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# **Etiology and Pathogenesis of Aortic Aneurysm**

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Additional information is available at the end of the chapter

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## **1. Introduction**

Aortic aneurysm is a multifactorial disease, with both genetic and environmental risk factors contributing to the underlying pathobiology.

Aortic aneurysms are atherosclerotic in origin, in older patients. Recognized predisposing factors are: hypertension, hypercholesterolemia, diabetes, and smoking.

Aneurysms are increased in frequency in patients with Marfan, Loeys-Dietz, Ehler-Danlos type IV, and Turner Syndrome, in Familial aortic disease (Hiratzka et al., 2010), and in repaired and nonrepaired congenital heart diseases (Hinton, 2012).

Less common causes, as Takayasu disease, giant cell arteritis, Behçet's disease, ankylosing spondylitis, rheumatoid arthritis, and infective aortitis should be considered (Hiratzka et al., 2010).

Histological examination demonstrates that the pathophysiological processes in aortic aneurysm involve all layers of the aortic wall in a variable proportion.

Although the aortic aneurysm morphological characteristics have been well-recognized, the mechanism which elicits its formation is incompletely understood. However, it is generally accepted that an aneurysm results from an association of genetic predisposition, stresses within the aortic wall, proteolytic degradation of the structural components, and/or inflammation and autoimmune response.

A review of the relevant scientific publications, concerning the etiology, pathogeny, histology, and molecular markers is presented in this chapter. These data provide valuable mechanistic insight into the pathogenesis of aortic aneurysm, reveal diagnostic markers, and identify new therapeutic targets.

## 2. Aortic anatomy

The thoracic aorta has four anatomical segments, as following: the aortic root, the ascending aorta, the aortic arch, and the descending aorta (Gray, Bannister, 1995; Hiratzka et al., 2010). The aortic diameter is influenced by age, gender, body mass index, location of measurements, and type of imaging technique (Hannuksela et al., 2006).

The aortic root contains the sinuses of Valsalva, the aortic valve annulus, and the aortic valve cusps measuring  $3.50\text{--}3.72 \pm 0.38$  cm in female and  $3.63\text{--}3.91 \pm 0.38$  cm in male (Hannuksela et al., 2006).

The ascending aorta contains the tubular portion extending from the sinotubular junction to the origin of the brachiocephalic artery measuring 2.82 cm (Hannuksela et al., 2006).

The aortic arch has a course in front of the trachea and to the left of the trachea and oesophagus, contains the origin of the brachiocephalic artery, and branches into the head and neck arteries (Hannuksela et al., 2006).

The descending aorta has a course anterior to the vertebral column, through the diaphragm to the abdomen, contains the isthmus between the origin of the left subclavian artery and the *ligamentum arteriosum* measuring, in mid-descending area,  $2.45\text{--}2.64 \pm 0.31$  cm in female and  $2.39\text{--}2.98 \pm 0.31$  cm in male and, in diaphragmatic region,  $2.40\text{--}2.44 \pm 0.32$  cm in female and  $2.43\text{--}2.69 \pm 0.27\text{--}0.40$  cm in male (Hannuksela et al., 2006).

The abdominal aorta is situated in front of the lower border of the last thoracic vertebra and descends in front of the vertebral column from the aortic hiatus of the diaphragm to the fourth lumbar vertebra, to the left of the middle line and branches into the two common iliac arteries (Gray, Bannister, 1995). The lesser omentum and stomach, together with the branches of the celiac artery and the celiac plexus are anteriorly placed and below these, the inferior part of the duodenum, the mesentery, the splenic vein, the pancreas, the left renal vein, and aortic plexus are disposed (Gray, Bannister, 1995). The anterior longitudinal ligament and left lumbar veins are posteriorly disposed. The azygos vein, thoracic duct, cisterna chyli, and the right crus of the diaphragm are situated to the right side and the inferior vena cava is situated below (Gray, Bannister, 1995). The left crus of the diaphragm, the ascending part of the duodenum, the left celiac ganglion, and some coils of the small intestine are disposed to the left (Gray, Bannister, 1995).

The normal adult infrarenal aorta has a 12 cm length, a diameter of 2 cm, and a thickness of 2 mm (Humphrey, Taylor, 2008).

The abdominal aorta has the following branches: visceral (celiac, mesenteric, renals, middle suprarenals, internal spermatics, and ovarian), parietal (lumbar, middle sacral, and inferior phrenics), and terminal (common iliacs) (Gray, Bannister, 1995).

### 3. Aortic embryology

The development of the aorta and aortic valves includes aortopulmonary septation, followed by semilunar valve and two large arteries formation (Hinton et al., 2012). A process of endothelial-mesenchymal transition is responsible for the development of endocardial cushions. Cell proliferation and extracellular matrix development results in valve cusps layer formation (Hinton, Yutzey, 2011). Consequently, while cells from the semilunar valve cusps are endothelial-derived, the smooth muscle cells of the proximal aorta originate from neural crest (Majesky, 2007), with reciprocal influences of both types of cells on the development of both cell populations (Jain et al., 2011). In aorta and valve development several signalling pathways are involved, such as TGF-beta and Notch (Garg et al., 2005), and Wnt (Hinton et al., 2012).

### 4. Aortic histology

The histological structure of the human adult aortic wall comprises three layers. Intima is composed of a monolayer of endothelial cells supported by a special type of connective tissue (subintima), with a basement membrane between the two types of tissues (Hannuksela et al., 2006). The endothelium is continuous with endocardium and represents the interface between the vascular wall and blood (Saito et al., 2013). The endothelium is actively involved in production and reaction to inflammation mediators, such as growth factors, adhesion molecules, and a wide panel of cytokines (Saito et al., 2013). The basement membrane is composed of type IV collagen and laminin. The subendothelial layer contains collagen type I and II, elastic fibers, and abundant extracellular matrix rich in proteoglycans. Supplementary, dual phenotypic myocytes, myointimal cells, and macrophages are also components of the subendothelial layer.

The internal limiting membrane is composed of condensed elastic fibers forming a crenelated structure delimiting the intima from media. Media is composed of fenestrated concentrically disposed elastic lamellae with interposed smooth muscle cells (abundant in abdominal aorta), multiple types of collagen, and proteoglycans (Humphrey, Taylor, 2008), and external elastic lamina (Hannuksela et al., 2006). Media occupies approximately 80% of the wall thickness and contains up to 70 elastic lamellae.

Adventitia is composed of connective tissue rich in type I collagen fibers admixed with elastin and fibroblasts (Humphrey, Taylor, 2008), containing *vasa vasorum* and *nervi vasorum*. Periadventitial tissue facilitates the aortic fixation in mediastinum and abdomen.

The aortic valve is semilunar and is composed of connective tissue forming three components: a fibrosa of fibrillar collagen, a spongiosa with proteoglycans, and a ventricularis layer made up of elastic fibers (Hinton, Yutzey, 2011). The aortic root has a different morphology compared to the aorta, consisting of the fibrous valve annulus region, situated at the cusp and aortic wall junction and of arterial tissue within the sinuses of Valsalva (Nesi et al., 2009), without elastic lamellae (Hinton, 2012).

## 5. Aortic aneurysm gross findings

According to the location, aortic aneurysms may be thoracic (25.9%), abdominal (62.7 %), thoracoabdominal (8.3%), and unspecified (3.0%) (Hiratzka et al., 2010).

Aortic aneurysm may exhibit two patterns, as following (Waller et al., 1997):

1. The most common type is cylindrical or fusiform pattern involving the entire aortic circumference and being diagnosed in almost all abdominal aortic aneurysms, distal to the renal arteries.
2. The saccular type is involving a limited portion of the circumference of the aorta and is diagnosed in the arch and in the descending aorta, associated to atherosclerosis, or in the abdominal aorta, mostly proximal to the renal arteries. The saccular type may be further subdivided into two subtypes, as following (Edwards, 1979):
  - True type is a bulge of aorta located in an area of medial weakness, exhibiting a mouth of a similar diameter as the size of the aortic bulge.
  - False type contains adventitia and a portion of media and an intra-aneurysmal thrombus, with a mouth diameter smaller than the diameter of the aortic bulge.

As chronic aneurysms are frequently associated in their evolution with atherosclerosis, the traumatic saccular aneurysm which may develop is wrongly considered as atherosclerotic in origin (Waller et al., 1997).

Within aneurysms, thrombi develop serving as a protective mean against the intra-aortic pressure (Waller et al., 1997). Due to progressive development, the outermost layers of the thrombus become organized with the consequent development of a “tree trunk” appearance (Waller et al., 1997). If it is dislodged, thromboembolic complications may occur (Waller et al., 1997).

## 6. Aortic aneurysm histopathology

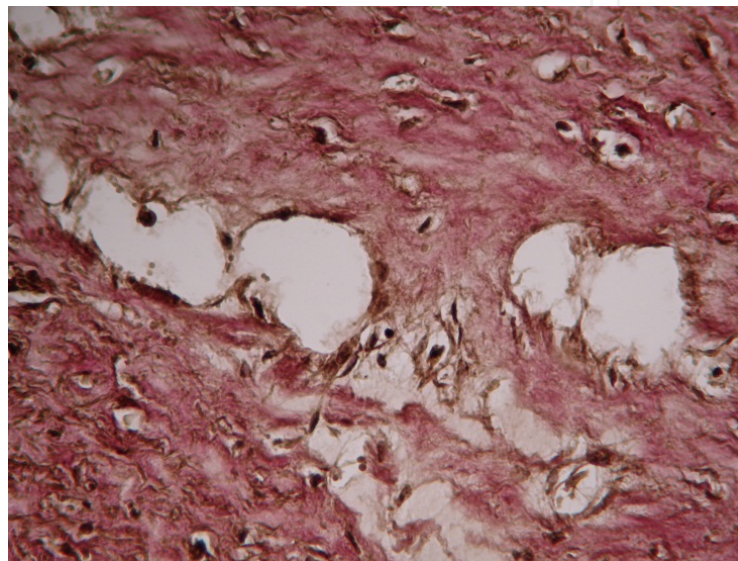
The thoracic aortic aneurysm has been termed cystic medial necrosis which is currently considered as a misnomer because the histopathology of the disease is not characterized by necrosis or cysts (Hiratzka et al., 2010). The term medial degeneration is more accurate as the process involves disruption of elastic fibers and accumulation of proteoglycans (Hiratzka et al., 2010). Although degenerative changes, not related to hypertension, are identified in approximately two thirds of ageing population, variably associated to fibrosis and atherosclerosis (Klima et al., 1983), there are quantitative differences comparative to aortic aneurysm (Savunen, Aho, 1985).

### 6.1. Light microscopy

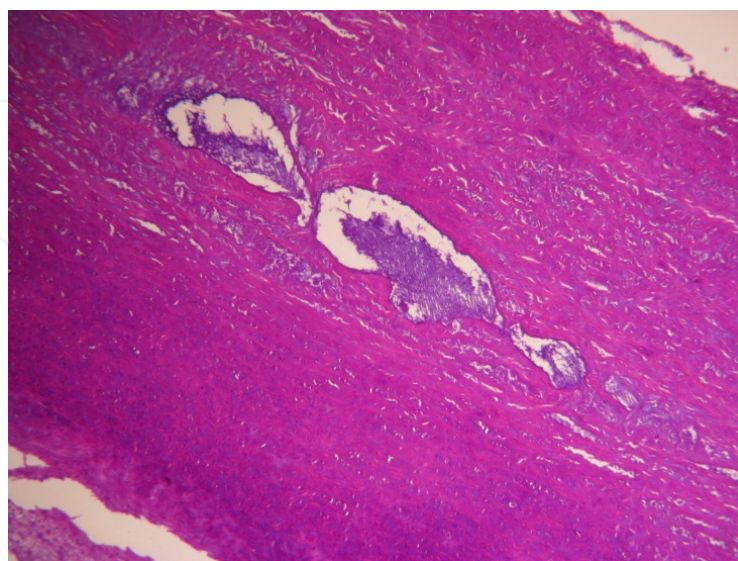
Histological examination demonstrates that pathophysiological processes in aortic aneurysm involve all layers of the aortic wall, contrasting to those observed in occlusive atherosclerosis.



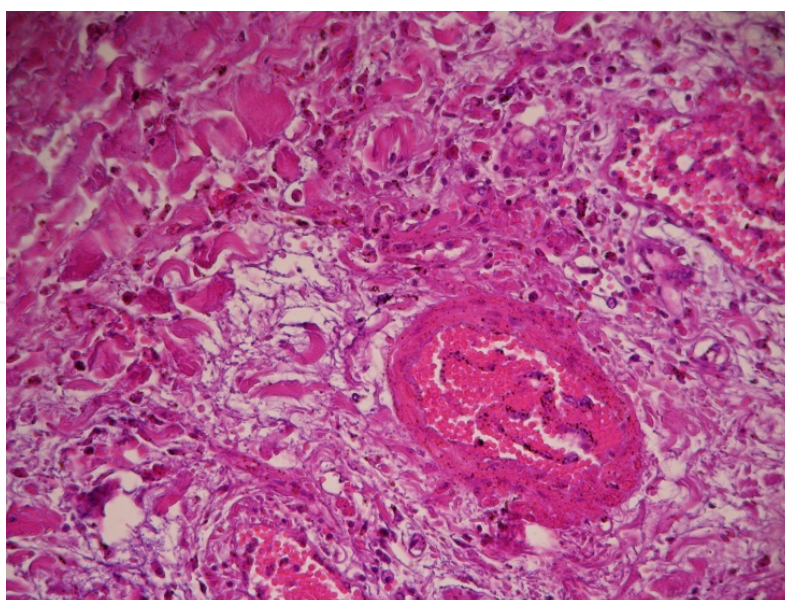
From our experience, the biopsies demonstrate significant degradation of extracellular elastin (Fig. 1) and collagen fibers, cystic medial change (Fig. 2) (Amalinei et al., 2009) and fibrosis, reduction in the number of vascular smooth muscle cells, medial and adventitial infiltration by mononuclear lymphocytes and macrophages forming vascular associated lymphoid tissue, and thickening of the *vasa vasorum* (Fig. 3). An increase in medial neovascularisation has also been reported in aneurysmal tissue biopsies. Moreover, medial splitting by haemorrhage associated to elastic fragmentation and fibrosis was observed in dissecting aneurysms from our files (Fig. 4).



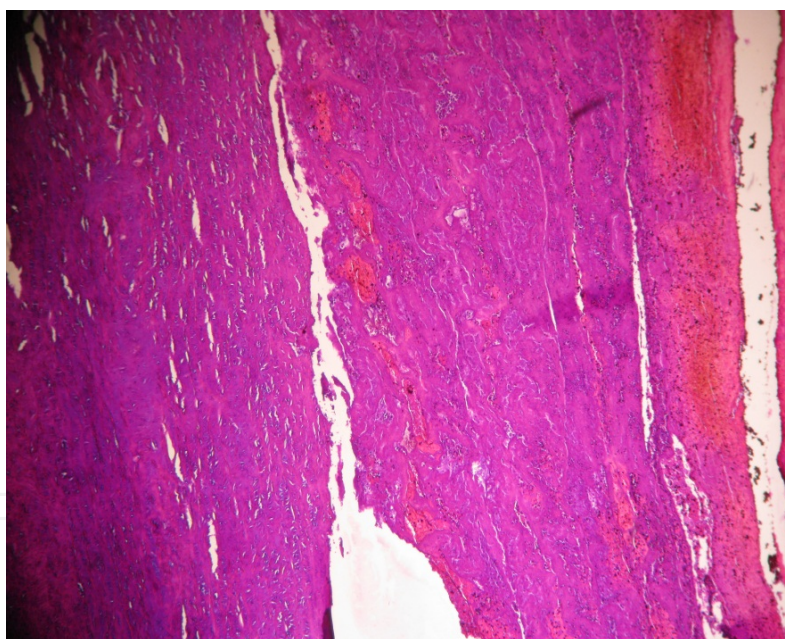
**Figure 1.** Elastic fibers fragmentation (Elastic-van Gieson staining)



**Figure 2.** Cystic medial degeneration (HE staining)



**Figure 3.** Adventitial inflammatory infiltrate and thickening of the *vasa vasorum* (HE staining)



**Figure 4.** Dissecting aneurysm (HE staining)

Cystic changes are characterized by accumulation of basophilic material (in haematoxylin-eosin staining), showing Alcian blue positivity and metachromatic characteristics (in toluidine blue staining) between the elastic lamellae of the aortic media (Savunen, Aho, 1985). Occasional elastin deposits are identified in areas with fibers disruption or severe fragmentation when associated to atherosclerotic lesions, in orcein (Savunen, Aho, 1985) or in Elastic-van Gieson staining.



According to the amount of material accumulated, the lesions may be classified into three degrees, as following (Savunen, Aho, 1985):

- Grade I shows minute cysts, involving up to five foci of elastic fibers degeneration extended to two to four lamellae within the total width of the media.
- Grade II involves maximum the width of one lamellar unit, being extended to more than five foci.
- Grade III is extended more than the width of a lamellar unit and it is also involving the smooth muscular tissue.

There are two types of degeneration, according to the location of the aortic damage, as following (Doerr, 1974):

- microcystic (Gsell-type);
- disseminated cystic (Erdheim-type).

The elastic fiber degeneration is positively correlated to an increase in collagen content, less severe in Marfan-related disease and more advanced in atherosclerotic aorta (Savunen, Aho, 1985). The fibrosis may be also graded, as following (Savunen, Aho, 1985):

- Grade I fibrosis involves less than one third of the medial thickness.
- Grade II fibrosis is extended to more than one third until maximum two thirds of the media.
- Grade III fibrosis involves more than two thirds of the aortic media.

The smooth muscle is progressively lost corresponding to the structurally ineffective reparative elastogenesis, as normal elastin inhibits smooth muscle apoptosis (Humphrey, Taylor, 2008).

The medial degeneration is variable associated to atherosclerosis and inflammation (Hiratzka et al., 2010).

## 6.2. Electron microscopy

Normal elastin comprises 3-4 nm diameter filaments showing a parallel disposition of the fibers and a periodicity of about 4 nm (Gotte et al., 1974). Although the filamentous component is not observed in elastic lamellae, the normal aorta shows elastin streaks attached to the elastic lamellae (Dingemans et al., 1981).

In aortic aneurysms, the elastic lamellae show irregular surfaces, granulofilamentous densities, and amorphous centre holes or a normal appearance exhibiting only a variable width (range 1.2- 1.5  $\mu$ m) (Savunen, Aho, 1985). New elastin formation is indicated by bundles composed of non-banded microfibrils (Savunen, Aho, 1985).

The electron microscopy shows a network of proteoglycan matrix associated to a variable amount of collagen tissue (Savunen, Aho, 1985). The collagen bundles are disposed both between elastic lamellae and in areas of elastic fibers degeneration and normal 64 nm periodicity of individual fibers has been identified (Savunen, Aho, 1985).



The smooth muscle shows degenerated cells, fragments of organelles, debris, with focal nuclei loss in Grade I, extended to less than one third in Grade II, and more than two thirds in Grade III medial necrosis (Savunen, Aho, 1985). Although smooth muscle cells are focally lost, there is no indication of a reduced total amount of muscular tissue (Hiratzka et al., 2010). Moreover, an initial hyperplastic smooth muscle cell remodelling of the aortic wall has been suggested by morphometry (Dong et al., 2002; Pannu et al., 2005; Guo et al., 2007).

### 6.3. Ascending aortic aneurysms particularities

The aneurysms of the ascending aorta are usually fusiform, being associated to degenerative or inflammatory processes, and occasionally calcified (Tazelaar, 2004).

The most common histopathological feature noticed in ascending aorta aneurysm is cystic medial degeneration. The patients' age ranges from 6 to 89 years, with a male dominance (M:F, 1.7:1) (Tazelaar, 2004).

The medial degenerative changes are variably associated with wall thinning, elastic lamellae disruption, and consecutive glycosaminoglycans deposition. Another finding is coagulative necrosis or laminar medial necrosis, exhibiting nuclei loss and elastic lamellae degeneration, in elderly or hypertensive patients (Tazelaar, 2004).

The consequence is the wall expansion, resulting in aortic root dilatation, anuloaortic ectasia, or ascending aortic aneurysm (type A).

According to the risk factors, patients with inherited connective tissue diseases are younger (mean age 42 years) and the lesions are more severe than those diagnosed with bicuspid aortic valve (56 years) or hypertension (65 years) (Tazelaar, 2004).

If disruption occur adjacent to small intramedial *vasa vasora*, either scant lymphoplasmacytic infiltrates or microfocal medial hemorrhage may occur, without active aortitis features.

Intima may be normal or unrelated co-existent atherosclerosis may be identified.

From our experience, during the aortic aneurysms evolution, descending aorta dilation is commonly progressive, and is accompanied by the formation of a non-occlusive, intraluminal, laminated thrombus, continuously remodelled and increasing in size. Localised hypoxia has been demonstrated in regions of the aorta covered by the thrombus and this has been suggested to contribute to physiological stresses within the arterial wall (Tazelaar, 2004).

Intramedial dissection is another manifestation of ascending aortic aneurysm most commonly diagnosed in men (63 %) with a mean age of 63 years (range 22–87 years) (Tazelaar, 2004). A higher susceptibility is registered in patients with hypertension (70% of cases), inherited connective tissue diseases, bicuspid aortic valve, cystic medial degeneration, and arteritis (Tazelaar, 2004).

The false channel developed in the outer third of the media results in hematoma with fresh platelet fibrin thrombus, sometimes with the detachment of the adventitial layer, and occasional intimal tear (Tazelaar, 2004), added to the background process of cystic degeneration, being rarely associated to laminar medial necrosis or giant cell aortitis (Tazelaar, 2004).

Variable degrees of healing may result in development of a thick, new intima possibly associated to atherosclerosis, mimicking the natural lumen or of obliterative dense linear fibrosis, or of an acute process developed against a background of chronic dissection (Tazelaar, 2004).

Despite extensive sampling, normal histological media is also reported in ascending aortic aneurysm, although associated with bicuspid valve, hypertension, or atherosclerosis (Tazelaar, 2004).

Isolated aortitis with foci of medial necrosis and no evidence of a temporal arteritis or other systemic inflammatory disease may be associated to ascending aorta aneurysm without dissection (Tazelaar, 2004). The histopathological findings reported are the following: 0.4 cm mean aortic thickness, laminar medial necrosis (50% of cases), and cystic medial degeneration (30%) (Tazelaar, 2004). Variable giant cells aortitis (44 to 75% of cases) and granulomas formation (20% of cases) have also been reported (Tazelaar, 2004).

#### **6.4. Abdominal aortic aneurysms particularities**

Abdominal aortic aneurysms are usually atherosclerotic in origin, being found in up to 3% of patients older than 50 years. Beside age, other predisposing factors are: hypertension, hypercholesterolemia, diabetes, and smoking (Heuser, Lopez, 1998).

As the abdominal aorta shows a wider pulse pressure, a thinner wall thickness, a different elastic/muscular tissue ratio, with only 28-30 concentric elastic lamellae (Humphrey, Taylor, 2008), there is a higher predisposition both for atherosclerosis and aneurysm (Heuser, Lopez, 1998).

The infrarenal segment is involved in 80-90% of cases and approximately 50% of cases show extension to the iliac arteries (Heuser, Lopez, 1998), with aneurysm being defined by a diameter greater than 3 cm and a tendency toward diffuse involvement (Humphrey, Taylor, 2008).

The histopathology of abdominal aortic aneurysm reveals a dilated lumen, a degenerated media containing disorganized collagen fibers, proliferation of fibroblasts and extracellular matrix production or external media and adventitia containing chronic inflammation (Tsuruda et al., 2006), and the development of an intraluminal thrombus (Humphrey, Taylor, 2008). The initial event is debated, either inflammation and early loss of elastin, or either a ruptured atherosclerotic plaque (Humphrey, Taylor, 2008).

Approximately 5% of patients develop a dense lymphocytic adventitial inflammation and adhesion to the duodenum or inferior vena cava, being called inflammatory aneurysms.

Numerous evidences support the significant role of Renin-angiotensin system in abdominal aortic aneurism (Blanchard et al., 2000; Lu et al., 2008). Angiotensinogen and Angiotensin II type I receptor (AT1) are overexpressed in aneurysms in comparison to healthy or atherosclerotic aorta (Kaschina et al., 2009).

In animal experiments, exogenous Angiotensin II stimulates aneurysm development (Daugherty, Cassis, 1999; Daugherty et al., 2000), while AT1a deletion inhibits its progression

(Cassis et al., 2007). Consequently, Angiotensin converting enzyme (ACE) inhibitors is preventing the aneurysmal disease progression and the AT1 blockers are currently under testing (Thompson et al., 2010; Iida et al., 2012).

## 7. Natural history

Aortic aneurysms are usually asymptomatic, as they initially have a slow expansion. Due to a complex association of pathogenic factors the process becomes faster, the aneurysm may continue to enlarge, and the diagnosis may be frequently be given by autopsy, due to lethal complications (Hiratzka et al., 2010).

**Aortic dissection** is an acute aortic syndrome caused by the disruption of the medial layer of the aortic wall with hemorrhage causing the separation of the layers (Hiratzka et al., 2010).

From our experience, an intimal lesion is found in most of the patients, resulting in tracking of the blood in a dissection plane inside medial layer (Hiratzka et al., 2010); it may rupture externally through the adventitia or back, through the intimal layer causing a septum or flap between the two lumens. The false lumen may be obstructed by a thrombus. The intimal disruption is visible on autopsy in 96% of cases (Roberts, Roberts, 1991). Atheromatosis may lead to dissection, intramural hematoma, or penetrating atherosclerotic ulcer (Hiratzka et al., 2010).

The DeBakey classification is based on the location of the intimal tear and its extension, into the following three types (Hiratzka et al., 2010):

Type I dissection is originating in the ascending aorta and extends to the aortic arch and the descending aorta.

Type II dissection is originating in the ascending aorta and it is limited to its territory.

Type III dissection is originating in the descending aorta and it is limited to its territory (Type IIIa), or it extends below the diaphragm (Type IIb).

The Stanford classification has two types: Type A involves the ascending aorta and Type B does not involve the ascending aorta (Hiratzka et al., 2010).

The risk factors of the aortic dissection comprise situations associated to medial degeneration, such as: inflammatory vasculitides, genetic conditions, pregnancy, polycystic kidney disease, chronic corticosteroid or immunosuppression, infections, or extreme stress of the aortic wall (hypertension, coarctation of the aorta, cocaine use, pheochromocytoma, weight lifting, deceleration, or torsional injury (Hiratzka et al., 2010).

**Rupture** of aorta may result in extravasation of blood into the pericardial sac, mediastinum, pleural sac, pulmonary trunk, main pulmonary arteries, cardiovascular defects, lung, esophagus (in thoracic aneurysms), inferior vena cava, retroperitoneum, duodenum (in abdominal aneurysms) (Roberts, 1981; Waller et al., 1997). The risk of rupture is correlated to the size of the dilated segment, to the type of aneurysm, as fusiform aneurysms are

correlated to a higher pressure directed against the wall of the bulge (Roberts, 1979; Waller et al., 1997), to the possible compression against a rigid adjacent structure, such as vertebra, and infection (Bless et al., 1968).

**Intramural hematoma** is identified in 10-20% of patients, most commonly in descending aorta, in older patients, without a false lumen or intimal tears, possibly originating from *vasa vasorum* hemorrhage (Nienaber, Sievers, 2002) or from microscopic lesions within intima. The evolution is variable: resolution (in 10% of cases), dissection (in 11-88% of cases of ascending segment involvement and in 3-14% of cases of descending aorta involvement), or aortic dilatation and rupture (Hiratzka et al., 2010).

**Obstruction** by hematoma of the aortic lumen may lead to true aortic stenosis and intussusception or an obstruction of the lumen of aortic branches may result in: acute myocardial infarction and sudden death (in coronary obstruction), oliguria and renal infarction (in renal artery obstruction), bowel ischemia and infarction (in mesenteric obstruction), syncope and stroke (in innominate and/or common carotid obstruction), upper limb gangrene, paralysis, and paraplegia (in innominate and/or subclavian obstruction), leg gangrene and paralysis (in common iliac obstruction) (Roberts, 1981; Waller et al., 1997).

**Aortic regurgitation and separation of a branch of aorta from aorta** are other complications which may occur (Roberts, 1981; Waller et al., 1997).

**Penetrating atherosclerotic ulcer** is diagnosed mostly in the descending thoracic aorta with atherosclerotic lesions associated to ulcerations penetrating the internal elastic lamina resulting in hematoma formation within the media (Stanson et al., 1986).

**Pseudoaneurysms of the thoracic aorta** are associated to deceleration or torsion aortic trauma, following aortic surgery, or in infectious aortitis and penetrating ulcers (Hiratzka et al., 2010).

## 8. Etiologic factors and pathogenesis

### 8.1. Genetic susceptibility

Several genetic anomalies are known to be associated to aortic aneurysm, such as: Marfan, Loeys-Dietz, Ehlers-Danlos, Turner, and familial aortic aneurysm and dissection. Recently, a panel of genes has been involved in the development of the disease. Supplementary, inherited cardiovascular conditions are also considered as risk factors of aortic aneurysms.

#### 8.1.1. Genetic syndromes associated to aortic aneurysm

**Marfan syndrome** is a high penetrance heritable disease of the connective tissue or may appear due to sporadic mutations in 25% of patients (Hiratzka et al., 2010).

Mutations of the *FBN1* gene encoding the fibrillin-1 glycoprotein of the microfibrils from the periphery of the elastic fibers are causing the disorder (Dietz, Pyeritz, 1995).



*MFS2* represents a second locus recently identified in Marfan syndrome. This is caused by mutations of the transforming growth factor-beta type II receptor (*TGFBR2*) showing a locus which may be common to that identified in Loeys-Dietz syndrome (Mizugaki et al., 2004).

The diagnosis criteria of Marfan syndrome are cardiovascular, ocular, and skeletal clinical findings along with family history, and *FBN1* mutations (De Paepe et al., 1996).

The cardiovascular features are thoracic aortic aneurysm and/or dissection, valvular disease (mitral valve prolapse), and aortic regurgitation, as a consequence of an enlarged aortic root causing distortion of the aortic valve cusps.

The skeletal features result from the excessive growth of the long bones and are manifested as kyphoscoliosis, pectus deformities, dolichocephaly, dolichostenomelia, and arachnodactyly, associated to manifestations of the connective tissue disorders, such as dural ectasia, hernia, striae atrophica, and joint laxity (De Paepe et al., 1996).

The lens dislocation and ectopia lentis are specific ocular findings that are useful to differentiate Marfan from Loeys-Dietz syndrome (Loeys et al., 2006).

The common clinical presentation of Marfan syndrome is that with involvement of both sinuses of Valsalva and of the tubular aortic portion, resulting a pear-shaped or an inverted light bulb ascending aortic aneurysm, possible complicated with type A dissection and rupture (Tazelaar, 2004). The prognosis is better if the dilatation is limited to the sinuses of Valsalva (Roman et al., 1993).

Beside the histopathological findings commonly found in aortic aneurysm (severe cystic medial degeneration without an inflammatory infiltrate), prolapse of the mitral and aortic valves may be associated in non-complicated cases (Tazelaar, 2004).

Type B dissection necessitating early surgical repair (at a threshold of an external diameter of 5.0 cm) (Milewicz et al., 2005) and rarely abdominal aortic aneurysm may occur in some of the patients.

**Loeys-Dietz syndrome** results from mutations of *TGFBR1* or *TGFBR2* genes, has an autosomal dominant transmission mechanism (Loeys et al., 2006), and is clinically manifested with a characteristic clinical triad (Singh et al., 2006). The triad comprises hypertelorism, uvula anomalies, and head and neck arterial tortuosity and aneurysms. The patients may also show skeletal anomalies similar to Marfan syndrome, dural ectasia, cervical spine anomalies, joint laxity, craniosynostosis, malar hypoplasia, retrognathia, blue sclera, and translucent skin (Loeys et al., 2006).

The vascular abnormalities include patent *ductus arteriosus*, atrial septal defects, aortic root aneurysms complicated with aortic dissection even if the aortic diameter is less than 5.0 cm (Loeys et al., 2006).

**Type IV Ehlers-Danlos syndrome (vascular form)** is an autosomal dominant disease due to a defect of collagen type III encoded by *COL3A1* gene (Hiratzka et al., 2010) and the clinical findings are: thin skin, easy bruising, characteristic facial appearance, and rupture of gastro-

intestinal tract, uterus, and arteries, leading to death until 48 years-old with or without documented aneurysms (Pepin et al., 2000).

**Turner syndrome** is characterized by a 45, X karyotype, manifested with a short stature, webbed neck, low-set ears, low hairline, broad chest, ovarian failure, and cardiovascular disease with hypertension. The cardiovascular anomalies are: bicuspid aortic valve, aortic coarctation, aortic dilatation diagnosed as an ascending/descending aortic diameter ratio greater than 1.5 (Ostberg et al., 2004), and aortic dissection.

Aortic root dilatation may also occur in other types of Ehlers-Danlos syndrome (other than the vascular form), in **Beals syndrome** (congenital contractural arachnodactyly due to mutations of *FBN2*) (Gupta et al., 2004), in **Autosomal dominant polycystic kidney disease** (less common than cerebral aneurysm) (Lee et al., 2004), in **Noonan syndrome** (Purnell et al., 2005), in **Alagille syndrome** (McElhinney et al., 2002), and in Shprintzen-Goldberg syndrome (Doyle et al., 2012).

#### 8.1.2. Nonsyndromic familial aortic aneurysm and dissection

**Nonsyndromic familial aortic aneurysm and dissection** is inherited in an autosomal dominant manner with decreased penetrance (Milewicz et al., 1998) and exhibits genetic heterogeneity (Guo et al., 2009).

The *TAAD4* defective gene located at the locus 10q23-24 is *ACTA2* (actin, alpha 2, smooth muscle aorta). *ACTA2* was identified in 14% of familial thoracic aneurysms Type A or Type B and dissections, being associated to the following features: patent *ductus arteriosus*, bicuspid aortic valve, *liveo reticularis*, and *iris flocculi* (Hiratzka et al., 2010).

The *TAAD2* locus defective gene is *TGFBR2*, being identified in 4% of familial thoracic aneurysms and dissections, showing the following features: arterial tortuosity, aneurysms, and thin, translucent skin (Pannu et al., 2005; Hiratzka et al., 2010).

The mutant gene at 16p is *MYH11* (smooth muscle cell-specific myosin heavy chain 11) gene, identified in 1% of familial thoracic aortic aneurysms and dissections, and associated to patent *ductus arteriosus* (Zhu et al., 2006). The mutant myosin molecules due to *MYH11* mutations inhibit the filament formation preventing the smooth muscle cells contraction mechanism (Zhu et al., 2006). As *Caenorhabditis elegans* studies have demonstrated that a proper folding and assembly of thick filaments require a distinct ratio  $\beta$ -myosin/UNC45 (its cellular chaperone), researchers have hypothesized that this imbalance might lead to the  $\beta$ -myosin degradation and contraction dysfunction due to *MYH11* overexpression (Kuang et al., 2011).

The 16p13.1 duplications are overlapping in thoracic aortic disease, schizophrenia, and attention-deficit hyperactivity disorder (Kuang et al., 2011). In familial thoracic aortic aneurysms and dissections, both inherited and *de novo* duplications of 16p13.1 were identified (Kuang et al., 2011), supporting the hypothesis of its influence in changing the age of onset and of dissection risk. In cases where familial single gene mutations have been identified (Kuang et al., 2011), other risk factors are required for the clinical phenotype expression (Girirajan et al., 2010).

### 8.1.3. Novel validated genes in aortic aneurysm

In the development of abdominal aortic aneurysms a panel of genes has been recently identified, as following: *FOSB*, *LYZ*, *MFGE8*, *ADCY7*, *SMTN*, *NTRK3*, *GATM*, *CSRP2*, *HSPB2*, *PTPRC*, *CD4*, *RAMP1*, and *NCF4* (Hinterseher et al., 2013).

*FOSB* belongs to FOS family and it is highly increased (both its mRNA and immunohistochemical staining of FOSB protein) in human abdominal aortic aneurysm (Hinterseher et al., 2012). Transcription factors associated to FOS are known to be involved in apoptosis, cell proliferation and differentiation (Ameyar et al., 2003). Vascular smooth muscle cells apoptosis may be related to transcription factors associated to FOS family proteins, such as AP1 (Hinterseher et al., 2013).

*LYZ* is encoding human lysozyme produced by macrophages, as a function of innate immunity. The enzyme acts on the bacterial wall, as the enzyme breaks down peptidoglycans (Levy et al., 1999). In the pathogenesis of abdominal aortic aneurysm, pathogens have been considered as initiators, so an increased *LYZ* mRNA and immunohistochemical staining of *LYZ* protein would be expected (Hinterseher et al., 2012). Two hypotheses have been launched to explain this finding, either the accumulation of microorganisms into the thrombus associated to the expanded aortic segment triggering a focal aortitis (Marques da Silva et al., 2003), or either phagocytic cells recruitment triggered by vascular smooth cells apoptosis, as an autoimmune reaction (Hinterseher et al., 2013).

*MFGE8* represents the milk fat globule epidermal growth factor 8 which encodes lactadherin produced by macrophages (Hinterseher et al., 2013). This protein recognizes surface proteins of apoptotic cells, binds them to integrins, as a marker for their removal (Dasgupta et al., 2006). *MFGE8* protein function is important, as the failure of apoptotic cells removal triggers inflammatory and autoimmune mechanisms (Hanayama et al., 2004). Both the gene expression and *MFGE8* protein immunostaining are down regulated in abdominal aortic aneurysms, suggesting a failure of lactadherin function and a consecutive lack of appropriate marking of cells which need to be removed (Hinterseher et al., 2013).

*ADCY7* is a gene encoding an enzyme which catalyzes the conversion of ATP to cAMP (Beeler et al., 2004) and the corresponding cell adhesion protein is represented in human platelets (Hellevuo et al., 1995). *ADCY* protein is involved in calcium and chemokine signaling pathways (Beeler et al., 2004). This membrane-bound adenylate cyclase activates vascular smooth muscle contraction (Akata, 2007) and it is significantly up regulated in human abdominal aortic aneurysms (Hinterseher et al., 2013).

*SMTN* is involved in the smooth muscle cells development, differentiation, structural maintenance, and contraction mechanism (Krämer et al., 2001). Mouse experiments have demonstrated the risk of cardiac hypertrophy and hypertension development (Rensen et al., 2008). *SMTN* is down regulated in abdominal aortic aneurysms and in intracranial aneurysms (Shi et al., 2009; Hinterseher et al., 2013).

*NTRK3* represents a tyrosine kinase receptor involved in cellular development and differentiation (Hinterseher et al., 2013). Multiple cardiac malformations associated to a reduced

amount of stem cells have been described in *Ntrk-3* deficient mouse (Youn et al., 2003) and in human abdominal aortic aneurysm, suggesting its involvement in the differentiation process of vascular smooth muscle cells (Hinterseher et al., 2013).

*GATM* is a gene involved in embryonic development, tissue regeneration, and metabolic activities, such as serine, threonine, proline, and arginine pathways (Hinterseher et al., 2013). *GATM* belongs to the amidinotransferase family, as a mitochondrial enzyme which is involved in creatine precursor (guanidinoacetic acid) synthesis (Humm et al., 1997). In heart failure, even post-therapy, a high *GATM* level has been demonstrated (Cullen et al., 2006). Similarly, in abdominal aortic aneurysms, a high expression of both the gene and its correspondent protein has been demonstrated, supporting its contribution to the high serum creatinine values (Nakamura et al., 2009).

*CSRP2* is a gene involved in myoblast differentiation and development (Hinterseher et al., 2013). Both the gene and its corresponding protein are down regulated in injuries of the arterial walls, both in mouse and in human abdominal aortic aneurysms (Hinterseher et al., 2013).

*HSPB2* is a gene encoding a stress protein of skeletal muscle cells with poorly delimited biological functions in humans although a cardio-protective role has been demonstrated in *ex vivo* experiments (Benjamin et al., 2007). *HSPB2* is down regulated in human aortic aneurysms (Hinterseher et al., 2013).

*PTPRC* (*CD45*) codifies a membrane protein with multiple functions, including the regulation of cell cycle, focal adhesion (extracellular domains similar to those of cell adhesion molecules) (Bouyain, Watkins, 2010), and sequestered calcium releasing into the cytosol (Barell et al., 2009). *PTPRC* is up regulated in human aortic aneurysms (Hinterseher et al., 2013), with a concurrently low level in patients' peripheral blood (Giusti et al., 2009). In a genome-wide association study, the *PTPRG* subtype revealed interaction with contactin 3 (Bouyain, Watkins, 2010) harboring polymorphism associated to abdominal aortic aneurysms. As the *PTPRC* protein is strongly positive in inflammatory infiltrate of the abdominal aortic aneurysms but has been also observed in control aortas, it is considered as an unspecific marker of the aortic wall inflammation (Treska et al., 2002; Hinterseher et al., 2013).

*CD4* is a gene which encodes a membrane protein involved in calcium signaling, cell adhesion, and immune reactions (Hinterseher et al., 2013). Several studies have demonstrated its up regulation in abdominal aortic aneurysms (Abdul-Hussien et al., 2010; Hinterseher et al., 2013), with a suggested involvement in an autoimmune mechanism.

*RAMP1* belongs to the calcitonin receptor modifying proteins family and the corresponding protein encoded is involved in blood pressure regulation, by inducing vascular relaxation (Hinterseher et al., 2013). *RAMP1* is down regulated in abdominal aortic aneurysms (Hinterseher et al., 2013).

*NCF4* gene encodes a protein belonging to a multi-enzyme complex, as a cytosolic regulatory component of the superoxide-producing phagocyte NADPH-oxidase (NOX complex) (Hinterseher et al., 2013). *NCF4* is up regulated in human abdominal aortic aneurysms (Hinterseher et al., 2013). As a gene variant has been identified in men diagnosed with



rheumatoid arthritis (Olsson et al., 2007), its involvement in an autoimmune mechanism might influence the abdominal aortic aneurysm development (Hinterseher et al., 2013).

#### 8.1.4. Aortic aneurysm and cardiovascular diseases

Different cardiovascular conditions are associated to an increased risk of aortic aneurysm, such as bicuspid aortic valve, aberrant right subclavian artery, coarctation of the aorta, and right aortic arch (Hiratzka et al., 2010).

Recently, the association of aortic aneurysm to several repaired and non-repaired congenital heart diseases has led to the term “aortopathy” (Zanjani, Niwa, 2012).

**Bicuspid aortic valve** is a congenital anomaly identified in 0.5-1.4% of population (Pisano et al., 2011).

According to the morphology, several types of bicuspid aortic valve have been identified, as follows: fusion of the right and left coronary cusps (approximately 70% of cases), fusion of the right and non-coronary cusps, and rare cases of fusion of the left and non-coronary cusps (Roberts, Ko, 2005). The valves are prone to regurgitation in young people or stenosis in older people, with concurrent ascending aortic aneurysm in 10- 35% of cases (Svensson, 2008), as a latent manifestation of the malformation (Hinton, 2012).

The patients diagnosed with bicuspid aortic valve have degenerative developmental changes, with elastolysis, smooth muscle cells anomalies in the media of the aorta and the pulmonary artery (De Sa et al., 1999). The matrix metalloproteinases (MMPs) activation followed by extracellular matrix abnormal remodeling might be initiated by deficiency of elastin, fibrillin, emilin, known as fibers proteins (Fedak et al., 2003; Fondard et al., 2005). Supplementary, asymmetric blood flow demonstrated by computational fluid dynamics is contributing to the aortic aneurysm formation (Hope et al., 2010; Viscardi et al., 2010).

As bicuspid aortic valve and aneurysm share the pathogenesis and show overlapping genetic causes, the supposition of a single disease has been proposed (Hinton et al., 2012). In order to examine the mechanism of the disease, specific mouse models have been used, as following: *ACTA2*-deficient mouse is a model of aorta malformation and *eNOS*-deficient mouse (Lee et al., 2000) is a model of bicuspid aortic valve. Further studies are needed to develop the hypothesis of an associated diseases model (Hinton et al., 2012). Family-based research has identified 10q23-24 locus as the genomic site of *ACTA2*, as already mentioned, and *NOTCH1* on 9q34 (Garg et al., 2005; Martin et al., 2007), with complex inheritance underlying bicuspid aortic valve and thoracic aortic aneurysm (Sans-Coma et al., 2012). Genetic heterogeneity, variable expressivity, combined to epigenetics result in different clinical risks (Hinton et al., 2012). The identification of the variable genetic and clinical patterns might facilitate prognosis evaluation and management of complex aortopathies.

**Aberrant right subclavian artery** may arise as the fourth branch of aorta causing dysphagia due to its course behind the esophagus and its enlargement forming the Kommerell diverticulum (Freed, Low, 1997). This congenital abnormality is associated to aortic aneurysms, dissection, and rupture.

**Coarctation of the aorta** may be associated to aortic aneurysms if untreated or after repair surgery (Ou et al., 2006).

**Right aortic arch** is identified in 0.5% of population and may be associated with two types of symptoms. An enlarged aorta or the vascular ring formed by the atretic *ductus arteriosus* result in esophagus or trachea compression in Type I anomaly or the aberrant left subclavian artery running posterior to the trachea and compressing it in Type II right aortic arch (Felson, Palayew, 1963).

### **Aortopathy**

Aortic aneurysm is one of the late complications in repaired or non-repaired congenital heart diseases (Zanjani, Niwa, 2012), such as bicuspid aortic valve (Gurvitz et al., 2004), coarctation of the aorta (Istner et al., 1987), tetralogy of Fallot (Ramayya et al., 2011), *truncus arteriosus* (Carlo et al., 2011), double-outlet right ventricle (Taussig-Bing anomaly)- ventricular septal defect- pulmonary stenosis (Losay et al., 2006), hypoplastic left heart syndrome (Cohen et al., 2003), ventricular septal defect (Eisenmenger syndrome), and single ventricle- pulmonary stenosis (Niwa et al., 2001).

Genetic anomalies are associated to intrinsic aortic wall defects, aortic overflow resulting in aortic wall dilatation (Chowdhury et al., 2008).

The histopathological appearance is similar but milder than that observed in Marfan syndrome (Niwa et al., 2001). As the aortic dilatation is correlated to aortic regurgitation, and aortic and ventricular disfunctions, the result is a complex pathophysiological abnormality creating the new concept of “aortopathy” (Zanjani, Niwa, 2012).

## **8.2. Atherosclerosis role in the aortic aneurysm pathogenesis**

The degenerative atherosclerotic disease results in hypoxia, as the diffusion of blood from the lumen is prevented by the plaques. The consequence is the onset of aortic wall structural anomalies which may lead to arterial dilatation, in a traditional view (Heuser, Lopez, 1998).

Higher coronary disease prevalence has been found in abdominal aortic aneurysm when compared to their thoracic counterpart (Agmon et al., 2003). Supplementary, a higher incidence of atherosclerosis in type B dissections compared to type A dissection has been identified, in autopsy studies (Nakashima et al., 1990). There is a statistical difference demonstrated in C-reactive protein (CRP)/Interleukin-6 (IL-6) ratio in cases of descending aortic aneurysms when compared to ascending aortic aneurysms (Artemiou et al., 2012). Moreover, CRP/IL-6 ratio shows a positive correlation to the size of aneurysms (in both ascending and descending aorta), with the cut-off value of 0.8 (Artemiou et al., 2012).

Although a variable degree of inflammation is seen in all atherosclerotic aneurysms (Rijbroek et al., 1994), rare cases of inflammatory abdominal aortic aneurysm have been diagnosed mainly in elderly patients with only few cases being diagnosed in young patients (Sharif et al., 2008). The characteristics of inflammatory abdominal aortic aneurysm are the following: thick aortic wall containing a variable mononuclear infiltrate, periaortitis, with possible association of perianeurysmal fibrosis or involvement of ureters and duodenum (Sharif et al., 2008). It is

currently considered that inflammatory abdominal aortic aneurysm, associated with variable perianeurysmal fibrosis, and idiopathic retroperitoneal fibrosis are all components of the chronic periaortitis spectrum (Jois et al., 2004). In 19% of patients this process is part of a systemic autoimmune disorder but sometimes the autoimmune diseases cannot be identified (Sharif et al., 2008). A possible reaction to the antigens released from the atherosclerotic plaques has been also considered (Sharif et al., 2008).

The disturbed fibrinolytic balance in extracellular matrix remodelling has been demonstrated in atherosclerotic human aortic aneurysm (Hayashi et al., 2008). Two plasminogen activators, tissue-type and urokinase-type (both corresponding genes being enhanced in atherosclerotic human aortic aneurysms), transform plasminogen into plasmin. Consequently, plasmin, as a trypsin-like proteolytic enzyme, degrades the extracellular matrix and activates MMPs (Hayashi et al., 2008). Annexin II, a receptor for fibrinolytic proteins, binds plasminogen and tissue-type plasminogen activators, amplifying the catalytic effect of plasminogen activation. Recently, annexin II has been identified in pathophysiological intervention of macrophages in inflammatory process associated to human atherosclerotic aneurysms, suggesting a correlation between its expression and disease progression (Hayashi et al., 2008).

### 8.3. Inflammatory and autoimmune conditions in the aortic aneurysm pathogenesis

#### 8.4. Infective thoracic aortic aneurysm (infected aneurysm or infectious aortitis)

Inflammatory diseases associated to aortic aneurysms are Takayasu arteritis, giant cell arteritis, Behçet disease, ankylosing spondylitis (Hiratzka et al., 2010), and rheumatoid arthritis (Tazelaar, 2004).

**Takayasu arteritis** involves elastic arteries (aorta and its branches) being more prevalent in women, in the third decade of life, exhibiting a moderate Asian overexpression (Kerr et al., 1994). The distribution of the aortic segments involved by Takayasu arteritis in Japanese population is: the descending aorta, followed by the abdominal, and then ascending aorta (Matsumura et al., 1991). The abdominal aorta and renal arteries are more commonly affected in Indian population (Kerr et al., 1994).

The American College of Rheumatology criteria may be used to diagnose Takayasu arteritis if three of the following criteria are found: age younger than 40 years, diminished brachial artery pulse, intermittent claudication, subclavian artery or aortic bruit, variation of blood pressure higher than 10 mm Hg between arms, and stenosis identified by angiography (Kerr et al., 1994). Supplementary, increased CRP and erythrocyte sedimentation rate are useful for diagnosis, mainly in acute phase (Kerr et al., 1994).

Several types have been described according to the extension of the disease (Tazelaar, 2004):

- Type I involves the aortic arch, the proximal brachiocephalic, and the common carotid, with IA subtype, involving the ascending aorta and associated with aortic valve regurgitation.
- Type II involves the descending thoracic and abdominal aorta.
- Type III involves the entire aorta.

- Type IV involves the pulmonary arteries, with the possible association of aorta and systemic vessels.

The histopathological findings in active arteritis have been described as: a thick wall (mean 0.7 cm, range 0.4-0.9 cm) mainly due to inflammation involving the media and adventitia, containing lymphocytes, macrophages, plasma cells, eosinophils, and neutrophils. Rare granulomas may be identified (14% of cases), showing central necrosis. Other findings are: laminar necrosis (40-50 %) and rare cystic degeneration (Tazelaar, 2004).

Obstruction of large arteries by a mural thrombus followed by its organization and association to medial and circumferential adventitial fibrosis, and intimal hyperplasia may occur in evolution (Tazelaar, 2004). Healing process may be associated with aneurysm formation (type IA) (Tazelaar, 2004).

The pathogenesis of Takayasu arteritis is attributed to a clonal T-cell-mediated panarteritis, initiated in adventitial *vasa vasorum* (Hiratzka et al., 2010). The destruction process leads to aneurysm, while fibrosis causes stenosis (Hiratzka et al., 2010).

**Giant cell arteritis** or temporal arteritis is a vasculitis of elastic vessels and its secondary and tertiary branches (Hiratzka et al., 2010), more prevalent in Scandinavian population, suggesting a genetic component (Nordborg et al., 1994).

The diagnosis is accomplished in case of positivity of three or more of the following criteria: localized headache, age more than 50 years, attenuation of the temporal artery pulse, increased erythrocyte sedimentation rate (greater than 50 mm/h), and positive biopsy (Achkar et al., 1994). The biopsy may be performed even during therapy, as it remains positive within 7 days of steroid therapy initiation (Achkar et al., 1994).

Isolated aortitis histopathological findings may be seen in systemic giant cells arteritis. Caucasians, over 50 years old, with women: men ratio of 4:1 may be diagnosed with systemic giant cells arteritis, being associated in 10-15% of patients with temporal arteritis and polymyalgia rheumatica (Tazelaar, 2004).

Giant cell arteritis and Takayasu arteritis share an inflammatory response with T-cell clonal expansion initiated in adventitia and amplified by cytokines and MMPs, resulting in granuloma formation and followed by vessel destruction (Salvarani et al., 1995). The granulomatous reaction protects the affected vessel from the inciting antigen but results in wall destruction (Hiratzka et al., 2010).

**Behçet disease** is another inflammatory vasculitis which may also result in thoracic aortic aneurysm (Hiratzka et al., 2010). The eponymous syndrome is most common in Turkey and diagnostic criteria comprise aphtous stomatitis, associated to another two of these three lesions: uveitis or retinal vasculitis, recurrent genital ulcers, or skin manifestations, such as pseudofolliculitis, pathergy, or erythema nodosum (Criteria for diagnosis of Behçet's disease, 1990; Sarica-Kucukoglu et al., 2006).

Variable arteries and veins involvement may occur in approximately one third of patients (Hiratzka et al., 2010), such as thrombosis and varices (Sarica-Kucukoglu et al., 2006).



Aortic inflammation of media and surrounding *vasa vasorum* is composed of lymphocytes, macrophages, eosinophils, and giant cells. The inflammation leads to multiple aneurysms, stenotic lesions, and brachiocephalic arteries occlusion (Tunaci et al., 1995).

### Ankylosing spondylitis

There is strong association of major histocompatibility complex *HLA B-27* and the lack of rheumatoid factor in spondyloarthropathies, including Ankylosing spondylitis (Khan, Ball, 2002).

The diagnosis is set by finding four of the following five criteria: subtle onset, with morning stiffness, back pain prolonged more than three months, showing improvement with exercise, and diagnosis in young age (Roldan et al., 1998). Variable constitutional symptoms, acute anterior uveitis, aortic root involvement, nodular aortic valve, and aortic valvular regurgitation may also be associated (Roldan et al., 1998).

### Rheumatoid arthritis

Rarely, a variable extension of inflammation of media and adventitia, composed of mononuclear cells, macrophages, and neutrophils, associated to granulomas (up to 50% of cases), laminar necrosis, and increased aortic wall thickness may occur in rheumatoid arthritis (Tazelaar, 2004).

**Infective thoracic aortic aneurysm (infected aneurysm or infectious aortitis)** may be caused by fungal, bacterial, spirochetal, viral, or mycobacterium microorganisms (Hiratzka et al., 2010).

It was firstly described by Osler, as *mycotic endarteritis* (Osler, 1885). The disease may involve the ascending thoracic aorta, aortic arch, and descending aorta, usually in opposite sites to the great vessels in the aortic arch or to the abdominal visceral arteries, in the common shape of saccular or rare fusiform types, or pseudoaneurysms (Hiratzka et al., 2010).

The pathogenic mechanism involves contiguous spread from adjacent infected lymph nodes, pericarditis, mediastinitis, empyema, or abscesses, by septic emboli from a endocarditis, or by hematogenous spread in intravenous drug abuse or sepsis (Hiratzka et al., 2010).

Preexisting atherosclerotic plaque, trauma, or aneurysm may facilitate the onset of the infectious process (Hiratzka et al., 2010).

The organisms responsible for the aortitis are variable, such as bacteria of *Staphylococcus aureus*, *Salmonella*, *Pneumococcus*, and *Escherichia coli* species (Hiratzka et al., 2010), or fungi (in immunodeficient hosts) either *Candida* or *Aspergillus* (Byard et al., 1987).

*Treponema* species mainly affect ascending thoracic aorta, with the syphilitic aortitis onset 10-25 years after the initial infection (Hiratzka et al., 2010).

An increased thickness of the aortic wall associated to narrower or occluded lumina may occur in syphilitic aortitis, which mostly involves the aortic arch and descending thoracic aorta.

Histopathological findings consist of: variable elastic fibers degeneration, compensatory fibrosis, *vasa vasorum* with increased thickness, partial or complete lumen obliteration, and

perivascular chronic inflammatory infiltrate (Tazelaar, 2004). Atherosclerosis is sometimes superimposed. Occasionally, gummas and diffuse secondary intimal fibrosis with linear folds creating the “tree bark” appearance may be identified (Tazelaar, 2004).

Tuberculous aortitis may spread by direct extension from lymph nodes, pericarditis or empyema, affecting the distal aortic arch and descending thoracic aorta (Allins et al., 1999).

Human immunodeficiency virus has been also associated to ascending thoracic aorta dilations (Brawley, Clagett, 2005).

### **8.5. Matrix Metalloproteinases (MMPs) involvement in aortic aneurysm pathogenesis**

Aortic aneurysms risk factors are currently correlated to initiation associated to elastin and collagen proteolytic degradation, altered expression of contractile proteins in smooth muscle cells, destruction of the extracellular matrix, and inflammation or progression and rupture, related to added angiogenesis.

The action of proteolytic enzymes, notably matrix metalloproteases and serine proteases, has been associated with the destruction of the extracellular matrix (Amalinei et al., 2007). Typically, protease activity is regulated by endogenous inhibitors (e.g.  $\alpha$ 2-macroglobulins,  $\alpha$ 1-antitrypsin and tissue inhibitors of metalloproteinases) (Amalinei et al., 2010), and unbalanced proteolysis within the aortic media suggests that over-expression of proteinases, or deficiency in protease inhibitors may be involved in aortic aneurysm pathophysiology.

MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, and MMP-12 have been associated to the aortic aneurysm pathogeny.

Gelatinase-A (MMP-2) and gelatinase-B (MMP-9) show a strong expression in media of aortic aneurysms, on the surface of disrupted elastic fibers (Ikonomidis et al., 2007; Lemaire et al., 2007).

MMP-2 results from an overexpression by the resident (mesenchymal) cells of the aortic wall, while MMP-9 is attributed to a strong expression of macrophages (Thompson et al., 1995), similar findings being also found in mouse models (Longo et al., 2002).

Gene expression analyses in animal models have demonstrated the up regulation of mRNA encoding MMP-1, MMP-3, and MMP-9, together with an enhanced cysteine protease cathepsin-D, -H, -K, and -S level, corresponding to an increased extracellular matrix degradation (Trollope et al., 2011).

Immunohistochemistry demonstrated the expression of MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, and MMP-12 in macrophage-rich areas of abdominal aortic aneurysms (Curci et al., 1998).

Recent proteomics studies on tissue lysates have revealed increased levels of MMP-12 (macrophage metalloelastase) in abdominal aortic aneurysms. The MMP-12 overexpression was associated to enhanced levels of type XII collagen (correlated to exposure to high tensile forces), aortic carboxypeptidase-like protein (ACLP) (associated to collagen fibers and considered a possible regulator of fibrosis), fibronectin (accumulated in injured tissues),

tenascin (correlated to the macrophage functions), thrombospondin 2 and periostin (related to cellular adhesion) (Didangelos et al., 2011). Furthermore, concomitant poor expression of glycoproteins which mediate the link between hyaluronic acid and proteoglycans, namely perlecan, aggrecan, and versican has been demonstrated (Didangelos et al., 2011).

### **8.6. ADAMs (a disintegrin and metalloproteases) involvement in aortic aneurysm pathogenesis**

ADAMs are produced by smooth muscle cells in a healthy aorta (Lipp et al., 2012). Supplementary, ADAMs 10, 12, 15, and 17 expression are significantly correlated to the amount of smooth muscle tissue in the aortic wall (Lipp et al., 2012), without any influence on the expression of macrophages or other inflammatory cells or of the neovascularisation extent. Their complex biological roles have been demonstrated, including: proteolysis, cell adhesion, zymogen activation, cell migration, cell-matrix relation, angiogenesis (Oksala et al., 2009), and a possible role in the pathogenesis of atherosclerosis.

The experiments analysing the role of ADAM family of metalloproteases in aneurysm pathogenesis showed ADAMs 8, 9, 10, 12, 15, and 17 expressions in inflammatory cells and in neovessels of abdominal aortic aneurysm (Lipp et al., 2012).

As tissue inhibitors of metalloproteases, TIMP-1 and TIMP-3 counteract ADAMs activity, an increased TIMP-3 expression being found in abdominal aortic aneurysms (Lipp et al., 2012).

### **8.7. Angiogenesis in aortic aneurysm pathogenesis**

An important pathway in the aortic aneurysm pathogenesis is attributed to angiogenesis.

Angiogenesis is regulated by ephrin-B1 and its cognate receptor, EphB2, members of a 21 gene family involved in morphogenesis by regulating cell adhesion and migration (Palmer, Klein, 2003; Sakamoto et al., 2008; Pasquale, 2010). In contrast to cytokines and chemokines that are soluble molecules, ephrins and Ephs are membrane-bound molecules that act locally by cell-to-cell interactions (Kepler, Chan, 2007; Janes et al., 2008). Thus, ephrins and Ephs modulate various types of cell interactions, conditioned by cytokines and chemokines, as macrophages-to-macrophages, macrophages-to-T-lymphocytes, and macrophages-to-endothelial cells (Sakamoto et al., 2012).

Human abdominal aortic aneurysm expresses high levels of ephrin-B1 and EphB2 in macrophages, T lymphocytes, and endothelial cells (Sakamoto et al., 2012).

Supplementary, ephrin-5 is up regulated in human abdominal aortic aneurysm (Armstrong et al., 2002).

### **8.8. Mast cells key role in aortic aneurysm pathogenesis**

Mast cells, as cellular components of the media and adventitia are also important players in aortic aneurysm pathogenesis *via* several mechanisms, such as: activation of metalloproteinases and of the Renin-Angiotensin system, contribution to smooth muscle cells apoptosis,

and release of proteolytic enzymes. Thus, drugs targeting the pathways of mast cell-derived mediators may be of value in future treatment of aortic aneurysm.

Two types of mast cells may be identified in human aorta (Kaartinen et al., 1994; Lindstedt et al., 2007): T type containing tryptase and TC type supplementary expressing chymase, carboxypeptidase A, and cathepsin G within cytoplasmic granules. The granules may also contain variable quantities of the following substances: tumor necrosis factor alpha (TNF- $\alpha$ ), transforming growth factor beta (TGF- $\beta$ ), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and chemokines (Swedenborg et al., 2012). Following mast cells activation, a prolonged synthesis and secretion of cytokines, chemokines, and eicosanoids takes place (Swedenborg et al., 2011).

As in normal human aorta, mast cells are located within intima and adventitia; their identification within media of abdominal aortic aneurysm in a higher amount in comparison to their expression in atherosclerosis demonstrates their involvement in the extracellular matrix degradation, smooth muscle cells apoptosis, renin-angiotensin system activity, and in neo-vascularization (Swedenborg et al., 2011). Moreover, their overall count increases along the aneurysm expansion, being associated to T cells and macrophages (Swedenborg et al., 2011).

Various types of cells are involved in producing chemotactic factors for mast cells, such as stem cell factor (SCF). Both the homing of the progenitor cells and their terminal differentiation are performed by SCF (Swedenborg et al., 2011).

Experimental studies on rats and mice which lack SCF or its receptor (c-kit) expression are used as mast cell deficient models (Swedenborg et al., 2011). In mast cell deficient rodents, elastase or CaCl<sub>2</sub> infusion cannot produce abdominal aortic aneurysm. Wild-type mast cells derived may restore the capacity of aneurysm formation. Alternatively, similar results have been obtained in experimental models in which mast cells degranulation has been pharmacologically prevented (Swedenborg et al., 2011).

Adrenomedullin, a 52-amino acid peptide firstly isolated from human pheochromocytoma, inhibits myofibroblastic differentiation and collagen synthesis and stimulates MMP-2 activity. In abdominal aortic aneurysms, an increased amount of adrenomedullin has been found in mast cells situated in the outer media and adventitia, showing a stronger expression in comparison to atherosclerotic aortas without aneurysmal changes (Tsuruda et al., 2006). This finding suggests anti-fibrotic function of adrenomedullin released from mast cells demonstrating its complex role in extracellular matrix modulation in the development of abdominal aortic aneurysms (Tsuruda et al., 2006).

## 8.9. Cytokines involvement in aortic aneurysms pathogenesis

Using comparative quantitative proteins profile within aortic aneurysm biopsies and aortic samples from cadaveric controls, significant differences in the expression of numerous proteins, including proinflammatory cytokines (IL-1 $\alpha$ , IL-1 $\beta$ , TNF- $\alpha$  and TNF- $\beta$ , oncostatin M, and IL-6), chemokines (ENA-78, GRO, IL-8, monocyte chemoattractant proteins [MCP-1, MCP-2], and regulated upon activation normal T cell expressed and secreted [RANTES]), anti-inflammatory cytokines (IL-10 and IL-13), and growth factors (VEGF, Angiogenin, GCSF



[granulocyte colony stimulating factor], EGF [epidermal growth factor], SCF, leptin, IL-3, IL-7, and thrombopoietin) were reported (Quillard et al., 2011).

IL-6 has synergic effect as IL-1 in regulating the hepatic synthesis of CRP (Artemiou et al., 2012). There are both experimental and clinical evidences supporting the CRP involvement in stenotic atherogenesis and the significance of its increased level as a marker of cardiovascular diseases (Venugopal et al., 2005). IL-6 is involved in acute and chronic inflammation associated to aneurysm formation (Smallwood et al., 2008). Both thoracic and abdominal aortic aneurysms are positively correlated to IL-6 high circulating levels (Artemiou et al., 2012).

#### **8.10. COX-2 involvement in aortic aneurysms pathogenesis**

COX-2 (cyclooxygenase-2) is expressed in smooth muscle cells of the media, in mouse models of abdominal aortic aneurysm (Ghoshal, Loftin, 2012).

Chronic infusion of Angiotensin II induces abdominal aortic aneurysm but the process can be significantly reduced by pre-treatment with a COX-2 inhibitor or by targeted genetic inactivation of COX-2 (Gitlin et al., 2007). COX-2 inactivation is associated to significant decrease of macrophage-dependent inflammation (Gitlin et al., 2007).

A reduced progression of abdominal aortic aneurysm has been also obtained by inactivation of microsomal prostaglandin E synthase-1 (mPGES-1) (Wang et al., 2007), acting on COX-2-dependent mechanism and being correlated to a reduced activity of MMP-2 (Wang et al., 2007).

The experimental findings that COX-2 inhibition results in significantly reduced MMP-2 expression supports the hypothesis that COX-2 is involved in smooth muscle cell dedifferentiation during the abdominal aortic aneurysm progression (Ghoshal, Loftin, 2012).

During abdominal aortic aneurysm progression, smooth muscle cells produce hyaluronic acid and show a variable expression of  $\alpha$ -actin, as characteristics of de-differentiation (Jain et al., 1996). Mouse experiments demonstrated that COX-2 inhibition results in  $\alpha$ -actin mRNA expression and a hyaluronic acid synthase reduced expression (Ghoshal, Loftin, 2012). These findings suggest the COX-2 pathway involvement in smooth muscle cells de-differentiation is associated to abdominal aortic aneurysm development (Ghoshal, Loftin, 2012).

#### **8.11. Macrophage role in aortic aneurysm pathogenesis**

Experimental subcutaneous infusion of Angiotensin II into mice induces histopathological changes that result in proteolytic generation of elastin and collagen degradation products which can attract circulating inflammatory cells, such as macrophages and mononuclear lymphocytes (Daugherty et al., 2011). The cellular changes involve the early macrophage infiltration into media and adventitia, demonstrated by CD68 immunostaining in the suprarenal aortic region (Daugherty et al., 2011).

Once activated, inflammatory infiltrates produce (amongst others) leukotriens, proinflammatory cytokines, chemokines, prostaglandin derivatives, immunoglobulins, cysteine and serine proteases, thereby perpetuating the wall degradation and vascular smooth cell apoptosis (Daugherty et al., 2011). This infiltration of proinflammatory cells and the observation that IgG

purified from aneurysm tissue is reactive to aortic extracellular matrix proteins suggest that its development may have an autoimmune component (Daugherty et al., 2011).

Macrophages along with smooth muscle cells produce elastolytic cathepsin L that results in elastic lamina fragmentation, muscle cell migration into neointima, and wall expansion (Liu et al., 2006). Cathepsin S produced by smooth muscle cells is amplifying the cathepsin L effect (Liu et al., 2006). Moreover, cathepsin L may process caspases and induce apoptosis in human abdominal aortic aneurysms and atherosclerosis. Both cathepsin L and VEGF-A (Kaneko et al., 2011), as macrophages products, are involved in neovascularization. The high expression of cathepsin L in atherosclerosis and abdominal aortic aneurysm, or its higher serum levels suggest a strong involvement in their pathogenesis (Liu et al., 2006).

There are several surface targets used for macrophage imaging, such as scavenger receptors (Tawakol et al., 2008), vascular cell adhesion protein-1 (VCAM-1) (Nahrendorf et al., 2006), inter-cellular adhesion molecule-1 (ICAM-1) (Choi et al., 2007),  $\alpha_v\beta_3$  integrin (Chen et al., 2010), and chemokine (C-C motif) receptor 2 (CCR-2) (Hartung et al., 2007). Supplementary, phagocytosis may be useful for cell detection by internalization of probes (Quillard et al., 2011), such as nanoparticles (Christen et al., 2009). The possibility of developing therapies based on drugs marked with imaging moieties opens up the perspectives of “theranostic” approaches (Quillard et al., 2011). An illustrative example is the use of agents targeting macrophages scavenger receptor 1A which may detect MMP-9 activity (Suzuki et al., 2008). Reactive oxygen species and proteases, including MMPs and cysteinyl cathepsins (Lutgens et al., 2007), could also be used in macrophages detection (Quillard et al., 2011).

### **8.12. Utility of animal models in the study of aortic aneurysms pathogenesis**

The study of the pathogenic mechanism operative in aortic aneurysm may be performed on experimental models, using normal transgenic animals or choosing one of the following methods: intra-aortic elastase infusion, topical aortic treatment with  $\text{CaCl}_2$ , or angiotension infusion (Swedenborg et al., 2011).

The advantage of animal research is that the study of the progressive stages of aneurysm is possible but the limits of this type of studies is that the results cannot be directly applied in interpreting human aortic aneurysm and interspecies biological and physiological variations must be considered (Trollope et al., 2010; Swedenborg et al., 2011).

The experiments on large animal models are helpful in development of new surgical techniques, being performed by turbulent flow method, vein patch, or xenografts (Trollope et al., 2010).

Another possibility of research is to study the plasma concentration of various markers or of the surgical specimens with the limitation that they represent just the end stage of the disease, as the intervention is recommended when the diameter is significantly increased (Daugherty et al., 2011; Swedenborg et al., 2011).

In experimental models, the initial disintegration of elastic fibers has been identified (Daugherty et al., 2011). The following stage is the medial rupture occurring several days after the

progressive lumen expansion and followed by thrombi and adventitial dissection (Barisone et al., 2006; Daugherty et al., 2011). After thrombi resolving, abundant infiltration by macrophages, lymphocytes, disarrayed collagen deposition, and neovascularization follow (Saraff et al., 2003; Rateri et al., 2011; Daugherty et al., 2011). Supplementary, atherosclerotic lesions associated to hypercholesterolemia may be detected (Rateri et al., 2011; Daugherty et al., 2011).

The heterogeneity of angiotensin II induced abdominal aortic aneurysm is illustrated by their classification into four types, as following (Daugherty et al., 2011):

- type I- a small single dilation ( $\times 1.5$ -2 times of a normal diameter);
- type II- a large single dilation ( $> 2$  times of a normal diameter);
- type III- multiple dilations;
- type IV- aortic rupture.

The angiotensin II induced abdominal aortic aneurysm model may validate the therapeutic usage of renin angiotensin inhibitors (Daugherty et al., 2011).

Using mouse model with Angiotensin II-induced abdominal aortic aneurysm formation, the involvement of oxidative stress-induced changes in biomechanical and microstructural alterations characteristic for abdominal aortic aneurysm development have been investigated (Maiellaro-Rafferty et al., 2011). Although the aortic pressure-diameter mechanics has been preserved, an increased mean circumferential strain in the outer abdominal aortic wall has been registered (Maiellaro-Rafferty et al., 2011). Moreover, the strong expression of aortic smooth muscle cell-specific catalase might prevent the development of the mechanical alterations resulted from Angiotensin II perfusion (Maiellaro-Rafferty et al., 2011), suggesting reactive oxygen species production association to early remodelling process and mechanical adaptation (Maiellaro-Rafferty et al., 2011). As expected, up regulated reactive oxygen species have been found in abdominal aortic aneurysms (Gavrila et al., 2005) stimulating MMP action via the NADPH oxidase and thus promoting extracellular matrix degradation (Grote et al., 2003).

Numerous cellular abnormalities and ultrastructural alterations in extracellular matrix cross-linking might be added to the mentioned biomechanical events (Maiellaro-Rafferty et al., 2011). Enzymatically-related mechanisms have been identified in the genesis of abdominal aortic aneurysms both in animal models and in humans. These are related to the stimulator role of dysfunctional collagen and elastin cross-linking in aneurysmal progression in mice showing lysyl oxidase-deficiency (Maki et al., 2002). Moreover, cysteine protease inhibitor cystatin C human deficiency has been correlated to abdominal aortic aneurysms (Lindholt, Henneberg, 2001). Several other elements may complicate the aneurysm genesis, such as reduced proteoglycans (Tamarina et al., 1998), collagen microarchitecture anomalies (Lindeman et al., 2010), and inflammation (Freestone et al., 1995).

Additionally, the activation of endothelial NF- $\kappa$ B in transgenic mice results in an increased expression of adhesion molecules initiating macrophage infiltration and inflammation in adventitia and media, demonstrating the endothelium role in remodelling of the vascular wall and in aneurysm development (Saito et al., 2013).

## 9. Conclusion and perspectives

Aortic aneurysm is a multifactorial disease, with both genetic and environmental risk factors contributing in variable degrees to the underlying pathobiology, leading to proteolytic degradation of aortic wall components, stresses within the aortic wall, and variable intervention of inflammation and/or autoimmune response.

Although the aortic aneurysm morphological characteristics have been well-recognized, the mechanisms underpinning these changes are extremely complex and only partially discovered.

Numerous research data provide valuable mechanistic insight into the genetic, environmental, and mechanistic pathogenesis of aortic aneurysm, reveal diagnostic markers, and identifies new therapeutic targets, such as recently described “theranostic” approaches.

The translation of data resulted in animal models to human pathology may lead to the refinement of clinical risk categories and consequently to development of novel management strategies for the prevention and treatment of aortic aneurysms.

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