 2011) (Charo and Taub, 2011) (Maskrey et al., 2011). During recent years, inflammation has emerged as a major driving force in atherosclerotic lesion development throughout the different stages of the disease (Libby et al., 2011) (Charo and Taub, 2011) (Moubayed et al., 2007) (Little et al., 2011), from early fatty streak to advanced fibro-fatty plaque formation. Of the cells participating in atherogenesis, monocyte-derived macrophages and T-lymphocytes are the most prominent cells that secrete various pro- or anti-atherogenic cytokines that can influence the disease development and affect plaque stability (Ferri et al., 2009) (Pasqui et al., 2006) (Kleemann et al., 2008) (Galkina and Ley, 2009) (Woollard and Geissmann, 2010) (Weber et al., 2008).

Being the most abundant inflammatory cell type in the plaque, macrophages are the most important source of cytokine production in atherosclerotic lesions (Tedgui and Mallat, 2006) and can produce pro-inflammatory cytokines such as TNF- α , IL-1, IL-6, IL-12, IL-15, IL-18, as well as the anti-inflammatory cytokines like IL-10 and transforming growth factor- β (TGF- β). It has been well documented that pro-inflammatory cytokines can promote development of atherosclerosis (Little et al., 2011) while anti-inflammatory cytokines like TGF- β (Bobik et al., 1999) and IL-10 (Nishihira et al., 2006) can have an anti-atherogenic effect.

One of the earlier studies showed that IL-10 mRNA was detected by RT-PCR in 4 of 5 human atherosclerotic specimens but not in plaque-free aortic specimens (Uyemura et al., 1996). When human monocytes isolated from PBMC were incubated with oxLDL, IL-10 protein production was increased (Uyemura et al., 1996). The presence of IL-10 in advanced human atherosclerotic plaque was subsequently verified by another group (Mallat et al., 1999b). They showed also by using RT-PCR, that IL-10 mRNA was present in 12 of 17 atherosclerotic plaques, mainly in macrophages (Mallat et al., 1999b). These studies suggest that progressive inflammation during atherosclerosis causes macrophages to express IL-10.

IL-10 is a potent anti-inflammatory cytokine. Increased IL-10 serum level is a beneficial prognostic determinant in patients with acute coronary syndromes (Heeschen et al., 2003). A line of publications has shown that IL-10 expression by plaque macrophages limits the inflammatory response and promotes plaque healing (de Vries, 1995) (de Waal Malefyt et al., 1991) (Gerard et al., 1993) by inhibiting IL-12 (Uyemura et al., 1996) and inducible nitric oxide synthase (iNOS) production (Mallat et al., 1999b) (Ito and Ikeda, 2003). Attenuation of atherogenesis by IL-10 was attributed to its anti-inflammatory effects, most notably its ability to inhibit the release of several pro-inflammatory cytokines (including IL-1 β , TNF- α , and IL-8) from monocytic cells, and to induce the production of IL-1 receptor antagonist (Terkeltaub, 1999) (van der Poll et al., 1994) (Wang et al., 1995). IL-10 also suppresses the production of the chemokine KC/GRO- α (Kishore et al., 1999) which is implicated in intimal macrophage accumulation and the progression of complex atherosclerotic lesions in advanced disease (Boisvert et al., 1998). MCP-1 is chemotactic for monocytes and highly expressed in macrophage-rich areas of the lesion. IL-10-induced inhibition of MCP-1 (Ajuebor et al., 1999) (Han et al., 2009) (Han et al., 2010) (Zimmerman et al., 2004), a key player in monocyte recruitment to early atherosclerotic lesions (Gosling et al., 1999), has been regarded as an important protective mechanism of atherogenesis by IL-10.

2.1.2 Inhibition of matrix metalloproteinases and tissue factor

Pathological studies have provided evidence that extracellular matrix content and its degradation are related to vulnerability and instability of plaques (Libby, 1995). It has been well documented that clinical instability of atherosclerosis is related to the activation of local inflammatory and immune cells with increased expression of MMPs (Libby, 1995) and TF (Ardissino et al., 1997) in the culprit plaque as well as increased systemic production of MMPs (Kai et al., 1998) and thrombin (Biasucci et al., 1996) (Caligiuri et al., 2003). Macrophages are important sources of MMPs within atherosclerotic lesions, including MMP-2, MMP-8, MMP-9, MMP-12, MMP-13, and MMP-14 (Gough et al., 2006) (Little et al., 2011). MMPs affect lesion development and progression by degrading extracellular matrix proteins, leading eventually to the development of unstable, rupture-prone atherosclerotic lesions (Boyle, 2005) (Little et al., 2011). Tissue factor is a prothrombotic molecule expressed by various cell types within atherosclerotic plaques and has been thought to play an essential role in thrombus formation after atherosclerotic plaque rupture (Kamimura et al., 2005). There is evidence that IL-10 may have protective effects against plaque rupture and thrombus formation (Waehre et al., 2002). IL-10 can inhibit the secretion of MMPs (Waehre et al., 2002) (Han et al., 2009) (Han et al., 2010) (Holven et al., 2006), the synthesis of TF (Kamimura et al., 2005) (Ramani et al., 1993), and the production of thrombin (Pajkrt et al., 1997) from PBMC and macrophages. Decreased collagen synthesis and increased activity of macrophage-derived matrix degrading metalloproteinases are responsible for fibrous cap thinning and fragility. Therefore, low levels of IL-10 may lead to augmented MMP activity which may in turn promote plaque instability to cause acute cardiovascular events in certain individuals (Holven et al., 2006) (Mallat et al., 1999a). In addition, the balance between Th1 (IFN- γ) and Th2 (IL-10) polarization in T helper cells may play an important role in atherogenesis. IFN- γ may destabilize plaques not only by inhibiting collagen production (Amento et al., 1991) in human vascular smooth muscle cells, but by stimulating MMP production in macrophages (Libby, 1995) (Saren et al., 1996) and modulating the fibrinolytic response of endothelial cells (Arnman et al., 1995) (Gallicchio et al., 1996).

2.1.3 Anti-apoptotic properties

Both IL-10 transgenic animal models and mice deficient in either IL-10 or IL-10 receptor have highlighted the anti-apoptotic feature of IL-10. Both apoptosis and necrosis occur in the atherosclerotic plaque (Geng and Libby, 1995) (Isner et al., 1995) (Han et al., 1995) (Bjorkerud and Bjorkerud, 1996; Cai et al., 1997; Geng and Libby, 1995; Han et al., 1995; Isner et al., 1995). IL-10's anti-apoptotic properties have been reported in cultured macrophages (Arai et al., 1995) (Han et al., 2009) (Han et al., 2010) and in T lymphocytes (Cohen et al., 1997). Inflammatory nitric oxide has apoptotic effects (Geng et al., 1996) (Albina et al., 1993) and can induce cell death, at least in part through local peroxynitrite formation (Luoma et al., 1998) (Kockx et al., 1998). One mechanism by which IL-10 can protect from excessive cell damage and death in the plaque is by inhibition of iNOS production (Cattaruzza et al., 2003). The production of ROS is increased in atherosclerotic arteries (Minor et al., 1990), leading to endothelial damage, oxidation of lipid components (Witztum and Steinberg, 2001), and recruitment of inflammatory cells to the site of injury. IL-10 may down-regulate immune responses in atherosclerosis by inhibiting antigen presentation to T cells (de Waal Malefyt et al., 1991), and by inhibiting production of reactive oxygen intermediates which result in oxidation of LDL (Bogdan et al., 1991). In addition, IL-10 activates signal transducer and activator of transcription 3 (STAT3), which suppresses endoplasmic reticulum (ER) stress-induced apoptosis in macrophages by inducing the expression of cell-survival molecules (Li et al., 2008). The increased expression of the anti-apoptotic genes Bcl-1 and Mcl-1 in response to IL-10 contributes to the suppression of apoptosis by IL-10 in lipid-laden foam cells (Halvorsen et al., 2005). Furthermore, because excessive accumulation of free cholesterol can cause apoptosis in cells, one other way in which IL-10 may exert its anti-apoptotic effects is by stimulating ABCA1/ABCG1 production which increases the cholesterol efflux from lipid laden foam cells (Rubic and Lorenz, 2006) (Han et al., 2009) (Han et al., 2010).

2.1.4 Polarization of macrophage by IL-10

In response to cytokines and microbial products, macrophages have the ability to be polarized into one of two subgroups: classically activated M1 and alternatively activated M2 form (Benoit et al., 2008). The concept of macrophage polarization has been widely accepted in recent years (Mantovani et al., 2005) (Martinez et al., 2008). M1 macrophages are induced by IFN- γ , microbial stimuli (e.g. LPS) or cytokines such as TNF- α and GM-CSF. M2 macrophages are induced by IL-4, IL-10, IL-13, immune complexes, glucocorticoid or secosteroid (vitamin D3) hormones (Mantovani et al., 2005; Martinez et al., 2008). One of the notable features of M1 macrophage is its low level of IL-10 expression and high levels of IL-12 and IL-23 expression. As efficient producers of reactive oxygen and nitrogen intermediates and inflammatory cytokines, M1 macrophages are associated with protection during acute infectious diseases, and can induce and polarize Th1 response as well as mediate immune response against intracellular parasites and tumors (Benoit et al., 2008).

By contrast, M2 macrophage phenotype is characterized by abundant expression of IL-10 and low levels of IL-12 and IL-23 production. By expressing high levels of scavenger, mannose and galactose-type receptors, M2 macrophages participate in polarized Th2 response and exert immunoregulatory functions (Martinez et al., 2008) (Mantovani et al., 2005) by promoting killing and encapsulation of parasites (Noel et al., 2004). They are actively involved in tumor progression, tissue repair and remodeling (Wynn, 2004). Chronic

infectious diseases are associated with macrophage reprogramming towards an M2 profile (Benoit et al., 2008).

Both M1 and M2 macrophages are present in atherosclerotic lesions (Khallou-Laschet et al.). Exposure of macrophages to oxLDL renders M2 macrophages pro-inflammatory (van Tits et al., 2011). Compared with pro-inflammatory M1 macrophages, anti-inflammatory M2 macrophages are more susceptible to foam cell formation (van Tits et al., 2011). Interestingly, however, a recent report indicates that M2 phenotype may exert an athero-protective action in experimental atherosclerosis (Khallou-Laschet et al.). On the other hand, PPAR γ activation plays an essential role in promoting polarization of circulating blood monocytes to become M2 macrophages (Bouhrel et al., 2007) (Charo, 2007) (Chinetti-Gbaguidi and Staels). Convincing clinical evidence and animal experiments from PPAR γ -deficient mice and from the mice treated with PPAR γ ligands have demonstrated the beneficial role of PPAR γ activation in preventing atherosclerosis (Staels, 2005) (Ricote et al., 1998). Because IL-10 increases ABCA1-mediated cholesterol efflux through PPAR γ activation (Han et al., 2009) (Han et al., 2010), it is likely that PPAR γ -driven M2 macrophage formation plays an important role in athero-protective action by IL-10.

2.1.5 Modulation of lipid metabolism

The loading of macrophages with lipoprotein-derived cholesterol alters macrophage functions during atherogenic processes. The fact that IL-10 production is increased in lipid laden macrophages suggests that IL-10 may be involved in lipid metabolism in these cells. In fact, oxLDL can promote immune activation by inducing pro-inflammatory cytokines IL-12 and TNF- α , and anti-inflammatory cytokine IL-10 production by mononuclear leukocytes from human atherosclerotic plaque (Fei et al., 2003). During recent years, the involvement and importance of IL-10 in lipid metabolism, particularly in macrophages, has been increasingly recognized.

With regard to lipid metabolism and foam cell formation, two steps are critical in maintaining lipid homeostasis in macrophages: 1. cholesterol uptake mediated by scavenger receptors and 2. cholesterol efflux mediated by ABCA1/ABCG1. Scavenger receptors such as scavenger receptor A and CD36 on macrophages mediate the uptake of modified lipoproteins from the vessel wall (Nagy et al., 1998). In addition, reverse cholesterol transport through ABCA1 and ABCG1 is an important mechanism to export cytotoxic cellular free cholesterol to lipid poor apoAI and lipidated HDL particles (Chinetti et al., 2001; Kennedy et al., 2005). It is well documented that cholesterol efflux via ABCA1 and ABCG1 is essential to slow the development of atherosclerosis by decreasing lipid loading (Yvan-Charvet et al., 2007) (Zhao et al., 2010) (Calkin and Tontonoz, 2010) (Fitzgerald et al., 2010) (Ye et al., 2011). Although the role of scavenger receptors appears complicated because of conflicting results from gene knockout or transgenic mouse studies (Hansson and Hermansson, 2011) the general consensus among recent publications is that these receptors are protective against atherosclerosis due to their ability to remove modified LDL from the vessel wall (Marleau et al., 2005) (Moore et al., 2005) (Van Eck et al., 2000) (Whitman et al., 2002) (Liao et al., 2000) (Teupser et al., 1999).

Recent *in vivo* results show that the role of IL-10 in regulating lipid metabolism remains elusive. Plasma lipoprotein levels including LDL, HDL and triglyceride have been measured in these animal models but the results appear controversial and are dependent on several factors such as the animal model used, route of administration and stage of atherosclerosis

investigated. In C57BL/6J mice, total plasma cholesterol and HDL cholesterol levels were not affected by IL-10 deficiency (Mallat et al., 1999a) (Pinderski Oslund et al., 1999). Systemic IL-10 overexpression lowered plasma VLDL and LDL cholesterol levels in LDLR^{-/-} mice (Von Der Thusen et al., 2001), but IL-10 overexpression in T cells did not alter circulating lipoprotein profiles (Pinderski et al., 2002). No changes in plasma (Namiki et al., 2004) or reduced cholesterol levels (Yoshioka et al., 2004) were observed in apoE^{-/-} mice with intramuscular gene transfer of IL-10 cDNA. Interestingly, the lack of IL-10 led to increased LDL cholesterol whereas VLDL was reduced in apoE^{-/-} mice with no significant changes observed in either total cholesterol or triglyceride levels (Caligiuri et al., 2003). However, systemic delivery of adeno-associated virus type 2-hIL-10 inhibited atherogenesis in LDLR knockout mice with no changes in plasma cholesterol levels (total cholesterol, LDL, HDL, and TG) compared with those with no treatment (Liu et al., 2006). In APOE*3-Leiden mice, IL-10 deficiency did not lead to significant changes in cholesterol levels but overexpression of IL-10 reduced cholesterol levels after feeding a high-fat, cholesterol-rich diet (Eefting et al., 2007). These confusing set of results suggest that IL-10-modulated lipid metabolism and plasma cholesterol levels vary widely and is dependent on the animal models utilized. The role of IL-10 in lipid metabolism needs to be rigorously elucidated, especially in relation to human atherosclerosis.

Recent publications provide convincing evidence that IL-10 can modulate cellular lipid metabolism, including cholesterol uptake and cholesterol efflux (reverse cholesterol transport). In 2005, Halvorsen et al. reported that IL-10 enhances oxLDL-induced formation of macrophage foam cells (Halvorsen et al., 2005). The authors propose that IL-10 not only enhances foam cell formation but also has anti-apoptotic effects by increasing the expression of anti-apoptotic genes Bcl-1 and Mcl-1 (Halvorsen et al., 2005). In 2006, Rubic and Lorenz showed that IL-10 can stimulate ABCA1/ABCG1 which increases the cholesterol efflux from lipid-laden foam cells. In addition, they observed a down-regulation of CD36-mediated oxLDL uptake in macrophages. According to their results IL-10 is able to decrease oxLDL uptake and increase reverse cholesterol transport in macrophages, thereby preventing foam cell formation (Rubic and Lorenz, 2006). These results appear to contradict the report by Halvorsen et al. in which IL-10 increases foam cell formation. These confusing findings were partially clarified by a study by Han et al. in 2009 in which they reported that IL-10 modulates lipid metabolism in macrophages by facilitating both cholesterol uptake and efflux (Han et al., 2009). This study clearly revealed that IL-10 not only can up-regulate ABCA1 in a PPAR- γ -dependent mechanism but can increase the expression of scavenger receptors (scavenger receptor A and CD36). In support of this Montoya et al. reported that IL-10 stimulates the expression of scavenger receptors and enhances foam cell formation (Montoya et al., 2009). These data support the hypothesis that increased cholesterol uptake by IL-10 may be athero-protective by actively removing the highly atherogenic lipoproteins from the artery wall. On the other hand, the increase in ABCA1-dependent cholesterol efflux by IL-10 is a crucial factor in the efficient disposal of cytotoxic free cholesterol through reverse cholesterol transport. Interestingly, a recent report indicated that anti-inflammatory M2 macrophages but not pro-inflammatory M1 macrophages rapidly accumulate oxidized LDL (van Tits et al., 2011). As IL-10 is one of the effectors that promote M2 macrophage polarization as mentioned above (Martinez et al., 2009) (Tabas, 2010), it is likely that IL-10 is involved in the lipid accumulation predominantly in M2 macrophages. These results present a comprehensive anti-atherogenic role of IL-10 in macrophages, along with a more

traditional role of IL-10 in inhibiting inflammatory molecules (e.g. TNF- α , iCAM-1, and MMP9) and reducing apoptosis (Han et al., 2009) (Han et al., 2010). A cartoon depicting the multi-faceted anti-atherogenic role of IL-10 in macrophages is shown in the figure below.

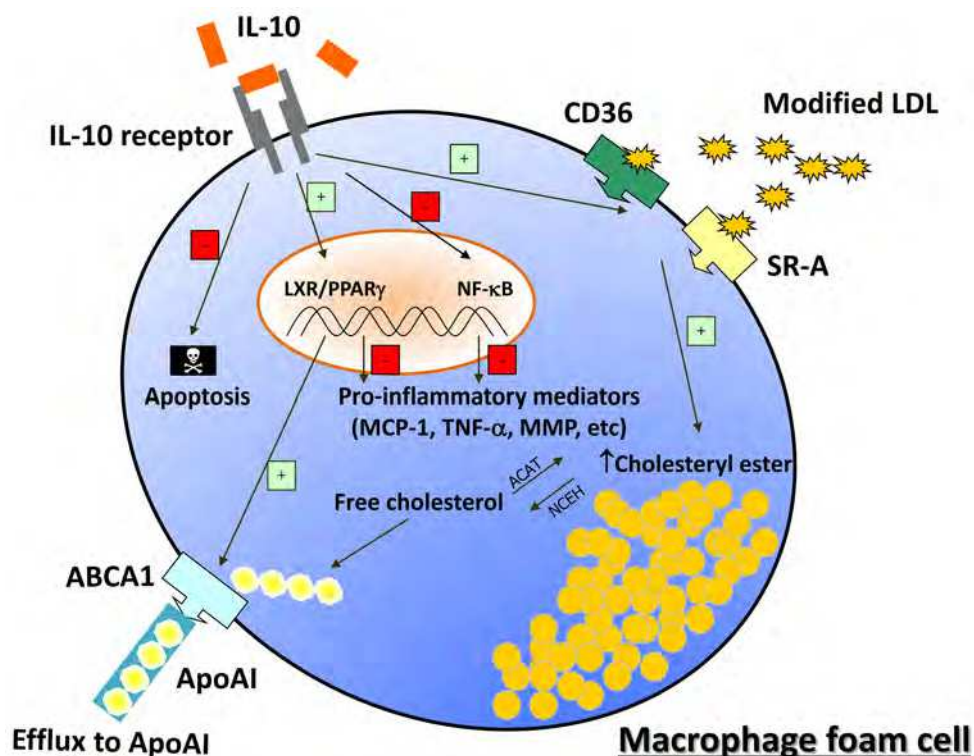


Fig. 1. Schematic overview of the protective role of IL-10 during atherosclerosis involving regulation of lipid metabolism in macrophages. Upon binding to its receptor, IL-10 up-regulates scavenger receptors, SR-A (SR-I and SR-II) and CD36, which account for an increase in modified LDL uptake by macrophages. This promotes cholesteryl ester accumulation and foam cell formation. IL-10 also promotes ABCA1-mediated free cholesterol efflux to apoA1 in a PPAR γ -dependent manner. In a more traditional role as an anti-inflammatory cytokine, IL-10 markedly suppresses the expression of pro-inflammatory molecules such as TNF- α , MCP-1 and MMPs, presumably through the inhibition of NF- κ B activity as documented before (Wang et al., 1995), and diminishes apoptosis in the lipid-laden foam cells (Han et al., 2009).

2.2 Influence on T lymphocyte function

Recent publications have shown that, although T cell numbers are far fewer than mononuclear phagocytes, they are also recruited to the intima and play an important role in the development of atherosclerosis. Therefore, the protective action of IL-10 in atherosclerosis is likely to involve T cell immune response.

2.2.1 Polarization and balance of T helper cells

T lymphocytes are found in lesions in an activated state and coexist with lesion macrophages, particularly in early phases of atherosclerosis. The key role for Th1 cytokines, such as IL-12 (Lee et al., 1999) or IFN- γ (Gupta et al., 1997) as well as the general role of lesion T lymphocytes in atherogenesis have been reviewed elsewhere (Daugherty and Rateri, 2002). As a prototypic anti-inflammatory cytokine, IL-10 down-regulates Th1 cytokines such as IL-12 and IL-18 leading to inhibition of Th1-biased immune response (Moore et al., 2001), and polarization of the Th1:Th2 balances toward Th2 (Daugherty and Rateri, 2002). Induction of a regulatory T cell type 1 response attenuates the development of atherosclerosis in apoE-knockout mice by decreasing the Th1 response, decreasing the production of IFN- γ and increasing IL-10 production (Mallat et al., 2003). Also, it may be that the reduction in atherosclerotic lesion formation in Fc γ RIII (CD16) $-/-$ mice crossed onto the LDLR $-/-$ mice is associated with increased production of IL-10 by the expansion of CD4 $^{+}$ T cells (Kelly et al., 2010).

The imbalance between pro- and anti-inflammatory forces influences plaque disruption and recurrent cardiovascular events (Trompet et al., 2007) with a shift towards the Th1 dominance seen in atherosclerosis patients (Ait-Oufella et al., 2011). In support of this concept is the report that serum IL-18/IL-10 ratio is an independent predictor of in-hospital adverse events in patients with acute coronary syndrome (Chalikias et al., 2005). Furthermore, an anti-inflammatory marker such as IL-10 is a better prognostic marker than inflammatory markers such as CRP and IL-18 to predict cardiovascular events in ACS patients (Tziakas et al., 2007). Likewise, it has been demonstrated that CRP accentuates inflammation, which is pivotal in atherothrombosis, by lowering IL-10, thereby altering the anti-inflammatory/pro-inflammatory balance (Singh et al., 2006). There is an inverse correlation between pro-inflammatory CRP and anti-inflammatory IL-10 levels in patients with atherosclerosis (Seyrek et al., 2005). More recently, an inflammatory imbalance between the TNF- α system and IL-10 has been characterized in children with familial hypercholesterolemia (Narverud et al., 2011).

Th1 biased phenotype is responsible for clinical instability (Liuzzo et al., 2000) and atherogenesis (Jonsson et al., 2001) (Hurt-Camejo et al., 2001) (Laurat et al., 2001) (Zhou et al., 1998) (Caligiuri et al., 2003) (Mallat and Tedgui, 2004) (Mallat et al., 2005). Interestingly, in IL-10 $-/-$ ApoE $-/-$ double KO mice, Th1-bias was accompanied by a higher susceptibility to atherosclerosis, but only at the early stage of the disease when macrophages dominate (which is when they are sensitive to Th1 and Th2 cytokines (Caligiuri et al., 2003)).

2.2.2 Regulatory T cells and Th17 cells

Recently, the role of regulatory T cells (Treg) and IL-17-producing T cells (Th17 cells) has been emphasized in atherosclerosis (Taleb et al., 2010) (Lahoute et al., 2011). Treg are important in protection against atherosclerosis at least in part through the production of IL-10 (Mor et al., 2007) (Taleb et al., 2010) (George, 2008) (Feng et al., 2009). It is also believed that the pro-atherogenic response by Th1 cells can be controlled by Treg (Binder et al., 2004). IL-17-producing Th17 cells also play an important role in atherosclerosis (Hansson and Hermansson, 2011). Irradiated LDLR $-/-$ mice transplanted with IL-17R deficient bone marrow exhibit reduced lesion size in aortic root, increased IL-10 production, and decreased IL-6 production (van Es et al., 2009). This suggests that signaling via the IL-17 receptor in bone marrow derived cells enhances atherosclerosis. Similarly, blockade of IL-17 results in reduced atherosclerosis in apoE $-/-$ mice (Smith et al., 2010) (Erbel et al., 2009). However, the role of IL-

17 in atherogenesis is controversial in that increased level of IL-17 is associated with a stable human plaque phenotype while defective Th17 cell differentiation may be implicated in increased susceptibility to vascular inflammation (Taleb et al., 2009). In addition, Th17 response is protective against vascular inflammation and the progression of atherosclerosis (Taleb et al., 2010). Similarly, a deficiency of SOCS3 in T cells leads to IL-17-dependent reduction in lesion development and vascular inflammation by increasing IL-17 and IL-10 production, and by inducing an anti-inflammatory macrophage phenotype (Taleb et al., 2009)

3. Human studies and in vivo animal models

The role of IL-10 in atherosclerosis has been investigated using different animal models as listed on the table below. In 1996, Uyemura et al. (Uyemura et al., 1996) first described that IL-10 was produced in human atherosclerotic lesions and that ox-LDL induced IL-10 release from monocytes in vitro. The down-regulation of IL-12 by IL-10 (Sieling et al., 1994) (D'Andrea et al., 1993) (de Waal Malefyt et al., 1991) observed in this study and others suggest that the balance between IL-12 and IL-10 production contributes to the level of immune-mediated tissue injury in atherosclerosis. IL-12 and IL-10 are two important cytokines produced by activated monocytes that regulate the Th1 and Th2 responses, respectively (D'Andrea et al., 1992) (Gately et al., 1991) (Germann et al., 1993) (Hsieh et al., 1993) (Seder et al., 1993) (Sieling et al., 1994) (de Waal Malefyt et al., 1991) (Barnes et al., 1992). IL-12 is a T cell growth factor (Gately et al., 1991) that is primarily produced by activated monocytes (D'Andrea et al., 1992) which selectively induces the Th1 cytokine pattern (Gately et al., 1991) (Germann et al., 1993) (Hsieh et al., 1993) (Seder et al., 1993) (Sieling et al., 1994). One important mechanism of IL-10 action is that it inhibits the local production of IL-12 which may potentiate the chronic inflammatory Th1 cell and macrophage responses leading to tissue injury in atherosclerosis (Uyemura et al., 1996). The complicated issue of athero-regulation by both IL-12 and IL-10 was further exhibited by an observation that IL-12 is expressed at an earlier stage of atherosclerosis than IL-10 in apoE^{-/-} mice (Lee et al., 1999). This suggests that IL-12 and IL-10 may play an active role in regulating the immune response during the different phases of atherosclerosis.

In 1999, Mallat et al. reported the expression and potential effects of IL-10 in advanced human atherosclerotic plaques (Mallat et al., 1999b). Immunohistochemical staining from this study indicated that macrophages in advanced human atherosclerotic plaques are the main source of IL-10. The local anti-inflammatory response of IL-10 and its effect on protection from excessive cell death in the plaque was supported by the data that high levels of IL-10 expression were associated with low levels of iNOS expression and cell death.

Studies involving IL-10-deficient and IL-10-overexpressing mouse models on either apoE^{-/-} or LDLR^{-/-} background have greatly advanced our understanding of the mechanism of IL-10 function in atherogenesis. In 1999, two labs independently reported that IL-10 is protective in atherosclerosis (Mallat et al., 1999a; Pinderski Oslund et al., 1999). Since then, more than ten groups utilized different animal models and various IL-10 delivery systems in an attempt to understand how IL-10 affects atherosclerosis. The first report using the IL-10-deficient mice fed an atherogenic diet showed an increased lipid accumulation, higher T-cell infiltration, abundant IFN- γ expression, and decreased collagen content in the lesion compared with wild-type mice (Mallat et al., 1999a). Transfer of murine

Publication	Approach	Animal model	Underlying mechanism
Mallat et al. 1999, Circ Res (Mallat et al., 1999a)	IL-10-encoding plasmid transferred to muscle cells using electrotransfer procedures	C57BL/6 mice	Inhibit inflammation, plaque collagen content and stability
Pinderski Oslund et al. 1999, ATVB (Pinderski Oslund et al., 1999)	Systemic overexpression of IL-10	C57BL/6J mice	Block monocyte adhesion to human aortic endothelial cells
Von der Thusen et al. 2001, FASEB J (Von Der Thusen et al., 2001)	Systemic adenovirus-mediated transfer of IL-10	LDLR ^{-/-} mice	Monocyte deactivation by inhibition of TNF- α and lowering of serum cholesterol levels
Pinderski et al. 2002, Circ Res (Pinderski et al., 2002)	Murine IL-10 transgene under human IL-2 promoter, bone marrow transplantation (overexpression of IL-10 by T cells)	LDLR ^{-/-} mice	Polarization to Th2 phenotype; lowered activation of monocytes; decreased apoptosis of macrophage foam cells within lesion
Caligiuri G et al. 2003, Mol Med (Caligiuri et al., 2003)	IL-10 deficiency	ApoE ^{-/-} mice	Increased Th1 response; increased TF and MMP activity; increase in LDL and decrease in vLDL in IL-10 ^{-/-} -ApoE ^{-/-} mice
Namiki M et al 2004 Atherosclerosis (Namiki et al., 2004)	Intramuscular gene transfer of IL-10 cDNA	ApoE ^{-/-} mice	Change in the Th1 response by inhibiting IL-12 and IFN- γ expression
Yoshioka et al. 2004, Gene Ther (Yoshioka et al., 2004)	Systemic delivery of adeno-associated virus vector (tibial muscle injection)	ApoE ^{-/-} mice	Inhibition of inflammation and oxidative stress
Liu et al. 2006, Atherosclerosis (Liu et al., 2006)	Systemic delivery (tail vein injection)	LDLR ^{-/-} mice	Anti-inflammatory (MCP-1) and cholesterol-lowering effects
Namiki et al. 2004, Atherosclerosis (Namiki et al., 2004)	Transfer of murine IL-10 cDNA plasmid to femoral muscle with Hemagglutinin virus of Japan (HVJ)-liposome	ApoE ^{-/-} mice	Reduced macrophage infiltration and altered Th1 response
Han X, et al. 2010, FASEB J (Han et al., 2010)	Overexpression of IL-10 by macrophages, bone marrow transplantation	LDLR ^{-/-} mice	Inhibition of inflammation and apoptosis; modulation of lipid metabolism in foam cells (both lipid uptake and cholesterol efflux)
Du L, et al. 2011, Human Gen Therapy (Du et al., 2011)	Expression of IL-10 in carotid arteries achieved with helper-dependent adenoviral vector	Rabbit	No athero-protective effect

IL-10 through in vivo intramuscular electrotransfers of pCor-IL-10 plasmid DNA achieved a 60% reduction in lesion size in IL-10-deficient mice. In agreement with these findings, Pinderski Oslund et al. observed that diet-induced atherosclerotic lesions were larger in IL-10 null mice than in control mice (Pinderski Oslund et al., 1999). In addition, they also observed that transgenic murine IL-10 expression which was selectively driven in T cells by human IL-2 promoter decreased atherosclerotic lesion formation (Pinderski Oslund et al., 1999).

In 2001, von der Thusen and colleagues reported that increased plasma concentrations of IL-10 as a result of adenoviral gene transfer in LDLR^{-/-} mice led to reduction in atherosclerotic lesion size by inhibiting the production of TNF- α (Han et al., 2010; Von Der Thusen et al., 2001). The mechanism involves the inhibition of anti-inflammatory TNF- α production by IL-10 (Han et al., 2010; Von Der Thusen et al., 2001). At the same time, Pinderski et al. demonstrated that overexpression of IL-10 by activated T lymphocytes attenuated lesion formation by driving the shift to a Th2 phenotype with decreased IFN- γ production (by peripheral blood lymphocytes, splenocytes, and circulating monocytes) (Pinderski et al., 2002). Alteration of macrophage function was exhibited by markedly decreased apoptosis in macrophage foam cells within the lesions of IL-10 transgenic mice (Pinderski et al., 2002).

The athero-protective results obtained with IL-10-deficient mice on the C57BL/6J background (Mallat et al., 1999a; Pinderski Oslund et al., 1999) were confirmed in IL-10 and apoE double knockout mice as demonstrated by Caligiuri et al. (Caligiuri et al., 2003). Several significant findings were revealed by this study: (1) Th-1 response and lesion size were dramatically increased in double knockout mice compared with apoE^{-/-} controls at the early phase of lesion development; (2) the proteolytic and procoagulant activity was elevated in advanced lesions as indicated by an increase in TF and MMP activities, suggesting that IL-10 may reduce atherogenesis and improve the stability of plaques; and (3) lipid metabolism regulated by IL-10 was implicated in this study as LDL cholesterol was increased but VLDL was decreased in the double KO mice without significant changes in total cholesterol or triglyceride levels (Caligiuri et al., 2003).

In an attempt to utilize IL-10 as a therapeutic agent, several techniques have been used by different groups to deliver the IL-10 gene in vivo. One study showed that intramuscular gene transfer of IL-10 cDNA reduces atherosclerotic lesion formation in apoE^{-/-} mice (Namiki et al., 2004). IL-10 gene transfer quelled the Th1 response by inhibiting IL-12 and IFN- γ expression in transgenic mice (Namiki et al., 2004). These results were confirmed in another study in which adeno-associated virus vector-mediated IL-10 gene transfer via intramuscular injection inhibited atherosclerosis in apoE^{-/-} mice (Yoshioka et al., 2004) by lowering MCP-1 expression in both the vascular wall of the ascending aorta and serum. In agreement with these results, a systemic delivery of adeno-associated virus type 2-hIL-10 inhibited atherogenesis in LDLR^{-/-} mice by combating inflammation and oxidative stress (Liu et al., 2006). Similar effects of IL-10 deficiency and overexpression on neointima formation were seen in the hypercholesterolemic apoE*3-Leiden mice as well (Eefting et al., 2007).

Anti-atherosclerotic properties of IL-10 were further displayed in high fat diet-fed LDLR^{-/-} mice in which IL-10 was overexpressed in macrophages by utilizing a macrophage-specific retroviral vector that allows long-term in vivo expression of IL-10 in macrophages through transplantation of retrovirally transduced bone marrow cells (BMCs) (Han et al., 2010). The

IL-10 expressed by macrophages in the plaques derived from transduced BMCs inhibited atherosclerosis in these mice, at least in part by reducing the inflammation and apoptosis in IL-10-overexpressing macrophages. These results are consistent with previous findings (Han et al., 2009) and provided evidence that IL-10 production in macrophages is protective against atherosclerosis. Their results also highlight a novel therapeutic technique against atherosclerosis using an effective stem cell transduction system that allows prolonged production of IL-10 from macrophages.

It is worth emphasizing that most strategies mentioned above had systemic effects on multiple cells including T cells, monocytes and endothelium resulting from overexpression of IL-10 in circulation. For example, overexpression of IL-10 in activated T lymphocytes inhibited monocyte activation and led to a shift to either Th2 phenotype (Pinderski et al., 2002) or Th1 phenotype (Zhou et al., 1998). As a cytokine with diverse effects on most hematopoietic cell types, IL-10 can inhibit the activation and effector function of T cells, monocytes, and macrophages (Moore et al., 2001). In addition, IL-10 can regulate the growth and/or differentiation of B cells, NK cells, cytotoxic and helper T cells, mast cells, granulocytes, dendritic cells, keratinocytes, and endothelial cells (Moore et al., 2001). Therefore, alterations in circulating IL-10 levels can influence the function of other immune cells which may in turn influence atherosclerosis. In the study by Han et al. there was no detectable IL-10 in circulating plasma at any time point during the atherogenic diet feeding whereas IL-10 was readily detected in IL-10-overexpressing macrophages in atherosclerotic lesions. This suggests that IL-10 was expressed in differentiated macrophages but not in circulating monocytes. Therefore, their technique of overexpressing IL-10 only in differentiated macrophages is useful to evaluate the unique role of locally-produced IL-10 in atherogenesis, and clearly shows that IL-10 acting in the vessel wall can decrease the development of atherosclerosis despite ongoing hyperlipidemia.

However, a recent study using a rabbit model showed that prolonged and stable expression of IL-10 in rabbit carotid arteries achieved with a helper-dependent adenoviral vector had neither an atheroprotective effect nor any effect on adhesion molecules or any other atherogenic cytokines (Du et al., 2011). Possible explanation accounting for the discrepant results may be inadequate protein expression *in vivo* or lack of suitability of this rabbit model to detect IL-10's therapeutic effects. This study suggests that gene therapy involving IL-10 delivery may bring about different results in different species.

4. Therapeutic considerations

In light of the findings that systemic and intralésional delivery of IL-10 can be anti-atherogenic, it is tempting to speculate that IL-10 treatment may have the potential to be a novel therapeutic agent against atherosclerosis in the future. IL-10 expression after intramuscular DNA electrotransfer or other techniques leads to a persistent expression of this protective cytokine in circulation and in local lesion (Deleuze et al., 2002; Han et al., 2010; Pinderski et al., 2002). It is likely that systemic delivery of IL-10 will result in suppression of immune response and increase the opportunity of infection, particularly involving intracellular pathogens such as *Chlamydia* and *Listeria monocytogenes* (Terkeltaub, 1999). Compared with systemic delivery of IL-10, local expression of IL-10 in atherosclerotic lesions may have much less impact on the general immune response. On the other hand, a robust local expression driven by retrovirus or adenovirus makes it difficult to regulate IL-10 expression in a temporally and spatially controllable manner as desired. Accordingly, the

safety and effectiveness of exogenous IL-10 administration utilizing these techniques will need to be evaluated in the future before they are adopted in human patients for the treatment of atherosclerosis.

5. References

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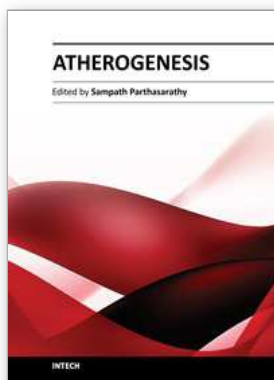
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This monograph will bring out the state-of-the-art advances in the dynamics of cholesterol transport and will address several important issues that pertain to oxidative stress and inflammation. The book is divided into three major sections. The book will offer insights into the roles of specific cytokines, inflammation, and oxidative stress in atherosclerosis and is intended for new researchers who are curious about atherosclerosis as well as for established senior researchers and clinicians who would be interested in novel findings that may link various aspects of the disease.

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Slavka Krautzeka 83/A
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No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821