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Mast Cell Density and Distribution in Human Abdominal Aortic Aneurysm

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1. Introduction

Atherosclerosis exhibits many inflammatory characteristics, in which macrophages and T-lymphocytes are found at the shoulder region of atherosclerotic plaque, and are associated with its rupture and thrombosis (Libby et al. 2010). On the other hand, abdominal aortic aneurysm (AAA) shows distinct histological features; inflammatory cell infiltration was observed predominantly at the outer media and adventitia (Michel et al. 2010). Several experimental studies have suggested important roles of inflammatory cells (macrophages, T-lymphocytes and neutrophils) in AAA development (Longo et al. 2002; Xiong et al. 2004; Eliason et al. 2005). Mast cell, unique effector components of the immune system, play a critical role in defending hosts against pathogens by releasing a number of immunoregulatory mediators (Marshall & Jawdat 2004). Mast cells synthesize a number of substances, which include histamine, heparin, tryptase, chymase, carboxypeptidase, cathepsin G, leukotriene C_4, prostaglandin D_2, tumor necrosis factor-α and interleukin (IL)-4,-5,-6,-13, some of which are stored in secretory vesicles (Krishnaswamy et al. 2006). Recently, mast cells have been recognized not only to be involved in host defense but also to initiate the inflammatory response by recruiting macrophages and T-lymphocytes (von Stebut et al. 2003; Henz et al. 2001) and by releasing pro-inflammatory cytokines, growth factors, angiogenic mediators and proteases (Krishnaswamy et al. 2006). Specifically, tryptase and chymase have been examined for their unique biological actions to modulate extracellular matrix formation and induce apoptosis of vascular smooth muscle cells (Cairns & Walls 1997; Leskinen et al. 2001; Tchougounova et al. 2005). In this chapter, we characterize mast cell density and distribution in the human aneurysmal abdominal aorta, compared with atherosclerotic abdominal aorta, and discuss the potential role of this type of cell to understand the pathophysiology of AAA.

2. Materials and methods

This study was approved by the Human Investigation Review Committee of the University of Miyazaki (No. 99) and conformed with the principles outlined in the Declaration of Helsinki (World Medical Association Declaration of Helsinki. 1997).

2.1 Human tissue preparation

Aneurysmal tissues were obtained from the anterior side of aortic walls of 60 Japanese suffering from AAA associated with atherosclerosis during elective repair surgery. AAA tissues were fixed in 10 % formalin or frozen in liquid nitrogen immediately after resection. Aortic tissues with various degrees of atherosclerosis were collected from the anterior side of the aorta at autopsy performed within 6 hours postmortem: 26, early stage atherosclerosis including diffuse intimal thickening or fatty streak; 30, advanced atherosclerosis formed by an extracellular lipid core (Stary et al. 1995). Hypertension was defined as a blood pressure >140/90 mm Hg or the need for antihypertensive medication. Diabetes mellitus was defined as fasting plasma glucose 126 mg/dL or higher and/or two-hour postprandial plasma glucose readings of 200 mg/dL or higher and/or the need for medicine in the medical records.

2.2 Immunohistochemistry

Single Staining: Aortic tissues fixed in 10% formalin were embedded in paraffin wax. The tissue sections (3 μm thick) were microwaved at 95 ^{o}C for one hour in 10 mmol/L citrate buffer (pH 6.0) to stain mast cell tryptase, prior to incubation with the primary antibody. The sections were incubated at 4 ^{o}C overnight with the monoclonal antibody against tryptase (80 μg/mL, Clone AA1; DAKOcytomation), followed by incubation with horseradish peroxidase-labeled polymer conjugated secondary antibody (Dako Envision+ System) for 30 min at room temperature. Immunoreactivity was visualized with 3,3′-diaminobenzidine (Dako), counterstained with Mayer's hematoxylin. For IL-4 staining, frozen sections of AAA tissues were fixed in acetone and incubated with the monoclonal antibody against human IL-4 (10 μg/mL, clone 3007.11; R&D Systems, Inc.).

Double Staining: To identify the phenotype of mast cells in aortic tissues, double staining was performed using a Histofine kit (Nichirei, Tokyo, Japan) according to the manufacturer's instructions. In double staining of tryptase (80 μg/mL, Clone AA1; DAKOcytomation) and chymase (1:100, Clone CC1; abcam), enzymatic activity of alkaline phosphatase for tryptase was visualized with new fuchsin in red (New Fuchsin Kit; Nichirei) and for chymase with 3, 3′, 5, 5′-tetramethylbenzidine in blue (TMB substrate kit; Vector Laboratories).

2.3 Morphometric analysis

Mast cell numbers in at least 10 microscopic fields were counted at a magnification of x400 and expressed as a density (cells per mm^2) in the intima, outer media and adventitia of early (diffuse intimal thickening and fatty streak), advanced atherosclerotic abdominal aorta and AAA. In counting the cell number, the intima was defined as the region of the arterial wall from the endothelial surface to the luminal margin of the media;(Stary et al. 1992) however, the internal elastic lamina becomes unclear or absent in the advanced atherosclerotic aorta, so we counted mast cells located on the luminal side of atheromatous plaques. On the other hand, the adventitia was defined as the area outside the external elastic lamina and inside the border of inner dense and outer loose connective tissues, and the number of cells in the outer media and adventitia was combined because the external elastic lamina was mostly unclear in AAA specimens. Capillary vessel number positive for CD34 antigen was also evaluated in the outer media and adventitia, and was expressed as a density (/mm^2).

2.4 Western blot

Denatured protein extract (30 μg) from the AAA and non-dilated atherosclerotic aorta was subjected to sodium dodecyl sulfate-polyacrylamide gel as described (Tsuruda et al. 2008).

The separated proteins electrically transferred onto polyvinylidene difluoride (PVDF) membranes were incubated with anti-mouse monoclonal IL -4 antibody (2 μg/mL, clone 3007.11; R&D Systems, Inc.), followed by incubation with horseradish peroxidase-coupled second antibody. Immunoreactive bands were visualized by the ECL Plus detection kit (Amersham), and intensities of the bands were analyzed densitometrically (Chemi Doc™ Documentation System; BIO-RAD).

3. Statistical analysis

All data were analyzed with JMP 7.0.1 and GraphPad prism 5. Comparisons between groups were assessed with the chi-square test or Kruskal-Wallis test, and the mast cell density and capillary number were correlated with the Spearman rank correlation coefficient test. Protein expression between the two groups was analyzed with Student's t-test. The data are expressed as the mean ± SEM or as the median with the quartile range, 1.5 interquartile and outlying values. Statistical significance was accepted at $p<0.05$.

4. Results

4.1 Patients' characteristics

Clinical parameters of the patients enrolled in this study are shown in the Table 1. The advanced atherosclerosis and AAA groups were significantly older than the early stage atherosclerosis group, but there was no difference in age between AAA patients and those with advanced atherosclerosis. The AAA group showed a significantly higher rate of hypertension than the early or advanced atherosclerosis group, whereas the ratio of diabetes mellitus was equivalent in advanced atherosclerosis and AAA groups.

	Early (n=26)	Advanced (n=30)	Aneurysm (n=60)
Age	40±4	77±2 **	76±1 **
Sex (M/F)	19 / 7	24 / 6	46 / 14
Smoking (%)	34.6	53.3	66.7
Hypertension (%)	6.7	63.3	90.0 **,##
Diabetes mellitus (%)	7.7	13.3	11.7 *

Table 1. Patients' characteristics. Data are expressed as the mean ±SEM. *$p<0.01$, **$p<0.0001$ vs. early stage of atherosclerosis, ##$p<0.0001$ vs. advanced atherosclerosis

4.2 Mast cell density in atherosclerotic abdominal aorta and AAA

Figure 1 shows representative pictures of tryptase-positive mast cells at the intima and outer media and adventitia of early atherosclerosis (diffuse intimal thickening, DIT), advanced atherosclerosis and AAA. As shown in Figure 2A, the density of mast cells at the intima

tended to decrease according to the degree of atherosclerosis, and was further diminished in AAA. On the other hand, the cell number significantly increased at the outer media and adventitia of the AAA group, compared with those in the early or advanced atherosclerotic aorta (Figure 2B).

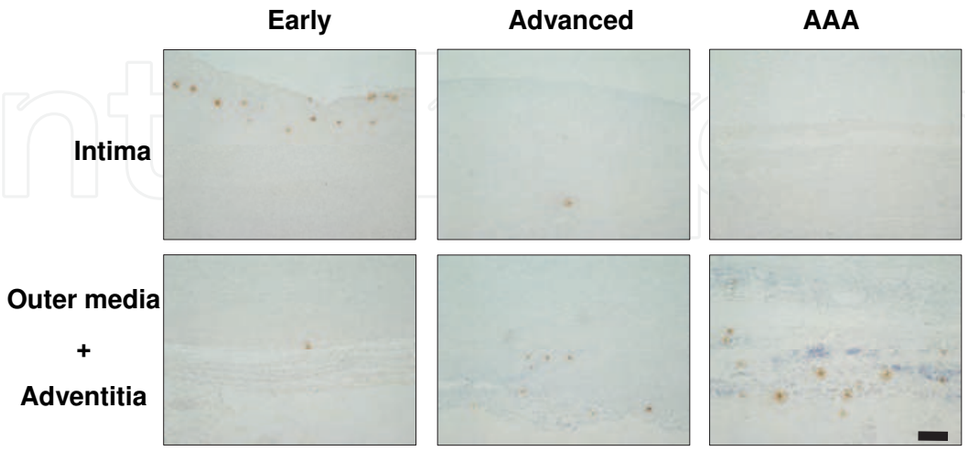

Fig. 1. Representative pictures of tryptase-positive mast cells at intima and outer media and adventitia of early atherosclerosis (diffuse intimal thickening, DIT), advanced atherosclerosis and AAA. Scale bar, 200 μm.

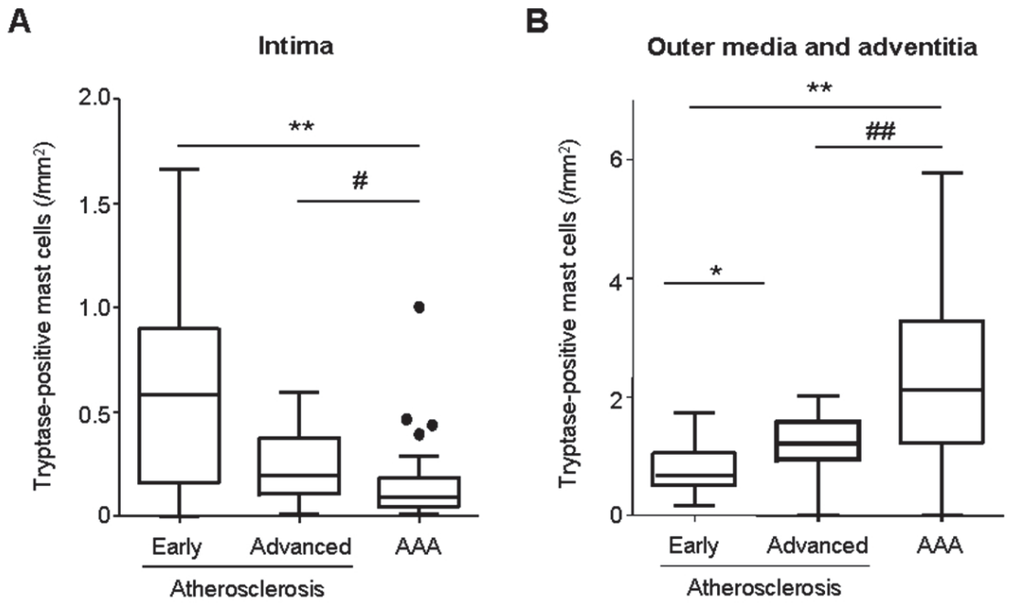

Fig. 2. Mast cell density in early or advanced atherosclerosis and AAA. Number of tryptase-positive mast cells was counted at intima **(A)** and outer media and adventitia **(B)**, respectively in early (n=26) or advanced (n=30) atherosclerosis and AAA (n=60). Data are expressed as the median with the quartile range, 1.5 interquartile and outlying values. *p<0.05, **p<0.01 vs. early stage atherosclerosis, #p<0.05, ##p<0.01 vs. advanced atherosclerosis.

4.3 Phenotype of mast cells in AAA

Figure 3A-C illustrate the representative pictures of the mast cell phenotype in the AAA specimens. As shown in Figure 3D, most of the mast cells distributed at the outer media and adventitia of AAA were positive both for tryptase and chymase (97.9%), while the remainder of the mast cell subtypes, tryptase-positive/chymase-negative (0.27%) or tryptase-negative/chymase-positive (1.9%) were a minor population. The proportion of mast cell phenotypes was similar in early or advanced atherosclerotic aortae.

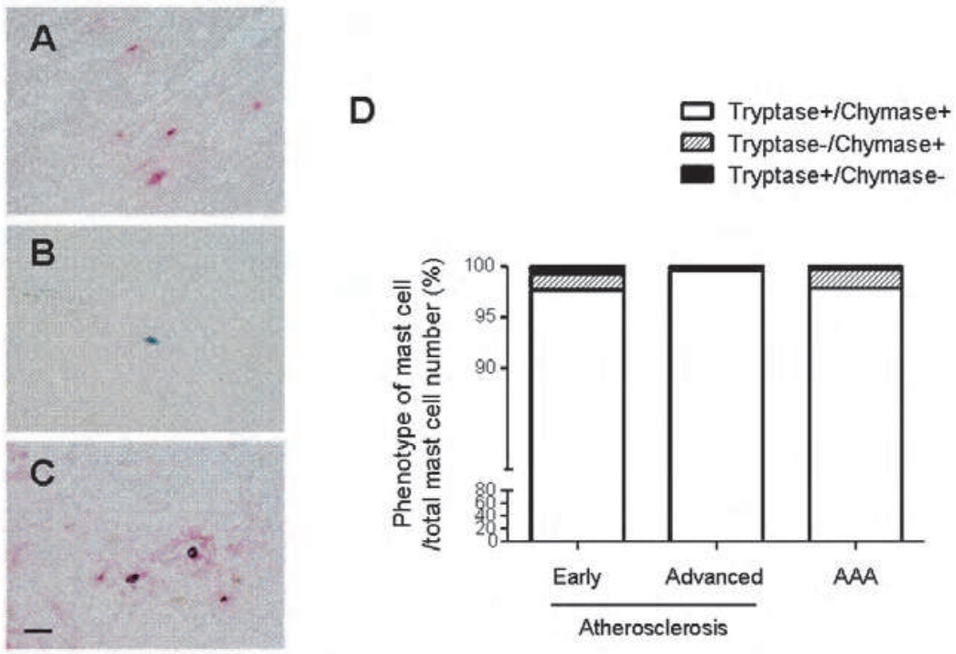

Fig. 3. Phenotype of mast cells in early or advanced atherosclerosis and AAA. Representative pictures of tryptase-positive/chymase-negative **(A)**, tryptase-negative/chymase-positive **(B)** and tryptase-positive/chymase-positive mast cells **(C)**. Scale bar, 20 μm. **D,** Percentage of mast cell phenotype in early (n=10) or advanced (n=5) atherosclerosis and AAA (n=26).

4.4 Expression and distribution of IL-4 in AAA

Figure 4A illustrates that the protein expression of IL-4 was significantly increased in AAA compared to the atherosclerotic aorta. The immunoreactivity of IL-4 was widely distributed in the endothelial cells of microvessels and fibroblast-like cells at the outer media and adventitia of AAA (Figure 4B).

4.5 Correlation between numbers of capillary vessel and mast cell

Figure 5A shows that the number of capillary vessels distributed at the outer media and adventitia (so called "vasa vasorum") was significantly increased in the advanced atherosclerotic aorta group compared with the early stage of atherosclerosis; however, the number did not change significantly between advanced atherosclerosis and AAA. As shown in Figure 5B, mast cell density correlated with the capillary vessel number at the outer media and adventitia of all cases (n=116, r=0.349, p=0.0001).

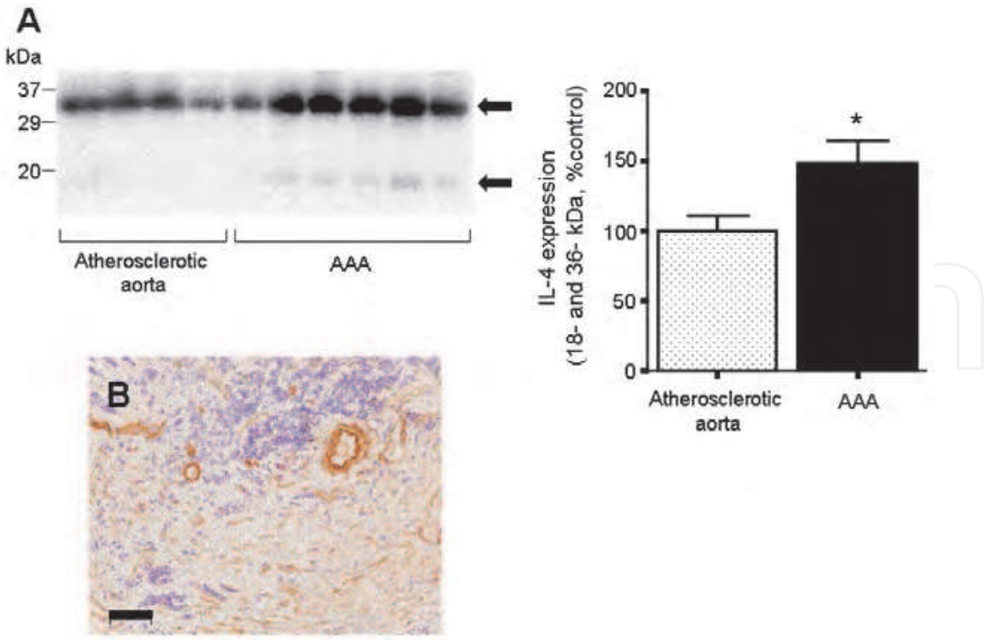

Fig. 4. Protein expression of IL-4 and its distribution in AAA specimen. **A,** Western blot for IL-4 in non-dilated atherosclerotic aorta (n=5) and AAA (n=6). Arrows indicate the mono-form (18 kDa) and dimer (36 kDa) of IL-4, respectively. The two forms of IL-4 expression were combined to present the data. Data are expressed as the mean ± SEM. *p<0.05 vs. non-dilated atherosclerosis. **B,** Immunolocalization of IL-4 in AAA. Scale bar, 50 μm.

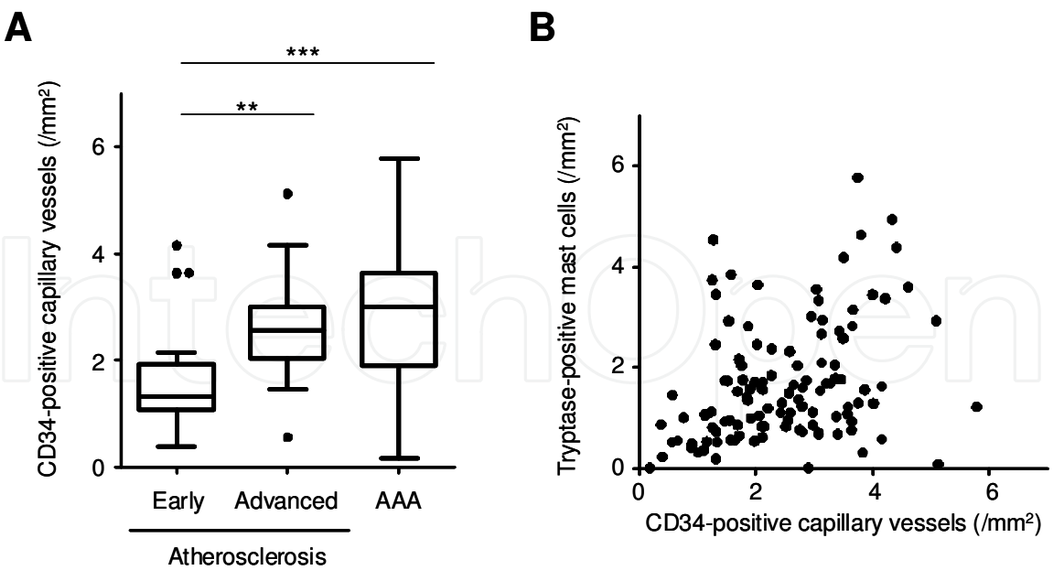

Fig. 5. **A,** Capillary vessel number determined by CD34-positive staining in the outer media and adventitia of early or atherosclerosis and AAA. Data are expressed as the median with the quartile range, 1.5 interquartile and outlying values. **B,** Correlation between numbers of mast cells and capillary vessels in the outer media and adventitia in early or advanced atherosclerosis and AAA (n=116, r=0.3494, p=0.0001).

5. Discussion

Up to 8 % of men older than 65 years harbor AAA, and it is associated with several risk factors, such as smoking and hypertension (Nordon et al. 2010). AAA progresses asymptomatically and patients with AAA eventually die due to rupture. At the tissue level, inadequate remodeling of the extracellular matrix in aortic walls appears to be involved in the development, progression or rupture of AAA (Kadoglou & Liapis 2004; Choke et al. 2005; Longo et al. 2002; Xiong et al. 2004; Daugherty & Cassis 2004; Brown & Powell 1999; Singh et al. 2001; Freestone et al. 1995); however, to date, the underlying mechanism is not fully understood and there is no effective pharmacological therapy to inhibit/reverse enlargement of the aneurysmal aorta in humans. The immune system is assumed to participate because of the inflammatory infiltration of macrophages and T lymphocytes that can produce enzymes degrading the extracellular matrix at the outer media and adventitia of human and experimental AAA (Longo et al. 2002; Ocana et al. 2003; Xiong et al. 2004).

As a component of the immune system, mast cells are widely distributed throughout the body and have an important role in defending hosts against pathogens. In the cardiovascular tissues, this type of cell is present at the intima of normal/fatty streak (Kaartinen et al. 1994), whereas it is more prominent at the adventitia of atherosclerotic aorta (Atkinson et al. 1994) and in the vulnerable plaques of atherosclerotic coronary and carotid arteries (Kaartinen et al. 1998; Jeziorska et al. 1997). Our data support a previous study (Kaartinen et al. 1994) which shows that mast cells at the intima decreased according to the degree of atherosclerosis, assuming that a loss of endogenous heparin production by mast cells stimulates pro-coagulant activity on atherosclerotic plaques. More importantly, we demonstrated that the cell number was significantly increased at the outer media and adventitia of AAA, compared with either the early or advanced stage of atherosclerosis. The proportion of activated mast cells (seen as "degranulation") has been reported to be frequently observed in the adventitia of AAA compared to in advanced atherosclerosis (15±2 % vs. 0.4±0.3% total number of mast cells) (Tsuruda et al. 2008). Thus, mast cells distributed "outside of aortic wall" appear to be associated with the AAA pathogenesis.

Mast cells mature with tissue-specific phenotypes from circulating multipotent haematopoietic progenitor cells in response to signals communicated by quiescent microvascular environment cells where they become resident (Krishnaswamy et al. 2006). Stem cell factor (SCF), a ligand for the proto-oncogene c-kit, is widely produced in various types of cells, such as fibroblasts (Nocka et al. 1990), endothelial cells and stromal cells (Heinrich et al. 1993), and is the main factor for the growth and differentiation of mast cells (Zsebo et al. 1990). Circulating mast cell precursor has been reported to mature in tissues by SCF (Zsebo et al. 1990) and other cytokines such as IL-4 (Conti et al. 2003; Yanagida et al. 1995). In accordance with the report (de Paulis et al. 1999), we have shown that the immunoreactivity of SCF was detected in the cytoplasm of mast cells (Tsuruda et al. 2008), suggesting autocrine or paracrine regulation of differentiation and maturation of cells in aortic tissues. Schönbeck et al. (2002) showed the augmented expressions of IL-4 and IL-10 in inflammatory cells of AAA tissues. Importantly, these cytokines enhanced the growth-promoting effect of SCF on mast cells (Conti et al. 2003; Yanagida et al. 1995), and we further demonstrated that IL-4 was widely present in the endothelial cells of microvessels and fibroblast-like cells in AAA specimens. In contrast, we could not detect IL-10 expression in AAA tissues in this study (data not shown). It seems likely that mast cells can mature or differentiate in the aneurysmal aortic wall, at least partly through SCF and IL-4 stimulation.

Human mast cells exhibit tissue-specific functional heterogeneity; they are divided conventionally into two different phenotypes depending on the proteases in their secretory vesicles. In this study, the majority of mast cells distributed at the outer media and adventitia of AAA were positive both for tryptase and chymase. One of the histopathological features of AAA is the degeneration of the media by apoptosis of smooth muscle cells (Lopez-Candales et al. 1997) and fragmentation of elastic fibers digested by matrix metalloproteinase (MMP) (Baxter et al. 1994), resulting in loss of integrity to maintain the architecture of the aortic wall. Mast cell tryptase stimulates fibroblast proliferation (Cairns & Walls 1997) as well as MMP-1,-3 activation (Johnson et al. 1998). On the other hand, mast cell chymase may have a wide range of actions in AAA tissues: induction of apoptosis of smooth muscle cells (Leskinen et al. 2001), conversion of angiotensin I to angiotensin II (Takai et al. 1999) and of pro-MMP-2 and -9 to the mature forms (Tchougounova et al. 2005), whereas mast cells themselves are found to express MMPs-2 and 9 (Fang et al. 1999). We have reported that interferon-γ produced from mast cells stimulated MMP-9 synthesis by macrophages in the co-culture (Tsuruda et al. 2008). Angiogenesis appears to be another important histopathological characteristic of AAA (Paik et al. 2004; Reeps et al. 2009). Mast cells are capable of synthesizing factors associated with angiogenesis (Hiromatsu & Toda 2003), and indeed, are often positioned around capillary vessels. We found a positive correlation between mast cell density and capillary number at the adventitial layer, speculating that mast cells might contribute to initiate the inflammatory response by stimulating the growth of the vasa vasorum, and thereby recruit macrophages and T-lymphocytes from outside the aortic wall (Satta et al. 1998; Reeps et al. 2009). However, it remains to be elucidated whether angiogenesis itself is relevant to AAA development, because the vessel number was statistically insignificant between AAA and advanced atherosclerosis in this study. Based upon the observation in human tissues, we propose that mast cells infiltrating at the outer media and adventitia of the AAA wall contribute to the development or progression of aneurysm formation, coordinating with other inflammatory cells. Furthermore, the inhibition of mast cell accumulation, maturation and activation in the aortic wall with a mast cell stabilizer would be a potential pharmacological target for preventing/attenuating the development of AAA (Tsuruda et al. 2008; Sun et al. 2007).

6. Conclusion

Mast cells are predominantly present at the outer media and adventitia, and are susceptible to maturation/activation by interaction with cytokines in AAA tissues. In addition, the mediators expressed by mast cells and neovascularization might contribute to enhance the inflammatory response in AAA. These results underline the pathophysiological role of this type of immune cell in the development/progression of aneurysm formation.

7. Acknowledgements

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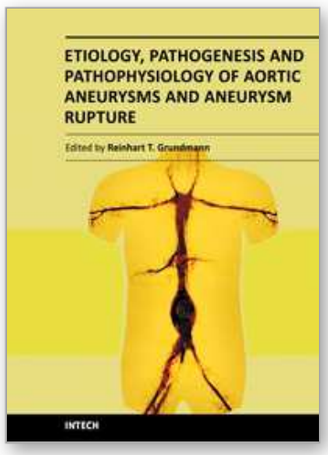

Etiology, Pathogenesis and Pathophysiology of Aortic Aneurysms and Aneurysm Rupture

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This book considers mainly etiology, pathogenesis, and pathophysiology of aortic aneurysms (AA) and aneurysm rupture and addresses anyone engaged in treatment and prevention of AA. Multiple factors are implicated in AA pathogenesis, and are outlined here in detail by a team of specialist researchers. Initial pathological events in AA involve recruitment and infiltration of leukocytes into the aortic adventitia and media, which are associated with the production of inflammatory cytokines, chemokine, and reactive oxygen species. AA development is characterized by elastin fragmentation. As the aorta dilates due to loss of elastin and attenuation of the media, the arterial wall thickens as a result of remodeling. Collagen synthesis increases during the early stages of aneurysm formation, suggesting a repair process, but resulting in a less distensible vessel. Proteases identified in excess in AA and other aortic diseases include matrix metalloproteinases (MMPs), cathepsins, chymase and others. The elucidation of these issues will identify new targets for prophylactic and therapeutic intervention.

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