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Review

Novel anti-inflammatory therapies for the treatment of atherosclerosis

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ABSTRACT

The underlying role of inflammation in atherosclerosis has been characterized. However, current treatment of coronary artery disease (CAD) predominantly consists of targeted reductions in serum lipoprotein levels rather than combating the deleterious effects of acute and chronic inflammation. Vascular inflammation acts by a number of different molecular and cellular pathways to contribute to atherogenesis. Over the last decades, both basic studies and clinical trials have provided evidence for the potential benefits of treatment of inflammation in CAD. During this period, development of pharmacotherapies directed towards inflammation in atherosclerosis has accelerated quickly. This review will highlight specific therapies targeting interleukin-1β (IL-1β), P-selectin and 5-lipoxygenase (5-LO). It will also aim to examine the anti-inflammatory effects of serpin administration, colchicine and intravenous HDL-directed treatment of CAD. We summarize the mechanistic rationale and evidence for these novel anti-inflammatory treatments at both the experimental and clinical levels.

1. Introduction

Atherosclerosis is an inflammatory disease that results in the development of plaques and progressive stenosis of the coronary arteries. Inflammation has been implicated in every stage of atherosclerosis, ranging from onset of plaque to rupture. Traditional models of inflammation begin with endothelial cell dysfunction within the vascular wall resulting in up-regulation of leukocyte adhesion molecules followed by infiltration of cholesterol and diapedesis of monocytes across the arterial intima, with subsequent development of pro-inflammatory foam cells and eventual atherosclerotic plaque formation [1–3]. The use of P-selectin and leukotriene inhibitors, intravenous HDL, serpins and colchicine have all been proposed as therapeutic options to impede different steps in the inflammatory process in atherosclerosis [4].

Other inflammatory pathways have been elucidated more recently. The role of cytokines that promote atherosclerosis, including Interleukin-1β (Il-1β), IL-6 and tumor necrosis factor-α (TNF-α), has become increasingly clear. Additionally, the importance of immune cells, particularly T-helper and regulatory T-cells, has been noted in atheroma development, altering traditional mechanistic views of vascular inflammation. Current evidence has also highlighted the role of innate, adaptive and humoral immunity in atherogenesis. These inflammatory pathways serve as burgeoning targets for future therapy.

Despite the efficacy of therapies targeting serum lipid abnormalities, atherosclerosis remains the most significant cause of death in the world [5]. The potential benefit of targeting inflammation in atherosclerosis may be demonstrated by examining cardiovascular outcomes in patients receiving 1) statins for coronary artery disease (CAD) and 2) therapy for systemic inflammatory conditions. In patients with known CAD, a dose-dependent decrease in LDL-cholesterol (LDL-C) levels and concurrent reduction in cardiovascular events has been associated with statin use. However, the TNT and IDEAL trials suggested that despite treatment with high-dose statins and concurrent reductions in LDL-C levels, the risk of ischemic events still exists in CAD patients, with event rates ranging between 8.7% and 9.3% over ~5-year median follow-up, suggesting potential utility for additional therapies targeting atherosclerosis [6,7]. Outside this lowering effect on LDL-C, the potential anti-inflammatory effects of statins were examined in the Jupiter trial. Major cardiovascular events were significantly reduced in patients without overt hyperlipidemia but with elevated high-sensitivity C-reactive protein (hs-CRP) levels when treated by rosuvastatin [8]. A

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secondary analysis of this study demonstrated that patients with reductions of both hs-CRP levels <2 mg/L and LDL-C < 1.8 mmol/L had greater clinical benefit when compared with those who achieved just one of this targets [9].

In patients with underlying chronic systemic inflammatory conditions, such as rheumatoid arthritis (RA), systemic lupus erythematosus, psoriasis and inflammatory bowel disease, rates of myocardial infarction (MI) are increased when compared with those in the general population. In these patients, vascular inflammation is noted early in disease with diminished nitric oxide production causing endothelial dysfunction, demonstrated by impaired flow-mediated coronary dilation, and further propagation of the inflammatory cascade results in premature atherosclerotic plaque formation. Treatment of systemic extra-cardiac conditions with anti-inflammatory therapies such as methotrexate and TNF-α inhibitors has been associated with possible reductions in the development of CAD and cardiovascular outcomes [10,11].

This review attempts to highlight therapies targeting components of traditional and emerging inflammatory pathways involved in atherogenesis, including inhibition of IL-1β, IL-6, TNF-α, P-selectin and 5-lipoxygenase (5-LO), as well as examining the potential utility of serpin, intravenous HDL, methotrexate and colchicine treatments. It also summarizes pre-clinical evidence for therapies that promote atheroprotective immunity, including T-cell-targeted treatments and immunization strategies against atherosclerosis.

1.1. Interleukin-1β

The IL-1 family of proteins consists of IL-1α and IL-1β, proinflammatory cytokines which act on endothelial and vascular smooth muscle cells (VSMCs). IL-1α proteins bind to an IL-1 receptor. IL-1 receptor type II and IL-1 receptor antagonist (IL-1Ra) serve as competitive inhibitors to counter the effects of IL-1α and IL-1β [12]. After synthesis, IL-1α is predominantly bound to the plasma membrane of producing cells and acts locally. In contrast, IL-1β is secreted into the plasma, predominantly by monocytes and macrophages, and acts systemically [13]. IL-1β plays an important role in up regulating leukocyte adhesion molecules on endothelial cells, proliferation of VSMCs and production of other cytokines [14,15] which have all been implicated in the development of atherosclerosis (Fig. 1) [13].

IL-1β was found to be elevated in porcine models immediately after angioplasty and was suggested to play a role in inflammation after arterial injury. IL-1 Ra deficient mice, which are exposed to the excessive effects of IL-1β, have increased neointimal thickening after endothelial injury due to balloon angioplasty-related injury and increased vascular inflammation [16,17]. Direct intracoronary administration of Il-1 had similar increase in neointimal thickening and arterial vasospasm in porcine models [18].

Inhibiting the actions of Il-1β has been shown to attenuate plaque growth in animal models. Reduced intimal thickening was noted after carotid artery injury in mice deficient of IL-1β and type 1 IL-1 receptor [19]. Administration of IL-1Ra to ApoE knockout mice resulted in attenuation of fatty lesion formation (Table 1) [20]. Ablation of the IL-1 receptor in mice predisposed to atherosclerosis also attenuated plaque progression [21]. Furthermore, a single administration of the IL-1β modulator gevokizumab improves endothelial regrowth and reduces neointima formation in rats following carotid denudation (Table 1) [22]. In addition to its role in atherosclerosis, IL-1 may affect myocardial remodeling after MI. In animal models, use of IL-1β trap or administration of type 1 IL-1 Ra have been shown to reduce myocardial dysfunction by preventing apoptosis and fibrosis associated with post–MI remodeling (Table 1) [23–25].

In humans, arteries with atherosclerotic lesions have greater IL-1β concentrations when compared to normal coronary arteries [26]. Despite this, causality between arterial IL-1β levels and development of atherosclerosis has not been determined. In contrast with animal studies, IL-1Ra levels have been noted to be higher in patients with acute coronary syndrome (ACS) in comparison to asymptomatic patients or those with chronic stable CAD [27]. Increased plasma levels of IL-1Ra at the time of PCI have also been associated with major adverse cardiovascular events in patients with symptomatic CAD [28]. Higher levels may be attributed to increased production of IL-1Ra by myocytes at infarct border zones in response to tissue injury caused by IL-1-related pathways [29]. It remains to be seen whether higher levels of IL-1β and its receptors merely serve as a surrogate markers for disease or whether they are involved in causal pathways regulating CAD development. Polymorphisms of IL-1Ra have been associated with increased risk of restenosis (>50% luminal narrowing) after percutaneous coronary intervention (PCI) in a large cohort of individuals with single-vessel disease [30], but these associations are not consistent and have conflicted with a subsequent meta-analysis [31].

Clinically, administration of anakinra, a non-glycosylated form of human recombinant IL-1Ra that competitively inhibits the actions of IL-1β, to patients with rheumatoid arthritis but no known CAD was associated with improved coronary flow reserve, endothelial function and reduced levels of inflammatory biomarkers compared to placebo [32]. In this study, parameters of left ventricular function, including mitral annular systolic velocity and E-to-E_M ratio, were improved in patients receiving anakinra at 30 days. In the larger clinical MRC-ILA-HEART Study, therapy with anakinra early after ACS patients did not reduce hs-CRP or subsequent cardiac events (Table 2) [33]. Currently, the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) is a large clinical trial examining the effects of the selective human monoclonal IL-1β antibody, canakinumab, on rates of recurrent cardiovascular events in stable post–MI patients who have persistently elevated hsCRP (>2 mg/L) (Table 2) [34]. Canakinumab has been shown to reduce IL-6 and fibrinogen, both inflammatory markers, in patients with diabetes and high cardiovascular disease risk [35].

1.2. Interleukin-6

Other members of the interleukin family are also thought to be involved in the initiation and progression of atherosclerosis. Interleukin-6 (IL-6) plays a prominent role in the development of atherosclerotic plaques, as well as plaque rupture. Although IL-6 is expressed at low levels in healthy individuals, it is up-regulated in the setting of inflammation and further propagates the inflammatory response in atherosclerosis and other chronic systemic inflammatory disorders.

IL-6 is produced most commonly by macrophages in atherosclerotic plaques and also by endothelial cells, fibroblasts and adipose tissue [36,37]. IL-6 acts by binding to IL-6 receptors (IL6R) and then complexing with gp130, a transmembrane molecule, leading to the activation of JNK, ERK and p38MAPK signaling systems. It promotes endothelial dysfunction, VSMC migration and macrophage transition to foam cells (Fig. 1) [38]. IL-6 is also involved in the acute phase response to inflammation, including the regulation of C-reactive protein.

In vitro, free cholesterol loaded macrophages were shown to be sources of significant IL-6 synthesis and production. In human VSMCs cultures, administration of angiotensin II has been noted to increase IL-6 production [39]. The combined treatment of IL-6 with