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Mast cells as pivotal players in atherogenesis. Review

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Abstract: The mast cell is an immune cell involved primary in host defense of organism. Moreover, it plays an important role in atopic diseases. Recently, accumulating evidence established the contribution of the mast cell in atherogenesis. Through its release of mediators, activated mast cells can have proatherogenic effects on its surroundings in the vessel wall. In this review, we will discuss the current knowledge on mast cell function in atherogenesis and atherosclerosis — caused cardiovascular diseases.

Keywords: atherosclerosis, mast cells, cardiovascular disease.

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Introduction

In 1876 Paul Ehrlich discovered new inflammatory cells and named them "mast cells" [1, 2]. Mast cells are able to respond to exogenous signals from bacteria, viruses and parasites, using recognition receptors (like Toll-like receptors, immunoglobulins and others) [3].

Mast cells (MC) were initially "designed" by nature in defence against pathogens. However, especially in modern times, they represent important mediators in atopy (allergy and asthma), once they become dysregulated in response to an excess of allergen or allergen-specific Inmmunoglubulin E (IgE) [3]. Mast cells contain granules with mediators, such as the vasoactive histamine, heparin, the proteases chymase, tryptase and the cathepsins, as well as cytokines such as Tumor Necrosis Factor α (TNFα), chemokines (e.g. Interleukin 8 (IL-8)) and other growth factors like Vascular Endothelial Growth Factor (VEGF) and Fibroblast Growth Factor (FGF) [4].

In 1978 Kitamura and colleagues described mast cell deficient animals. These were so called W/Wv mice, devoid of tissue and skin mast cells [5]. These mice had 1% of the normal number of

skin mast cells compared to wild-type mice. In other tissues mast cells were absent. W/Wv mice carried a mutation in the C-Kit gene. It caused a defect in hematopoietic stem cells, resulting in dysregulated hematopoiesis. The anemic Sl/Sld mouse had a comparable phenotype to the W/Wv mouse. The difference was, however, that in this strain bone marrow transfer does not rescue the phenotype. This suggested the absence of environmental factors needed to induce mast cell differentiation and maturation in Sl/Sld mice [6, 7]. Recently, a new mast cell deficient mouse was discovered. It contains the spontaneously arisen W-sash (Wsh) inversion mutation. However, here mast cell deficiency is not accompanied by anemia and sterility [8]. These Kit(W-sh/W-sh) mice can be repopulated with mast cells by injection of either bone marrow cells or cultured bone marrow derived mast cells. Therefore, they represent an interesting tool for animal studying mast cell biology *in vivo* in many diseases.

Mast cells in atherosclerosis

In 1953, Constantinides described that mast cells are involved in experimental atherosclerosis [8]. He suggested that the heparin could be atheroprotective. In 1954, he and his coworkers described that in myocardial tissue from patients suffering from atherosclerosis there is a reduced numbers of mast cells compared to patients without atherosclerosis [9]. It was a "founding stone" for decades-longing strong belief that mast cells are „atheroprotective". Therefore, atopic patients were comfortingly informed by doctors, that „at least" they should not develop atherosclerosis [8]. Unfortunately, it all occurred to be a false premise. In recent years, the paradigm shifted towards a pro-atherogenic role of mast cells [10].

Mechanisms of participation in atherogenesis

For a long time mast cells have been identified with atherosclerosis [11]. Mast cells can recruit neutrophils and circulating leukocytes. They take place in the initiation of atherogenesis and are part of the atherosclerotic inflammation. Upon activation, MC secretes its granules into the subendothelial space of the arterial intima. What is important, activated MC stimulate endothelial cells to express adhesion molecules [12. 13]. Mast cells secrete tryptase, which damages endothelial integrity. Due to tryptase — induced degradation of the endothelium, LDL particles may appear in subendothelial space [14]. Histamine increases the transendothelial transport of plasma LDL into the subendothelial space. There it is bound by the heparin component of the insoluble granule remnants and degraded by chymase. The proteolytically modified LDL particles become unstable and fuse on the remnant surface.Then the macrocomplex is phagocytosed and degraded by the macrophage with the subsequent formation of a foam cell [15, 16]. High density lipoprotein, responsible for the efflux of LDL-derived cholesterol from the macrophage foam cell, is also proteolyzed by mast cell chymase. The high-affinity component of the HDL-dependent cholesterol efflux is so impaired. Therefore, the balance between cholesterol influx and efflux is disturbed. A cholesterol-filled foam cell is formed. The foam cell contribute to the formation of an extracellular lipid core [17, 18].

MC also take plase in formation of neovessels within the plaques [19]. Data from clinical trials showed that using of antibodies against VEGF (inhibiting angiogenesis) can increase risk of thromboembolic complications. Moreover, it seems that inhibition of angiogenesis is not a good therapeutic strategy for cardiovascular diseases. It has occurred that VEGF — induced angiogenesis in human arteries may rather play a protective role [19].

Mast Cell Activators in Cardiovascular Disease

Since MC are considered to be proatherogenic, the question arises how they are activated in the place of formation of atherosclerotic plaque. There are several pathways by which they can be activated [20, 21]. One of them is the immunoglubulin E (IgE)-dependent pathway. It takes place *via* allergen-triggered crosslinking of IgE molecules. They are bound to high-affinity FcεRI receptors on the mast cell surface.

Oxidized LDL (oxLDL) has been also shown to induce MC activation. They cause leukocyte recruitment [22]. Next, there is an induction of secretion of proatherogenic cytokines *via* toll-like receptor type 4 (TLR4) [23]. Moreover, individual components of modified LDL particles can act as MC activators. One of them is lysophosphatidic acid (LPA) [24].

Another MC type of activation acts *via* the complement system. MC within the plaque express receptors for complement components. In particular, it is the receptor for C5a, C5aR [25]. As we already know, activated complement is present within the atherosclerotic plaque [26], fulfilling the complement-mediated MC activation hypothesis.

Last but not least, MC degranulation may be regulated *via* neuronal activation (particularly in the adventitia). In humans, MC connect with nerve fibers [27]. They are substance P-positive. Local substance P — mediated MC activation resulted in plaque destabilization. It was indicated by increased intraplaque hemorrhage, which did not occur in mast cell-deficient ApoE-/- Kit(W-sh/W-sh) mice. These mice (described above) have no mast cells [28].

Mast cells and myocardial infarction

Acute cardiovascular syndromes (ACS) remain one of the leading causes of death in Western societies. The main cardiovascular disorder causing these acute cardiovascular events is the development of atherosclerosis [29]. Lipid accumulation, matrix degradation, and infiltration of different proinflammatory cells are considered pivotal in the atherogenesis and the pathogenesis of plaque rupture [30, 31]. A novel therapeutic target could be MC, which has been shown to increase within the arterial wall during atherosclerotic plaque progression [32–37].

Mast cells in aortic valve stenosis

Aortic valve stenosis (AS) shares many features with atherosclerosis. It includes infiltration of inflammatory cells such as macrophages and T-lymphocytes, accumulation of oxidized lipids and extensive tissue remodeling [38, 39]. In analogue to atherosclerosis, in the diseased aortic valve area mast cells are also demonstrated, as can be visualized by CD117 immunoreactivity [40].

Mast cells in aortic aneurysms

Aortic aneurysm development is a chronic degenerative condition. It is characterized by weakening and dilation of the aortic wall that results in a life-threatening risk of rupture. It is associated with atherosclerosis [41]. The first study to report a causal relation between MC density in the aortic wall and aneurysm rupture was published in 1981 [42]. In this article Faleiro *et al.* showed a pronounced presence of MC in arteries of the circle of Willis of patients that died of subarachnoid hemorrhage after aneurysm rupture.

Recently, Sun *et al*. studied the role of MC in an animal model of abdominal aortic aneurysm (AAA) formation. AAA was induced by elastase perfusion in MC deficient Kit(W-sh/W-sh) mice and control mice [43]. It has occurred that the MC-deficient mice failed to develop AAA. It was because of reduced aortic expansion and internal elastic lamina degradation.

Summary

Overwhelming evidence from pathology and experimental studies points to a pivotal role for MC not only in immune diseases, but also in various cardiovascular disorders [44]. Perivascular and intimal MC contribute substantially to the atherogenesis and plaque destabilization. MC contribute to intraplaque hemorrhage, plaque destabilization and rupture. Moreover, they contribute to aortic valve stenosis as well as aneurysm formation.

Could MC be a novel therapeutic road for treament of cardiovascular diseases [36]? We do hope that near future could response to this important question.

Author's contributions

J.J. and M.B. provided the overall concept and frasmework of the review; J.J. wrote the manuscript; M.B. revised the manuscript. All authors read and approved the final version of the manuscript.

Abbreviations

AAA — abdominal aortic aneurysm
ACS — acute cardiovascular syndrome
AS — aortic valve stenosis
HDL — High Density Lipoproteins
IgE — immunoglobulin E
LDL — Low Density Lipoproteins
LPA — lysophosphatidic acid
MC — mast cells
oxLDL — oxidized low-density lipoprotein
TLR4 — toll-like receptor
TNF — tumor necrosis factor
VEGF — Vascular Endothelial Growth Factor

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