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Review

Mast cell proteases: Physiological tools to study functional significance of high density lipoproteins in the initiation of reverse cholesterol transport

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Abstract

The extracellular fluid of the intima is rich in lipid-poor species of high density lipoproteins (HDL) that promote efficient efflux of cholesterol from macrophages. Yet, during atherogenesis, cholesterol accumulates in macrophages, and foam cells are formed. We have studied proteolytic modification of HDL by mast cell proteases as a potential mechanism of reduced cholesterol efflux from foam cells. Mast cells are present in human atherosclerotic lesions and, when activated, they expel cytoplasmic granules that are filled with heparin proteoglycans and two neutral proteases, chymase and tryptase. Both proteases were found to specifically deplete in vitro the apoA-I-containing preβ-migrating HDL (preβ-HDL) and other lipid-poor HDL particles that contain only apoA-IV or apoE. These losses led to inhibition of the high-affinity component of cholesterol efflux from macrophage foam cells facilitated by the ATP-binding cassette transporter A1 (ABCA1). In contrast, the diffusional component of efflux promoted by α-HDL particles was not changed after proteolysis. Mast cell proteases are providing new insights into the role of extracellular proteolysis of HDL as an inhibiting principle of the initial steps of reverse cholesterol transport in the atherosclerotic intima, where many types of protease-secreting cells are present.

Keywords: Mast cells; Chymase; Tryptase; High-affinity cholesterol efflux; HDL proteolysis; Preβ-HDL; Reverse cholesterol transport

Contents

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1. Introduction

Atherosclerosis is a long-lasting disease of the inner layer of the arterial wall, the intima, and is characterized by accumulation of low density lipoprotein (LDL)-derived cholesterol in the intimal macrophages [1]. The cholesterol-filled macrophages are called foam cells and are the hallmark of atherosclerosis. By removing cholesterol from macrophages, HDL particles promote the transfer of cholesterol from the arterial intima back to the liver and initiate reverse cholesterol transport. This pathway comprises several steps in which various proteins operate in the plasma membrane of cells, the extracellular fluid of tissues, or the blood plasma compartment [2].

According to the cholesterol balance theory of atherogenesis, atherosclerosis is a cholesterol storage disease of the arterial intima in which cholesterol accumulation results from an imbalance between cholesterol influx and efflux [3]. There are indications that proteolytic modification of LDL and HDL by mast cell proteases may induce such an imbalance, at least in a system in which LDL, HDL and macrophages are present [4]. We focus in this review on the mast cell protease-dependent modifications of HDL.

Since macrophages do not posses a negative feed-back system to down-regulate the inflow of cholesterol, efforts to enhance cholesterol removal from these cells are potentially of great therapeutic value. Indeed, a preliminary clinical trial to stimulate the reverse cholesterol transport by infusion of the naturally occurring variant apoA-I Milano has produced significant regression of coronary atherosclerosis [5].

Various plasma proteins and lipoproteins may act as acceptors of cholesterol released from cells; yet HDL are the most efficient physiological acceptors [6]. This function may itself explain the protective role of HDL in atherosclerosis and, indeed, compromised cholesterol efflux can be sufficient to reduce the efficiency of reverse cholesterol transport [7]. The plasma enzyme lecithin cholesterol acyltransferase (LCAT) promotes esterification of cholesterol in the nascent HDL and, by enhancing the core of the developing spherical HDL, leads to formation of mature HDL particles [8]. The lipid transfer proteins, namely cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP), also contribute to HDL remodelling by promoting exchange of cholesteryl esters and phospholipids among HDL subclasses or with apoB-containing lipoproteins [9]. The occurrence of multiple steps in reverse cholesterol transport with various participating proteins suggests this pathway could be affected by proteolytic degradation of several of its components.

Human atherosclerotic lesions contain endothelial cells, smooth muscle cells, and inflammatory cells such as macrophages, T lymphocytes and mast cells [10]. These cells secrete active proteases capable of degrading components of the extracellular matrix of the intima [11]. The mast cell is the first type of a cell present in the arterial intima that has been found to inhibit cholesterol efflux from macrophage foam cells in vitro [12].

2. Mast cell as a powerful source of neutral proteases

Human mast cells are an inflammatory cell type filled with cytoplasmic secretory granules that contain two species of neutral serine proteases, tryptase and chymase, and smaller amounts of carboxipeptidase A and cathepsin G [13]. Importantly, mast cells are found in both early and late human coronary atherosclerotic lesions, with densities in human coronary arteries nine-fold higher in areas where foam cells are present than in areas without foam cells [14]. Numerous stimuli activate mast cells including complement proteins C3a and C5a, monocyte chemotactic protein-1 (MCP-1) and oxidized LDL [15]. Upon activation, mast cells degranulate and their proteases are secreted in active forms as components of the exocytosed granules, which are then called granule remnants. Indeed, extracellular chymase and tryptase in exocytosed mast cell granules have been detected by immunostaining of the human coronary intima [14]. Some secreted tryptase is apparently released from exocytosed granules and can be also detected by immunoelectron microscopy in the extracellular matrix surrounding activated mast cells [16].

In several pathological conditions chymase and tryptase have been claimed to be responsible for tissue disruption, inducing chronic leg ulcer [17], and conjunctival epithelial cell detachment and apoptosis [18]. Interestingly, high levels of circulating tryptase are suggested to be the consequence of low-grade inflammatory activity in atherosclerotic plaques [19]. Furthermore, it has been shown recently that exposure to tobacco-derived substances, a known risk factor for atherosclerosis, induces upregulation of secreted proteinases in mast cells [20]. Observations in animal models of hypertension and atherosclerosis indicate that chymase may be also involved in lipid deposition in the intima [21,22].