Editorial

Mast cells feel the strain

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Received 16 April 2002; accepted 17 April 2002

See article by Huang et al. [1] (pages 150–160) in this issue.

Mast cells are implicated to be involved in the pathogenesis of atherosclerosis and acute coronary syndromes. However, the contribution of mast cells in the initiation of atherogenic mechanisms, and the role of mediators they release is not fully understood. In this issue of Cardiovascular Research, Huang et al. [1] provide evidence that mast cells can contribute to stress related cardiac disease. They showed that mast cells become activated in response to acute restraint stress in mice. This effect was enhanced in ApoE knock-out mice. These mice were seen to have higher levels of histamine and a greater number of mast cells, compared to wild type. The findings provide important evidence that acute coronary syndromes can be mediated by neuroinflammatory reactions.

Mast cells are found within every major organ of the body. Within the heart they can be localised to the interstitial space between myocytes, generally in regions associated with the coronary arteries [2]. Mast cells are also found within media and adventitia of the coronary vessels, with the majority residing in adventitia [3]. Mast cell numbers have been shown to increase during heart failure, with great numbers found in patients with ischaemic cardiomyopathy [4]. Greater numbers of mast cells are also associated with the shoulder region of atherosclerotic plaques [5]. Those coronary vessels that are associated with myocardial infarction have been shown to increase their numbers of degranulated mast cells within the adventitia of regions associated with plaque rupture. Within atherosclerotic lesions mast cells are associated with activated complement, T-lymphocytes and macrophages [6,7]. Mast cells release a repertoire of atherogenic mediators including proteases, chemokines, cytokines, prostanoids, platelet activators, vasoactive agents and growth factors [8].

Mast cell activation may also have a role to play in the initiation and progression of heart disease. Histamine has been shown to promote vascular smooth muscle cell growth, and blockade of H1-receptors has been shown to reduce intimal thickening in a mouse model of vascular injury [9,10]. It has been demonstrated that mast cell degranulation can induce apoptosis of rat cardiomyocytes and stimulate proliferation of non-myocardial cells, a situation that would lead to the progression of myocardial fibrosis and a loss in contractile function [11]. This effect was attributable to the protease action of rat mast cell chymase. In a study examining coronary arteries obtained from patients at autopsy, a 5–10-fold increase in mast cell numbers in cap, core and shoulder regions of atherosclerotic lesions were observed. In the shoulder region, 85% of the mast cells were activated [12]. Chymase and tryptase released by mast cells may destabilise atheromatous plaques due to their action on the extracellular matrix. Both chymase and tryptase can directly activate matrix metalloproteinases (MMPs), cleave and activate procollagenase, or stimulate the release of TNF-α which in turn activate macrophages to secrete MMPs [7,13,14].

The contents of mast cells may have an important role to play in coronary artery vasoconstriction associated with acute coronary syndromes. Intra-coronary injections of histamine have been shown to induce vasoconstriction of atherosclerotic segments of the artery, but not in non-diseased regions [15,16]. Indeed, histamine has been shown to act as a ‘double agent’ in human arteries, producing both relaxation and contraction [17]. The sensitivity of atherosclerotic regions of the vessel wall is most likely due to either endothelial dysfunction at these sites, and/or up-regulation of histaminergic receptors in spastic areas of diseased coronary arteries. Other vasoactive agents released by mast cells, namely prostaglandin D2 and leukotriene C4 will also contribute to the contractile effects of histamine. It has been shown that leukotriene C4

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constricts human arteries and veins [18]. Its contractile effect in the coronary circulation is only observed in atherosclerotic coronary [19].

Mast cells participate in the early events of the atherosclerotic process. Increased numbers of mast cells have been identified in fatty streaks, indicating their involvement in foam cell formation [20]. Mast cell activation stimulates the transport of LDLs across the endothelium and into extravascular areas [21]. Heparin proteoglycans released from mast cell granules bind LDLs and are then phagocytosed by macrophages [22]. Mast cell granules can also partially degrade apolipoprotein B, leading to fusion of LDL particles and uptake by macrophages [20]. Indeed, it has been shown that mast cell stabilising agents have the ability to inhibit foam cell formation [22].

Mast cells release a number of different proteases such as cathepsin G, cardioxypeptidase, tryptase and chymase. These enzymes can stimulate extra-cellular matrix degradation and vascular remodelling but also have the capacity to generate angiotensin II. Chymase in particular is associated with cardiovascular disease due its ability to generate angiotensin II. In a similar fashion to chymotrypsin, chymases hydrolyse peptide bonds at the COOH-termini of hydrophobic aromatic residues. The degree of selectivity over which amino acids are hydrolysed is a function of the extended substrate binding site of the chymase molecule. Thus, human chymase can form angiotensin II by cleavage of the bond between Phe−His of the precursor molecule, but it is unable to inactivate angiotensin II since it does not cleave Tyr−Ile bond in angiotensin II. It is also inactive against substance P, bradykinin, vasoactive intestinal peptide, lutenizing hormone-releasing hormone, somatostatin and alpha-melanocyte-stimulating hormone [23]. Human chymase has been located in the mesenchymal interstitial cells and endothelial cells within the heart [2]. Mast cells represent an important source of chymase with respect to its potential to generate angiotensin II within the coronary vessel wall. Chymase-containing mast cells have been localised to human atherosclerotic lesions, with the more severe lesions containing the greatest number of mast cells, and to regions of coronary vessels associated with myocardial infarction [5,24]. Increased numbers of mast cells have been observed in a dog carotid artery balloon injury model, primarily in the adventitial region of the vessel wall [25]. This increase was suggested to be the result of their migration into the adventitia. Tranilast, an anti-allergenic agent, was shown to reduce the increase in mast cell numbers and neointimal formation in this model. It has also been shown that interacting fibroblasts and mast cells, through regulation of stem cell factor and c-kit expression, are essential for the further development of mast cells. The beneficial effects of tranilast are thought to arise from its ability to down regulate the activity of fibroblasts [26,27].

Angiotensin II has the capacity to play a role at a number of key stages in the atherosclerotic process. In the very early stages of the disease, angiotensin, via stimulation of adhesion molecules, can aid in the recruitment of monocytes/macrophages into the vessel wall [28]. Angiotensin may assist in the development of these cells into foam cells by enhancing oxidant stress by activation of NADP/NADPH oxidase, which leads to oxidation of LDL [29]. Increases in oxidant stress will also down-regulate the protective effects of endothelium-derived nitric oxide. Superimposed on these mechanisms are the direct effects of angiotensin II on the vascular smooth muscle cells. Its mitogenic action, together with stimulation of messengers such as transforming growth factor-β and plasminogen activator inhibitor-1 mediate the remodelling of the vessel wall seen in the latter stages of the disease [30–32].

Mast cells therefore have the capacity to release a wide range of mediators that can contribute to the onset and progression of atherosclerotic disease. Understanding the events that initiate their activation is key to comprehending the mechanisms that allow mast cell degranulation to precipitate acute angina and myocardial infarction. The observation that acute stress can act as a trigger to their activation provides an insight into how acute stress can precipitate acute coronary syndromes. Investigations into the identification of the mediator(s) and the signalling mechanisms involved in the translation of stress into activation of mast cells are required. Additional studies are warranted to elucidate how chronic stress may induce continued mast cell activation, and if such a mechanism is important in atherogenesis. Such studies will permit assessment of the potential benefit of mast cell stabilising agents in the treatment of atherosclerosis.

References


