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Role of Cathepsin K, L and S in Blood Vessel Remodeling

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1. Introduction

The development of cardiovascular diseases is characterized by the loss of structural integrity of blood vessels that requires extensive remodeling of the extra-cellular matrix (Michel et al., 2011; Garcia-Touchard et al., 2005). The entire aorta and some medium-sized arteries have elastic properties and mechanical strength allowing these vessels to withstand a surge of blood ejected from the heart. Such properties of blood vessels are contributed mostly by two major components of the extracellular matrix: elastin and collagen (Barbour et al., 2007; Wagenseil & Mecham, 2009; Sawabe, 2010). Elastin fibers are responsible for the elastic properties and collagen fibers provide mechanical strength to the arterial wall (Arteaga-Solis et al., 2000). These two proteins have a fibrillar structure and in their mature forms are very resistant to proteolysis. Thus elastin has a half-life around 50 years (Wagenseil & Mecham, 2009). However in some pathological conditions, excessive proteolytic activity results in extracellular matrix breakdown that is a key factor of arterial wall damage and the development of potential rupture. Sites of atherosclerotic and aneurysmatic lesions are characterized by increased elasto- and collagenolytic activity (Diehm et al., 2007; Shimizu et al., 2006; Barbour et al., 2007; Sukhova et al., 1998). The dominant histological feature of aneurysmatic lesions is a chronic medial and adventitial inflammation resulting in medial degeneration and smooth muscle cell apoptosis. One of the most important contributors to aneurysmatic degeneration is an excessive loss of extracellular matrix. Fragmentation of elastin and collagen fibers is a characteristic feature of aneurysm formation and their loss is the ultimate cause of aneurysmatic rupture as well as rupture of atherosclerotic plaques (Shimizu et al., 2006; Sakalihasan et al., 2005; Diehm et al., 2007). Recently it has been shown that together with some matrix metalloproteinases, cathepsin K, L and S are the primary proteolytic culprits responsible for the breakdown of extracellular matrix proteins in blood vessels (Abdul-Hussien et al., 2010; Rizas et al., 2009; Sukhova & Shi, 2006). Cysteine proteinases cathepsin K, L and S belong to the most potent elasto- and/or collagenolytic proteinases with potent abilities to degrade extracellular matrix. These enzymes attracted attention due to their upregulation within the aortic wall under different pathological conditions (Lutgens et al., 2007; Lafarge et al., 2010; Liu et al., 2004). Their expression was revealed in macrophages, smooth muscle cells and endothelial cells in atherosclerotic and aneurismal lesions in humans. These results instigated a series of studies on the involvement of cathepsin K, L and S in the development of cardiovascular diseases based on animal models of atherosclerosis and abdominal aortic aneurysm

formation (Lutgens et al., 2007; Lafarge et al., 2010; Liu et al., 2004). The lack of these proteases resulted in a plaque size reduction and delay of plaque progression as well as in reduced level of medial elastin degradation and smooth muscle cell transmigration from the media to the intima (Lutgens et al., 2006a; Rodgers et al., 2006; Samokhin et al., 2008; Sukhova et al., 2003). These results were corroborated by in vitro experiments that revealed the differences in collageno- and elastolytic activities of smooth muscle cells and macrophages from mice expressing and lacking these cathepsins.

The availability of specific cathepsin inhibitors allowed the conduction of *in vitro* and *in vivo* experiments that confirmed the involvement of cathepsins in aortic extracellular matrix destruction and atherosclerosis progression (Samokhin et al., 2010b) Immunostaining for cathepsin K revealed its high level of expression in multinucleated giant cells in human specimens from carotid arteries and abdominal aortic aneurysm as well as in mouse atherosclerotic plaques (Samokhin et al., 2010c; Chapman et al., 1997). High level of cathepsin K expression is a marker of active osteoclasts; in these giant cells cathepsin K is a major enzyme responsible for bone resorption (Bromme et al., 1996). Similarly, cathepsin K-expressing giant cells were found close to damaged elastin laminae in aorta, suggesting an important role for this enzyme in the development of cardiovascular diseases (Samokhin et al., 2010c; Chapman et al., 1997).

2. Extracellular matrix of the aortic wall

Elastin and fibrillar collagen are the main components of the arterial wall responsible for its mechanical properties (Wagenseil & Mecham, 2009; Arteaga-Solis et al., 2000; Sawabe, 2010). Elastin is the major protein that confers elastic properties to the arterial wall. It is produced by smooth muscle cells of the tunica media in form of the soluble precursor tropoelastin and after polymerization by lysyl oxidase, forms interconnecting concentric rings around the arterial lumen. A high number of cross-links (15-20 per tropoelastin unit) is responsible for elastin insolubility, long half-life and resistance to proteolysis (Wagenseil & Mecham, 2009; Arteaga-Solis et al., 2000; Sawabe, 2010). Elastin fibers are formed by elastin and associated microfibrils. Microfibrils form a scaffold for elastin polymerization and they are mainly composed of fibrillin and a collagen type IV (Sawabe, 2010; Pasquali-Ronchetti & Baccarani-Contri, 1997). This three-dimensional network of interconnecting elastin fibers is designed to transfer stress throughout the arterial walls and is responsible for their dilation and recoil (Wagenseil & Mecham, 2009; Shadwick, 1999). The aortic wall is characterized by the abundant presence of elastic fibers associated with smooth muscle cells in the medial area (Barbour et al., 2007, Sakalihasan et al., 2005). Elastic fibers are also interconnected with collagen bundles (Wagenseil & Mecham, 2009).

Collagen is made up of a triple helix of three polypeptide chains. Types I, II and III collagens belong to "fibrillar" collagens that are the most abundant (van der Rest & Garrone, 1991). Types I and III collagens provide tensile strength and maintain the structural integrity of the blood vessels. In aorta these two types of collagens are mostly found in media and adventitia (Wagenseil & Mecham, 2009; Barbour et al., 2007; Sakalihasan et al., 2005). Types IV, V, and VI are nonfibrillar collagens highly present in the basement membrane. Fibrillar collagens type I and III are highly resistant towards proteolysis. They can be degraded only by specific collagenases that are able to cleave within the triple helix of native fibrillar collagen (Abdul-Hussien et al., 2007).

Medial elastin and collagens types I and II in the media and adventitia determine much of the structural integrity and stability of arteries (Shimizu et al., 2006; Arteaga-Solis et al.,

2000). The increased turnover of elastin and collagen results in aortic dilation and possible rupture (Shimizu et al., 2006). The fragmentation and loss of collagen and elastin fibers is one of the most important and consistent histological features of aneurismal changes in aorta (Dobrin & Mrkvicka, 1994; Barbour et al., 2007).

Because of the long half-life of collagen fibers and the extremely long half-life of elastin, loss of these two extracellular matrix proteins almost certainly results from increased degradation rather than decreased synthesis. Indeed, the predominant role of increased proteolysis is well described for the pathogenesis of aneurysm formation (Barbour et al., 2007; Sakalihasan et al., 2005; Michel et al., 2011). Traditionally, matrix metalloproteinases were considered the main culprits in blood vessel extracellular matrix cleavage (Kadoglou & Liapis, 2004; Newby, 2008), whereas some recent data point out to the important role of cathepsin K, L and S in this pathological process (Chapman et al., 1997; Shimizu et al., 2006; Abisi et al., 2007).

3. Cathepsin K, L and S are strong extracellular matrix-degrading enzymes

Cathepsin K, L and S are lysosomal cysteine proteases of the papain family. These enzymes share many common features but also have significant differences in distribution, activity and corresponding physiological functions. Cathepsin K has the highest level of expression in osteoclasts and plays a major role in collagen turnover in bones (Bromme et al., 1996). This protease is also expressed at lower levels in macrophages, epithelial cells, fibroblasts, smooth muscle cells which can be elevated under pathological conditions (Chapman et al., 1997). Thus, high cathepsin K concentration was found in rheumatoid arthritic joints, in epithelioid and multinucleated giant cells in lungs, and in thyroid glands (Buhling et al., 2004; Samokhin et al., 2010a; Tepel et al., 2000). Cathepsin K is not detectable in normal blood vessels, but is highly expressed in macrophages, smooth muscle cells, endothelial and multinucleated giant cells in atherosclerotic lesions and in giant cell aortitis (Sukhova et al., 1998; Platt et al., 2007; Chapman et al., 1997; Samokhin et al., 2010c). Cathepsin K is the most efficient elastinolytic enzyme (Bromme et al., 1996) and, in contrast to other cathepsins, has the ability to cleave triple-helical collagens both outside and inside the helical regions (Lecaille et al., 2008; Garnero et al., 1998). This unique feature enables cathepsin K to perform complete cleavage of collagens, a process that usually requires a cooperative action of several extracellular matrix-degrading enzymes.

Cathepsin S is predominantly expressed in spleen and antigen-presenting cells, including B cells, macrophages, dendritic and epithelial cells (Chapman et al., 1997; Gupta et al., 2008). In these cells, cathepsin S plays an important role in the proteolytic degradation of the invariant chain, thus regulating antigen presentation to CD4^{+} T-cells by MHC II molecules (Honey & Rudensky, 2003; Hsing & Rudensky, 2005). In addition to its role in the immune response, cathepsin S can be secreted by such cells as macrophages, smooth muscle cells, endothelial cells and some tumor cells (Gupta et al., 2008) and plays an important role in extracellular matrix remodeling. Similarly to cathepsin K, cathepsin S shows strong collagenolytic and elastolytic activities and in contrast to cathepsin K and L, this protease is more stable and retains activity at neutral pH (Chapman et al., 1997; Taleb & Clement, 2007). Under pathological conditions, cathepsin S is upregulated in lung and blood vessel tissues and its stability at neutral pH may significantly contribute to the degradation of the extracellular matrix (Deschamps et al., 2010; Samokhin et al., 2011; Hirakawa et al., 2007; Williams et al., 2009).

Cathepsin L is ubiquitously expressed and similarly to cathepsin S, plays an important role in the immune system by degrading the invariant chain in MHC class II processing (Honey & Rudensky, 2003; Hsing & Rudensky, 2005). Mice lacking cathepsin L have epidermal hyperplasia with periodic hair loss, older animals develop dilative cardiomyopathy (Lankelma et al., 2010; Reinheckel et al., 2005). This enzyme is also involved in the development of kidney diseases in mice and humans and is upregulated in a variety of cancers (Reiser et al., 2010). Cathepsin L is a potent elastase (equivalent to cathepsin S) and collagenase (similar to cathepsin K) (Chapman et al., 1997). The physiological role of mouse cathepsins L is most likely replaced by cathepsin V in human tissues (Tolosa et al., 2003).

A common feature of these cathepsins is their strong ability to degrade elastin and collagen fibers. Cathepsins have attracted attention as extracellular matrix-degrading enzymes only recently. Previously it was assumed that they are inactive outside of cells due to their instability at neutral pH. However under pathological conditions, the acidification of the pericellular environment creates optimal conditions for lysosomal cathepsins. Thus, the destruction of elastin-rich arteries is associated with the accumulation of macrophages. In inflammatory conditions, macrophages secrete cathepsin K, L and S and at the same time increase expression of vacuolar-type H^+-ATPase (Punturieri et al., 2000; Reddy et al., 1995). H^+-ATPase acidifies the local environment and creates optimal conditions for cathepsin activities. Such increased expression of H^+-ATPase has been revealed by immunohistochemical analysis in AAA in infiltrating monocytes and to a lesser extend in SMCs (Abdul-Hussien et al., 2010).

In addition to their direct destructive role in blood vessel remodeling, cathepsins may promote the development of cardiovascular diseases by degrading lipoproteins and through their involvement in the regulation of apoptosis (Linke et al., 2006; Conus & Simon, 2008; Repnik & Turk, 2010).

4. Increased expression of cathepsin K, L and S under pathological conditions in blood vessels

4.1 Atherosclerosis

Increased expression of cathepsin K and S in human atherosclerotic lesions was first described in 1998 (Sukhova et al., 1998). Until that time cathepsin K, L and S were already known as strong collagenases and elastases and researchers found a correlation between increased immunostaining for cathepsin K and S and increased elastase-degrading activity in atheromatous tissues extracts. The use of cathepsin and MMP inhibitors revealed that cathepsins had significantly greater contribution to elastolytic activity of atherosclerotic lesions extracts. Cathepsin K and S immunoreactivities were mostly localized in the fibrous cap region that suggested their important role in plaque destabilization (Sukhova et al., 1998; Rodgers et al., 2006). In addition, smooth muscle cells cultured with IFN-γ or interleukin-1β secreted active cathepsin S and showed significantly increased ability to degrade elastin. This elastolytic activity was abrogated by a selective cathepsin S inhibitor (Sukhova et al., 1998). In a similar experiment, a selective cathepsin S inhibitor or endogenous cathepsin inhibitor cystatin C significantly decreased SMC migration across an elastin gel (Cheng et al., 2006). In human atherosclerotic plaques cathepsins were localized in macrophages, SMCs and endothelial cells (Platt et al., 2007; Sukhova et al., 1998). The destructive role of cathepsin K in macrophage foam cells was confirmed by immunohistochemical analysis that revealed accumulation of collagen type I degradation products close to cathepsin K immunoreactivity. These results

were supported by an *in vitro* experiment where incubation of human macrophage foam cells on a collagen matrix resulted in the accumulation of collagen degradation products (Barascuk et al., 2010). Cathepsin K expression in endothelial cells in human atherosclerotic plaques also correlated with internal elastic lamina destruction (Platt et al., 2007).

Similarly to cathepsin K and S, cathepsin L shows weak or no immunostaining in normal human arteries but its immunoreactivity increases significantly in atherosclerotic lesions and localizes in the fibrous cap and tunica media (Liu et al., 2006). Double immunostaining revealed that cathepsin L is mostly expressed in macrophages of the plaque shoulder regions, endothelial and smooth muscle cells. Serum cathepsin L level correlated with the development of atherosclerotic lesions (Liu et al., 2006). Furthermore, expression of cathepsin L correlated with apoptosis, formation of the necrotic core, decrease in collagen content and rupture of the fibrous cap (Li et al., 2009; Liu et al., 2006).

4.2 Aortic aneurysm

Increased expression of cathepsin K, L and S was found in abdominal aortic aneurysm and in popliteal artery aneurysm (Sukhova and Shi, 2006; Abdul-Hussien et al., 2010). Similarly to atherosclerosis, these enzymes were identified as major proteolytic culprits in abdominal aortic aneurysm and their expresion correlated with excessive collagen degradation (Abdul-Hussien et al., 2007). The activities of cathepsin S and L were increased in abdominal aortic aneurysms and ruptured abdominal aortic aneurysms, whereas cathepsin K activity was not elevated despite a significant increase in the level of activated cathepsin K protein in aortic extracts (Abdul-Hussien et al., 2007; Abisi et al., 2007). Increased expression of cathepsin L in abdominal aortic aneurysm was localized in SMCs, Ecs and macrophages (Li et al., 2009).

5. Studies of cathepsin K, L and S in mouse models of cardiovascular diseases

5.1 Atherosclerosis

The results of human studies prompted *in vivo* studies of the involvement of cathepsins in cardiovascular diseases using murine disease models. Apolipoprotein E- and low density lipoprotein receptor-deficient mice are widely used as animal models of atherosclerosis. These mice develop severe hypercholesterolemia and atherosclerosis similar to human atherosclerosis and atherosclerotic lesions progression can be accelerated by high fat diet. Firstly, the high expression of cathepsin L and S was shown in aorta of apolipoprotein E-deficient mice. Immunohistochemical analysis showed positive staining for cathepsins L and S in the intima and within fibrous caps and cathepsin S was also detected in the medial area (Jormsjo et al., 2002). Soon after that, the effect of cathepsin S deficiency on atherosclerosis development was reported in experiments with low density lipoprotein receptor-deficient mice (Sukhova et al., 2003). Low density lipoprotein receptor-deficient mice lacking cathepsin S showed significant reduction of plaque size and area, preserved integrity of elastic lamina and reduced smooth muscle cell and collagen contents in the intima when compared to mice expressing cathepsin S. Absence of cathepsin S also resulted in decreased macrophage and leukocyte accumulation in atherosclerotic plaques (Sukhova et al., 2003). The atheroprotective effect of cathepsin S deficiency was also confirmed by experiments with apolipoprotein E-deficient mice lacking this protease. (Rodgers et al., 2006). Atherosclerotic lesions in brachiocephalic arteries of apolipoprotein E-deficient and cathepsin S double deficient mice were significantly smaller and had fewer acute plaque ruptures. These mice also had a lower

number of buried fibrous caps, which are believed to be a marker of unstable atherosclerotic plaques. The fibrous caps in plaques of double knockout mice were also thicker compared to cathepsin S-expressing mice that most likely rendered higher stability to those plaques (Rodgers et al., 2006). Recently, the role of cathepsin S in atherosclerosis was investigated in chimeric low density lipoprotein receptor-deficient mice lacking this protease in leukocytes (de Nooijer et al., 2009). The absence of cathepsin S in leukocytes did not change the lesion size but reduced the necrotic core and changed plaque morphology. Chimeric mice contained more macrophages and less intimal smooth muscle cells and collagen. The lower number of intimal smooth muscle cells correlated with the marked decrease in the number of elastin lamina ruptures providing evidence for an important role of leukocyte-derived cathepsin S in elastin lamina disruption in atherosclerosis (de Nooijer et al., 2009).

The role of cathepsin K in atherosclerotic lesions development was investigated in apolipoprotein E-deficient mice (Lutgens et al., 2006b; Samokhin et al., 2008; Lutgens et al., 2006a). Cathepsin K deficiency reduced the total plaque area in the aortic arch of mice receiving normal diet (Lutgens et al., 2006a) as well as the plaque size in the brachiocephalic artery after 16 weeks of high fat diet (Samokhin et al., 2008). In both experiments mice lacking cathepsin K had a smaller number of elastin lamina ruptures and increased collagen content compared to cathepsin K-expressing mice. Cathepsin K-deficient mice on normal diet had a borderline significant decrease in plaque macrophage content but the individual size of macrophages was increased and showed increased lipid uptake (Lutgens et al., 2006b). Atherosclerotic plaques in the brachiocephalic artery of mice on high fat diet had a significant decrease in their macrophage content and an increase in collagen content after 8 weeks of high fat diet. Smooth muscle cell loss in medial area was significantly lower in cathepsin K-deficient mice after 16 weeks of high fat diet that correlated well with the decreased number of elastin lamina breaks (Samokhin et al., 2008). Atherosclerotic plaques in brachiocephalic arteries had thicker fibrous caps and a smaller number of buried fibrous caps in cathepsin K-deficient mice. Similarly to cathepsin S, the effect of cathepsin K deficiency in leukocytes was studied in chimeric low density lipoprotein receptor-deficient mice (Guo et al., 2009). Leukocytes cathepsin K deficiency did not affect the plaque size but decreased elastin lamina fragmentation as well as collagen content and increased plaque macrophage content and the necrotic area. The effect of cathepsin L deficiency was studied on low density lipoprotein receptor-deficient mice (Kitamoto et al., 2007). Double knockout mice developed reduced atherosclerotic lesions with smaller lipid core compared to cathepsin L-expressing mice. They also had a lower number of elastin lamina ruptures and a decreased amount of plaque macrophages, CD4+ T-cells, smooth muscle cells and collagen. In *in vitro* experiments, cathepsin L-deficient smooth muscle cells showed delayed transmigration through an elastin layer, whereas cathepsin L-deficient monocytes and lymphocytes demonstrated reduced ability to migrate through collagen type I and IV coated transwell membranes. Based on these results, authors suggested that cathepsin L plays a significant role in medial smooth muscle cells and blood-borne leukocytes migration during development of atherosclerotic lesions (Kitamoto et al., 2007).

5.2 Aortic aneurysm

Increased expression of cathepsin K, L and S in blood vessels have been shown in several animal models of aneurysm induction. Cathepsin K and S were upregulated in a porcine model of abdominal aortic aneurysm (Sadek et al., 2008) and cathepsin L showed increased expression in a rabbit model of elastase-induced saccular aneurysm (Kadirvel et al., 2004).

The role of cathepsin K in aneurysm formation was investigated in a mouse model of aneurysm induction (Bai et al., 2010). Surprisingly, cathepsin K deficiency did not prevent aneurysm formation after angiotensin II infusion. Cathepsin K-lacking mice had the same aneurysm size and severity. The absence of cathepsin K did not prevent elastin degradation, whereas the collagen content was significantly increased in the aneurysm area in cathepsin K-lacking mice (Bai et al., 2010).

6. Cathepsin inhibitors in the prevention of pathological aortic remodeling

The highly destructive potential of cysteine cathepsins requires their tight regulation and one of such restrictive mechanisms is a presence of cathepsin inhibitors. Cystatin C is the most important inhibitor of cysteine cathepsins. It is a small protein expressed in virtually all organs and found in high concentration in biological fluids including blood (Shi et al., 1999). Cystatin C is present in normal blood vessels but its concentration significantly decreases in atherosclerotic and aneurismal lesions (Lindholt et al., 2001). Serum cystatin C level inversely correlated with abdominal aortic diameter in patients with abdominal aortic aneurysm (Shi et al., 1999). Animal experiments have shown that lack of cystatin C expression in apolipoprotein E-deficient mice results in more advanced atherosclerotic lesions with increased elastin lamina degradation and higher macrophage content (Bengtsson et al., 2005; Sukhova et al., 2005). In an angiotensin II-induced model of abdominal aortic aneurysm such mice showed aggravated destruction of elastin, increased cathepsin activity, fewer number of smooth muscle cells in tunica media and increased macrophage content and number of CD4$^+$ T cells (Schulte et al., 2010). Recently cathepsin K, L and S attracted a lot of attention as a potential therapeutic target in cardiovascular, bone and cartilage diseases (Turk, 2006; Bromme & Lecaille, 2009). The atheroprotective effect of a potent and selective cathepsin S inhibitor was tested in apolipoprotein E-deficient mice (Samokhin et al., 2010b). Animals receiving high fat diet containing the cathepsin S inhibitor developed significantly smaller plaques in brachiocephalic arteries, had smaller number of elastin ruptures, and lower levels of macrophages in plaques. Mice treated with cathepsin S inhibitor also showed a reduced number of buried fibrous caps providing evidence of more stable plaques. In this study, the cathepsin S inhibitor was also tested in peritoneal macrophages where cells showed reduced elastolytic activity (Samokhin et al., 2010b). This study also revealed some gender-related differences in atherosclerotic lesions development in response to inhibitor treatment. Female mice showed an almost 2-fold greater reduction in plaque sizes compared to the male group. The effectiveness of the cathepsin S inhibitor was verified by the build-up of intermediate invariant chain breakdown products in spleen. Cathepsin S plays an important role in MHC class II-associated antigen presentation by participating in proteolytic processing of invariant chain and its inhibition results in accumulation of invariant chain breakdown products (Honey & Rudensky, 2003). The inhibition of cathepsin S reflected most of the phenotype observed in experiments with cathepsin S-deficient mice (Sukhova, 2003; Rodgers, 2006) suggesting the high specificity of the inhibitor and the potential feasibility of the treatment of atherosclerosis with cathepsin inhibitors.

7. Cathepsin K is highly expressed in multinucleated giant cells in aortic wall

The presence of multinucleated giant cells within the aortic wall is described in giant cell arteritis and atherosclerosis. In these two diseases, multinucleated giant cells are formed by

the fusion of macrophages in inflammatory infiltrates of the arterial wall (Weyand et al., 2005; Eberhardt & Dhadly, 2007; Soilleux et al., 2002). It was shown by immunohistochemical analysis and *in situ* hybridization that multinucleated giant cells from different organs and from patients with different pathological conditions have strong cathepsin K expression (Buhling et al., 2001; Chapman et al., 1997).

7.1 Multinucleated giant cells in human atherosclerotic plaques show strong staining for cathepsin K

The analysis of atherosclerotic plaques from carotid arteries and lesions from patients with abdominal aortic aneurisms revealed the presence of multinucleated giant cells (Fig. 1). Similarly to giant cells arteritis, they were mostly localized in the media-intima junction (Samokhin, 2010c). The lesions contained Langhans-type multinucleated giant cells recognizable by their circular arrangement of nuclei and foreign body-type giant cells with random arrangement of nuclei.
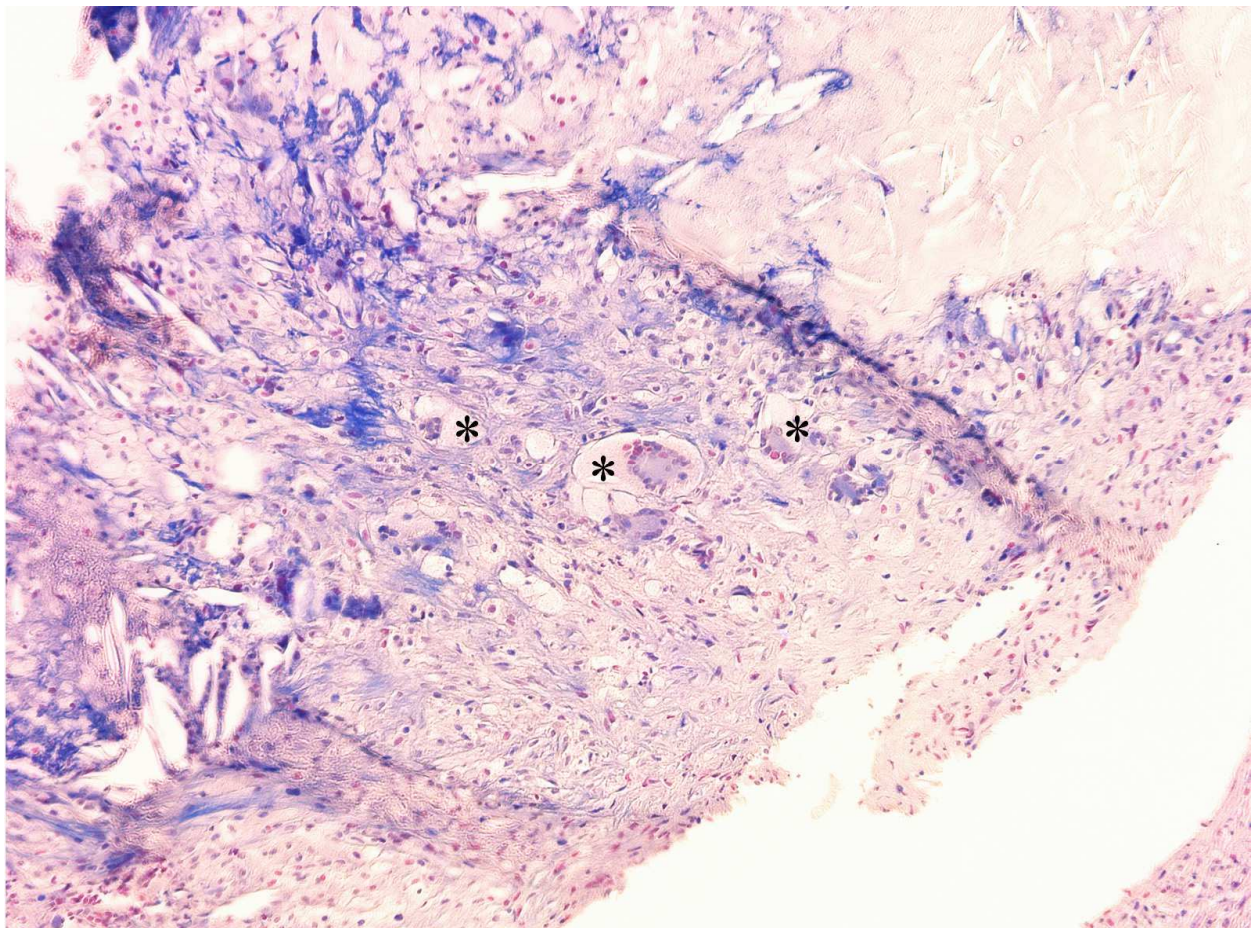

Fig. 1. Multinucleated giant cells in atherosclerotic lesions from carotid artery (trichrome staining, x10, asterisks show multinucleated giant cells).

Immunohistochemical analysis revealed strong expression of cathepsin K in multinucleated giant cells (Fig. 2). These results suggest an important role of cathepsin K from multinucleated giant cells in aortic wall damage in atherosclerosis and abdominal aortic aneurisms.
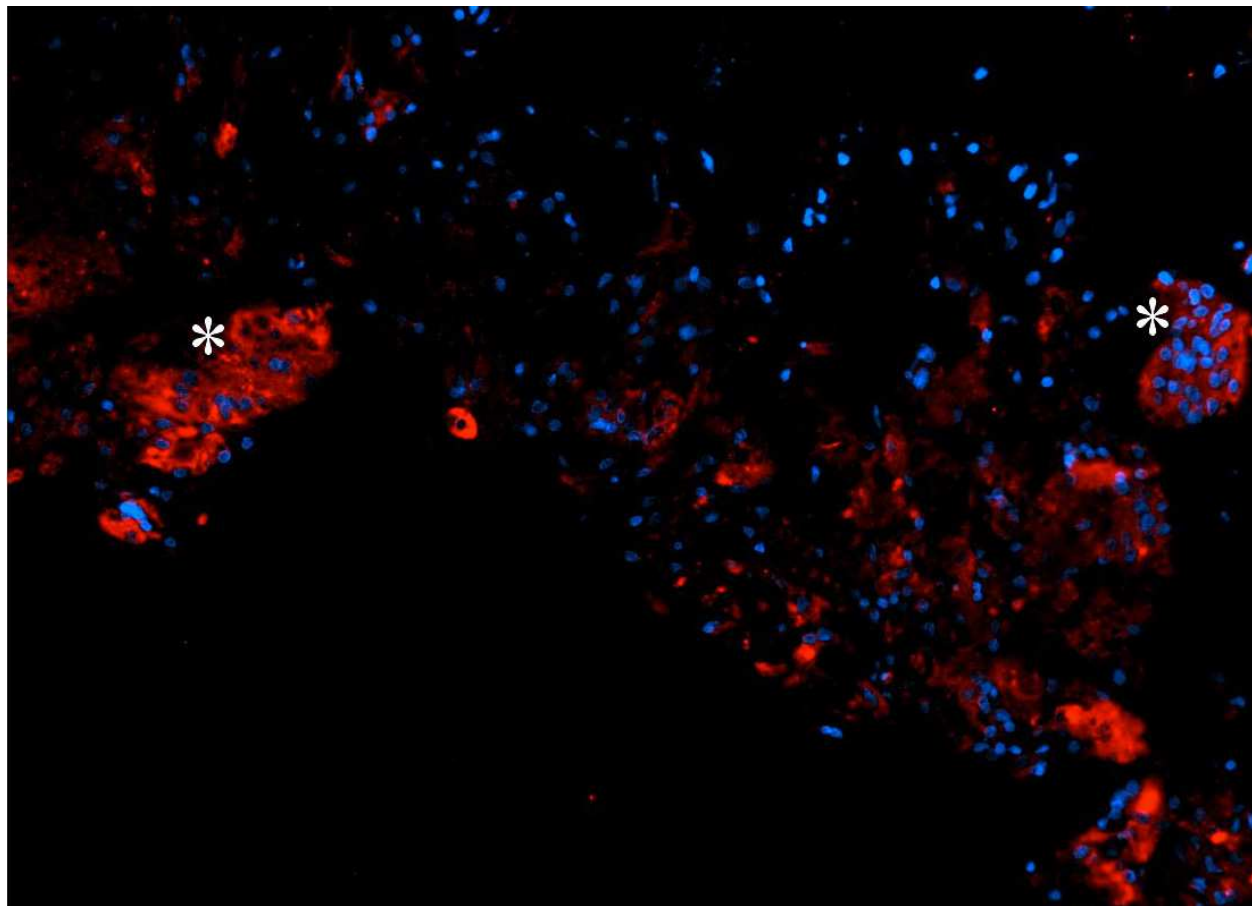
Fig. 2. Cathepsin K-positive multinucleated giant cells in atherosclerotic lesions from carotid artery (red – cathepsin K, blue - nuclei, x20, asterisks show multinucleated giant cells).

7.2 Multinucleated giant cells in mouse atherosclerotic plaques

Apolipoprotein E-deficient mice on cholate-containing high fat diet developed atherosclerotic lesions containing multinucleated giant cells (Fig. 3). These giant cells were observed in atherosclerotic plaques within the brachiocephalic artery and the aortic root and were easily detectable by intensive cathepsin K immunostaining (Samokhin et al., 2010c). They were mostly localized in the fibrous cap region and close to the elastin laminae. The presence of multinucleated giant cells correlated with the disruption of elastin fibers (Fig. 4) and the absence of smooth muscle cells within the tunica media. Similarly, in giant cell arteritis, multinucleated giant cells have been implicated in internal elastic laminae damage and their presence strongly correlated with smooth muscle cell migration (Kaiser et al., 1999; Penn & Dasgupta, 2003; Nordborg & Nordborg, 2003).

Cathepsin K plays a major role in the destructive potential of osteoclasts and is suggested as a marker of macrophage differentiation (Brömme et al., 1996; Buhling et al., 2001). In contrast to macrophages, multinucleated giant cells in atherosclerotic lesions of apolipoprotein E-deficient mice do not show strong immunostaining for cathepsin L and S (Samokhin; 2010c). These results suggest that cathepsin K plays a crucial role in the destructive potential of multinucleated giant cells in the aortic wall.
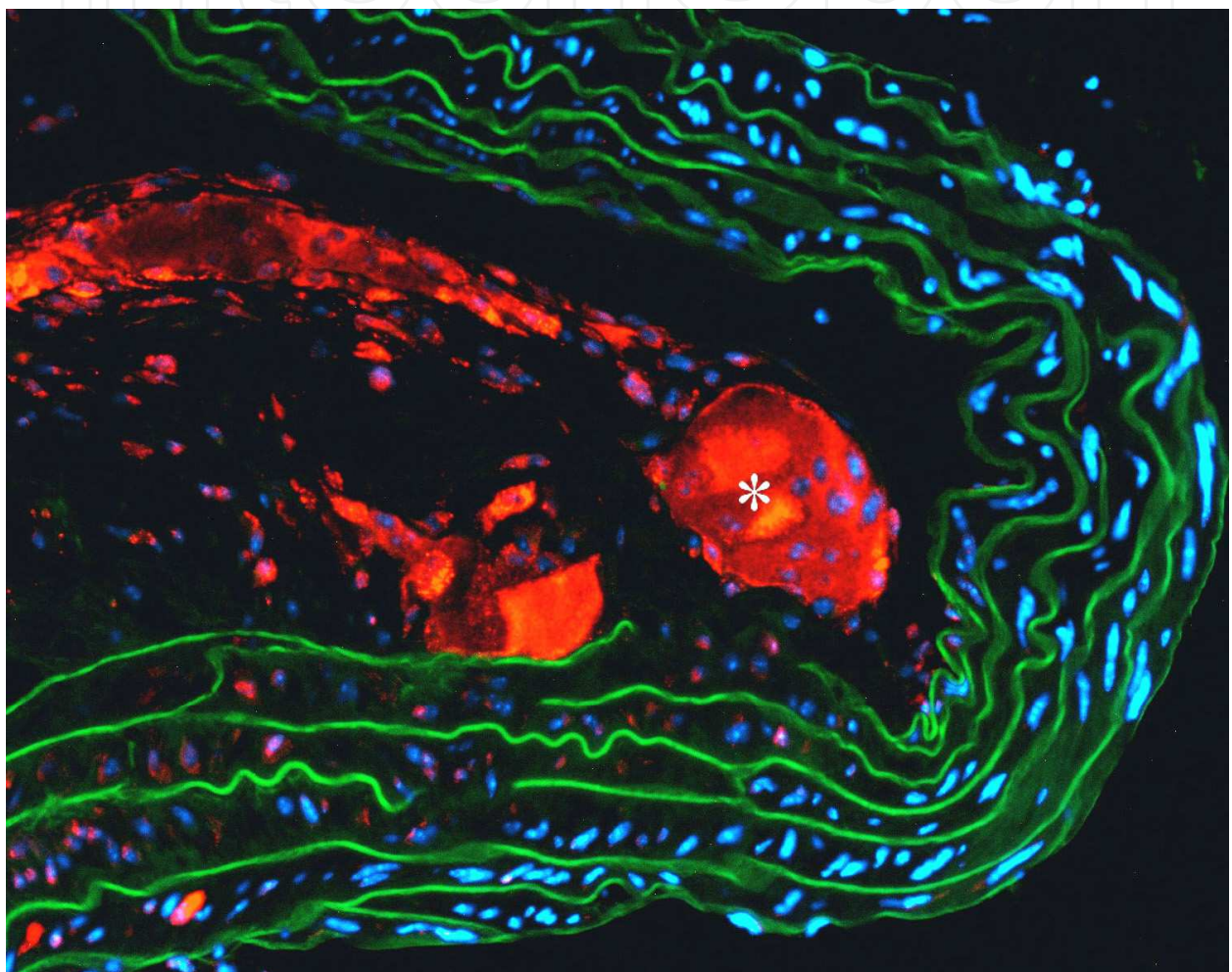
Fig. 3. Cathepsin K immunostaining of atherosclerotic lesions in brachiocephalic artery of ApoE-/- mice (red- cathepsin K, green – elastin fibers autofluorescence, blue – nuclei, x20, asterisk shows multinucleated giant cell).
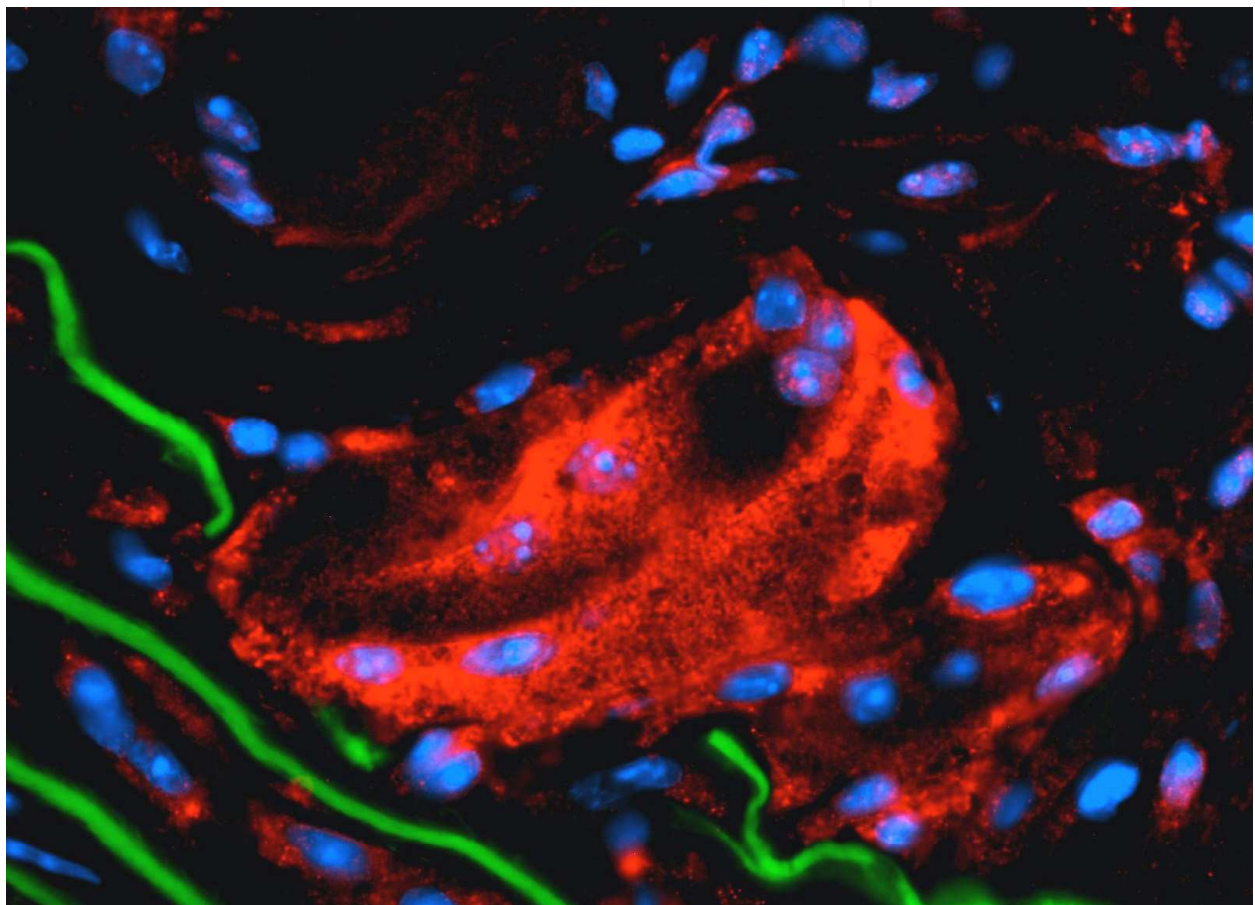
Fig. 4. Cathepsin K-positive multinucleated giant cell at the site of an elastin fiber break (red- cathepsin K, green – elastin fibers autofluorescence, blue- nuclei, x63).
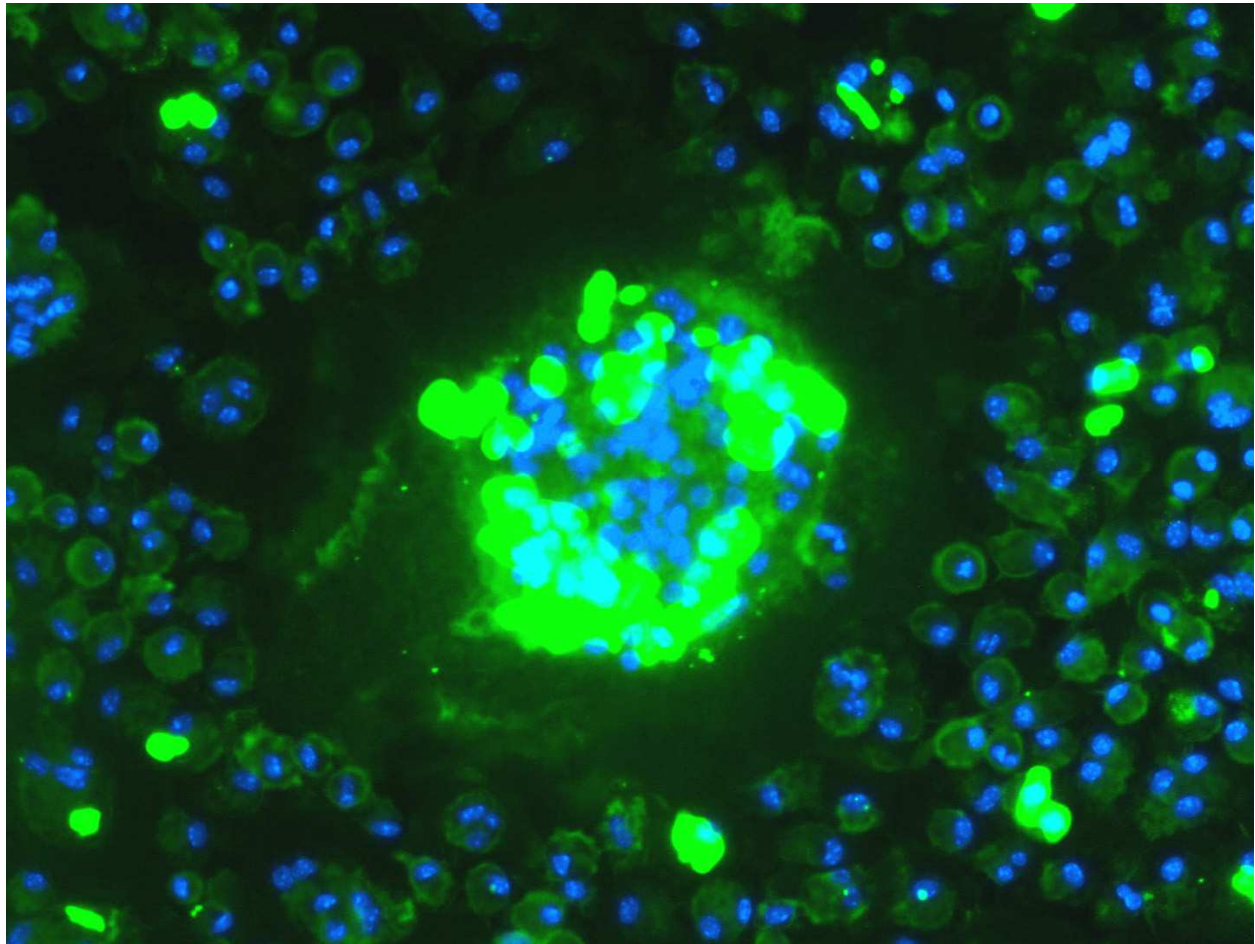
Fig. 5. Predominant accumulation of elastin-FITC complexes on/inside of multinucleated giant cell (olive green – phalloidin-FITC, neon green – elastin-FITC, blue nuclei, x20).

The involvement of cathepsin K in the increased elastolytic potential of multinucleated giant cells was further supported by an in vitro experiment where peritoneal macrophages were incubated with IL-4 to induce fusion and multinucleated giant cell formation. The fusion of macrophages resulted in dramatic increase in their elastolytic activity as was revealed by the cleavage of FITC-labeled elastin. On the third day of macrophage fusion, cells from cathepsin K-deficient mice showed a 30% reduction in their elastolytic activity compared to cells derived from cathepsin K-expressing animals (Samokhin, 2010c). Notably, most of the elastin fibers were attached to or engulfed by MGCs (Fig. 5) demonstrating that the observed increase in elastolytic activity was due to the process of giant cell formation.

8. Conclusion

The results of recent studies in humans and animal models provide evidences for the pivotal roles of cathepsin K, L and S in aortic extracellular matrix remodeling during pathological conditions. Their elasto- and/or collagenolytic activities render them into main culprits of matrix destruction observed in cardiovascular diseases and make these proteases attractive pharmaceutical targets for therapeutic interventions.

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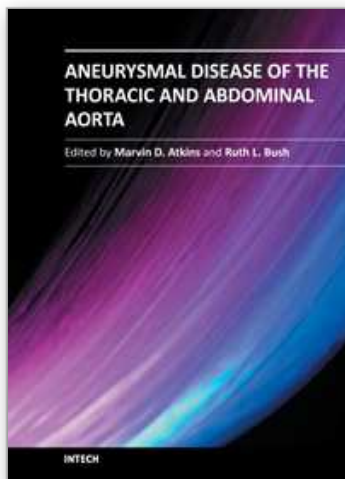
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Aneurysmal Disease of the Thoracic and Abdominal Aorta

Edited by Dr. Ruth Bush

The first successful open surgical repair of an abdominal aortic aneurysm was in 1951 by Dubost and represented a tremendous milestone in the care of this challenging disease. The introduction of endovascular repair in 1991 by Parodi furthered the care of these patients by allowing for lower morbidity and mortality rates and also, enabling surgeons to extend surgical treatment to patients traditionally deemed too high of a surgical risk. This new book on Aortic Disease covers many interesting and vital topics necessary for both the practicing surgeon as well as a student of vascular disease. The book starts with background information on the evolution of aortic management from traditional open surgical repair to modern endovascular therapies. There is also a chapter covering the data supporting current treatment modalities and how these data have supported modern management. Also, the use of endovascular means for care of the challenging situation of ruptured aneurysms is discussed. In addition to management of abdominal aneurysm, there is a chapter on treatment of aneurysms of the ascending aorta. Along with surgical treatment, one must also understand the molecular basis for how blood vessels remodel and thus, the role of cathepsins in aortic disease is elucidated. Lastly, chapters discussing the perioperative management of radiation exposure and ultrasound-guided nerve blocks as well as the need for high-quality postoperative nutrition will lend well to a full understanding of how to management patients from presentation to hospital discharge. We hope you enjoy this book, its variety of topics, and gain a fuller knowledge of Aneurysmal Disease of the Thoracic and Abdominal Aorta.

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