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Review

Interactions between inflammation and lipid metabolism: Relevance for efficacy of anti-inflammatory drugs in the treatment of atherosclerosis

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ABSTRACT

Dyslipidemia and inflammation are well known causal risk factors the development of atherosclerosis. The interplay between lipid metabolism and inflammation at multiple levels in metabolic active tissues may exacerbate the development of atherosclerosis, and will be discussed in this review. Cholesterol, fatty acids and modified lipids can directly activate inflammatory pathways. In addition, circulating (modified) lipoproteins modulate the activity of leukocytes. *Vice versa*, proinflammatory signaling (*i.e.* cytokines) in pre-clinical models directly affects lipid metabolism. Whereas the main lipid-lowering drugs all have potent anti-inflammatory actions, the lipid-modulating actions of anti-inflammatory agents appear to be less straightforward. The latter have mainly been evaluated in pre-clinical models and in patients with chronic inflammatory diseases, which will be discussed. The clinical trials that are currently conducted to evaluate the efficacy of anti-inflammatory agents in the treatment of cardiovascular diseases may additionally reveal potential (beneficial) effects of these therapeutics on lipid metabolism in the general population at risk for CVD.

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1. Introduction

Both hyperlipidemia and inflammation are well known risk factors for the development of atherosclerosis and have been shown to play a causal role in the progression of atherosclerotic plaques [1]. In this review, we will first describe interactions between lipid metabolism (dyslipidemia) and inflammatory processes that influence the development of atherosclerosis. It is well known that lipid-lowering drugs attenuate inflammation by reducing plasma cholesterol and fatty acid levels, as well as via multiple off-target effects that reduce inflammation. Since anti-inflammatory drugs currently receive more and more attention with respect to the treatment of atherosclerosis, we will summarize possible secondary effects of anti-inflammatory drugs on lipid metabolism that may additionally influence its efficacy in the treatment of atherosclerosis.

2. Lipids and atherosclerosis

The prevalence of hyperlipidemia and cardiovascular disease (CVD) increases as a consequence of increased nutrient intake in the western societies, where the average diet contains a high percentage fat and cholesterol. Hyperlipidemia is an important risk factor for the development of atherosclerosis and is characterized by increased plasma cholesterol and triglyceride (TG) levels. These lipids are carried by 'atherogenic' lipoproteins (chylomicrons, VLDL, their remnant lipoproteins and LDL) that can enter the arterial wall and accumulate inside, thereby causing lipid deposition and initiating early atherosclerosis [2]. LDL is prone to oxidative modifications by for example reactive oxygen species (ROS) resulting in oxidized LDL (oxLDL) that can induce endothelial cell activation in the vessel wall. OxLDL can also be taken up by macrophage scavenger receptors such as scavenger receptor A (SRA) and CD36, turning macrophages into foam cells, thereby contributing to the formation of the so called 'foamy atherosclerotic plaques'. Hyperlipidemia is frequently accompanied by decreased plasma levels of HDL, which is then called "dyslipidemia". HDL is considered to be atheroprotective mainly by increasing reverse cholesterol transport, a process whereby HDL acts as cholesterol acceptor and transports cholesterol from atherosclerotic lesions back to the liver for excretion into the bile [3]. However, HDL is also emerging as a key player in modulating inflammation-related responses, which may additionally impact atherosclerosis [4]. In cardiovascular patients, dysfunctional HDL shows a diminished capacity for reverse cholesterol transport and a correlated loss of anti-inflammatory function [5]. Therefore, lipid-lowering therapy is the main treatment strategy for combating atherosclerosis, while raising HDL or improving the functionality of HDL are evolving additional strategies.

3. Inflammation and atherosclerosis

Atherosclerosis is increasingly being considered as an inflammatory disease, since inflammatory processes play a key role in various stages of plaque development. These include the activation of endothelial cells (ECs) leading to expression of adhesion molecules such as intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 that attract inflammatory cells (*e.g.* neutrophils, T-cells and monocytes) into the early atherosclerotic lesion. Within the plaque, smooth muscle cells (SMCs) and ECs secrete proinflammatory mediators that stimulate monocyte differentiation into macrophages. These macrophages further develop into foam cells upon uptake of oxLDL and locally amplify the inflammatory response, thereby attracting more immune cells and inducing migration of SMCs into the plaque [6,7]. Intracellular inflammatory pathways (*e.g.* IKK and JNK signaling) play a key role in the development of atherosclerosis, with multiple different transcription factors involved including Nuclear factor-kappaB (NF-κB), activator protein-1 (c-Jun/AP-1) and early growth response 1 (EGR1).

These transcription factors are expressed and activated in multiple cell types in the atherosclerotic plaque such as ECs, SMCs and immune cells, in which they regulate expression of adhesion molecules (*e.g.* ICAM-1 and VCAM-1), chemokines (*e.g.* macrophage chemoattractant protein (MCP)-1), and proinflammatory cytokines (*e.g.* tumor necrosis factor (TNF)α, IFN-γ, interleukin (IL)-1β and IL-6), all of which play an important role during the various stages of plaque formation. Moreover, NF-κB and c-Jun N-terminal kinases (JNKs) regulate the expression of several factors involved in apoptosis and cell proliferation and play a role in the formation of foam cells and activation of inflammatory cells within the plaque. More complete overviews of inflammatory pathways involved in the progression of atherosclerosis have been reviewed elsewhere [8–11].

The inflammatory stimuli that contribute to the progression of an atherosclerotic lesion can have a local origin, as described above, or a non-vascular origin. Non-vascular sources of inflammation that are risk factors for atherosclerosis include diet-induced inflammation, chronic infection and chronic inflammatory diseases (*e.g.* rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE)), which will be described in paragraph 5.

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