REVIEW ARTICLE

Inflammation: A Novel Therapeutic Target/Direction in Atherosclerosis

Bin Li[a], Weihong Li[b], Xiaoli Li[a] and Hong Zhou*[,a]

[a]*Department of Pharmacology, College of Pharmacy, Third Military Medical University, Chongqing 400038, China;* [b]*Assisted Reproductive Center, The First Affiliated Hospital, Chongqing Medical University, Chongqing 400016, China*

Abstract: Over the past two decades, the viewpoint of atherosclerosis has been replaced gradually by a lipid-driven, chronic, low-grade inflammatory disease of the arterial wall. Current treatment of atherosclerosis is focused on limiting its risk factors, such as hyperlipidemia or hypertension. However, treatment targeting the inflammatory nature of atherosclerosis is still very limited and deserves further attention to fight atherosclerosis successfully. Here, we review the current development of inflammation and atherosclerosis to discuss novel insights and potential targets in atherosclerosis, and to address drug discovery based on anti-inflammatory strategy in atherosclerotic disease.

1. INTRODUCTION

Atherosclerosis and subsequent cardiovascular diseases are the leading causes of death worldwide. For a long time, atherosclerosis is considered as a predominantly lipid-driven disease, which is characterized as lipid deposition in the arterial wall. Thus, previous therapies were supposed to focus on the prevention of risk factors, such as hyperlipidemia, hypertension, etc. However, the risk of atherothrombotic complications still remains high, causing millions of deaths around the world each year. The viewpoint of atherosclerosis has been replaced gradually by a lipid-driven, chronic, low-grade inflammatory disease of the arterial wall over the past two decades [1]. Over time, anti-inflammatory strategies are increasingly being considered as an attractive strategy to further reduce the residual risk of atherosclerotic cardiovascular disease (ASCVD) [2, 3]. It is known that statins are the most efficient therapeutic drugs by reducing the levels of atherogenic lipoproteins and preventing major cardiovascular events. In addition, statins also have anti-inflammatory effects independent of LDL lowering that may contribute to the treatment of atherogenesis and other cardiovascular diseases [4, 5]. However, treatment targeting the inflammatory nature of atherosclerosis is still very limited and deserves further attention to fight atherosclerosis successfully [6].

Although lipoproteins and lipid-related factors are very important in the pathogenesis of atherosclerosis, we plan to discuss and review some developments focusing on this review to describe the current development of inflammation mechanisms of atherosclerosis and some trials targeting inflammation in atherosclerosis and ASCVD patients, to discuss novel insights and potential targets in atherosclerosis and to address drug discovery based on anti-inflammatory strategy in atherosclerotic disease.

2. PATHOLOGICAL PROCESS OF ATHEROSCLEROSIS

2.1. Lipid Theory and Atherosclerosis

The term "atherosclerosis" is derived from the Greek words atheroma meaning "soft, or porridge-like" to describe the physical appearance of the intima of arteries. The "lipid theory" of atherosclerosis has predominated as a major risk factor and has driven most of the therapeutic approaches. Lipid accumulation at sites of non-laminar flows is currently the most characterized [7]. Briefly, low density lipoprotein (LDL) becomes modified by oxidization as a normal metabolic consequence. Oxidized lipids are among the earliest initiating factors of the development of atherosclerosis. Next, the atherosclerotic lesion begins with the entry to LDL-cholesterol into the vascular intima. Subsequently, the accumulated LDL is oxidized and the oxidation of this LDL-cholesterol leads to the expression of adhesion and chemotactic molecules. Then, blood monocytes and various types of leukocytes adhere to the endothelium and take up oxidized LDL (OxLDL) leading to the formation of cholesterol-laden foam cells and atherosclerotic plaques. The subsequent activities including cellular signaling, cellular recruitment, enzyme production, and protein modification ignite a flurry of activity that serves to further progress atherosclerotic plaque development [8, 9].

Nowadays, many therapeutic approaches have been tested to treat atherosclerosis and prevent its complications. However, the risk of atherothrombotic complications still remains high. In the latest research, Ramsden *et al.* reported that replacement of saturated fat in the diet of linoleic acid effectively lowers serum cholesterol but does not support the hypothesis that this translates into a lower risk of death from coronary heart disease or all causes [10]. Extensive research has highlighted promising new therapeutic targets, each being implicated at different stages of the atherosclerotic plaque formation and progression.

2.2. The Role of Inflammation in Atherosclerosis

In the past three decades, the increasing research data suggest that atherosclerosis is an inflammatory disease [11, 12] and the immune system and inflammatory was gradually recognized to play a pivotal role in the development and progression of atherosclerosis [13, 14]. Atherosclerosis is characterized by the accumulation of monocytes/ macrophages, smooth muscle cells and lymphocytes within the arterial wall. Lipid uptake by monocytes/macrophages promotes their differentiation into large, lipid-laden foam cells in the vessel wall. The accumulation of inflammatory cells leads to the production of reactive oxygen species and cytokines [15]. Therefore, the previous view that the development of the atherosclerotic lesion

*Address correspondence to this author at the Department of Pharmacology, College of Pharamacy, The Third Military Medical University, P.O. Box: 400038, Chongqing, China; Tel/Fax: +86-23-68752266; E-mail: zhouh64@163.com

Table 1.   **Targets and relative agent based on the inflammation mechanism in atherosclerosis.**

Target		Agent	References
Th1 cytokines	IL-1β	Canakinumab (IL-1β mAb)	[55]
		Anakinra (IL-1R antagonist)	[57, 58]
		Rilonacept (IL-1 trap)	[63, 64]
	IL-6	Tocilizumab (IL-6R mAb)	[67]
	IL-12	Ustekinumab (CNTO-1275) (p40 subunit of IL-12 and IL-23 Ab)	[73, 74]
		Briakinumab (ABT-874) (both IL-12 and IL-23 mAb)	[75, 76]
	IFN-γ	Fontolizumab (anti-IFN-γ Ab)	[82, 83]
	TNF-α	Tanercept, Infliximab and Adalimumab (TNF-α neutralizing Ab)	[86, 87]
Th2 cytokines	IL-4	CYM5442 and FTY720	[94]
	IL-13		[95]
	IL-33		[97, 98]
B cells	CD20	Rituximab	[29, 103]
	BAFF-R	Tabalumab (BAFF mAb)	[108, 109]
TLRs pathway	TLR4	Eritoran (a most advanced TLR4 antagonist)	[112]
	TLR2	TLR2 and MyD88 neutralizing Ab	[113]
		OPN-305 (a TLR2-specific mAb)	[114]
	NF-kB	DHMEQ(NF-kB inhibitor)	[115]
		Pterostilbene	[118]
		Artesunate	[119, 120]
	IkB kinase β/2	IkB kinase β/2 Ab	[116]
	p38	p38 inhibitors	[117]
	TRAF6 and IRAK1	miR−146	[114]
Co-stimulatory molecules	CD28–CD80/CD86	Abatacept (a fusion protein of CTLA-4–Ig)	[124]
		Belatacept (anti-CD80 and anti-CD86 fusion protein)	[127]
		RhuDex (a small-molecule inhibitor of CD80)	[129]
	CD154–CD40	Ruplizumab (anti-CD154 mAb)	[133, 134]
		ABI793 (anti-CD154 mAb)	[135]
		CP-870,893 (agonistic anti-CD40 Ab)	[136]
		Dacetuzumab (agonistic anti-CD40 Ab)	[137]
		ChiLob 7/4 (agonistic anti-CD40 Ab)	[138]
		Ch5D12 (antagonistic anti-CD40 Ab)	[139]
	OX40L–OX40	Anti-OX40L Ab or OX40 immunoglobulin fusion proteins	[142]
	CD137L–CD137		[144, 145]
Leukocyte recruitment and migration	MCP-1/CCL2		[153]
	CCR2	MLN1202 (CCR2 antanonist)	[155]
	CCL19 and CCL21		[161]
	CCL17		[158, 160]

(Table 1) Contd....

Target		Agent	References
	P-Selectin	RO4905417 (P-selectin antagonist)	[151]
		Sialyl-Lewis X (mimicry of the common ligand of all selectins)	[152]
		Small-molecule inhibitors of the CCL17– CCL4 interaction	[160, 161]
PLA2	sPLA2	Varespladib (sPLA2 inhibitor)	[167]
	Lp-PLA2	Darapladib (Lp-PLA2 inhibitor)	[168-170]
		SB-4808 (Lp-PLA2 inhibitor)	[171]
Leukotrienes	5-LO	VIA-2291 (5-LO inhibitor)	[174]
	15-LO	PD145176 (15-LO inhibitor)	[175]
	FLAP	DG-031 (FLAP inhibitor)	[176]
HSP		Mycobacterial HSP-65	[179]
Other targets	Rho–ROCK pathway	SLx2119 (ROCK 2 inhibitor)	[180]
	p38 MAPK	SB-681323 (p38 MAPK inhibitor)	[181]
	CB-1 receptor	Rimonabant (CB-1 antagonist)	[182]
	CB-2 receptor	THC (CB2 agonist)	[183]
	ROS	Succinobucol(antioxidant)	[184, 185]
	ANGPTL4	miR-134	[186]
	PDCD4	miR−16	[187]
	Tregs and tolerogenic DCs	Vaccines targeting autoimmunity	[188]

solely depends on lipid deposition has been replaced by the current concept that activation of immune and inflammatory responses has a central role in plaque initiation and progression. Many anti-inflammatory strategies have emerged as potential treatments of atherosclerotic disease, in addition to the existing lipid-lowering therapies.

2.2.1. The Role of Innate Immune System in Atherosclerosis

Increasing evidence strongly supports the important role of the innate immune systems in lesion formation [6, 16]. Monocyte and macrophages are key cellular effectors in atherosclerosis. "Inflammatory" monocytes are preferentially recruited into atherosclerotic plaques through the chemokine receptors CCR2, CCR5 and CX3CR1 and their ligands [17]. "Resident" monocytes are also recruited into atheroma via CCR5 less frequency than 'inflammatory' monocytes [18]. Such accumulation results in the formation of the atherosclerotic plaque [19].

Monocytes and endothelial cells are not the only cells that participate in lesion formation. In the acute phase following an ischemic event, hematopoietic tissues of the bone marrow and spleen are able to expand the pool of proinflammatory monocytes that paradoxically aggravate atherosclerosis [20]. Next, circulating monocytes are exposed to a typical atherosclerotic danger signal oxLDL and obtained a trained hyperresponsive state [21]. These findings imply that circulating innate immune cells can be programmed toward a pro-atherogenic state.

Then, monocytes are continuously recruited to atherosclerotic plaques [22]. The number of monocytes correlates with plaque burden and inhibition of monocyte influx can result in a decrease in atherosclerosis [23, 24]. In more advanced plaques, plaque macrophages may proliferate locally leading to macrophage abundance.

The progression of atherosclerotic plaques is driven by an imbalance between formation and clearance of apoptotic macrophages, a phenomenon described as 'defective efferocytosis' [25]. Mentioned above these findings regarding innate immunity's role in atherosclerosis may provide some novel potential therapeutic targets.

2.2.2. The Role of Adaptive Immune System in Atherosclerosis

The adaptive immune system can also play the key role by antibody responses or cell-mediated immune responses. The key components of adaptive immune system are T-cells, B-cells and the antigen-presenting cells (APCs). Other inflammatory cells, mast cells and different subsets of dendritic cells (DCs), also contribute to lesion formation through antigen recognition and cytokine production [26].

In antibody responses, activated B cells secrete antibodies to block special antigen the interaction with their receptor on the host cell. B-cells can appear individually or aggregate in atherosclerotic plaques [27]. B-cells are divided into B1 and B2 subsets. B1 cells predominantly produce IgM antibodies and are protective against atherosclerosis [28]; B2 cells predominantly produce highly specific IgG antibodies and promote atherosclerosis [29].

B1 cells have three different subtypes, B1a, B1b and innate response activator. B1a cells predominantly produce the IgM antibodies, which are atheroprotective. The role of B1b cells in atherosclerosis remains unknown [30, 31]. B2 cells have two subtypes. B2 conventional play a pro-atherogenic role by taking part in CD4 T-cell activation and effector T-cell proliferation [31]. Regulatory B-cells (Bregs) secreted IL-10 and might play an athero-protective role [32]. B-cells might be potential therapeutic target and maybe used via B2-cells in vaccination strategies against atherosclerosis.

In the cell-mediated immune responses, activated T-cells respond directly to antigens presented on APCs and secrete signal molecules. T-cells are found in atherosclerotic lesions and play a pivotal role in the progression of atherosclerosis [33]. They have an ability to differentiate from different helper T-cells subtypes, such as Th1, Th2, Th17 and Treg. Effects of Th1 cells are clearly pro-atherogenic, whereas Treg cells are athero-protective. Th2 cells present in atherosclerotic lesion play both atheroprotective and athero-promoting roles as a target for the treatment of atherosclerosis remains controversial [34]. The role of Th17 cells in atherosclerosis is still not clear. Thus, interfering with Th cells cytokine or chemokine signalling is an emerging approach for development of the treatment of atherosclerosis.

In addition, there are multiple antigenic stimuli that have been associated with the pathogenesis of atherosclerosis. Most of them come from modified self-antigen molecules such as oxLDLs, beta2 glycoprotein1 (β2GP1), lipoprotein a (LP(a)), heat shock proteins (HSPs), *et al*. In addition, several foreign antigens, such as bacteria and viruses, have also been associated with atherosclerosis, specially in atherogenesis as causative or bystander participants in its development [19].

The NLR family, pyrin domain containing 3 (NLRP3) inflammasome is an interleukin (IL)-1β and IL-18 cytokine processing complex that is activated in inflammatory conditions [35]. Recent studies have suggested that the NLRP3 inflammasome signaling pathway components NLRP3, caspase-1, IL-1β, and IL-18 were strongly expressed in carotid atherosclerotic plaques [36] and NLRP3 inflammasome plays an important role in the development of vascular inflammation and atherosclerosis [37].

2.2.3. Effect of Inflammation Mediated by Toll Like Receptors in Atherosclerosis

Toll like receptors (TLRs) are the best-characterized pattern recognition receptors of the innate immune system and play a central role in innate and adaptive immune responses. TLRs represent an important link between atheroma and inflammation [38]. All populations of leukocytes, including monocytes/macrophages, DCs and T and B lymphocytes, appear to express TLRs [39].

Over the past few years, there is increasing evidence to indicate that TLRs and their ligands play key roles in various aspects of atherosclerotic lesion formation and development. Both exogenous and endogenous TLR ligands have been detected in atherosclerotic lesions [40, 41]. Saturated fatty acids induce inflammatory gene expression through TLR4 activation [42]. ApoCIII can induce pro-inflammatory signals in monocytes by TLR2 [43]. Minimally modified LDLs induce TLR4 activation in macrophages via the MyD88-dependent pathway or the MyD88-independent pathway [44]. Oxidized LDL increased chemokine gene expression in macrophages through a TLR4/6 heterodimer [45].

TLR 2 and TLR4 are the most extensively studied TLRs in atherosclerosis [40]. TLR2 plays a critical role in the progression of atherosclerosis in Apo E$^{-/-}$ mice. Blocking TLR2 is effective against dampening activation of human atherosclerotic lesions and in reducing the area of myocardial infarction in murine models of acute ischemia [46]. ApoE$^{-/-}$ mice with advanced atherosclerosis also display increased TLR2 and TLR4 expression on circulating cells [47]. Since genetic deletion of TLR2 and TLR4 is athero-protective in murine models of atherosclerosis [48, 49], antagonism of these receptors is an attractive prospect for treating atherosclerosis.

Hence, TLRs are able to sense modified lipids, enhance foam cell formation, induce leukocyte recruitment, and increase cytokine and matrix metalloproteinase production within atherosclerotic lesions. TLRs and their ligands are present and contribute to atherosclerotic lesion formation, which provide an attractive therapeutic target for treating disease.

3. DRUG DISCOVERY AND POTENTIAL TARGETS BASED ON THE INFLAMMATION MECHANISM IN ATHEROSCLEROSIS.

Since atherosclerosis is a complex, chronic inflammatory disease, its treatment may be faced for many different inflammatory molecules and targets. At present, the research targeted on these molecules and targets is mainly some antibodies or inhibitors. But in recent years, some natural substances, plants, traditional Chinese herbs have also been used in the study of atherosclerosis treatment (Table **1**).

3.1. Th1 Cytokines and Relative Drug Discovery

3.1.1. IL-1

IL-1 is a primary pro-inflammatory cytokine after injury [50] and plays an important role in atherogenesis [51]. The level of IL-1 was elevated in the human atherosclerotic arteries, and the IL-1 receptor antagonist (IL-1ra) gene was associated with a lower incidence of restenosis after coronary stenting [52]. IL-1β is another important cytokine promoting inflammation in atherosclerosis [51, 53]. However, the inhibition of IL-1β does not adversely affect lipid levels [54].

Canakinumab, a monoclonal antibody which neutralizes IL-1β, is ongoing a large secondary prevention trial in patients with prior acute myocardial infarction [Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)] [55].

Anakinra, an interleukin-1 receptor antagonist, can ameliorate the endothelial function in patients with rheumatoid arthritis (RA) [56] and reduce the inflammatory response in acute MI patients [57, 58]. Although anakinra therapy had no effect on the recurrence risk [59], one possible reason is different in acute versus chronic settings [60]. In addition, short-term use of anakinra has done a HEART study in patients presenting with myocardial infarction by the Medical Research Council [61].

Rilonacept is an IL-1 trap and used in the treatment of rheumatoid arthritis and other inflammatory diseases as an antagonist of IL-1 [62]. The effects of rilonacept on CRP level and endothelial function are evaluated in a randomized clinical trial [63]. Also, treatment with recombinant IL-1ra has been shown to be a successful antiatherosclerotic therapy in mice [64].

3.1.2. IL-6

A high circulating concentration of IL-6 is associated with increased risk of coronary heart disease. Recent studies provided strong evidence for a causal role of IL-6 signalling in coronary heart disease [65]. Targeting treatment of IL-6 receptor (IL-6R) also provided a promising therapeutic approach to prevention of coronary heart disease [66]. Results from two mendelian randomisation studies demonstrate that inhibition of IL-6 or IL-6R is considered as a promising therapeutic target to decrease ASCVD complications [65, 66].

Tocilizumab, a monoclonal antibody to block IL-6R, is currently solely licensed for treatment of RA [67]. However, Tocilizumab also increases cholesterol levels in RA patients, which may antagonize a potential beneficial effect of the intervention [67]. This target may seem promising in cardiovascular diseases. Currently, a randomized, placebo-controlled study is evaluating the impact of tocilizumab in 120 patients after a MI on major adverse cardiovascular events within the first 30 days (ClinicalTrials.gov Identifier: NCT02419937).

3.1.3. IL-12

IL-12 plays a central role in the differentiation of the T-cells into Th1 cells and triggers the expression of Th1 cytokines [68]. IL-12 deficiency in ApoE$^{-/-}$ mice was able to reduce atherosclerosis [69]. Administration of IL-12 significantly increased the size of atherosclerotic lesions [70]. In LDLr$^{-/-}$ mice, the IL-12 antibody resulted in a significant reduction of atherosclerotic lesion size [71].

The aforementioned results suggest that IL-12 is involved in the development of atherosclerosis and as a good target for the treatment of atherosclerosis.

Ustekinumab (CNTO-1275) is a new antibody against the p40 subunit of IL-12 and IL-23. It is approved by the US FDA as a drug for the treatment of psoriatic arthritis and moderate-to-severe plaque psoriasis [72]. Ustekinumab was also tested in Phase II clinical trials for other inflammatory diseases, such as multiple sclerosis [73] and sarcoidosis [74].

Briakinumab (ABT-874) is another human monoclonal antibody targeting both IL-12 and IL-23 for the treatment of autoimmune diseases [75]. It was tested for the treatment of moderate-to-severe psoriasis, but it was withdrawn from Phase I clinical trials in 2011 [76].

These results suggest that IL-12 is a good target for the treatment of atherosclerosis. The progress of antibody development for the treatment of inflammatory diseases provides the opportunity for anti-IL-12 antibodies to be tested for then treatment of atherosclerosis.

3.1.4. IFN-γ

IFN-γ is a prototypic Th1 cytokine and is present in atherosclerotic lesions upon activation by oxLDL [77]. In the ApoE–/– mouse model, IFN-γ deficiency resulted in a more stable plaque phenotype [78]. Treatment targeted at IFN-γ with IFNγR gene transfer in ApoE$^{-/-}$ mice resulted in significant 60% reduction of atherosclerosis [79]. Therefore, INF-γ is considered to play a pro-atherogenic role as a good target for the treatment of atherosclerosis [80].

Sortilin is the common receptor of IFN-γ and IL-6. In the ApoE$^{-/-}$ mice, sortilin deficiency decreased the level of IFN-γ and IL-6 and resulted in a reduction of the size of the atherosclerotic lesion [81]. Thus, blocking sortilin is suggested to be a promising strategy to treat atherosclerosis. However, until now, there are no small molecules available that directly target IFN-γ.

Fontolizumab, an anti-IFN-γ antibody, was tested for the treatment of RA or psoriasis [82]. However, its development was stopped because the Phase I clinical trials did not meet the endpoint. Fontolizumab was also tested for treatment of psoriasis but did not show a significant effect [83].

3.1.5. TNF-α

In patients with rheumatoid arthritis, endothelial dysfunction and increased atherosclerosis are observed. TNF-α is a potent pro-inflammatory cytokine that plays a key role in rheumatoid arthritis. And TNF-α also is closely associated with the mechanisms of accelerated atherosclerosis in the rheumatoid arthritis [84, 85].

Patients with rheumatoid arthritis were treated with the TNF-α blocking agent, including infliximab (a TNF-α neutralizing antibody), etanercept and adalimumab. A significant increases of total and HDL cholesterol levels were observed [86]. The endothelial function has been improved in such patients treated with infliximab [87].

Some anti-atherosclerotic drugs in clinical have been reported to inhibit the inflammatory response by targeting these inflammatory cytokines. Ezetimibe attenuates atherosclerosis associated with lipid reduction and decreasing circulating inflammatory cytokines in the lesions, such as monocyte chemoattractant protein (MCP-1) and tumor necrosis factor (TNF-α) [88]. Atorvastatin can also protect against a moderate atherosclerotic lesion by lowering serum cholesterol, decreasing inflammatory cytokines, and inhibiting macrophage accumulation in the lesions [89]. Tanshinone IIA is one of the major diterpenes in Salvia miltiorrhiza. The anti-atherosclerotic effect of tanshinone IIA is associated with the inhibition of TNF-α-induced vascular cell adhesion molecule-1 (VCAM-1), intercellular cell adhesion molecule-1(ICAM-1) and C-X3-C motif ligand 1(CX3CL1) expression [90].

3.2. Th2 Cytokines and Relative Drug Discovery

3.2.1. IL-4

IL-4 is a Th2 cytokine expressed in atherosclerotic lesions [69], but its role in atherogenesis remains controversial. The results from the deficiency of IL-4 in ApoE$^{-/-}$ and LDLr$^{-/-}$, and exogenous administration of IL-4 in ApoE$^{-/-}$ mice, are contradictory [69, 91]. IL-4 intervention attenuated ox-LDL-induced atherosclerotic lesions in ApoE$^{-/-}$ mice via inhibition of MAPK signaling pathways, thereby protecting against atherosclerosis [92].

Sphingosine 1-phosphate (S1P) induced anti-atherogenic and atheroprotective M2 macrophage polarization via IL-4 secretion and its signaling, and induced IL-4Rα [93]. However, CYM5442 and FTY720, S1P receptor type 1 agonist, failed to affect atherosclerosis in moderately hypercholesterolemic LDL-R$^{-/-}$ mice, which suggest that S1P mimetics exert atheroprotective effects only under conditions of increased cholesterol burden exacerbating vascular inflammation [94].

3.2.2. IL-13

IL-13 deficiency in LDLr$^{-/-}$ mice [95] increased atherosclerosis. Whereas administration of IL-13 into LDLr$^{-/-}$ mice reduced atherosclerotic lesion size and induced a stable plaque phenotype [95]. These results indicated that IL-13 play an athero-protective role in atherosclerosis, thus their activity has to be boosted for the potential therapy of atherosclerosis.

3.2.3. IL-33

IL-33 is a cytokine that induces a shift of Th1 into Th2. In humans, a reduced level of IL-33 was associated with an increased risk of atherosclerosis. In ApoE$^{-/-}$ mice, treatment with recombinant IL-33 could increase IL-4, IL-5 and IL-13 and reduce atherosclerotic lesion size [96].

Recent studies indicate that IL-33 can play protective effect in atherosclerosis via interaction with membrane-bound ST2 receptor and IL-1 receptor accessory protein (IL-1RAcP) or induction of Th2-type immune response and IL-5 and IL-13 synthesis [97]. The IL-33/ST2 pathway is a new therapeutic target in cardiovascular disease [98].

3.3. Targets and Drug Discovery of B Cells in Therapy for Atherosclerosis

3.3.1. CD20

CD20 is an antigen expressed on mature B-cells and pre-B-cells [99] , which is considered a good target for the treatment of atherosclerosis [100]. Administration of an anti-CD20 antibody for B cell depletion allows significant reduction of atherosclerotic plaque size in a mouse model [101]. These results suggest that B cell depleting therapies via CD20 are a potential target for the treatment of atherosclerosis.

Currently, B-cell depletion therapy via anti-CD20 is in use for the treatment of autoimmune diseases, such as RA [102]. The only CD20 targeted drug approved by the FDA is rituximab (RTX) to use for treatment of RA [103]. In atherosclerosis, B-cell depletion resulted in a reduction of the pro-atherogenic Th1 immune response and IL-17 production. Anti CD20-specific monoclonal antibody therapy reduces atherosclerosis in both LDLr$^{-/-}$ and ApoE$^{-/-}$ mice, but did not affect the production of anti-atherogenic anti-oxLDL antibodies [29].

3.3.2. B-Cells Activating Factor Receptor (BAFF-R)

BAFF-R is expressed on mature B-cells and binds BAFF that is crucial survival factor for maturation and survival of B2 cells [104]. In the ApoE$^{-/-}$ mice, depletion of BAFF-R leads to a significant reduction in mature B2 cells [105]. The BAFF-R knockout in both ApoE$^{-/-}$ and LDLr$^{-/-}$ mice significantly reduced atherosclerotic lesion size and decreased plaque inflammation cells [105, 106]. In ApoE$^{-/-}$ mice, anti-BAFF-R antibody treatment resulted in a reduc-

tion of atherosclerotic lesions [107]. These data suggest that BAFF-R is a good target for treatment of atherosclerosis by selective depletion of B2 cells.

Tabalumab, a human IgG4 monoclonal antibody for BAFF, was used in Phase II clinical trials for moderate-to-severe RA [108] and in Phase III clinical trials for systemic lupus erythematosus (SLE) [109]. As B-cell-mediated immune responses are involved in both SLE and atherosclerosis, anti-BAFF antibody might also be effective in the treatment of atherosclerosis.

3.4. Drug Discovery and Targets Based on the Role of TLRs in Atherosclerosis

Given the role of TLRs pathway in the pathogenesis of atherosclerosis, therapeutic targeting of TLRs by drugs could have tremendous clinical potential as an anti-atherosclerotic approach [46]. Apart from TLR2 and TLR4 are the most attractive therapeutic targets. TLR downstream signaling pathways offer additional possibilities for targeting blockade. The adaptor proteins, myeloid differentiation factor 88 (MyD88) and Toll IL-1 receptor (TIR) domain containing adaptor inducing IFN-β (TRIF), are also key molecules leading to the activation of NF-kB and interferon regulatory factor-3, respectively. NF-kB nuclear translocation and its activation is also more prominent in acute complications of atherosclerosis [110].

Eritoran, a most advanced TLR4 antagonists [111], works by interfering with the interactions between TLR4 and its co-receptor MD−2. In a Phase II clinical trial, eritoran reduced the mortality rate due to sepsis by 6.4% compared with the placebo group [112]. Neutralizing antibodies of TLR2 and MyD88 revealed that the predominant role of TLR2 and MyD88 in human atherosclerosis [113]. In clinical trials, OPN-305, which is a TLR2-specific monoclonal antibody, inhibits pro-inflammatory cytokine production in a range of inflammatory diseases [114].

Dehydroxymethylepoxyquinomicin (DHMEQ), a NF-kB inhibitor, can reduce atherosclerosis without affecting plasma lipid levels in ApoE-deficient mice [115]. Blockade of IkB kinase β/2 abolishes cytokine production in human atherosclerosis [116]. The p38 and JNK pathways are also activated following TLR activation. p38 inhibitors are currently in Phase II clinical trials for rheumatoid arthritis and psoriasis [117]. Developing drugs based on these targets in the pathway may have therapeutic potential.

Pterostilbene, a novel natural plant conduct, inhibits high fat-induced atherosclerosis inflammation via NF-κB signaling pathway in TLR5 deficient mice [118]. In 2013, Wang reported that artesunate combination with ursolic acid might have the potential to further develop for the treatment of atherosclerosis [119]. Feng also found that Artesunate counteracts the effect of IFNα to inhibit migration inhibitory factor production by blocking STAT1 phosphorylation and thus may have therapeutic potential for systemic lupus erythematosus -associated atherosclerosis [120]. However, our research found that artesunate can attenuate the progression of atherosclerosis lesions formation alone or combined with rosuvastatin through inhibition of pro-inflammatory cytokines and pro-inflammatory chemokines. This effect is closely related with its inhibition on TLR-NF-κB pathway (Phytomedicine, No: PHYMED-D-15-01018R1, 2016, accepted).

miRNAs is a novel therapeutics that target TLRs. miR−146 can negatively regulate the mRNA levels of both TRAF6 and IRAK1, which are two critical proteins involved in TLR signaling [114]. miR−146 along with miR−155, another inhibitory miRNAs, may be consequently used in atherosclerosis to inhibit TLR signaling and the induction of pro-inflammatory gene expression [121]. Recent results have suggested that maintenance of cholesterol homeostasis can be regulated by miRNA [122].

3.5. Drug Discovery and Targets Based on co-Stimulatory Molecules in Atherosclerosis

Co-stimulatory molecules predominantly modulate the immune responses by activating T- and B-cell functions, but also affect DC and macrophage functions and play a crucial role in the progression of atherosclerosis. Thus, blocking this interaction seems to have therapeutic potential in the treatment of atherosclerosis

3.5.1. CD28–CD80/CD86

CD28–CD80/CD86 pathway is a potential target for the treatment of atherosclerosis [123]. CTLA-4 negatively regulates T-cell CD80/86–CD28 pathway, which plays an important role in the post-intervention accelerated atherosclerosis [124]. Deficiency of CD80 and CD86 in LDLr$^{-/-}$ mice significantly reduced atherosclerosis [123]. However, LDLr$^{-/-}$CD80$^{-/-}$CD86$^{-/-}$ mice have twofold increase of atherosclerotic lesion [125]. Thus, blocking CD80/CD86–CD28 co-stimulatory molecules by its negative regulator seem to have beneficial effects.

Abatacept, a fusion protein of the extracellular domain of CTLA-4 and Fc fragment of human IgG1 (CTLA-4–Ig), is approved by FDA for the treatment of RA [126]. Furthermore, Abatacept also could reduce the development of atherosclerotic plaques in a post-intervention atherosclerosis model [124].

Belatacept is another FDA-approved anti-CD80 and anti-CD86 fusion protein used as an immune suppressant after kidney transplantation [127].

RhuDex, a small-molecule inhibitor of CD80, had completed Phase II clinical trial for the treatment of RA [128] and was tested in an *ex vivo* inflammation model in human atherosclerotic lesion [129].

3.5.2. CD154–CD40

The CD154–CD40 interaction plays the pivotal role in atherosclerosis. CD154 deficiency in ApoE$^{-/-}$ mice resulted in a 5.5-fold reduction of advanced atherosclerosis [130]. Anti-CD154 antibody treatment in LDLr$^{-/-}$ mice [131] or ApoE$^{-/-}$ mice [132] significantly reduced initial atherosclerotic plaque size and advanced atherosclerotic lesion. Currently, some anti-CD154 antibodies were tested in the inflammatory diseases.

Ruplizumab (hu5c8), an anti-CD154 monoclonal antibody, was tested for the treatment of SLE and inflammatory bowel disease [133, 134].

ABI793 (anti-CD154 mAb) was tested for the treatment of renal transplantation model in monkeys [135]. However, treatment of these anti-CD154 antibodies in the inflammatory disease showed side effects.

On the other side, anti-CD40 antibodies, both agonistic (CP-870,893 [136], Dacetuzumab (SGN-40) [137], ChiLob 7/4 [138]) and antagonistic (Ch5D12 [139]), are under the development for inflammatory and cancer therapies. Their preliminary results imply further exploration, especially in combination with other drugs [140].

3.5.3. OX40L–OX40

OX40L–OX40 pathway plays role in development of atherosclerotic lesions. Overexpression of OX40L resulted in increased development of atherosclerotic plaques in C57Bl/6 mice [141].

Anti-OX40L antibody (RM134 or RM134L) treatment reduced progressing or advanced atherosclerotic lesions by inhibition of IL-4-mediated Th2 isotope switching and reduction of anti-oxLDL IgM in the LDLr$^{-/-}$ mouse model [142]. Currently, the anti-OX40L antibodies or OX40 immunoglobulin fusion proteins block the OX40L–OX40 interaction in several inflammatory diseases, such as inflammatory bowel disease, graft-versus-host disease and RA [142]. Positive results obtained in inflammatory diseases suggest that anti-OX40L antibody treatment might be successful in the treatment of atherosclerosis.

3.5.4. CD137L–CD137

Some researches suggest that CD137L–CD137 interaction plays an important role in atherogenesis. In ApoE$^{-/-}$ mice model, treatment with a CD137 agonist 2A significantly increased inflammation [143]. CD137 deficiency in both ApoE$^{-/-}$ and LDLr$^{-/-}$ mice significantly reduced atherosclerosis [144]. Increased presence of CD137 in patients with acute coronary syndrome suggests a correlation between the CD137L–CD137 interaction and atherogenesis in human [145]. These data imply that CD137L–CD137 is a good target for treatment of atherosclerosis.

3.6. Targets Base on the Recruitment and Migration of Inflammatory Cell

Immune system-mediated inflammatory reactions during the development of atherosclerosis had been linked to inflammatory cell recruitment and migration through the arterial wall [146]. These factors include the selectins, adhesion molecules, some cytokines and chemokines such as monocyte chemoattractant protein-1 (MCP-1), stromal cell derived factor 1 (SDF-1), macrophage inhibitory factor (MIF) and their receptors [147]. These factors are rapidly expressed in pro-atherosclerotic conditions and thought to play a critical role in several steps of atherosclerosis [115, 148].

3.6.1. Selectin Family

The selectin family is involved in the selective recruitment of certain types of leukocytes into the atherosclerotic lesions [149]. Blocking the best-characterized ligand for selectins, P-selectin glycoprotein ligand-1 (PSGL-1), can dramatically inhibit the growth of arterial neointima after wire-induced arterial injury in ApoE$^{-/-}$ or ApoE/PSGL-1 double-deficient mice [149, 150]. Based on its effects on atherosclerosis, the inhibition of P-selectin and PSGL-1 signaling can attenuate inflammatory responses as the potential therapeutic targets as an anti-atherosclerosis therapy.

Two randomized clinical trials are ongoing to test the efficacy and safety in humans of RO4905417, a novel P-selectin antagonist [151]. The SELECT-Acute Coronary Syndrome (SELECT-ACS) randomized trial evaluates the drug efficacy in reducing procedural damage in 500 ACS patients treated with RO4905417. The SELECT-Coronary Artery Bypass Graft (SELECT-CABG) study is testing the efficacy of this compound in preventing saphenous vein graft disease in 380 patients undergoing elective or urgent coronary artery bypass graft surgery.

Sialyl-Lewis X (sLx), mimicry of the common ligand of all selectins, is an emerging therapeutic strategy, although this has yet to be tested in preclinical models of atherosclerosis [152].

3.6.2. MCP-1

Monocyte chemoattractant protein-1 (MCP-1/CCL2) is one of the key chemokines that regulate migration and infiltration of monocytes/macrophages. Both CCL2 and its receptor C-C motif chemokine receptor-2 (CCR2) have been demonstrated to be involved in various diseases, including atherosclerotic cardiovascular disease [153]. Monocyte recruitment by interaction between MCP-1 and CCR2 is an important step in early plaque development and therefore gained interest as a therapeutic target [154].

MLN1202 is a monoclonal antibody directed against CCR2. In a phase II trial, treatment with MLN1202 could significantly reduce the level of high-sensitivity CRP in patients at risk for atherosclerotic cardiovascular disease [155]. However, no study has been initiated to determine whether this approach will reduce cardiovascular event rates.

Wang L reported that effect of olive leaf extract can inhibit the progress of atherosclerosis, which is related to the suppressed expressions of inflammation factors, monocyte chemoattractant protein (MCP)-1, vascular cell adhesion molecule (VCAM)-1, nuclear factor-kappa B (NF-kappaB) and tumor necrosis factor alpha (TNF-alpha) [156] .

3.6.3. CCL17

Chemokine (C-C motif) ligand 17 (CCL17) is exclusively expressed on the mature subset of cDCs and plays a pivotal role in the development of atherosclerosis [157]. It was demonstrated that CCL17 promotes atherosclerosis via regulation of Treg homeostasis [158]. In addition, the treatment of anti-CCL17-specific antibody could result in significant reduction in atherosclerotic plaques of ApoE$^{-/-}$ mice [159]. Thus, CCL17 chemokine is a new potential target for treatment of atherosclerosis.

Targeting of CCL17 in a selective manner seems to be a good approach from immune homeostasis modulation in atherosclerosis [158]. Until now, there is no information about a small molecule or another modulator that is directly targeted at CCL17. However, research results of virtual ligand screening research about small-molecule inhibitors of the CCL17–CCL4 interaction suggest that validation of CCL17 as a target to inhibit atherogenesis is feasible [160, 161].

3.6.4. CCL19 and CCL21

The level of CCL19 and CCL21 is significantly increased in human atherosclerotic carotid plaques [162]. Recent studies showed that modulation of CCL19 and CCL21 chemokines in LDLr$^{-/-}$ mice model reduced the level of pro-inflammatory cytokines, such as IL-12 and IFN-γ, which resulted in atherosclerotic plaque stabilization [161].

In humans, the increased level of CCL19 and CCL21 is correlated with atherosclerotic carotid plaques [161]. The modulation of CCL19 and CCL21 chemokines in LDLr$^{-/-}$ mice model reduced the level of pro-inflammatory cytokines, such as IL-12 and IFN-γ, which resulted in atherosclerotic plaque stabilization [161, 163].

3.7. Phospholipase A2 (PLA2)

Members of PLA2 family can modify phospholipids and generate atherogenic pro-inflammatory lipids. Therefore, their inhibition maybe represent a promising target for the prevention of atherogenesis [164]. Currently, secretory PLA2 (sPLA2) and lipoprotein-associated PLA2 (Lp-PLA2) are investigated for their anti-atherogenic therapeutic potential [165]. Accumulating evidence of Lp-PLA2 in the development of atherosclerotic lesions has encouraged the exploration of Lp-PLA2 inhibition as a potential therapeutic strategy [166].

Varespladib, a sPLA2 inhibitor, exhibited anti-inflammatory effects mediated in part via enhancement of LDL clearance by the LDL receptor in phase II trial in patients in stable coronary heart disease [167].

Darapladib, the a Lp-PLA2 inhibitor, reduced levels of IL-6 and CRP in a phase II trial in patients with stable coronary heart disease [168]. Currently, darapladib is being evaluated in two phase III trials for its effect on cardiovascular events: the STabilization of Atherosclerotic plaque By Initiation of darapLadIb TherapY trial (STABILITY) trial in patients with chronic coronary heart disease [169] and the Stabilization Of pLaques usIng Darapladib – Thrombolysis In Myocardial Infarction (SOLID-TIMI 52) study in patients after an acute coronary event [170].

A small placebo controlled study showed that the Lp-PLA2 inhibitor SB-4808 activity in atherosclerotic plaque taken at the time of carotid endarterectomy [171]. Additional studies will be necessary to show that agents from this class can favorably affect inflammatory biomarkers, atherosclerosis and ultimately clinical outcomes.

3.8. Leukotrienes

Leukotrienes are arachidonic acid-derived lipid mediators of inflammation and play the pivotal role in the unstable and inflamed atherosclerotic plaque [172]. Pro-inflammatory lipid-derived mediators, including 5-Lipoxygenase (5-LO, regulatory enzymes in

leukotriene biosynthesis) and 15-Lipoxygenase (15-LO), lipoxygenase interaction products (lipoxins) and 5-LO associated protein (FLAP), play significant roles as potential anti-atherosclerotic target to reduce atherosclerotic plaque inflammation [173].

VIA-2291, a most prominent selective and reversible 5-LO inhibitor, could reduce leukotriene production in patients with coronary heart disease and indicate favourably to affect atherosclerosis [174].

PD146176, a potent and selective 15-LO inhibitor, lacks significant nonspecific antioxidant properties. It suppresses atherogenesis and limits atherosclerotic lesion development in the rabbit. It reduces oxidant stress-induced apoptosis in endothelial cells and inhibits proliferation in 15-LO overexpressing PC3 cells [175].

Meanwhile, DG-031, an inhibitor of 5-LO associated protein (FLAP), significantly reduces the inflammatory biomarkers in dose-dependent manner in patients with specific at-risk variants of two genes [176].

3.9. Heat-Shock Proteins (HSP)

The HSPs form a highly conserved family of proteins and are found in atherosclerotic lesions [177]. The HSP-60/65 can stimulate both anti- and pro-atherogenic effects [177, 178]. Therefore, much effort was invested to identify anti-atherogenic T-cell and B-cell HSP-60 epitopes that could induce athero-protective effects. In ApoE$^{-/-}$ mice model, administration of mycobacterial HSP-65 could reduce atherosclerotic plaque size [179]. Subcutaneous immunization of mycobacterial HSP-65 in ApoE$^{-/-}$ mice had a different effect on different phases of the progression of atherosclerosis [179]. Aforementioned results imply that HSP might be a good target for the treatment of atherosclerosis.

3.10. Other Potential Targets and Relative Drugs Discovery

The Rho–ROCK pathway may play a significant role in the pathogenesis of atherosclerosis. ROCK inhibition may be useful for treating arteriosclerotic and other inflammatory diseases. The ROCK 2 inhibitor SLx2119 has shown the ability to attenuate arterial plaque formation and to reduce vascular smooth muscle cell and monocyte migration as well as foam cell formation [180].

p38 MAPK inhibitor SB-681323 is evaluated in a variety of inflammatory conditions and in patients with coronary heart disease [181].

Rimonabant, cannabinoid-1 (CB-1) receptor antagonist, has demonstrated reduction of body weight, improvement of insulin resistance and lipid parameters as well as anti-inflammatory effects [182]. Activation of the CB-2 receptor on macrophages and T lymphocytes within atherosclerotic lesions attenuated atherosclerosis progression in a murine model [183].

The antioxidant succinobucol significantly reduced atherosclerosis in several animal models [184]. Furthermore, atherosclerosis regression was observed in patients treated with succinobucol in a clinical trial, although the result did not differ significantly from that observed with standard of care [185].

miR-134 may regulate lipid accumulation and proinflammatory cytokine secretion in macrophages by targeting the Angiopoietin-like 4 (ANGPTL4) gene, which suggested a promising and potential therapeutic target for atherosclerosis [186]. Targeting of Programmed cell death 4 (PDCD4) by miR−16 may suppress the activation of inflammatory macrophages though mitogen-activated protein kinase (MAPK) and NF-κB signaling in atherosclerosis. Thus, PDCD4 may prove to be a potential therapeutic target in the treatment for atherosclerosis [187].

Vaccination against atherosclerosis is a hopeful method of prevention of CVD. Vaccines targeting autoimmunity including atherosclerosis are tolerance induction to self-antigens and amplification of the regulatory responses such as Tregs and tolerogenic DCs

[188]. Another main targets for vaccination in atherosclerosis are (ox)LDL (apoB100) [189]. Vaccination or mucosal immunization with athero-antigens comes under candidate therapeutic methods for antigen-specific prevention of atherosclerosis. Immune suppression mediated by Tregs could be another method to regulate pathogenic chronic inflammation in atherogenesis. The intestinal immune system has been attracting much attention as a novel therapeutic target to treat atherosclerosis [188].

CONCLUSION

For a long time, atherosclerosis has been known to be lipid-driven disease, this therapy is mainly focusing on the lipid lowering methods. However, embracing the evidence suggests that inflammation is involved in the different aspect of atherosclerotic process. Discovery of the inflammatory nature of atherosclerosis gave rise to some potential targets that can modulate atherosclerosis. About the future clinical effects of medications with anti-inflammatory strategies in patients with atherosclerosis, it still remains much to be learned. More selective and targeted approaches are warranted to overcome some potential side-effects, such as opportunistic infections, whilst maintaining efficacy.

In this article, we have presented various targets based on the inflammation mechanism of atherosclerosis. We also discussed development of drug discovery about these targets treating atherosclerotic plaque and following disease syndrome. Some of these studies do not have definitive answers, because of their small populations and/or soft study end points. More agents that target on different inflammatory pathways or molecules will be evaluated in clinical trials within the next few years. Larger clinical trials will be required to confirm these encouraging results and test the hypothesis that anti-inflammatory approaches will improve outcomes of atherosclerotic patients treated with optimal standard of care.

As atherosclerosis is a complex, multi-targeted chronic disease driven by inflammation, its treatment will demand chronic administration. The challenge for therapy development for atherosclerosis is the need for an extraordinary safety profile. Except above mentioned antibodies and inhibitors targeted on these relative inflammatory molecules, there will be more novel, safety and multi-targets anti-inflammatory drugs, especially come from plant, herb or mineral etc natural substance, might be the potential source of drug research in the future.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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