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Minireview

Nuclear receptors in macrophages: A link between metabolism and inflammation

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Abstract **Subclinical inflammation is a candidate etiological factor in the pathogenesis of metabolic syndrome and in the progression of atherosclerosis. A central role for activated macrophages has been elucidated recently as important regulators of the inflammatory process in atherosclerosis. Macrophage differentiation and function can be modulated by a class of transcription factors termed nuclear receptors. These are activated by intermediary products of basic metabolic processes. In this review the contribution of peroxisome proliferator-activated receptors and liver X receptors to macrophage functions in inflammation and lipid metabolism will be discussed in light of their roles in macrophages during atherosclerosis.**

In the past decade much effort has been made to understand the mechanisms how lipids are handled by macrophages and how inflammation could promote the atherogenic process. Here, we also provide an overview of these two fields.

Keywords: Nuclear receptor; Inflammation; PPAR-γ; LXR; Atherosclerosis

1. Introduction

Disturbances in the basic metabolism lead to several disease states in western societies. Altered lipid turnover in the body results in pathological abnormalities. Among these, cardiovascular disease is the leading cause of death therefore understanding the progression of atherosclerosis has placed lipid metabolism and inflammation in the limelight.

Atherosclerosis is a degenerative disease of the tunica intima within arteries characterized by lipid accumulation in the wall initially observed by the development of fatty streaks within the subintimal tissues [1]. Development of fatty streaks is considered to be driven by a pathogenic interaction between circulating lipoproteins, hemodynamic factors, endothelial cells, vascular smooth muscle cells, macrophages, T lymphocytes and a constellation of metabolic abnormalities including insulin resistance, hypertension, dyslipidemia and central obesity collectively referred to as metabolic syndrome [2]. Handling of lipids by lesion macrophages is an important metabolic process in the context of hypercholesterolemia and the development of atherosclerotic lesions [3–5].

As a first step during atherogenesis a disturbance in endothel function results in the accumulation of low-density lipoprotein (LDL) in the sub-endothelial matrix. It is not clear how LDL gets modified but this leads to the appearance of minimally oxidized/modified (mmLDL) and subsequently fully oxidized LDL (oxLDL) containing multiple oxidized lipid molecules. Modified lipoproteins activate both endothelial cells and monocytes/macrophages resulting in further monocyte migration into the sub-endothelial space in response to locally produced chemoattractant molecules and cytokines like interferon γ (IFN-γ), interleukin-1β (IL-1-β), IL-6, tumor necrosis factor α (TNF-α) [6]. Macrophages are the first cellular components in lesion formation, they take up lipid particles through special cell surface proteins, scavanger receptors (SRs), as SR-A and CD36 that are not subjected to downregulation via a feed-back mechanism like LDL receptor. These processes evoke a characteristic inflammatory response by releasing inflammatory molecules to the extracellular environment such as monocyte chemoattractant protein-1 (MCP-1), which attract additional macrophages and other cells to the lesion [7,8].

Macrophages accumulate lipids from oxLDL leading to lipid-loaded foam cell formation, the characteristic cells of the early, cellular phase of lesions (Fig. 1B). Foam cells can also eliminate lipids from the sub-endothelial space through ATP-binding cassette transporters such as ABCA1, ABCG1 towards high-density lipoprotein (HDL) but if the transport is inhibited they accumulate lipids continuously resulting in increased cell death of inflammatory cells and the release of intracellular molecules that lead to a sustained chronic inflammation [4,9,10]. This chronic inflammation with secreted mediators and growth factors make smooth muscle cells migrate from the tunica media, proliferate and rearrange extracellular matrix (Fig. 1B,C). This results in the formation of the late, fibrous atherosclerotic plaques. This late lesion is characterized by calcification (sclerosis), which makes artery wall rigid and fragile. Finally, the originally stable lesion may change into

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Abbreviations: PPAR-γ, peroxisome proliferator-activated receptor γ; LXR, liver X receptor; DC, dendritic cell; IFN, interferon; IL, interleukin; LDL, low density lipoprotein; LDLR, LDL receptor; SR, scavenger receptor

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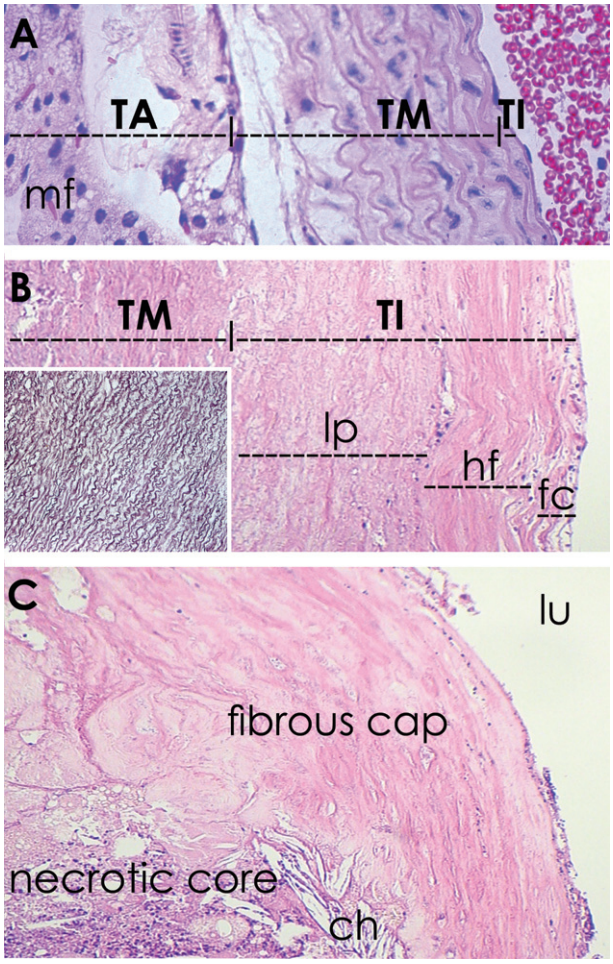

Fig. 1. The normal and pathological histology of the aortic arch. In mammals, as in mice (A) and humans (B and C) the aorta and the large arteries are built up from three tissue layers, the tunica intima (TI) covering the luminal surface (lu) of the vessels, the tunica media (TM) containing elastic layers and the tunica adventitia (TA). Human large arteries often have a subendothelial layer, which grows with age or atherosclerosis. Both connective tissue and smooth muscle cells are present in the intima. The border of the intima is delineated by the internal elastic membrane, which may not be conspicuous because of the abundance of elastic material in the tunica media (see inset in B). The tunica adventitia is a relatively thin connective tissue layer. In mice, mediastinal brown adipose cells (mf) can be involved in the formation of the tunica adventitia. Fibroblasts are the predominant cell type and many macrophages are also present. In mice, atherosclerotic plaques naturally cannot evolve, but in human lipid (lp) accumulation in the so-called fatty streaks of the subendothelial layer can occur with aging (B). In parallel with the accumulation of modified LDL, macrophages invade the tunica intima and differentiate into foam cells (fc). The vascular smooth muscle cells start to proliferate and form a hyalinized fibrous layer (hf) in the luminal surface of the subendothelial layer. The normal structure of elastic lamellae can be also degenerated. At the late phase of atheroprogression the subintimal layer is highly infiltrated by foam cells and the extracellular matrix proteins are degraded and show an eosinophilic hyalinic appearance (fibrous cap). Remnants of the apoptotic foam cells form a cholesterol (chol) rich necrotic core. Sections A, B, C are stained with hematoxylin–chromotrope, the inset is stained with orcein. Magnifications: 1000× (A), 250× (B and C), 400× (insert).

an unstable vulnerable plaque due to an imbalance between factors producing and degrading extracellular elements and this can easily rupture the covering endothelium leading to the formation of thrombus and intravascular coagulation.

There is growing appreciation that a special group of ligand-activated transcription factors play key roles in both the metabolic as well as the inflammatory processes.

2. Lipid metabolism of lesion macrophages: the pros and cons for peroxisome proliferator-activated receptor γ (PPAR-γ) in atherogenesis

Nuclear receptors are ligand-activated transcription factors. Small lipid-soluble molecules activate them. Members of this family can be located in the cytosol like classic steroid receptors (e.g. glucocorticoid receptor) or in the nucleus binding to the response elements of their target genes. Upon ligand binding receptors induce transcription of their target genes. Here, we are focusing on PPAR-γ and liver X receptor (LXR) since they have been shown to play a substantial role in lesion macrophages during atherosclerosis. Both of them form heterodimer with a common partner, retinoid X receptor (RXR).

PPAR-γ is most prominently expressed in adipose tissue and myelomonocytic cells, as macrophages and dendritic cells (DCs). PPAR-γ promotes uptake of oxLDL and subsequent differentiation of the macrophages to foam cells [11]. It is well known, that PPAR-γ is expressed in foam cells of atherosclerotic lesion [11,12]. Oxidized but not native LDL promotes its own uptake via scavenger receptor CD36 by PPAR-γ [11]. Two components from oxLDL, 9-hydroxy octadecadienoic acid (9-HODE) and 13-HODE were identified as endogenous activators and bona fide ligands for PPAR-γ [13]. There are also other scavenger receptors involved in LDL/oxLDL uptake, which will be discussed later. Thus, the consequence of oxLDL internalization is the activation of PPAR-γ that enhances further expression of CD36.

To provide genetic evidence that PPAR-γ is required for macrophage development and CD36 expression PPAR-γ-deficient embryonic stem (ES) cells were generated. Surprisingly, these can be differentiated into macrophages in vitro. In chimeric mice generated with mutant ES cells PPAR-γ-deficient cells are also able to contribute to the macrophage lineage in vivo [14]. However, retroviral transfer of the receptor facilitates induction of CD36 and oxLDL uptake in response to PPAR-γ-specific agonists. There is no change in the mRNA level of CD36 when PPAR-γ-deficient macrophages are treated with synthetic agonists such as thiazolidinediones (TZDs). These suggest that PPAR-γ is not necessary for macrophage development but required for the induction of CD36 and oxLDL uptake.

The model above would suggest that PPAR-γ is a pro-atherogenic factor. To define the in vivo role of PPAR-γ in atherogenesis PPAR-γ null bone marrow was transplanted into LDL receptor (LDLR) knockout mice, a murine model of atherosclerosis. Although animals received cholesterol-rich diet for 8 weeks, plasma total cholesterol levels were similar in control and PPAR-γ null bone marrow transplanted mice, however the degree of atherosclerosis was significantly increased in PPAR-γ-deficient bone marrow transplanted recipients [15].

TZDs were also reported to inhibit the development of atherosclerosis in LDLR-deficient male mice [16]. Chen and colleagues showed similar results in ApoE null mice, another murine model of atherosclerosis [17]. Targeted disruption of the PPAR-γ gene in macrophages resulted in reduced total