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REVIEW – OPEN ACCESS

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The Role of Macrophages in Atherosclerosis: An Overview

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ABSTRACT

Knowlege of the mechanism of atherosclerosis in chronic and inflammatory diseases is important in health care management. According to the World Health Organization, approximately 17.9 million people die from atherosclerosis annually. Macrophages played a major role in the immune response and pathophysiology of atherosclerosis. This review presents the role of macrophage in the development of atherosclerosis.

Keywords: Atherosclerosis, macrophage, macrophage lipophagy, lipid cycle in macrophage

INTRODUCTION

Atherosclerosis is a chronic and inflammatory disease caused by the accumulation of oxidized lipoproteins in the subendothelial layer of the arteries. According to the World Health Organization, approximately 17.9 million people die from atherosclerosis annually. In clinical practice, we often encounter cases of coronary artery disease, cerebrovascular disease, peripheral artery disease, or their complications. In the early stage of coronary artery disease, endothelial cells in the innermost layer of the arteries started to malfunction secondary to the presence of major risk factors such as diabetes, hypertension, hyperlipidemia, smoking, and genetic predisposition. Endothelial dysfunction leads to a decrease in nitric oxide synthesis in endothelial cells, an increase in the release of chemoattractant substances, an increase in permeability, and infiltration of of atherogenic lipoproteins into the subendothelium. In this process, circulating monocytes differentiate into macrophages to phagocytose lipoproteins accumulated in the subendothelium through scavenger receptors (SRs) and mediate their transfer to the liver. Macrophages that phagocytose lipoproteins become foam cells (1–7). Intracellular lipid accumulation, especially of free cholesterol, causes the release of a number of cytokines that initiate foam cell death. Dead cell debris causes the accumulation of new macrophages into the subendothelium. As this vicious cycle repeats itself, necrosis occurs and atheromatous plaque nuclei are converted into lipids, cholesterol crystals, and cell debris (8). While macrophages play a key role in the development of atherosclerosis, inflammatory cells other than macrophages such as endothelial cells and smooth muscle cells also contribute substantially to this process. In this review, we discuss the importance and role of macrophages in atherosclerosis.

CLINICAL and RESEARCH CONSEQUENCES

A literature search was performed in English databases including PubMed/Medline, ISI Web of Science, SCOPUS, and Google Scholar from 2000 to March 2020. The following key words were used: "atherosclerosis," "macrophage," "macrophage lipophagy," "lipid cycle in macrophage." Related sections of identified articles were utilized for this review.

Macrophages Types

Macrophages have a major role in the immunse response and pathophysiology of atherosclerosis. When macrophages are exposed to stimulating factors found in atherosclerotic plaque, macrophage types with different functions are formed (9). M1 macrophages are the first activated and proinflammatory phenotype. Studies in humans and mice have shown that the protein synthesis of M1 macrophages with proinflammatory properties leads to a larger and more unstable plaque formation. On the contrary, M2 macrophages play an antiatherogenic role by reducing plaque size and increasing plaque stabilization through their anti-inflammatory effects. M2 macrophages have a high number of SRs, galactose-type receptors, and mannose receptors. As a result, more tissue residues and apoptotic bodies are phagocytosed, thus preventing tissue damage. M2 macrophages are divided into four subgroups according to their function, namely, M2a, M2b, M2c, and M2d, and each of which have different effects on atherosclerosis. Mhem is another type of macrophage with antiatherogenic effect and

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is activated by intraplaque bleeding (10–13). Unlike M1 or M2, Mox macrophages are known as CXCR4-induced macrophages that can affect atherogenesis in two ways. Mox macrophages have lower phagocytosis ability than M1 and M2 macrophages (11, 14). Although the role of M1 and M2 macrophages in atherosclerosis are well recognized, intensive studies on the exact role of macrophage types are still ongoing.

Macrophage Lipophagy

At the initial stage of atherosclerosis (fatty streak), lipids, especially apolipoprotein B (Apo B)-rich lipoproteins, in plasma are passed to the subendothelium. Then, monocyte-derived macrophages and smooth muscle cells migrate to the subendothelium to remove oxidized low-density lipoproteins (oxLDL). As oxLDLs are phagocytosed by macrophages, structures called lipid droplets (LD) are formed within the macrophage. Macrophages containing LDs are defined as foam cells (6). Macrophages have many receptors that phagocytose oxLDL, but the major ones are SR type a (SR-A), cluster of differentiation 36 (CD36), and lectin-like oxidized LDL (oxLDL) receptor-1 (15). In particular, comparedwith LDL receptors (LDLRs), SR-A plays a greater role in phagocytosing oxLDL into the macrophage (4, 16,). Because increasing levels of intracellular cholesterol do not reduce the expression of SR-A, unlike the expression of other LDLRs, SR-mediated oxLDL uptake results in unlimited phagocytosis of lipoproteins and accumulation of extremely atherogenic lipoproteins in macrophages (17). Excessive lipid accumulation causes macrophage apoptosis. Cell contents released following apoptosis causes the infiltration of new macrophages into the subendothelium, creating a vicious cycle (18). The uncontrolled accumulation of oxidized lipoproteins in the atherosclerotic plaque increases the volume of the plaque, thereby narrowing the vessel lumen

Scavenger Receptor Type A

At present, it is accepted that SRs have important functions in many chronic diseases, such as phagocytosis of oxLDL in atherosclerosis, immune system response, inflammation, diabetes, and cancer. SR-A, which is an SR member and one of the most effective receptors in the phagocytosis of ox-LDLs, has five subgroups: SR-A1, SR-A3, SR-A4, SR-A5, and SR-A6. (19). SR-A1 (SCARA1) is found mainly on monocytes, macrophages, dendritic cells, and mast cells. The salient feature of SR-A1 is its ability to phagocytose oxLDL particles. The expression of SR-A3 (SCARA3) increases with oxidative stress and thus protects cells against the destructive effects of reactive oxygen species. In addition to being an endocytic receptor for lipoproteins, SR-A4 plays a role in the recognition and internalization of oxLDL by vascular endothelial cells. SR-A5 expression is limited to epithelial cells in the testis, thymus, respiratory tract, and adrenal gland. SR-A5 has important functions in host defense. In the absence of any inflammatory reaction, SR-A6 expression is limited to macrophages located in the lymph nodes and in marginal areas of the spleen. Similar to SR-A5, SR-A6 has important functions in host defense (20).

Lipid Cycle in Macrophages

Oxidized lipoproteins, LDL and VLDL, that are absorbed into the macrophages through SRs underwent macropinocytosis and phagocytosis in the lysosomes (21). The lipids within the lysosomes are exposed to lysosomal acid lipases and turn into free cholesterol and free fatty acids. Some of the free cholesterol particles formed in the cytoplasm are carried to the cell membrane. These cholesterol particles are transferred either to the lipid-weak apoA1 via ATP-binding cassette subfamily A member 1 (ABCA1) receptor or to mature high-density lipoproteins (HDL) via the ATP-binding cassette subfamily G1 (ABCG1) receptor (22). The remaining free cholesterol particles are esterified in the endoplasmic reticulum acetyl-coenzyme A cholesterol acyltransferase 1 and stored as cholesterol ester (CE) in the LD in the cytosol. Re-esterification protects the cells from the toxic effects of free cholesterol. Some free fatty acids are re-esterified and stored as triglycerides in LDs (23), and the remaining free fatty acids are transferred to the mitochondria for energy need. There are two known alternatives to the hydrolysis of CE stored in LDs: (1) hydrolysis that occurs after exposure of CE in LDs to neutral cholesterol ester hydrolase (nCEH) enzyme and (2) fusion of LDs with lysosomes secondary to autophagocytosis and subsequent hydrolysis with lysosomal acid lipase enzyme. Free cholesterol particles that are formed in both ways are transferred to the reverse cholesterol transport system via ABCA1 and ABCG1 receptors (24).

As the level of intracellular cholesterol increases, some transcription factors are activated, especially liver X receptor α and β (Lxra and Lxrb, respectively) and retinoid x receptor (Rxr) (25). Both Lxr and Rxr control the expression of ABCA1 and ABCG1 transporters (26–28).

Lipid Droplets

LDs are organelles with neutral lipids in the center with single-layer phospholipids and various functional proteins on its boundaries. They are found in many mammalian cells, especially macrophages, epithelia, fibroblasts, and hepatocytes. Proteins found around LDs can influence changes in LD size, intracellular movement, and interaction with other organelles. In mammals, perilipin (PLIN 1) and adipocyte differentiation-related protein/PLIN2 are more dominant (29). Free cholesterol particles accumulated in cells can create cytotoxic cholesterol crystals, causing inflammation and fibrosis in cells (30, 31). LDs can store the accumulated free cholesterol particles in the form of CE to protect the cells from this harmful effect. LD-loaded macrophages containing CE cause foam cell formation specific to atherosclerotic lesions.

CE can be converted into free cholesterol by hydrolysis and transferred to HDL. Free cholesterol particles transferred to HDL are then transported to the liver and bile and removed from the body (6). The hydrolysis of CE in the atherosclerotic lesion is the first step in removing CE from the body, and nCEH is the enzyme responsible for this step (32).

Genetic View of Macrophage Functions

As atherosclerosis is a chronic, inflammatory disease with still unclear pathophysiology, it is important to investigate the structure of the associated genes, the synthesis of related proteins, and their extraordinary role in the overall functioning of metabolism. The structure and functions of genes such as *APOB*, *OLR1*, *CD36*, *MSR1*, *LDLR*, *SCARA3*, and *SCARB1*, which play important roles in the transition of lipoproteins into the subendothelium and the phagocytosis of oxidized lipoproteins

Table 1. Genes affecting macrophage function in atherosclerosis (33)

Gene	Location	Exon count	Expression in organs	Function
APOB	2p24.1	29	Liver, small intestine, and duodenum	Ligand-defective Apo B caused by the gene or its regulatory region may cause hypercholesterolemia, hypobetalipoproteinemia, normotriglyceridemic hypobetalipoproteinemia, and diseases affecting plasma cholesterol and Apo B levels.
OLR1	12p13.2	6	Placenta, lung, appendix, bone marrow, brain, kidney, gall bladder, liver, adrenal, and urinary bladder	Defective oxidized low-density lipoprotein receptor 1 may cause atherosclerosis, myocardial infarction, and Alzheimer's disease.
CD36	7q21.11	19	Heart, fat, placenta, spleen, lung, gall bladder, lung, small intestine, and duodenum	Defective CD36 molecule may cause platelet glycoprotein deficiency.
MSR1	8p22	12	Lung, liver, gall bladder, placenta, adrenal, appendix, urinary bladder, spleen, brain, colon, testis, kidney, and heart	Defective macrophage scavenger receptor 1 or its isoforms may cause many macrophage-related physiological and pathological processes, including atherosclerosis, Alzheimer's disease, and host defense.
LDLR	19p13.2	18	Adrenal, lung, liver, gall bladder, stomach, appendix, heart, esophagus, prostate, colon, duodenum, small intestine, testis, placenta, bone marrow, endometrium, urinary bladder, pacreas, brain, and kidney	Defective low-density lipoprotein receptor may cause autosomal dominant disorder and familial hypercholesterolemia.
SCARA3	8p21.1	11	Endometrium, brain, gall bladder, placenta, prostate, urinary bladder, thyroid, lung, esophagus, appendix, lymph node, small intestine ovary, kidney, skin, adrenal, heart, colon, salivary gland, stomach, duodenum, fat, and salivary gland	Because of defective scavenger receptor class A member 3, the reactive oxygen species are not depleted and cells are not protected from oxidative stress.
SCARB1	12q24.31	15	Adrenal, liver, fat, testis, ovary, gall bladder, placenta, small intestine, lung, and heart	Because of defective scavenger receptor class B member 1, cholesterol transfer to, and from high-density lipoprotein cannot occur.

APOB: Apolipoprotein B; OLR1: Oxidized low density lipoprotein receptor 1; MSR1: Macrophage scavenger receptor 1; LDLR: Low density lipoprotein receptor; SCARA3: Scavenger receptor class A member 3; HDL: High-density lipoprotein; SCARB1: Scavenger receptor class B member1

in the atherosclerosis process, are presented in Table 1 (33). Defects in these genes cause a functional negative effect on cholesterol metabolism and disrupt the optimal functioning of the cholesterol cycle. Consequently, more oxidized lipoproteins accumulate in peripheral tissues and the disease course worsens. With the above information, genetic research should be prioritize to enable development of new strategies in the treatment of atherosclerosis.

CONCLUSION

Atherosclerosis is a common potentially serious disorder that may result in death due to partial or complete closure of the vessel, which is a result of the accumulation of fat, cholesterol, and other substances in the arterial wall. Macrophages have an outstanding role in the immune response and pathophysiology of atherosclerosis. Therefore, it is crucial to know how macrophages influence homeostasis in response to different stimuli and how macrophages help prevent atherosclerosis as a complication of disease states such as diabetes, obesity, dyslipidemia, and metabolic syndrome, and minimize atherosclerotic damage. Thus, information in various diseases, especially atherosclerosis, will enable setting of new goals and corresponding different treatment strategies to improve quality of life.

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