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Review

The role of adiponectin and adipolin as anti-inflammatory adipokines in the formation of macrophage foam cells and their association with cardiovascular diseases

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ABSTRACT

Obesity is one of the major public health concerns that is closely associated with obesity-related disorders such as type 2 diabetes mellitus (T2DM), hypertension, and atherosclerosis. Atherosclerosis is a chronic disease characterized by excess cholesterol deposition in the arterial intima and the formation of foam cells. Adipocytokines or adipokines are secreted by the adipose tissue as endocrine glands; adiponectin and adipolin are among these adipokines that are associated with obese and insulin-resistant phenotypes.

Adipolin and adiponectin are cytokines that exert substantial impact on obesity, progression of atherosclerosis, insulin resistance, and glucose metabolism. In this paper, we review the formation of macrophage foam cells, which are associated with atherosclerosis, and the macrophage mechanism, which includes uptake, esterification, and release.

We also summarize current information on adipose tissue-derived hormone and energy homeostasis in obesity. Finally, the role of adipokines, e.g., adipoline and adiponectin, in regulating metabolic, cardiovascular diseases is discussed.

1. Introduction

High-fat and high-cholesterol diets, especially used by people with a genetic susceptibility, leads to atherosclerosis and hypercholesterolemia. Atherosclerosis is a major cause of myocardial infarction (commonly known as heart attack) or stroke. On the other hand, cardiovascular disease has the highest mortality rate in the world, accounting for 16.7 million annual deaths worldwide [1–4]. Atherosclerosis (as a chronic disease of the arteries), shows that macrophages are generated by direct stimulation of the inflammatory signaling pathways [5,6]. It contributes significantly to atherogenesis through the uptake of the most atherogenic of all the lipoproteins and modified low-density lipoprotein (LDL) and via the secretion of cytokines and particle-forming enzymes [5,6].

Laminar flow and especially the arterial bifurcation sites are mostly disrupted by accumulated lipids and fibrous elements in the large vessels, and thus atherosclerosis is introduced as a highly important cardiovascular disease [7]. Low density lipoprotein cholesterol (LDL-c), as opposed to high-density lipoprotein cholesterol (HDL-c), increases the accumulation of cholesterol and causes inflammatory responses in the arterial wall. Increased LDL-c leads some cholesterols into blood vessels whereby changes such as accumulation and oxidation [8–11]. Nonetheless, Toll-like receptors (TLRs) are identified as pattern recognition receptors in the macrophage by modified LDL-c, thereby they activate the proinflammatory signaling pathways and macrophages surround the modified LDL-c. Accordingly, the accumulation of cholesterol is promoted by TLR signaling [8–10].

The signals of microbial products and stress-activated NLRP3 inflammasome can induce the activation of caspase 1, the cleavage of pro-IL 1β and pro-IL 18, and the subsequent secretion of IL 1β, IL 18, and possibly of pyroptosis (inflammasome consists of the NOD-like receptor NLRP3, caspase 1, and the adaptor protein ASC) [12–14].

Activation of the NLRP3 inflammasome is promoted via increased TLR activity, cytokine production, and the subsequent formation of intracellular cholesterol crystals. Many studies have investigated atherogenesis, i.e., the formation of abnormal fats in the arterial wall. For instance, lesions of atherosclerosis and platelet derivatives in foam cells have been studied [15,16]. Foam cells include accumulation of cholesterol in macrophages, which causes primary lesions of atherosclerosis in the subendothelial layer, subsequently leading to the

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internalization of various types of LDL-c and their accumulation in the artery. Fatty streak lesions are found in different stages of human life. As such, aorta, coronary arteries, and cerebral arteries are usually found in the first decade, the second decade, and the third or fourth decades of life, respectively [17,18]. In the early stages of atherogenesis, macrophages remove cholesterol deposits in the arteries, meaning that the accumulated CE-LDL in macrophages generate foam cells that lead to inflammation and coronary artery disease [6,19].

In this review paper, we focus on early stages in the formation of macrophage foam cells and adiponectin and adipolin as anti-inflammatory adipokines. Their association with cardiovascular disease is also discussed.

1.1. Foam-cell formation

The internalization of different forms of modified LDL-c into macrophages leads to foam cells formation in the intima, which accumulates in the arteries [21]. It is one of the serious hallmarks of atherosclerotic lesions [20,21]. Reduction of cholesterol release, excessive cholesterol esterification, and lack of control over uptake of oxidized low-density lipoprotein (ox-LDL) lead to the formation of foam cells from accumulated cholesterol ester [22,23]. The regulation of cholesterol metabolism in macrophages for cardiovascular disease and arteriosclerosis can be divided into three pathways. Firstly, the cholesterol uptake pathway refers to the internalization of 75 to 90% of the extracellular modified LDL-c in macrophage for the formation of foam cells. Internalization of extracellular modified LDL-c in the macrophage is induced by surface receptors such as Scavenger receptors (SRs), SR class A (SR-A), and CD36 via mediated phagocytosis and pinocytosis (Fig. 1) [24,25]. Secondly, free cholesterol (FC) and cholesterol ester (CE) converge into one another causing balance and regulation of the extracellular cholesterol content of the macrophage foam cells. The next step after internalization of the lipoprotein is hydrolysis via the lysosomal acid lipase (LAL) enzyme in the late endosome or lysosome.

The released FC into the ER, which is re-esterified by ACAT1, is stored as cytoplasmic lipid droplets. When the re-esterification process increases, thus increases the internalization and accumulation of re-esterified FC or CE in macrophages foam cells [26].

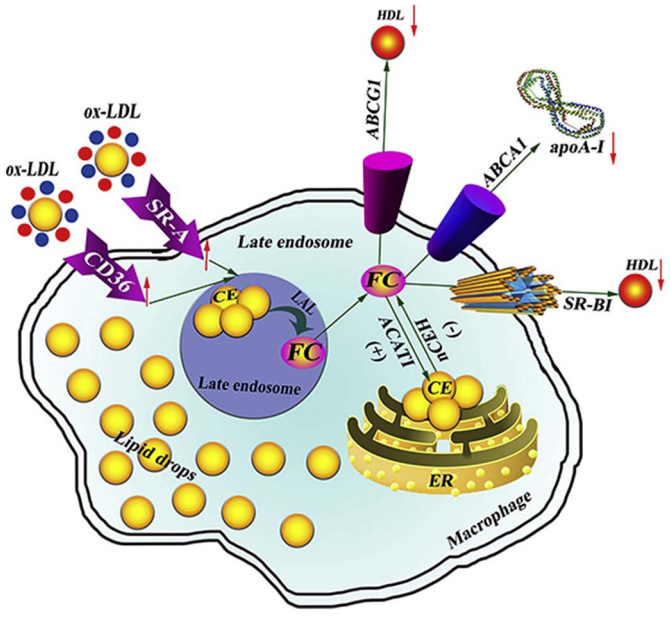

Fig. 1. The mechanism involved in macrophage foam cell formation [110].
Factors that cause excessive CE accumulation and increased formation of macrophage foam cells in atherogenic conditions include a) the internalization of Cholesteryl-ester (CE) rich lipoproteins by macrophage receptors such as CD36 and SR-A into cells and converting them to FC, b) re-esterification of FC to CE by acyl:cholesterol acyltransferase 1 (ACAT1) in the endoplasmic reticulum (ER); if this does not happen, FC level increases, ultimately causing apoptosis, and c) downregulation of ABCA1 and ABCG1, hence reduced cholesterol efflux.

The reason for the term *foam* is that the lipid occupies a large volume of the cell and appears "foamy" [26]. The slowest step in chemical kinetics is known as the rate determining step (RDS). In the FC outflow, RDS is catalyzed by the neutral cholesteryl ester hydrolase (nCEH), which converts the CE to FC and is released via transporters-mediated efflux. Thus, nCEH and ACAT1 are very important for cholesterol esterification [27,28].

Externalization of the accumulated cholesterol from macrophages occurs via transporters or passive diffusion. Therefore, free cholesterol is collected by apolipoprotein A-I (apoA-I) or HDL-c. The most important and principle responsibility is efflux of large volumes of cholesterol from macrophages onto extracellular acceptors through active transport [29,30]. Among the most important extracellular transporters are ATP-binding cassette (ABC) transporter A1(ABCA1), ABCG1 and scavenger receptor-BI (SR-BI).

Therefore, ABCG1, ABCA1 and SRB1 are necessary to remove cholesterol from macrophages [29,30]. Balance, esterification and release of cholesterol influx are significant to prevention from arteriosclerosis. Artherogenic reduces the expression of the ABCA1, ABCG1 and SR-BI as a result of the decreased amounts of cholesterol efflux. Increased expression of CD36 and SR-A, decreased nCEH levels, and increased levels of ACTA1 raise the amount of cellular esterified cholesterol [31,32]. Accordingly, the formation of lipid droplets in macrophages due to excessive accumulation of CE can be considered as an important contributor to foam cells formation [31,32]. With regard to the central role of these three distinct pathways in the regulation of cholesterol in macrophages, they can be used to treat atherosclerotic cardiovascular diseases (Fig. 1).

The accumulation of cholesterol and inflammation in macrophages are reduced by counter-regulatory mechanisms. The liver X receptor (LXR) is activated by specific oxysterols created by the formation of cholesterol. LXR is characterized by two isoforms, including LXRα and LXRβ [33]. LXRs reduce substantially the low-density lipoprotein cholesterol (LDL-c) receptor uptake by the LDL receptor, and regulate the reverse cholesterol transport and cellular cholesterol, which is activated by desmosterol (as intermediate cholesterol biosynthesis) and oxysterols (derived from cholesterol) [33]. Many promoters of the genes involved in the metabolism of cholesterol and lipogenesis have retinoid X receptors (RXRs) that are coupled with the transcription factors of LXRα and LXRβ. ATP-binding cassette transporters (ABC transporters) are a family of membrane transport proteins that contain isoforms such as A1, G1, G5 and G8. ABC transporters require energy (ATP) to transport cholesterol and other lipids across the cell membrane. These transporters are upregulated by a variety of anti-inflammatory activities such as LXR-RXR heterodimers. However, ABC subfamily A member 1 (ABCA1) and ABCG1 isoforms release cholesterol and consequently reduce cholesterol accumulation and attenuate TLR signaling [33].

Cholesterol efflux occurs from HDL particles and APOA1 (as a lipid-poor form of lipid that is the main protein of HDL) by transporters such as ABCG1 and ABCA1. Cholesterol is collected under the process of reverse cholesterol transport (RCT) via the lymphatics and bloodstream in their passway to peripheral tissues to the liver, and thus it is excreted by bile and feces [34,35]. LXR activity is suppressed by TLR activation, whereby the cholesterol efflux from macrophage is reduced, and in turn, TLR signaling is amplified [36,37]. Inflammatory response is enhanced by changing the cholesterol homeostasis (through the effects of acute phase response), which is a type of feedforward mechanism [38,39]. Changes in cholesterol homeostasis are effected by the innate immune system in order to amplify the inflammatory response. Thus, the RCT pathway is down-regulated by the acute phase response. Short-term cholesterol-facilitated immune responses are useful for wound healing and infection; nonetheless, if they are long-term, they may result in atherosclerosis [40].