EDITORIAL

ROLE OF MAST CELLS IN ATHEROSCLEROSIS: A CLASSICAL INFLAMMATORY DISEASE

E. SPINAS[1], S.K. KRITAS[2], A. SAGGINI[3], A. MOBILI[4], A. CARAFFA[5], P. ANTINOLFI[5], A. PANTALONE[6], M. TEI[7], A. SPEZIALI[7], R. SAGGINI[8], and P. CONTI[9]

[1]Department of Surgery and Odontostomatological Sciences, University of Cagliari, Italy; [2]Department of Microbiology and Infectious Diseases, School of Veterinary Medicine, Aristotle University of Thessaloniki, Macedonia, Greece; [3]Department of Dermatology, University of Rome Tor Vergata, Rome, Italy; [4]Cardiology Division, Post-graduate Medical School, University of Chieti-Pescara, Chieti, Italy; [5]Orthopedic Division, University of Perugia, Perugia, Italy; [6]Orthopedic Division, University of Chieti-Pescara, Chieti, Italy; [7]Nicola's Foundation, Onlus, Arezzo, Italy; [8]Department of Neurosciences and Imaging, Faculty of Medicine and Surgery, G. d'Annunzio University Chieti-Pescara, Chieti, Italy; [9]Immunology Division, Post-graduate Medical School, University of Chieti-Pescara, Chieti, Italy

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Atherosclerosis is an inflammatory disease and hyperlipidaemia is one of the main risk factors for aging, hypertension and diabetes. Variance in plasma LDL cholesterol concentration may be associated with differences in cardiovascular disease risk and high levels of lipids are associated with increased risk of developing atherosclerosis. Macrophages, which generate pro-inflammatory cytokines, mainly interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-alpha), are deeply involved in atherosclerosis, as well as mast cells which generate several cytokines, including IL-6 and IFN-gamma, and chemokines such as eotaxin, MCP-1 and RANTES involved in monocyte recruitment and differentiation in the arterial wall. In addition, mast cells participate in lipid retention and vascular cell remodeling, and are mediators of innate and adaptive immunity during atherosclerosis. Mast cells which accumulate in the human arterial intima and adventitia during atherosclerotic plaque progression, release vasoactive and angiogenic compounds, and pro-inflammatory mediators, such as arachidonic acid metabolites, histamine, cytokines/chemokines, platelet activating factor (PAF) and proteolytic enzymes. Mast cells can be activated by pro-inflammatory stimuli, including cytokines, hypercholesterolemia, and hyperglycemia, and trigger the endothelial expression of adhesion molecules such as P-selectin, vascular cell adhesion molecule-1 (VCAM-1) and chemokines which mediate the recruitment and adhesion of leukocytes. The participation of mast cells in atherosclerosis is still an enigma and it may be of therapeutic interest to clarify this process.

Inflammation is the reaction course of an infected or generally irritated and injured living tissue in the organism. The irritant can be of mechanical-physical, chemical, infectious, immunological or reactive nature. Microscopically, inflammation is mainly demonstrable by inflammatory cells which in

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Mailing address: Prof. Enrico Spinas,
Department of Surgery and Odontostomatological Sciences,
University of Cagliari,
Cso Vittorio Emanuele 340,
09123 Cagliari, Italy
Tel.: +39 330412295
e-mail: enricospinas@tiscali.it

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number and nature change depending on the stage and type of inflammation. Biochemically, inflammation is indicated by local increase of numerous tissue hormones, transmitters (e.g. produced by mast cells), complement components, arachidonic acid products, and cytokines. Most of these products belong to the so-called autacoids (autos, greek= self, akos, greek = drug). The term autacoids expresses the idea that the increase of substances like those mentioned above means self-treatment by the body of the inflamed site.

Atherosclerosis is an inflammatory disease and the term arteriosclerosis was first introduced by Jean Lobstein in 1829 and later, Virchow showed that cellular pathology is critical in this chronic disease. Atherosclerosis-related diseases, such as myocardial infarction, and strokes account for about half of the diseases in the United States and Western Europe and for a great deal of morbidity (1). It has been reported that high levels of cholesterol and triglycerides are associated with obesity and increased risk of developing atherosclerosis and shorter life (2). Therefore, hyperlipidaemia is one of the main risk factors for aging, hypertension and diabetes, and high level lipids are associated with an increased risk of developing atherosclerosis. Almost 40 years ago it was shown that T-cell accumulation was very important in early lesions, suggesting that lymphocytes play an essential role in atherosclerosis (3). In fact, immune pathways play a major role in the development and progression of atherosclerosis which is characterized by vascular wall infiltration by macrophages and T cells associated with lipid infiltration (4) and presents metabolic perturbations that mediate important and complex interactions with the immune system and the vascular wall.

It is a commonly accepted concept that atherosclerosis is a response of the vascular wall to a variety of initiating agents, and multiple pathogenetic mechanisms contribute to the formation of the plaques consisting of apoptosis, calcified regions, accumulated modified lipids, inflamed smooth muscle cells, endothelial cells (ECs), foam cells, leukocytes, ulceration, thrombosis, hemorrhage, aneurysmal dilatation and smooth muscle cell proliferation which are all critical events in the development of the atheromatous plaque (5). Smooth muscle cells synthesize large amounts of connective tissue matrix, including collagen, elastic tissue, and proteoglycans, which characterize the lesion of atherosclerosis (6). During the past 10 years, the recognition that variance in plasma LDL cholesterol concentration may be associated with differences in cardiovascular disease risk and that LDL has potentially important cardiovascular-damage functions (7). The reduction of serum cholesterol reduces atherosclerosis and myocardial infarction, strokes and mortality. Therefore, young and elderly should be treated and the lipid-lowering drugs and diet should be used.

Adhesion molecules generated by the dysfunction of NO and endothelial cells which line an artery as well as LDL-cholesterol which accumulates within the vessel wall and becomes oxidized, mediate atherosclerosis (8).

Macrophages, which are deeply involved in this disease, have two sub-populations, M1 and M2 macrophages, generate pro-inflammatory cytokines [mainly interleukin-1(IL-1) and tumor necrosis factor-alpha (TNF-α)], and participate in lipid retention and vascular cell remodeling, and are mediators of innate and adaptive immunity during atherosclerosis (9).

The generation of certain cytokines by mast cells, such as IL-6 and IFN-gamma and chemokines (eotaxin, MCP-1 and RANTES involved in monocyte recruitment and differentiation in the arterial wall), restores atherosclerosis progression in experimental animal model (10).

Mast cells (MCs) are multi-effector cells with wide distribution in the different body parts(11). Mast cells are necessary for the development of allergic reactions through cross-linking of their surface high affinity receptors for IgE (FcεRI) leading to immediate degranulation and slow release of newly synthesized vasoactive and angiogenic compounds, pro-inflammatory and nociceptive mediators, such as arachidonic acid metabolites, histamine, cytokines/chemokines, platelet activating factor (PAF) and proteolytic enzymes (12).

Mast cells accumulate in the human arterial intima and adventitia during atherosclerotic plaque progression (13) and are involved on the incidence of intra-plaque hemorrhage. Adventitial MCs are localized close to nerve endings in atherosclerotic coronary arteries and correlate with the number of

nerve fibers (14).

We previously reported that CC chemokines MCP-1 and RANTES are able to recruit MCs at the site of inflammation (15); since these chemokines are expressed within atheroma they may provide, along with eotaxin (CCL11), a chemotactic stimulus to the recruitment and adhesion of leukocytes including mast cells, directing their diapedesis and migration into the intima, where they take residence and divide (16).

Macrophages and mast cell-derived foam cells drive lesion progression by secreting pro-inflammatory cytokines; while mostly T cells and macrophages are involved adaptive immune responses (17). All these leukocytes, as well as endothelial cells, generate additional cytokines and growth factors which provoke the migration and proliferation of smooth muscle cells (18). Mast cells, which comprise part of the innate and adaptive immune system (19), can be recruited to inflamed endothelium and this recruitment has been shown to be proportional to the extent of atherosclerotic disease (20). There is overwhelming evidence for the underlying importance of mast cells in atherosclerosis which accumulate in atherosclerotic lesions (21). Mast cells can be activated by many stimuli, including complement protein factors C3a and C5a, MCP-1 and oxidized LDL (22). They are present in human arterial intima where they exert different physiological and pathophysiological roles by secreting a large panel of mediators including neutral proteases, cathepsins, histamine, heparin and several cytokines/chemokines, growth factors and inflammatory lipid mediators, including leukotrienes and prostaglandins (23). In atherosclerosis, the inflammatory cell infiltration of fibrous cap and adventitia are mostly activated monocyte (macrophages), mast cells and activated T cells (10). Atherosclerosis is characterized by a chronic inflammatory state in which metabolic factors and cytokines play an essential role in stimulation of the innate immune system (4). Elevated cholesterol (lipids) is associated with obesity, an increase risk of heart attack and atherosclerosis where the inflammatory components can be divided into an innate immune response involving monocytes, macrophages and mast cells, and an adaptive immune response that involves antigen-specific T cells in collaboration with mast cells which actively participate in plaque destabilization (24). In addition, mast cells can be activated by pro-inflammatory stimuli, including cytokines, hypercholesterolemia, and hyperglycemia, they degranulate and generate the above inflammatory compounds and trigger the endothelial expression of adhesion molecules such as P-selectin and vascular cell adhesion molecule-1 (VCAM-1) which mediate the adhesion of leukocytes (25). MCs, through the generation of histamine and fibroblast growth factor (FGF) activate the smooth muscle cell (SMC) surface receptors and accelerate their migration and proliferation; while the heparin proteoglycans released by mast cells inhibits the proliferation of smooth muscle cells *in vitro* (26). The elevation of cytokines/chemokines (eotaxin) and both chymase and tryptase in atheromatous plaque may contribute to leukocyte adhesion and migration, foam cell formation and SMC apoptosis (16). This suggests that these neutral serine proteases, tryptase and chymase which are potent inflammatory compounds, deeply influence the dynamic of atherosclerosis (27). In atherosclerotic plaque, it is likely that mast cells are recruited by chemokines in particular by eotaxin (CCL11) and its receptor CCR3 on mast cells (16). MC mediators participate in the initial fatty streak formation as well as in the destabilization of plaques and the absence of MCs in $Kit^{W\text{-}sh/W\text{-}sh}$ mice protect against abdominal aortic aneurysm formation and probably also atherosclerosis (28). Interestingly, Lee-Ruekert M. (29) reported that mast cell protease-mediated inhibition of cholesterol efflux from macrophage foam cells in the arterial intima and stimulated human mast cells can accelerate foam cell formation and prevent their regression in the proteoglycan-rich intimal areas.

We believe that inhibitors of mast cells products (30-31) such as chymase, tryptase, cytokines/ chemokines and other mediators (32), can be surely useful to alleviate atherosclerosis disease in humans.

However, at the moment, little is known about the involvement and recruitment of mast cells in atherosclerosis and to shed light on this enigma may be of therapeutic interest for the treatment and prevention of this social disease. Therefore, more studies are needed, since the exact role of mast cells and other inflammatory cell types within the

atherosclerotic lesion remains to be clarified.

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