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Mast cells in atherosclerotic cardiovascular disease – Activators and actions

Petri T. Kovanen[a,*], Ilze Bot[b]

[a] Wihuri Research Institute, Helsinki, Finland
[b] Division of BioTherapeutics, Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands

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ABSTRACT

Mast cells are potent actors involved in inflammatory reactions in various tissues, including both in the intimal and the adventitial layers of atherosclerotic arteries. In the arterial intima, the site of atherogenesis, mast cells are activated to degranulate, and thereby triggered to release an abundance of preformed inflammatory mediators, notably histamine, heparin, neutral proteases and cytokines stored in their cytoplasmic secretory granules. Depending on the stimulus, mast cell activation may also launch prolonged synthesis and secretion of single bioactive molecules, such as cytokines and derivatives of arachidonic acid. The mast cell-derived mediators may impede the functions of different types of cells present in atherosclerotic lesions, and also compromise the structural and functional integrity of the intimal extracellular matrix. In the adventitial layer of atherosclerotic coronary arteries, mast cells locate next to peptidergic sensory nerve fibers, which, by releasing neuropeptides may activate mast cells to release vasoactive compounds capable of triggering local vasoconstriction. The concerted actions of arterial mast cells have the potential to contribute to the initiation and progression of atherosclerosis, and ultimately to destabilization and rupture of an advanced atherosclerotic plaque with ensuing atherothrombotic complications.

1. Introduction

Mast cells, first described in 1878 by Paul Ehrlich as aniline-positive cells in connective tissues, are considered as the primary type of cell in IgE-dependent allergic reactions in the human body (Vyas and Krishnaswamy, 2006; Galli and Tsai, 2012). The early detection of mast cells in human atherosclerotic lesions by Constantinides led him to propose the involvement of mast cells in atherosclerotic cardiovascular diseases (ASCVD) (Constantinides, 1954). The curiosity on the contribution of mast cells to the pathobiology of ASCVD was renewed when it was discovered that activation of mast cells to degranulate in a culture medium containing low density lipoprotein (LDL) particles resulted conversion of the macrophages into foam cells (Kokkonen and Kovanen, 1987). Mechanistically, LDL particles were bound to the heparin component of the exocytosed granules, and subsequently the LDL-granule complexes were phagocytosed by cultured macrophages. These macrophages became filled with cytoplasmic lipid droplets consisting of re-esterified LDL-derived cholesterol, i.e. they were converted into foam cells. The exocytosed mast cells granules also proteolyzed high density lipoprotein (HDL), thereby inhibiting their ability to induce high-affinity cholesterol efflux from the foam cells (Lee et al., 1992). Jointly, these two mechanisms have the potential to promote the formation and maintenance of foam cells in an LDL- and HDL-containing tissue environment, such as the inflamed arterial intima, in which mast cells and macrophages coexist.

After the above-described initial observations on a possible role of mast cells in the intimal metabolism of LDL and HDL, much work has been performed in an attempt to explore the potential mechanisms via which mast cells can act as proatherogenic cells in the propagation of atherosclerosis, and even as triggers and regulators of atherothrombotic complications generated by vulnerable atherosclerotic lesions (Kovanen, 2007a). By aid of advanced cell culture systems and experimental mouse models of atherosclerosis, and by examining atherosclerotic arteries obtained either at autopsy or during surgical procedures, understanding of the possible roles of mast cells in the progression of atherosclerotic lesions has become more comprehensive (Shi et al., 2015; Bot et al., 2015). In this review, a number of mast cell stimulators and actions of the released mediators on cellular functions and extracellular structures relevant to atherogenesis will be described.

2. Mast cell origin, development, and morphology

Mast cells arise from hematopoietic progenitor cells in the bone marrow; yet, in contrast to the ontogenesis of most hematopoietic lineages which are well understood, the ontogenesis of the mast cell lineage in the bone marrow remains ill-defined, particularly in humans

* Corresponding author.
E-mail address: petri.kovanen@wri.fi (P.T. Kovanen).

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(Kitamura et al., 1978; Schmetzer et al., 2016). The mast cell progenitors released from the bone marrow into the circulation express specific surface markers including CD34, CD13 and CD117 (c-Kit), which is the receptor for the KIT ligand, also termed mast cell growth factor or stem cell factor (SCF) (Agis et al., 1993; Kirshenbaum et al., 1999). Actually, the tissue mast cells appear to originate from a single class of circulating mast cell-committed progenitors (Maaninka et al., 2013), and differentiate into mature mast cells with varying phenotypes only once having entered a certain tissue. When maturing in tissue, mast cells develop a strong constitutive expression of the high-affinity receptor for IgE, FcεRI, which explains their unique role as tissue based-cells in IgE-dependent acute allergic reactions, and also in chronic IgE-dependent inflammatory states, such as asthma (Galli et al., 2008). Regarding atherogenesis and other chronic non-allergic inflammatory diseases, such as rheumatoid arthritis, in which mast cells have been suggested to play a pathogenic role (Marshall and Jawdat, 2004; Metcalfe, 2008; Theoharides et al., 2012; Suurmond et al., 2016b), the relative contributions of IgE-dependent and non-IgE-dependent mast cell activation remain to be defined. Many variations on the theme appear to exist, as mast cell responses often only partially depend on IgE-receptor mediated signaling.

Chemotaxis of circulating mast cell progenitors, which have acquired proper signals via their chemoattractant receptors, is mediated by various chemoattractants, including cytokines, chemokines, and eicosanoids, the SCF being one of them (Okayama and Kawakami, 2006; Collington et al., 2011; Halova et al., 2012; Nilsson et al., 1994). Regarding the arterial wall, SCF has been reported to be expressed in wire-injured mouse femoral artery, and in injured rat carotid artery, in which both SCF and c-Kit were significantly increased (Wang et al., 2006; Hollenbeck et al., 2004). In human studies, SCF has been found to the expressed by both endothelial and smooth muscle cells in the aorta and in coronary arteries (Miyamoto et al., 1997). The authors demonstrated the presence of both the transmembrane and soluble form of SCF, the former one potentially serving for paracrine mast cell – smooth muscle cell interactions, and the latter one being available as a chemoattractant for mast cell progenitors. Chemotaxis of mast cell progenitors is also mediated by eotaxin, a chemokine initially described as a chemotactic factor for eosinophils (Juremalm and Nilsson, 2005). Eotaxin was observed to be overexpressed by smooth muscle cells in human atherosclerotic lesions, in which also a fraction of mast cells were immunopositive for the eotaxin receptor CCR3 (Haley et al., 2000). Inhibition of CCR3 using a specific CCR3 antagonist was seen to limit perivascular mast cell accumulation during atherogenesis, leading to a concomitant reduction in lesion development (Bot et al., 2008), and suggesting that CCR3 is directly involved in mast cell progenitor recruitment to the atherosclerotic plaque. Mast cells in the perivascular tissue themselves may also be involved in the recruitment of new mast cell progenitors, as activation of mast cells has been shown to result in additional mast cell accumulation in the atherosclerotic artery (Bot et al., 2007, 2010), although the exact mechanisms in this process have not been elucidated.

For tissue homing, human mast cell progenitors require alpha4-integrin, VCAM-1, and PSGL-1 E-selectin for adhesive interactions with cytokine-activated human vascular endothelial cells, as demonstrated under conditions that mimic physiologic shear flow (Boyce et al., 2002). These observations may explain the presence of mast cells at sites of atherosclerotic inflammation, where VCAM-1 and E-selectin are important inducible endothelial receptors (Galkina and Ley, 2007). Ultimately, the differentiation of a progenitor cell into a given phenotype of a tissue resident mature mast cell is determined by the microenvironmental growth factors and cytokines present in the tissue involved (Dahlin and Hallgren, 2015). Among the maturation factors, the most essential molecule for mast cell differentiation is the SCF, which exerts its differentiation-inducing activities by binding to its receptor (c-Kit) on mast cell surface (Lennartsson and Rönnstrand, 2012). Moreover, SCF is also of key importance for mast cell adhesion, differentiation, activation, and survival (Galli et al., 1995).

Common to all mature mast cells in tissues is their high content of cytoplasmic membrane-bound secretory granules that are filled with preformed, highly active biological effector molecules, notably histamine, heparin, and neutral proteases, notably the tryptic protease tryptase and the chymotryptic protease chymase (Wernersson and Pejler, 2014). Human mast cells are characterized based on their neutral protease content. All human mast cells contain tryptase and a variable fraction of them contains also chymase, which renders them distinguishable into tryptase- (MC_T) and tryptase- and chymase-containing (MC_{TC}) mast cells (Irani et al., 1986). Human mast cells express three forms of tryptase (α-, β- and γ- tryptase) and one form of chymase (Bischoff, 2007). Human mast cells possess the potential to express also cathepsin B, carboxypeptidase A3, and granzyme B (Maaninka et al., 2013). Mast cells in mice, the animal species which is mostly used to study mast cell related effects in disease, are divided into two subsets based on their anatomic and histologic location in the body (Gurish and Austen, 2012; Wernersson and Pejler, 2014). Thus, in mice mucosal mast cells (MMCs) are located in tissues with a mucosal surface, such as the intestine and lungs, while connective tissue mast cells (CTMCs) are typically located in the skin and perivascular areas of all tissues. Mouse mast cells express four chymases (mMCP-1, −2, -4, and -5) and two tryptases (mMCP-6 and -7). Interestingly, in mice all mast cells contain mixed protease expression profiles in a strain- and tissue-dependent manner, so that both chymases and tryptases are expressed both in MMCs and in CTMCs, with the notable exception of mouse small intestinal MMCs, which appear to express the chymotryptic mMCP-1 only (Gurish and Austen, 2012; Wernersson and Pejler, 2014). Since the neutral proteases are present intracellularly in the cytoplasmic secretory granules, their release from the cell is necessary for them to gain access to the pericellular milieu. Indeed, in response to a variety of signals, mast cells become activated and release a fraction of their secretory granules in an exocytotic process termed ‘degranulation’, thereby acutely influencing their microenvironment (Choi and Abraham, 2015). Importantly, most of the granule proteases are stored as fully processed enzymes capable of exerting full activity immediately upon release into the extracellular space (Caughey, 2016).

The mast cells are long-lived and reside in various body tissues and survive there for months or even years (Westerberg et al., 2015). Such longevity is possible through an anti-apoptotic machinery in which SCF functions as a survival factor by repressing apoptosis through the bcl-2 family of apoptosis-regulatory genes (Mekori et al., 2001). This anti-apoptotic machinery also becomes operative upon mast cell degranulation, and it allows mast cells to regenerate new granules and to undergo several cycles of degranulation, a characteristic not shared by, e.g. by neutrophils, which have a short life span and are destined to enter apoptosis both in the circulation and in tissues (Christenson et al., 2011). It is then conceivable that the very low concentration of mast cell progenitors in the circulation (Dahlin et al., 2016) is appropriate for the slow turnover of mast cells in tissues, albeit, at least in mice, peripheral tissues have a constitutive pool of mast cell progenitors whose numbers increase tremendously upon allergic inflammation (Dahlin and Hallgren, 2015).

3. Mast cells in human atherosclerotic lesions

Since tryptase is a molecule expressed specifically by mast cells in atherosclerotic tissues, immunostaining for it is used as a reliable method for the detection of mast cells (Walls and Amalinei, 2014). By counting tryptase-positive cells in the aortic wall, we found that mast cells are present in normal intima, in fatty streaks, and in the growing, but ultimately vulnerable, shoulder regions of atheromas, thus supporting the hypothesis that mast cells play a role both in the early and late stages of human atherogenesis (Kaartinen et al., 1994a). In these plaques, mast cell generally co-localized with T lymphocytes and macrophages, so providing a proper soil for interactions between the