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Mast cells and vascular diseases

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ABSTRACT

Mast cells are increasingly being recognized as effector cells in many cardiovascular conditions. Many mast-cell-derived products such as tryptase and chymase can, through their enzymic action, have detrimental effects on blood vessel structure while mast cell-derived mediators such as cytokines and chemokines can perpetuate vascular inflammation. Mice lacking mast cells have been developed and these are providing an insight into how mast cells are involved in cardiovascular diseases and, as knowledge increase, mast cells may become a viable therapeutic target to slow progression of cardiovascular disease.

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1. Introduction

Mast cells are often considered as the basophils of the tissue. They are particularly numerous in connective and submucosal tissues where they have been shown to play a key role in the regulation of innate and adaptive immune responses, immunity against pathogens, autoimmune diseases, cancer, diabetes and angiogenesis (Rodewald & Feyerabend, 2012). Importantly, mast cell products play a role in regulating vascular functions. Mast cells are frequently associated with diseased vessels and the possible contribution of mast cells to

Abbreviations: 5-LO, 5-lipoxygenase; AAA, abdominal aortic aneurisma; ABCA1, ATP-binding cassette transporter A1; ACE, angiotensin converting enzyme; ACEI, angiotensin converting enzyme inhibitors; AGTR1, angiotensin receptor type I; Ang, angiotensin; $ApoE^{-/-}$, apolipoprotein E deficient mice; ARBs, angiotensin receptor blocking drugs; bFGF, basic fibroblast growth factor; BMMC, bone marrow derived mast cells; BMP-2, bone morphogenic protein-2; CTMCs, connective tissue distributed mast cells; EC, endothelial cells; FLAP, 5-lipoxygenase activating protein; HDL, high density lipoprotein; HEIS, Hyper IgE syndrome; IgE, immunoglobulin E; IL, interleukin; $iPLA_2$, phospholipase A_2; LDL, low density lipoprotein; $Ldlr^{-/-}$, low density lipoprotein receptor-deficient mouse; LT, leukotriene; MCP-1, monocyte chemoattractant protein-1; MCps, Mast cells leave the bone marrow as progenitors; mMCP-4, mast cell protease-4; MMCs, mucosal mast cells; MMPs, matrix metalloproteinases; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor-κB; NGF, nerve growth factor; PAF, platelet activating factor; PARs, protease activated receptors; PRRs, pattern recognition receptors; PTCA, Percutaneous coronary transluminal angioplasty; RANTES, regulated upon activation, normal T cell expressed and secreted; ROS, reactive oxygen species; SCF, stem cell factor; Serpin A3, serine protease inhibitor A3; STAT 3, signal transducer and activator of transcription 3; TAA, thoracic aortic aneurysm; TLRs, toll-like receptors; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.

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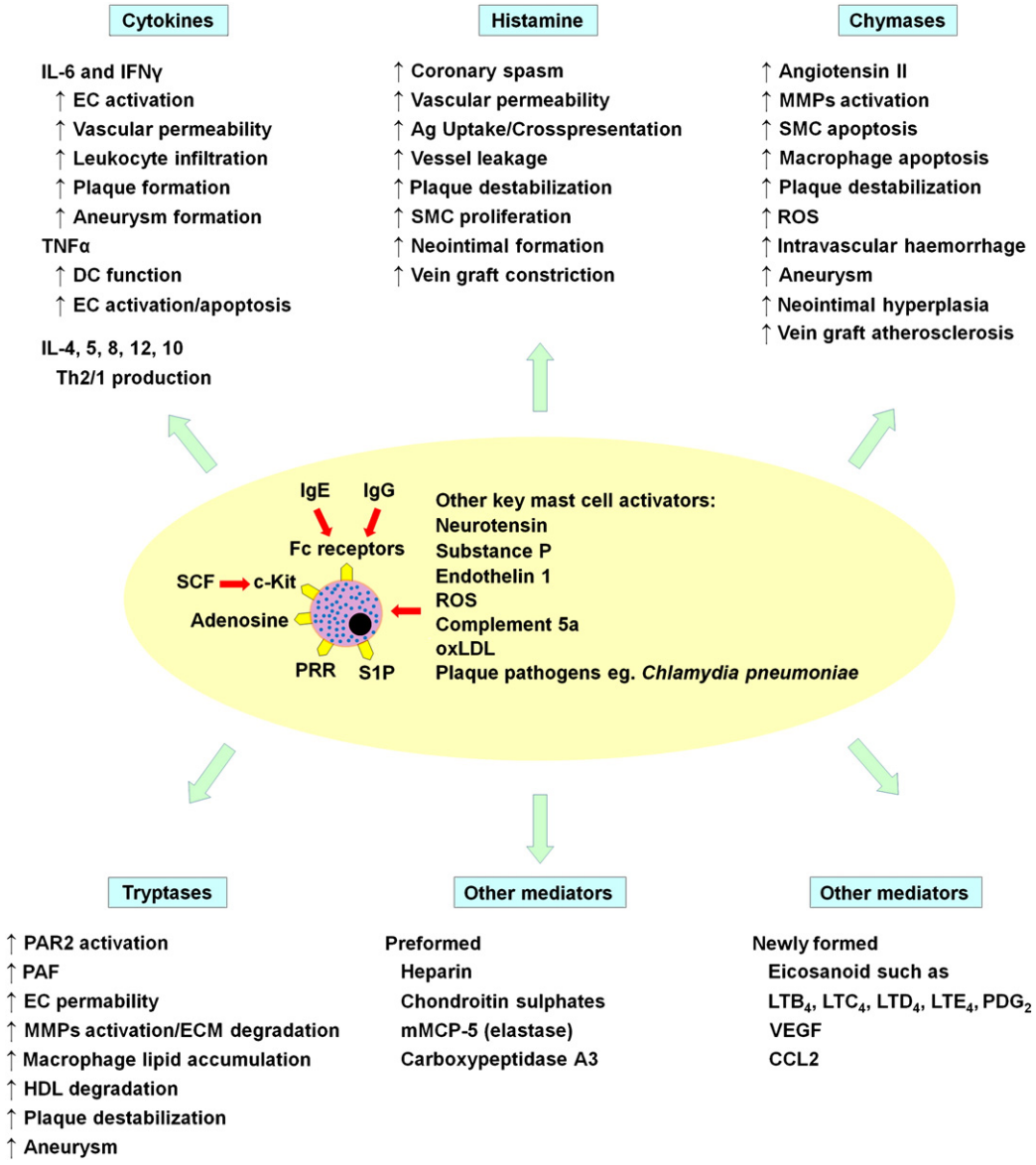

Fig. 1. Mast cells in vascular diseases. Mast cells, mainly located in plaque and adventitia of diseased vessels, activated by several stimuli play key roles in vascular pathologies by releasing a broad range or preformed or newly synthesized mediators. Cytokines such as IL-6 and IFN-γ have been shown to induce endothelial cell activation, promote vascular inflammation leading to plaque and aneurysm formation. Mast cell-derived TNFα promotes dendritic cell activation and antigen presentation, other interleukins can influence T cell effector response. Histamine induces vascular constriction, increases vascular permeability, promotes antigen uptake and SMC proliferation leading to plaque destabilization, neointimal formation and vein graft constriction. Mast cells proteases (chymases and tryptases), via different mediators, induce extracellular matrix degradation, vascular cell apoptosis and foam cell formation leading to plaque destabilization, aneurysm, neointimal formation and vein graft atherosclerosis. Finally, several other mediators produced by mast cells have been shown to be involved in vascular inflammation/remodelling.

vascular pathology have been recently suggested in arteriosclerosis (Kovanen, 2007; Lindstedt et al., 2007; Sun et al., 2007a; Bot & Biessen, 2011; Theoharides et al., 2011; Wang & Shi, 2011), aortic aneurysm (Swedenborg et al., 2011; Shi & Lindholt, 2012; Wang & Shi, 2012) and vein graft disease (de Vries et al., 2013). In this review we will summarize current knowledge on the role(s) for mast cells in vascular diseases including atherosclerosis, restenosis and vein graft hyperplasia (Fig. 1).

2. Mast cell biology

Mast cells are long-lived cells constitutively present in most tissues and are characterized by dense granules in their cytoplasm (Abraham & St John, 2010). Mast cells leave the bone marrow as progenitors (MCps), expressing the high-affinity receptor for immunoglobulin E (IgE), FcεRI, and the stem cell factor (SCF) receptor Kit. MCps are released in the blood stream from where they migrate into the peripheral tissues by transendothelial migration (Gurish & Austen, 2012). They then mature and become terminally differentiated under the influence of cytokines within the surrounding milieu.

Two major subclasses of mature tissue mast cells have been identified: connective tissue distributed mast cells (CTMCs), found in the skin, synovium and perivascular tissue (Nakano et al., 2009), and mucosal mast cells (MMCs), typically present in the lungs and intestinal mucosa (Knight et al., 2000; Gurish & Austen, 2012). Mast cells are phenotypically plastic as determined by their differential expression of receptors and granule contents. The localization of mast cells in tissues as well as their replication and differentiation into distinct phenotypes are typically determined by the chemical environment of their final tissue destination (Gilfillan & Beaven, 2011). SCF is the main survival and developmental factor for mast cells. Other molecules that promote mast cell maturation include nerve growth factor (NGF) and neutrophin-3 (Theoharides et