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Review

Cytokines, macrophage lipid metabolism and foam cells: Implications for cardiovascular disease therapy

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ABSTRACT

Cardiovascular disease is the biggest killer globally and the principal contributing factor to the pathology is atherosclerosis; a chronic, inflammatory disorder characterized by lipid and cholesterol accumulation and the development of fibrotic plaques within the walls of large and medium arteries. Macrophages are fundamental to the immune response directed to the site of inflammation and their normal, protective function is harnessed, detrimentally, in atherosclerosis. Macrophages contribute to plaque development by internalizing native and modified lipoproteins to convert them into cholesterol-rich foam cells. Foam cells not only help to bridge the innate and adaptive immune response to atherosclerosis but also accumulate to create fatty streaks, which help shape the architecture of advanced plaques. Foam cell formation involves the disruption of normal macrophage cholesterol metabolism, which is governed by a homeostatic mechanism that controls the uptake, intracellular metabolism, and efflux of cholesterol. It has emerged over the last 20 years that an array of cytokines, including interferon-γ, transforming growth factor-β1, interleukin-1β, and interleukin-10, are able to manipulate these processes. Foam cell targeting, anti-inflammatory therapies, such as agonists of nuclear receptors and statins, are known to regulate the actions of pro- and anti-atherogenic cytokines indirectly of their primary pharmacological function. A clear understanding of macrophage foam cell biology will hopefully enable novel foam cell targeting therapies to be developed for use in the clinical intervention of atherosclerosis.

Contents

Abbreviations: ABCA-1/G-1, ATP-binding cassette transporter A-1/G-1; ACAT-1, Acyl-CoA:cholesterol acyltransferase-1; AcLDL, acetylated LDL; ADRP, adipocyte differentiation related protein; ApoE/A–I, apolipoprotein E/A–I; BMMs, bone-marrow derived macrophages; CD, cluster of differentiation; CHOP, C/EBP-homologous protein; CPT-1, carnitine palmitoyl transferase-1; CRP, C-reactive protein; CXCL, chemokine (C–X–C motif) ligand; CVD, cardiovascular disease; DR3, Death Receptor 3; ECM, extracellular matrix; FAs, non-esterified fatty acids; HDL, high-density lipoprotein; HL, hepatic lipase; HMDMs, human monocyte-derived macrophages; HMG CoA, 3-hydroxy-3-methylglutaryl-CoA; ICAM1, intercellular adhesion molecule-1; IDL, intermediate density lipoprotein; IFN, interferon; IL, interleukin; IMT, intima-media thickness; JNK2, c-Jun N-terminal kinase 2; LIGHT, lymphotoxin-like inducible protein that competes with glycoprotein D for binding herpesvirus entry mediator on T cells; LDL, low density lipoprotein; LDLr, low density lipoprotein receptor; LPL, lipoprotein lipase; LXR, liver X receptor; MAPK, mitogen activated protein kinase; M1, classically activated macrophage; M2, alternatively activated macrophage; MCP-1, monocyte chemoattractant protein-1; M-CSF, macrophage-colony stimulating factor; MMP, matrix metalloproteinase; MPMs, murine peritoneal macrophages; NPC, Niemann Pick type C; NCEH, neutral cholesteryl ester hydrolase; oxLDL, oxidized LDL; PPAR, peroxisome proliferator-activated receptor; sIFN-γR, soluble interferon-γ receptor; SOCS3, suppressor of cytokine signaling 3; $sPLA_2$, secretory phospholipase A_2; SR, scavenger receptor; SR-PSOX, scavenger receptor for phosphatidylserine and oxidized LDL; T_h, T-helper; TGF-β1, transforming growth factor-β1; TL1A, TNF-like protein 1A; TNF, tumor necrosis factor; TNFR, tumor necrosis factor receptor; TNFSF, tumor necrosis factor superfamily; TWEAK, TNF-like weak inducer of apoptosis; UPR, unfolded protein response; VCAM-1, vascular cell adhesion molecule-1; VLDL, very low-density lipoprotein; VSMC, vascular smooth muscle cell.

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1. Atherosclerosis

1.1. Incidence of disease

The latest statistics from the World Health Organization indicate that more people die annually from cardiovascular disease (CVD) than any other ailment. In 2004, an estimated 17.1 million people died from CVD, representing nearly 29% of all global mortalities. Of these, an estimated 7.2 million were due to coronary heart disease and 5.7 million were due to stroke. Interestingly, of the total worldwide CVD related mortalities in 2004, 82% occurred in low- and middle-income countries. Based on these ever expanding figures, the World Health Organization has predicted that by 2030 almost 23.6 million people will die from CVD related illness worldwide [1]. The principal cause of heart disease, myocardial infarction and stroke in western society is atherosclerosis, a chronic inflammatory disease characterized by lipid and cholesterol accumulation within the walls of large and medium arteries [2]. This fact distinguishes atherosclerosis as the critical contributor to the number one cause of death on the planet and the magnitude of the World Health Organization statistics clearly emphasize the importance of continued scientific research into atherosclerosis and possible therapeutic targets.

1.2. History of atherosclerosis research

During the history of scientific and medical research into atherosclerosis, there has been a long-standing debate regarding the main, underlying causes of the disease [3]. Circa 1900, it was believed that atherosclerosis was simply a product of the aging process. Therefore, very few forms of treatment or prevention existed [3]. It was not until 1913 when the exemplary work of Anichkov demonstrated that high cholesterol levels were indeed a major cause of the disease [4,5]. In his study, Anichkov used a rabbit model of atherosclerosis to show that a high cholesterol containing diet increased the incidence of the disease [5]. This pioneering experiment paved the way for many lines of investigation into the effects of cholesterol during the initiation and progression of atherosclerosis [3]. Despite this compelling evidence, a strong debate raged within the scientific community about the importance of elevated cholesterol levels in atherosclerosis. In 1961, despite the level of scepticism that still remained, the American Heart Association accepted the causal link and recommended people at high risk alter their diet to reduce cholesterol intake [6]. Nevertheless, other groups still disputed that a change in diet would be impractical and would be unlikely to result in a reduced incidence of the disease [7]. It was not until 1984 that clarity was eventually reached when the National Institute of Health published the findings of the Coronary Prevention Trial [8]. This human study clearly showed a significant decrease in cardiovascular endpoints as a result of reduction in blood cholesterol levels [8]. A vast amount of research has since been carried out on cholesterol metabolism and has formed the foundation for modern atherosclerotic research.

1.3. Cholesterol metabolism

The non-pathogenic metabolic route that cholesterol takes within the body is very complicated (Fig. 1). Cholesterol can either be made *de novo*, or absorbed from the diet and, once in the body, it is then subjected to various modes of transport, storage and metabolism. It is important to understand these physiological mechanisms in order to assess where the system has lost its balance during the development of atherosclerosis [9]. Cholesterol, a sterol that is essential for membrane fluidity and lipid raft assembly and function [10], is synthesised in the endoplasmic reticulum from acetate in a series of around 30 enzymatic reactions [11]. The rate limiting step in the biosynthesis of cholesterol is the reaction catalyzed by 3-hydroxy-3-methylglutaryl-CoA reductase (HMG CoA reductase), which converts HMG CoA to mevalonate. Once synthesised, cholesterol can either be transported to peripheral tissues or the liver, or can accumulate in intracellular stores [11]. For intracellular storage, cholesterol undergoes conversion into cholesteryl esters through hydroxyl group acylation by the enzyme Acyl-CoA:cholesterol acyltransferase-1 (ACAT-1) [12]. Cholesterol is classically transported in the blood stream as a water soluble lipoprotein particle. There are various types of lipoproteins, such as chylomicron, very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), low density lipoprotein (LDL), and high density lipoprotein (HDL), which all perform different functions