Modulation of Autoimmunity and Atherosclerosis – Common Targets and Promising Translational Approaches Against Disease –

Daniel FJ Ketelhuth, PhD; Göran K Hansson, MD, PhD

Atherosclerosis is a chronic inflammatory disease of the arterial wall that is influenced by several risk factors, including hyperlipidemia and hypertension. Autoimmune diseases substantially increase the risk for cardiovascular disease (CVD). Although atherosclerotic CVD, such as myocardial and stroke, is much more prevalent than classical autoimmune conditions such as rheumatoid arthritis, psoriasis, and systemic lupus erythematosus, these types of pathology have many similarities, raising the possibility that therapies against autoimmune disease can have beneficial effects on CVD. Substantial clinical and experimental data support the potential for immunomodulatory approaches to combating both autoimmune and cardiovascular diseases, including classical immunosuppressants, anticytokine therapy, the targeting of T and B cells and their responses, and vaccination. In this review, we discuss experimental and clinical studies that have used immunomodulatory approaches to mitigate autoimmune reactions and examine their potential to prevent and treat atherosclerotic CVD. (*Circ J* 2015; **79**: 924–933)

Key Words: Atherosclerosis; Autoimmune disease; Cardiovascular disease; Immunomodulation; Therapy

In Europe, despite the recent decline in mortality rates in several countries, cardiovascular disease (CVD) remains the leading cause of death, accounting for approximately half of all deaths on the continent – over 4 million deaths per year.¹ Known as acute complications of atherosclerosis and atherothrombosis, 2 major CVDs, coronary artery disease (CAD) and stroke, are the chief causes of death worldwide.²

Atherosclerosis is a chronic inflammatory disease. Strong evidence indicates that the inflammatory process that characterizes this disease is initiated by the infiltration, retention, and accumulation of low-density lipoprotein (LDL) in the intima of the arterial wall.³ This accumulation effects the formation of an atherosclerotic plaque or lesion: a complex tissue that comprises lipids, calcified and fibrotic tissue, vascular cells, cellular debris, and a wide range of innate and adaptive immune cells.³

Atherothrombosis, defined as the disruption of an atherosclerotic lesion and superimposed thrombosis, promotes the lethal effects of atherosclerosis,⁴ including the development of CAD and stroke. Atherothrombosis is generally triggered by prothrombotic changes in the lesion, including weakening of the smooth muscle cells (SMCs) and collagen-rich fibrous cap, plaque rupture, and exposure of the lesion's procoagulant molecules to coagulation factors and platelets in the blood.³

Atherosclerosis is a multifactorial disease, in which genetic and environmental factors interact. Current preventive and treatment efforts against CVD have concentrated on targeting classical risk factors for the development of atherosclerotic

disease, such as smoking cessation, dietary changes and the prescription of drugs to treat hypertension, diabetes, and dyslipidemia, in middle-aged and older individuals with established CVD (secondary prevention) and those who are at high risk of developing a first episode of disease (primary prevention).⁵

Despite the significant survival benefit of blockbuster therapeutic approaches, such as statins,⁶ current therapies fail to prevent two-thirds of CVD cases, and at least 10% of healthy individuals may develop CVD in the absence of classical risk factors.⁷

We lack therapies that can target the undesired immune and inflammatory reactions in the artery wall and that, either alone or in combination with existing treatments, can substantially affect the burden of CVD. Considering this scenario, novel therapies are needed. In this review, we examine experimental and clinical studies of immunomodulatory approaches used to combat autoimmune diseases and their potential to prevent and treat atherosclerotic CVD (Table).

The Immune Inflammatory Process of Atherosclerosis

Initiation of the Disease: Fatty Streaks

The binding of apolipoprotein B-containing lipoproteins, particularly LDL that contains the apolipoprotein B-100 (ApoB100), to proteoglycans in the intima of the artery wall is considered the initiating event in atherosclerosis.⁸ Trapped in the intimal layer, LDL undergoes several modifications, including oxidation,

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Center for Molecular Medicine, Department of Medicine, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden

Mailing address: Daniel FJ Ketelhuth, PhD, Center for Molecular Medicine, L8:03, Karolinska University Hospital, S-17176 Stockholm, Sweden. E-mail: daniel.ketelhuth@ki.se

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Table. Overview of Potential Immunomodulatory Therapies for CVD: Results From Preclinical and Clinical Studies

Therapy	Preclinical	Clinical
Methotrexate	↓ atherosclerosis in rabbits ^{32,33}	↓ CVD risk in RA patients ³⁴
Colchicine	—	↓ CAD (combined with statins and other standard therapies) ⁵⁸
TNF blockade	↓ neointimal formation in rabbits ⁴⁰ ↔ neointimal formation in rabbits ⁴¹ ↓ atherosclerosis in <i>ApoE</i> ^{−/−} mice ⁴²	↓ CVD risk in RA ^{37,38} ↓ CVD risk in psoriatic patients ³⁹ ↓ glucose values in RA patients ⁴⁴ ↑ or ↓ plasma lipids in RA patients ^{45,46} ↑ incidence of heart failure ⁴⁷
IL-1 blockade	↓ atherosclerosis in <i>Ldlr</i> ^{−/−} mice ⁵²	↑ endothelial and coronary aortic function in RA patients ⁵⁹ ↓ plasma levels of IL-6, CRP, and fibrinogen in high CVD risk patients ⁶¹
IL-6 blockade	—	↑ HDL and LDL plasma levels ^{63,64} ↔ CVD in RA patients ⁶⁴
IFN γ blockade	↓ atherosclerosis in <i>ApoE</i> ^{−/−} mice ⁶⁸	—
IL-17 blockade	↓ atherosclerosis in <i>ApoE</i> ^{−/−} mice ^{72–74} ↓ plaque stability in <i>Ldlr</i> ^{−/−} mice ⁷⁵	—
IL-12/IL-23 blockade	↓ plaque stability in <i>Ldlr</i> ^{−/−} mice ⁷⁷	↑ or ↓ risk of CVD in psoriatic patients ⁷⁶
TCR vaccination	↓ atherosclerosis in huB100tg $\times$ <i>Ldlr</i> ^{−/−} mice ²³	—
CTLA4.Ig	↓ atherosclerosis in ApoE3 $\times$ Leiden mice ⁸⁸ ↓ blood pressure in C57Bl/6J mice ⁸⁹	↑ HDL levels, ↔ aortic stiffness in RA patients ⁸⁷
CD40L blockade	↓ atherosclerosis in <i>Ldlr</i> ^{−/−} mice ⁹⁵ ↓ atherosclerosis and ↑ plaque stability in <i>ApoE</i> ^{−/−} mice ⁹⁶	↑ fatal thrombotic events in SLE patients ⁹¹
OX40L blockade	↓ atherosclerosis in <i>Ldlr</i> ^{−/−} mice ⁹⁸	—
CD137 agonistic mAb	↑ atherosclerosis in <i>ApoE</i> ^{−/−} mice ¹⁰¹	—
IL-2/mAb immunocomplex	↓ atherosclerosis in <i>Ldlr</i> ^{−/−} mice ¹⁰⁵	↓ HCV-induced vasculitis ¹⁰⁷
Tr1 induction	↓ atherosclerosis in <i>ApoE</i> ^{−/−} mice ¹²¹	—
Anti-CD3	↓ atherosclerosis in <i>Ldlr</i> ^{−/−} mice ¹²²	—
CD31 receptor globulin	↓ atherosclerosis in <i>ApoE</i> ^{−/−} mice ¹²³	—
Vitamin D3	↓ atherosclerosis in <i>ApoE</i> ^{−/−} mice ¹²⁴	—
Immunization (active and passive) and tolerization	↓ atherosclerosis in <i>ApoE</i> ^{−/−} , <i>Ldlr</i> ^{−/−} , and huB100tg $\times$ <i>Ldlr</i> ^{−/−} mice ^{125–131,156–158}	—
B cell depletion (anti-CD20)	↓ atherosclerosis in <i>ApoE</i> ^{−/−} and <i>Ldlr</i> ^{−/−} mice ¹⁴⁴	↑ endothelial function in RA patients ¹³⁶ ↑ endothelial function, ↑ HDL, ↓ cIMT in RA patients ¹³⁷ ↑ CV events in RA patients ¹³⁸

CAD, coronary artery disease; cIMT, intima-media thickness in the common carotid artery; CRP, C-reactive protein; CVD, cardiovascular disease; HDL, high-density lipoprotein; IFN, interferon; IL, interleukin; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

lipolysis, and proteolysis by resident hydrolytic and oxidative enzymes.^{9,10} The modified LDL particles are then preferentially taken up by macrophages that accumulate intracellular cholesterol esters and become foam cells, a hallmark of atherosclerosis. In early life, the accumulation of foam cells gives rise to fatty streaks, which are the precursors of atherosclerotic lesions or atheromas.

Disease Progression: Development of the Atherosclerotic Lesion

In addition to the formation of foam cells, various bioactive functions have been ascribed to modified LDL, including stimulation of the endothelium, overexpression of adhesion molecules, such as VCAM-1 and ICAM-1, and activation of macrophages that release proinflammatory proteins (such as tumor necrosis factor (TNF), interleukin (IL)-1 β , IL-6, and CCL2), lipid mediators,¹¹ and proteolytic enzymes, such as matrix metalloproteases (MMPs).¹² These responses effect the recruitment and proliferation of cells in the intima. Thus, the accumulation of cells and lipids lead to the development of

atherosclerotic lesions, which increase in size and complexity over time.

Plaque antigens, such as ApoB100, can be transported alone or by dendritic cells (DCs), which can reach vascular draining lymph nodes or the spleen.¹³ Lysosomal proteases in the DCs generate ApoB100 peptides that are presented by major histocompatibility complex class II molecules (MHC-II) prior to the activation of CD4⁺ T cells. Through cross-presentation mechanisms, CD8⁺ T cells could also be primed locally by similar antigens.¹⁴

Subsequently, activated naïve T cells differentiate into effector and memory T cells that can re-enter the bloodstream and, when attracted by activated endothelium that expresses high levels of adhesion molecules and chemokine gradients, arrive at the atherosclerotic lesion.¹⁵

Remaining in the lymphoid organs, B cells, assisted by activated T cells, mount antibody-based responses against LDL-derived antigens. In addition to LDL, other plaque antigens have been suggested to elicit T and B cell reactions locally and in the periphery, such as β -2 glycoprotein I (β 2GPI) and heat

shock proteins (HSPs).¹⁶

Notably, at very late stages, atherosclerosis-associated lymphocyte aggregates form in the arterial adventitia. Termed “adventitial artery tertiary lymphoid organs (ATLOs)”, these lymphoid-like structures have distinct compartments, including T cell-rich areas and areas that resemble B cell follicles. ATLOs have been suggested to recruit large numbers of naïve T cells, CD4⁺ and CD8⁺ effector and memory T cells, natural and induced regulatory T cells (Tregs), and memory B cells at various stages of differentiation. Thus, primary activation of T and B cells has been hypothesized to occur in the vessel wall, within ATLOs, and in secondary lymphoid organs such as draining lymph nodes and spleen. ATLOs have been proposed to mediate the balance between pro- and anti-atherogenic responses in the vessel wall,^{17,18} but further studies are needed to examine this concept.

In the plaque, effector CD4⁺ Th1 cells release interferon- γ (IFN γ) and TNF, 2 proinflammatory cytokines with pro-atherogenic effects. Conversely, local activated Tregs can downregulate inflammation through local secretion of anti-inflammatory cytokines, such as transforming growth factor- β (TGF β) and IL-10, and by cell-to-cell contact.¹⁵

Advanced Disease: Plaque Instability and Rupture

The most common event leading to arterial thrombosis is the rupture of the plaque lesion’s fibrous cap. Advanced plaques normally have a fibrous cap: a layer of tissue that primarily comprises SMCs and collagen and prevents blood from making contact with the prothrombotic core of the plaque. Vascular SMCs synthesize several types of collagen. Their amounts, crosslinking and maturation state can influence the stability of the lesion.¹⁹ Plaque growth is associated with compensatory mechanisms, such as the remodeling of extracellular matrix proteins by MMPs and cytokine secretion by vascular and immune cells. Such remodeling can enhance collagen degradation and plaque erosion, and weaken the fibrous cap, promoting an unstable phenotype and increasing the susceptibility to rupture and thrombosis.¹²

Atherosclerosis: An Autoimmune Disease?

Witebsky defined autoimmune diseases as conditions in which (1) an autoimmune reaction occurs, in the form of an autoantibody- or autoreactive cell-mediated response, (2) the corresponding antigen is known, and (3) an analogous response that is mediated by the autoantibodies or autoreactive cells can cause similar disease in experimental animals.²⁰ Classical examples of autoimmune disease are systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren syndrome, Hashimoto thyroiditis, type 1 diabetes, multiple sclerosis (MS), and psoriasis.

Chronic inflammatory and autoimmune diseases present with mixed innate and adaptive immune responses. Thus, the classification of atherosclerosis as an autoimmune disease is debatable. However, in the past decades, significant discoveries have indicated that atherosclerosis indeed fulfills Witebsky’s postulates. Autoantibodies and autoreactive T cells against atherosclerotic plaque-derived antigens, such as HSPs, and LDL- or oxidized LDL-derived components (lysoPC, phosphorylcholine, ApoB100) have been identified,²¹ and the disease could be induced by transfer of oxLDL-reactive T cells,²² whereas blockade of ApoB100-reactive T cells has been shown to be protective.²³

Although atherosclerotic CVD is more prevalent than most of the classical autoimmune diseases, both have many similarities,

raising the possibility that therapeutic approaches to autoimmune disease will be successful in treating and preventing CVD. Of note, individuals who suffer from RA, SLE, psoriasis, and a few other autoimmune diseases have a greater and earlier incidence of atherosclerotic CVD. Nevertheless, the molecular mechanisms that mediate the acceleration of atherosclerosis and its manifestations in patients with autoimmune diseases are unclear.

Therapies for Autoimmune Disease and Atherosclerosis

Classical Antiinflammatory and Immunosuppressant Drugs

The only immunomodulatory drug that is used to prevent CAD and stroke is aspirin, although at its prescribed dose, its antiplatelet effects most likely prevail.

Statins, which have the main purpose of lowering blood cholesterol and LDL levels, have been implied to have anti-inflammatory effects.²⁴ Thus, interventions that can reduce CVD mortality and are restricted to immunomodulatory activity have not yet reached the clinic.

Classical antiinflammatory and immunosuppressive drugs, such as corticosteroids, cyclosporine, sirolimus, tacrolimus, azathioprine, cyclophosphamide, and methotrexate, remain valuable therapeutic options against autoimmune diseases, in addition to their use in preventing transplant rejection.²⁵

Post-injury lesions in rat arteries are strongly reduced by cyclosporine A treatment.²⁶ Drug-eluting stents containing sirolimus or its analogues have shown extraordinary effects in the prevention of restenosis.²⁷ Whereas immunosuppression may have the desired immunomodulatory effect that is needed to prevent and treat atherosclerotic CVD, certain classes of drugs, including glucocorticoids and nonsteroidal antiinflammatory drugs (NSAIDs), are not ideal for CVD; on the contrary, they can induce many undesirable side effects, such as thrombosis, dyslipidemia, hypertension, and diabetes.^{28,29}

Nevertheless, within this class of drugs, methotrexate, a safe and widespread first-line treatment for RA, is under investigation for its immunomodulatory activity against CVD. The Cardiovascular Inflammation Reduction Trial (CIRT; clinicaltrials.gov: NCT01594333) is randomly assigning post-myocardial infarction (MI) patients to treatment with low-dose methotrexate (15–20 mg/week) or placebo.³⁰ A separate trial in Brazil will evaluate methotrexate therapy in ST-segment elevation MI (TETHYS Trial; clinicaltrials.gov: NCT01741558) to determine whether this treatment can reduce the area of ischemia in the heart.³¹

Experimentally, the administration of methotrexate to New Zealand rabbits that were fed a high-cholesterol diet markedly reduced atherosclerosis.^{32,33} Thus, based on evidence that methotrexate decreases the risk of CVD in RA and psoriatic patients,³⁴ and directly influences atherogenesis in animals, methotrexate arises as a promising therapy.

Targeting Chief Proinflammatory Cytokines

Cytokines are the principal mediators of immunity. Thus, disturbances and imbalances in cytokine production can lead to immune dysfunction and disease. There is extensive data on the function of cytokines in autoimmune diseases, wherein several classes of cytokines have emerged as candidate targets for therapy, including TNF, IL-1 β , and IL-6,³⁵ all of which have been linked to atherogenesis.

In today’s standard management of RA, anti-TNF therapy, alone or, in most cases, combined with methotrexate, substantially improves patients’ lives, which, in certain cases, means

clinical remission. Various anti-TNF drugs are indicated for more than 15 diseases, including other classical autoimmune diseases, such as ankylosing spondylitis, psoriasis, and psoriatic arthritis.³⁶ Notably, anti-TNF therapy is associated with lower CVD risk in RA^{37,38} and psoriatic patients.³⁹

Experimentally, TNF blockade in vivo suppresses neointimal formation in the coronary arteries of transplanted hearts,⁴⁰ but not following balloon angioplasty in rabbits.⁴¹ In atherosclerosis-prone hypercholesterolemic *ApoE*^{-/-} mice, TNF deficiency or blockade mitigates atherosclerosis,⁴² suggesting that this therapy could potentially have beneficial effects on CVD in the general population.

The precise mechanisms of how anti-TNF lowers the risk of atherosclerotic CVD are unknown. Anti-TNF therapy is associated with a general reduction of inflammation; improved inflammatory parameters, such as C-reactive protein (CRP); and improved endothelial function.³⁷ Notably, increased TNF levels in plasma correlated with insulin resistance and greater plasma glucose prior to the onset of type 2 diabetes,⁴³ suggesting that the blockade of TNF, which is also secreted by fat cells within muscles, liver, and adipose tissue, has other cardioprotective effects. Consistent with this hypothesis, RA and Crohn disease patients who have concomitant type 2 diabetes and are treated with anti-TNF experience significant improvements in their fasting glucose values.⁴⁴

Interestingly, certain strategies of TNF blockade have been shown to raise plasma lipid levels,⁴⁵ whereas others have shown favorable effects on plasma lipid levels.⁴⁶ Thus, the use of cytokine blockers in CVD warrants consideration with regard to the monitoring of plasma lipids, which could limit or enhance the cardiovascular (CV) benefit. Further, TNF inhibition has been linked to undesired CV effects, such as a greater incidence of heart failure and lower heart compliance,⁴⁷ possibly warranting attention and restricting its use in certain cases.

Unfortunately, not all autoimmune disease patients react favorably to anti-TNF therapy. Certain RA patients fail to respond to the treatment, whereas others, despite initial improvement, experience relapses because of several factors, including the immunogenicity of the drugs, which causes patients to develop anti-antibodies.⁴⁸ However, these shortcomings have prompted the development of several classes of anti-TNF and drugs that target other major cytokines to treat autoimmune diseases, and which might have benefits in CVD.

Similar to TNF, IL-1 β is an important mediator of inflammation. Thus, inhibition of IL-1 β has emerged as a valuable therapeutic approach against many systemic and local inflammatory conditions, especially those that are considered “auto-inflammatory”, and certain autoimmune diseases.^{49,50} IL-1 receptor antagonism, which impairs IL-1 α - and IL-1 β -mediated activity, is an approved therapy for RA and might constitute a significant clinical alternative for chronic arthritis and cartilage erosion.⁵¹

In experimental atherosclerosis, the function of IL-1 has been examined by altering its level and activity using *ApoE*^{-/-} and *Ldlr*^{-/-} mice. Generally, these studies indicate that IL-1 α and IL-1 β have pro-atherogenic activity, whereas IL-1Ra (a natural inhibitor of IL-1 activity and an endogenous homolog of IL-1 that binds IL-1R without activating it) has anti-atherogenic functions.⁵²

Despite some discrepancies among the experimental models, the evidence for a pathogenic role of IL-1 signaling is strengthened by findings that have linked atherosclerosis with inflammasome activation.⁵³ The inflammasome is a cytosolic multiprotein complex, typically comprising a sensor protein

(most often an NLRP [NOD-like receptor]), pro-caspase-1, and an adaptor protein, called apoptosis-associated speck-like protein containing CARD (ASC). Formed in response to exogenous or endogenous stimuli, such as pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), the inflammasome cleaves pro-IL-1 β to generate mature and active IL-1 β that is later secreted.⁵⁴ In *Ldlr*^{-/-} mice, NLRP3 or ASC deficiency in hematopoietic cells has been shown to substantially decrease atherosclerosis.⁵⁵

Uric acid crystals have been shown to activate the NLRP3 inflammasome, triggering IL-1 β secretion.⁵⁶ In this context, IL-1 blockade was found to be an effective treatment for gout,⁵⁷ and colchicine, which is used to treat acute gout flares, was shown to block IL-1 β generation.⁵⁶ Interestingly, combined treatment with colchicine, statins and other standard therapies has shown promising results in the prevention of CAD.⁵⁸ Currently, there are several ongoing clinical trials investigating the benefits of colchicine for CVD.

In RA patients with coexisting CAD, IL-1 inhibition is associated with improved endothelial and coronary aortic function, and left ventricular myocardial deformation and twisting.⁵⁹ Anti-IL-1 β therapy is under investigation in the CANTOS trial (Canakinumab Anti-inflammatory Thrombosis Outcomes Trial; clinicaltrials.gov: NCT01327846), which is determining whether IL-1 β inhibition can reduce CV events and death among stable patients with CAD who remain at high risk, despite current secondary prevention strategies.⁶⁰ At the 4-month follow-up, IL-1 β blockade showed promising results; it significantly reduced inflammation (decreasing plasma levels of IL-6, CRP, and fibrinogen) without having significant effects on plasma lipid levels.⁶¹

Several studies have implicated IL-6 as another primary driver of inflammation in RA. Anti-IL-6 therapy is an approved treatment for patients with moderate to severe RA who have not responded adequately to other therapies, including anti-TNF.⁶² Paradoxically, regarding the potential use of anti-IL-6 in CVD, IL-6 blockade has been shown to upregulate ApoA1 and ApoB and, consequently, raise HDL and LDL plasma levels, respectively.^{63,64} These findings are consistent with previous work, in which IL-6 inhibited the production of apolipoproteins in hepatocytes in vitro.⁶⁵

In experimental atherosclerosis, the administration of recombinant IL-6 was found to accelerate atherogenesis in *ApoE*^{-/-} mice.⁶⁶ However, not all animal studies show such activity of IL-6 in the development of atherosclerosis (reviewed by Kleemann et al⁵²). This could be related to its pleiotropic nature, having pro- and antiinflammatory effects.⁶⁷

Long-term IL-6 blockade is considered safe and does not increase CV event rates in RA patients.⁶⁴ However, larger studies that assess the risk of IL-6 blockade in autoimmune disease patients are needed to support its use for preventing and treating CVD in the general population.

Adaptive as well as innate immunity is likely to play a significant role in atherosclerosis. T cell responses have been identified in atheromas, and particularly the Th1 subtype has been demonstrated to play a key role in the disease.¹⁵ Thus, modulation of Th1-specific signal transduction or its signature Th1 cytokine IFN γ could be a compelling therapeutic strategy for atherosclerotic CVD.

The development of IFN γ -inhibitory therapies has not advanced much experimentally and clinically. Nevertheless, injection of a plasmid that expresses a soluble receptor that neutralizes IFN γ impedes progression of the lesion and stabilizes atherosclerotic plaques in *ApoE*^{-/-} mice.⁶⁸

A humanized monoclonal antibody against IFN γ entered a

phase II clinical trial in RA patients (ClinicalTrials.gov: NCT00281294). However, that was later terminated, because the first phase did not meet its endpoint. Other anti-IFN γ drugs are now under investigation (ClinicalTrials.gov: NCT00818948), but whether this therapeutic class will attain clinical significance is unknown.

IL-17 blockade has also recently become a therapeutic approach in the treatment of autoimmune diseases. Experimental research has implicated IL-17 in the pathophysiology of several autoimmune diseases, including RA, EAE, psoriasis, and psoriatic arthritis.^{69–71} In experimental atherosclerosis, anti-IL-17A and sIL-17R reduce lesion size in *ApoE*^{−/−} mice.^{72–74} Paradoxically, IL-17A showed profibrotic properties and increased collagen expression and fibrous cap formation in *Ldlr*^{−/−} mice. Ablation of Smad7 enhanced TGF- β signaling in *Ldlr*^{−/−} mice, which, on being fed a high-cholesterol diet, upregulated IL-6 levels and induced a shift from a Th1 to Th17 cell response.⁷⁵ Treatment of Smad7-deficient chimeras with anti-IL-17A impeded fibrous cap formation, confirming that IL-17A has fibrogenic properties and suggesting that it may prevent plaque instability.⁷⁵

The potential atherosclerotic plaque-stabilizing activity of IL-17 raises concerns about the use of IL-17 blockade in chronic inflammatory diseases. Therefore, patients who undergo IL-17 blockade should be monitored carefully with regard to their CV status.

Based on experimental and clinical data, other cytokines may be potential targets in the development of therapies for CVD. Promising results have been achieved for IL-12/IL-23-blocking antibody (binding its common subunit, p40) in psoriasis patients. However, the data on the CV safety of this strategy in these patients are conflicting, in part because of the limited number of events and short follow-up times in trials.⁷⁶ Yet, in preclinical studies, IL-12 blockade by vaccination resulted in significant atheroprotection in *Ldlr*^{−/−} mice.⁷⁷

Elevated levels of IFN α have been reported in the sera of a subgroup of SLE patients, and hundreds of IFN-stimulated mRNA species are found in the blood of these patients.⁷⁸ SLE patients with high type I IFN activity in the serum display substantial endothelial dysfunction, which has been proposed as a mechanism of the increased risk for CVD in SLE patients.⁷⁹

Type I IFN signaling is upregulated in ruptured human atherosclerotic plaques, and accelerates disease in hypercholesterolemic mice, suggesting a deleterious function of this cytokine in atherosclerotic CVD.⁸⁰ Anti-IFN α therapy is under investigation in the “low” type I IFN subgroup of SLE patients, in whom it has been associated with clinical improvements.⁸¹ Additional studies are needed to understand the function of type I IFNs in atherosclerosis and determine whether this class of cytokines is a therapeutic target.

Targeting Effector T Cell Responses

Effector T cell responses are central in many inflammatory disorders, including autoimmune diseases,⁸² and atherosclerosis.¹⁵ Several attempts have been made to target T cells in autoimmune and other diseases, including their specific elimination with anti-CD4, using anti-thymocyte globulin, and anti-CD52.⁸³ However, many issues have limited their use, including long-lasting T cell depletion, cytokine release syndrome, immunogenicity to rabbit/equine antibodies resulting in serum sickness, immune thrombocytopenic purpura, thyroid dysfunction, and infections.⁸³

Immunization against the variable regions of the T cell receptor (TCR) induces antibody-dependent depletion of antigen-

specific T cells. This treatment can prevent collagen-induced arthritis⁸⁴ and EAE.⁸⁵ This approach has been tested for atherosclerosis, wherein immunization against a peptide from the T cell receptor β variable 31 (TRBV31), a TCR β chain that recognizes ApoB100, substantially mitigated experimental disease.²³

T cells, particularly naïve cells, depend highly on costimulation for their activation. Thus, targeting surface costimulatory molecules has been considered in an attempt to control T cell-mediated responses. A CTLA4-Fc fusion protein (cytotoxic T lymphocyte-associated antigen-Fc) that inhibits the binding of CD28 on the T cell to its complementary costimulatory molecules on antigen-presenting cells (ie, CD80 (B7.1) and CD86 (B7.2)) has been developed and is being examined as a first-line biologic for the treatment of RA.⁸⁶

A 6-month therapy regimen with a CTLA4-Fc fusion protein (CTLA4.Ig; abatacept) significantly affected disease activity in RA patients. In parallel, treatment with CTLA4.Ig improved plasma lipoprotein profiles by increasing significantly HDL levels.⁸⁷ However, no influence on aortic stiffness, which was used as a surrogate marker of CV risk, was observed after treatment with abatacept.

Targeting of the CD28-CD80/86 costimulatory pathway has yielded encouraging results in experimental atherosclerosis. Administration of CTLA4.Ig to hypercholesterolemic ApoE3*Leiden mice reduced atherosclerosis substantially, whereas CTLA4-blocking antibodies increased the atherosclerotic plaque size compared with controls.⁸⁸ Further, CTLA4.Ig was shown to regulate blood pressure through the modulation of T cell responses in mice.⁸⁹ Thus, this pathway emerges as a promising target in managing atherosclerotic CVD.

Other costimulatory molecules are being investigated in autoimmune and inflammatory diseases, including CD40, CD40L (CD154), OX40, and ICOS. Promising approaches have been developed preclinically by targeting some of these molecules to treat autoimmunity.⁹⁰ However, a trial of anti-CD40L monoclonal antibody (mAb) in patients with SLE was halted due to unexpected fatal thrombotic events.⁹¹ This may be logical, considering that most of the CD40L in blood is expressed on platelets, not T cells.⁹²

In experimental atherosclerosis, CD40-CD40L interactions induce a proinflammatory response, thus accelerating the disease,^{93,94} whereas CD40L blockade is associated with atheroprotection.⁹⁵ Notably, anti-CD40L has been proposed to influence plaque size and stability through the induction of collagen.⁹⁶

The costimulatory molecule, OX40L, has been identified as a genetic risk factor for CAD, RA, and MS,⁹⁷ and anti-OX40L therapy protects against disease in *Ldlr*^{−/−} mice.⁹⁸ Yet, targeting of a costimulatory molecule has yielded disparate results in different diseases. For instance, an agonistic anti-CD137 mitigated disease in murine autoimmune models,^{99,100} but exacerbated atherosclerosis in *ApoE*^{−/−} mice.¹⁰¹

A lethal systemic proinflammatory cytokine storm was unfortunately induced in healthy volunteers by targeting CD28 with agonistic anti-CD28.¹⁰² Therefore, the use of some therapeutics that are directed toward certain costimulatory molecules may be a powerful but dangerous approach to treating CVD.

Induction of Protective Treg Responses

Tregs are central in the maintenance of immune homeostasis, preventing autoimmunity. Thus, disruption in their development and function causes autoimmune and inflammatory diseases in humans and animals.¹⁰³ For example, polymorphisms in *Il2*, *cd25*, and *Ctla4* that alter Treg development and function

induce such pathologies.¹⁰⁴

Immunotherapies that expand Tregs or shift the balance between Tregs and effector T cells are potential alternative treatments for autoimmune diseases and atherosclerotic CVD.

When administered as an immune complex with anti-IL-2 mAb, IL-2 enhances the Treg pool and impairs experimental atherosclerosis.¹⁰⁵ IL-2-targeting therapies, as immune complexes with anti-IL-2 or alone at low doses, might be a suitable method of expanding Treg populations in vivo.¹⁰⁶ In a clinical trial, low-dose IL-2 effected Treg recovery and clinical improvement in 8 out of 10 patients with hepatitis C virus -induced vasculitis, an autoimmune condition that is brought on by infection with the virus.¹⁰⁷

Other therapeutic strategies have been proposed to expand Treg pools, including infusion of autologous Tregs that have been differentiated and expanded in vitro.¹⁰⁸ Although this approach is performed easily in preclinical research, wherein Tregs can be prepared from a large pool of cells from the spleens of donor mice, the expansion of human peripheral blood Tregs, a minor fraction of CD4⁺ T cells, has been difficult. Until these technological hurdles are overcome, this therapeutic prospect remains limited.

The balance between Tregs and effector T cells can be altered through a reduction in effector T cells and by attenuation of their effector activity by immunomodulatory approaches, including the use of immunosuppressants, and cytokine- and costimulatory molecule-targeting drugs.¹⁰⁸

The depletion of Tregs and abrogation of Treg-mediated responses accelerate atherosclerosis.^{18,109–112} Unexpectedly, depletion of Foxp3⁺ Tregs substantially increases cholesterol levels in *Ldlr*^{−/−} mice, particularly because of impaired clearance of chylomicrons and VLDL.¹¹² This finding highlights the important crosstalk between immunity and metabolism and its role in CVD.

Low Treg numbers and imbalance between Tregs and effector T cells have been associated with CVD events.^{113–116} There is also evidence that statin treatment correlates with higher Treg numbers.^{117–120} Overall, the existing experimental and clinical data indicate that Tregs may influence lipoprotein metabolism and vice versa.

Experimental approaches that induce and expand Tregs (through bystander activation of Tr1 cells in vivo,¹²¹ anti-CD3 infusion,¹²² CD31 receptor globulin,¹²³ oral administration of calcitriol (1,25-dihydroxycholecalciferol), an active form of vitamin D3,¹²⁴ and vaccination) limit inflammation and the development of atherosclerosis.

With regard to vaccination strategies, subcutaneous and mucosal administration of ApoB100 peptide,^{125,126} intravenous injection of IL-10-induced tolerogenic DCs that are loaded with native ApoB100,¹²⁷ mucosal tolerization against oxidized LDL,¹²⁸ subcutaneous immunization and mucosal tolerization against HSP65,^{129,130} and mucosal tolerization to β 2-glycoprotein I¹³¹ are atheroprotective in mice, an effect attributed at least in part to Treg expansion. Of note, mucosal administration of atherosclerosis-related antigens, orally and nasally, appears to be a very efficient method of inducing antigen-specific Tregs that combat atherogenesis.

Targeting B Cell Responses

The contribution of B cells in autoimmunity is well recognized. B cells pathological role has been attributed to their capacity to secrete autoantibodies, particularly those that can induce highly inflammatory immune complex deposits, through cytokine secretion, upregulation of costimulatory molecules, antigen presentation by MHC and CD1 molecules inducing

pathogenic T cell responses, and their ability to initiate the formation of lymphoid-like structures.¹³² Yet the discovery of a new B cell subtype, the regulatory B cell (Breg), which secretes IL-10 and TGF β and affects Treg development, has revealed another mechanism by which these cells can influence autoimmunity, inhibiting antiinflammatory activity.¹³³

B cell depletion by a chimeric anti-CD20 antibody (rituximab) has substantial clinical benefit in many autoimmune and chronic inflammatory diseases, including type I diabetes,¹³⁴ RA, and SLE.¹³⁵

Rituximab-mediated B cell depletion was recently shown to improve endothelial function for at least 12 weeks in RA patients, at the same time as improved RA clinical disease activity and most inflammatory markers.¹³⁶ Consistent with these findings, a smaller trial reported favorable effects of anti-CD20 therapy on endothelial function. Lowering of plasma total cholesterol, raised HDL levels, and decreased intima-media thickness in the common carotid artery were also observed in the trial.¹³⁷

Although rare, anti-CD20 therapy has shown adverse effects in the form of CV events, causing patients to be withdrawn from anti-CD20 clinical trials.¹³⁸ Nevertheless, with regard to the concern over the use of anti-CD20 therapy for CVD, there is debate on whether statins decrease the efficacy of anti-CD20 agents.^{139,140} More studies are needed to examine the potentially deleterious effects of statins on anti-CD20 drugs. If confirmed, the use of the approach in CVD could be limited.

The function of B cells has been evaluated in various animal models of atherosclerosis. The elimination of a large B cell population by splenectomy accelerates atherosclerosis in *ApoE*^{−/−} mice, whereas adoptive transfer of B cells rescues the disease.¹⁴¹ Similarly, B cell deficiency increases atherosclerosis in *Ldlr*^{−/−} mice.¹⁴² One later study has suggested that B1a cells and their secretion of IgM mediate the protective effects of B cells.¹⁴³

Although these data indicate an atheroprotective function of B cells in atherosclerosis, B cell depletion with anti-CD20 was shown to protect against atherosclerosis in *ApoE*^{−/−} and *Ldlr*^{−/−} mice,¹⁴⁴ suggesting the contrary. Notably, anti-CD20 therapy depletes mature B2 cells, whereas B1a cells are unaffected, suggesting that B2 cells are pro-atherogenic through modulation of T cell-dependent mechanisms, and that B1a cells mediate atheroprotection.

Consistent with this hypothesis, Sage et al demonstrated that a lack of B cell-activating factor receptor (BAFFR), which is critical for maintaining mature B2 B cells, substantially mitigates atherosclerosis in *Ldlr*^{−/−} mice.¹⁴⁵ Further, the targeting of B-lymphocyte stimulator (BLyS), another growth factor that is required for B cell survival, maturation, and activation, has shown significant clinical improvement in SLE patients.¹⁴⁶

Moreover, considering the function of B cells in atherosclerosis, antibodies against several oxidation-specific epitopes of LDL are found in animals and humans, both in the circulation^{147–151} and in atherosclerotic plaques.^{152,153} Although the mechanisms by which antibodies against LDL and other atherosclerosis-related antigens act in disease remain unclear, many experimental atherosclerosis studies have shown that vaccination is protective (see reviews^{154–156}).

Studies have suggested that the protective effects of vaccination can be mediated by the induction of protective Treg responses, as discussed, and also by the induction of protective antibodies. Thus, consistent with its potential atheroprotective function in atherosclerosis, antibody transfer has been shown to reduce disease burden.^{156–158} These findings have

prompted interest in the development of vaccination for atherosclerotic CVD, including many centers under the aegis of the European Union [European Consortium-VIA (Vaccination in Atherosclerosis)].

A greater understanding of the functions and mechanisms of various B cell subsets, the role of recognized antigens and antibody isotypes in atherosclerosis is needed to guide the development of clinically relevant immunomodulatory approaches against atherosclerosis.

Conclusions

Immunomodulation is a promising therapeutic approach against CVD. However, atherosclerosis is a chronic disease, and long-term therapies might increase the risk of complications that are related to immunosuppression. Hence, it is unknown which patients will benefit most from immunomodulation. An assessment of the CV effects of immunomodulatory therapies in autoimmune disease patients might teach us important lessons on their safety and efficacy in CVD.

Monitoring the effects of such therapies on classical risk factors for CVD is also critical. For example, certain cytokines are pleiotropic and might have significant functions in metabolic and immunologic pathways during disease and in health. Thus, a better understanding of the disease, particularly in defining the stages of atherogenesis that are to be targeted, is needed. Certain immunomodulatory approaches, such as vaccination, might be a realistic approach that can be implemented before the disease develops. Strategies that enhance Treg responses, which can re-establish immune homeostasis, might be beneficial in the treatment of atherosclerosis at various stages of the disease. Furthermore, specific effector molecules of the immune system may be useful as disease-modifying therapy targets, for instance by promoting plaque stabilization and improving lipid metabolism.

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Disclosures

Conflicts of Interest: None.

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