

# Spontaneous arterial dissection: phenotype and molecular pathogenesis

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**Abstract** Arterial dissection (AD) is defined as the longitudinal splitting up of the arterial wall caused by intramural bleeding. It can occur as a spontaneous event in all large and medium sized arteries. The histological hallmark of AD is medial degeneration. Histological investigations, gene expression profiling and proteome studies of affected arteries reveal disturbances in many different biological processes including inflammation, proteolytic activity, cell proliferation, apoptosis and smooth muscle cell (SMC) contractile function. Medial degeneration can be caused by various rare dominant Mendelian disorders. Genetic linkage analysis lead to the identification of mutations in different disease-causing genes involved in the biosynthesis of the extracellular matrix (FBN1, COL3A1), in transforming growth factor (TGF) beta signaling (FBN1, TGFBR1, TGFBR2) and in the SMC contractile system (ACTA2, MYH11). Genome wide association studies suggest that the CDKN2A/CDKN2B locus plays a role in the etiology AD and other arterial diseases.

**Keywords** Arterial dissection · Aortic disease · Medial degeneration · Transforming growth factor (TGF) beta signaling · Smooth muscle cell (SMC) · Matrix metalloproteinase (MMP) · Genetics

## Introduction

Spontaneous arterial dissection (AD) was considered as a very rare disease before modern imaging enabled its diagnosis in a growing number of patients. Pathognomonic signs of AD are (1) an intimal tear/intimal flap, (2) a mural hematoma or (3) a double arterial lumen. Most dissections are diagnosed in the ascending and descending thoracic aorta or in the cervical arteries with estimated annual incidences of 3–6/100,000 [1–4] followed by the intracranial, renal and coronary arteries. Dissections of the abdominal aorta that are not extensions of thoracic aortic dissections are rare [5] and will not be considered in this review. Some authors assume that a considerable number of ADs occur without major clinical signs and may remain undiagnosed even nowadays [6–8].

AD can entail serious complications like sudden heart death, aortic rupture, visceral ischemia, ischemic stroke, subarachnoid hemorrhage and renal failure. As a consequence AD has been studied over the years in different medical fields such as cardiology, neurology, heart and vascular surgery or pathology. This study tries to overcome the fragmentation of AD research and brings findings from different arteries and different bio-medical fields together. Histopathological and molecular studies—primarily based on thoracic aortic aneurysms and dissections (TAAD)—give insight to basic pathological processes underlying AD. We focus on the role of

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mutations and associated genetic polymorphisms, since genetics enables the identification of causal factors [9, 10]. Genetic research revealed that defects in (1) extracellular matrix (ECM) structure, (2) regulation of transforming growth factor (TGF)-beta signaling and (3) smooth muscle cell (SMC) function and proliferation are involved in the pathogenesis of AD. Our study focuses on the pathogenesis of AD, but we discuss aneurysms at several occasions, since both vascular diseases might depend on a similar underlying pathology.

## The disease phenotype

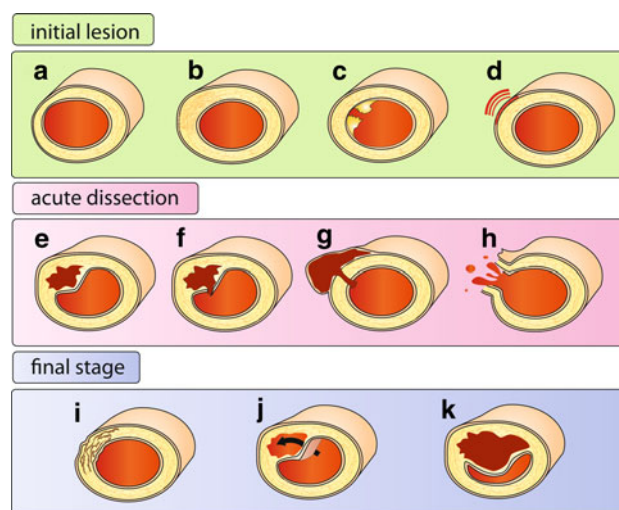
### Different forms and stages

AD is characterized by a hemorrhage within the arterial wall or by a tear in its intimal layer. The intimal tear may connect the true arterial lumen with a false or second lumen within the arterial wall.

AD often develops suddenly without warning signs and in absence of traditional vascular risk factors [11]. In contrast to the spontaneous and acute occurrence of AD, the morphology and histology of affected arteries usually reveal the presence of chronic, asymptomatic pathologic alterations associated with non-specific traits like arterial stiffness, dilation, premature arterial occlusion and medial degeneration. Figure 1 interprets the pathological findings as different morphological types and developmental stages of AD. Initial lesions that predispose for a dissection affect the medial layer of the artery and have been described as mediolytic (dissolution of components of the medial layer, Fig. 1a) or as dysplastic (abnormal proliferation of smooth muscle cells, leading to a thickened arterial wall, Fig. 1b). These medial changes might be promoted by inherited and environmental factors, but can also be caused by injury: either as a consequence of endovascular manipulations or due to atherosclerotic ulceration (Fig. 1c). Medial degeneration might result in local aneurysmatic dilatation of the vessel. Impaired blood supply from the adventitial vasa vasorum and chronic adventitial inflammation are considered as further factors that weaken the medial layer (Fig. 1d).

Triggering factors like an abrupt or extreme movement [12, 13], excessive physical activity [14–17], minor trauma or a hypertensive crisis are thought to induce an acute bleeding within the defective arterial wall (Fig. 1f). The resulting intramural hematoma can also develop without a communication with the arterial lumen (Fig. 1e). After local iatrogenic injury of the vessel wall a pseudoaneurysm may develop (Fig. 1g).

Different forms of AD prevail in distinct locations. Acute dissections of the aorta can develop into chronic



**Fig. 1** Forms and stages of arterial dissection. *Initial lesion* Several types of injury of the arterial wall may predispose to AD. Degenerative alterations may include loss of SMC with fragmentation and depletion of elastic fibers (a) or proliferation of SMCs with irregular and local thickening of medial and intimal layers (b). Mechanical injury due to endovascular operations, atheromatous ulcer (c), as well as peri-adventitial inflammation (d) and small adventitial bleedings [75] are further predisposing factors. Acute AD may present with an intimal tear and intimal flap (f) or as an intramural hematoma without apparent communication with the lumen (e). If AD causes aneurysmal dilatation of the artery (g), it is often referred to as pseudoaneurysm [2], but others use this notion to describe a hematoma with is located outside the arterial wall, due to a leaking hole in the arterial wall, usually due to an endovascular intervention. Arterial rupture (h) is a most serious complication of AD. *Final stage* AD may heal spontaneously (i) or develop into chronic forms with a double (false) lumen (j) or a persistent stenosis (k), occlusion or arterial dilatation

forms with a double lumen (Fig. 1j), a rarity for dissections in other arteries. Intramural hematoma without intimal tear (Fig. 1e) is very common in cervical arteries [18, 19], but not in the aorta [20]. The risk of rupture is elevated in aortic and intracranial AD, but not in the extracranial part of the carotid arteries. The different forms of AD probably correlate with local differences in vessel anatomy, vulnerability and blood flow shear forces.

AD is a dynamic event. The initial and local splitting up of the arterial wall can expand along the artery in downstream as well as in upstream direction. Extracranial dissections of the vertebral arteries can extend into the cranium and develop into intracranial dissections with the risk of subarachnoid or intracerebral hemorrhage. Aortic dissections can expand from the thoracic into the infrarenal segment or into its branches. Dissections may heal spontaneously (Fig. 1i) or develop into a permanent chronic dissection with double lumen with or without chronic expansion (Fig. 1j). Rupture is a serious acute complication of AD (Fig. 1h).

## Common characteristics

*Incidence*

Rigorous population based prospective studies about the epidemiology of AD are rare. Since most of the observations were made in hospital based study samples, asymptomatic and fatal cases might be underrepresented. Moreover, dissections have been usually investigated as causes for particular diseases by medical specialists. Reduced attention to symptoms concerning other organ systems might result in further recruitment bias. Epidemiological studies suggested that AD is rare in all arteries with a yearly incidence in the order of magnitude of 1:100,000 [1, 3, 7, 21, 22]. Most patients are male and develop AD during midlife. It is unclear, whether the age peak is similar for both sexes or whether the occurrence of AD in women is more evenly distributed over all ages. The incidences of aortic dissection and cervical AD show seasonal variation and are highest in winter [23, 24].

Given the low incidence of AD, the frequency of bilateral dissections (of the cervical, renal, coronary or intracranial arteries) is remarkably high (Table 1). Most bilateral dissections occur simultaneously or within a short time interval. Interestingly, the coincidence of dissections in different arteries is less frequent. These findings suggest that patients suffer a transient vasculopathy with an increased risk for a specific AD location. A predisposition for AD in general, independent of its specific location, seems to be very rare and was demonstrated only in some familial cases [2] and in some patients with connective tissue syndromes, as described below.

*Symptoms and complications*

Symptoms and complications of AD are summarized in Table 2. Pain is the leading symptom of AD in all arteries. It has a sudden onset and is described as unusual, severe, sharp or tearing, unbearable, or “worst ever” by most patients. The location of the pain usually correlates with the site of the dissection. Pain appears typically as an early sign of AD and is considered as a direct symptom of the arterial injury itself. AD may cause a wide range of complications, dependent on the type of lesion (vessel collapse or rupture) as well as its location. Malperfusion syndromes due to hemodynamic impairment usually develop gradually but without delay, whereas embolism originating from the dissected artery can cause abrupt ischemic symptoms days after the first symptoms of a cervical AD [25]. Myocardial ischemia, pericardial tamponade or cardiac failure and stroke are main complications of dissections of the ascending aorta (Stanford A), whereas patients with dissections of the descending thoracic aorta (Stanford B) present with ischemia of viscera, kidneys or lower limbs [1]. Renal failure is a complication of isolated renal artery dissection [26]. Most patients with cervical AD present with transient ischemic attack (TIA) or thrombo-embolic ischemic stroke [2, 4]. Subarachnoid hemorrhage is a serious complication of intracranial AD [22, 27]. All acute ADs, particularly those with increased risk for arterial rupture or ischemic injury of supplied downstream tissues, are emergency cases that require immediate surgery or aggressive medical therapy. However, due to its rarity and the broad range of its complications the immediate diagnosis of AD was not always possible.

**Table 1** Baseline characteristics

Artery	Ascending aorta	Descending aorta	Ren. A.	ICA	VA	Intracran. Aa.	Coron. Aa.
Incidence/100,000/year	3–4	1–2	<1	ca. 3	ca. 1	ca. 1	<1
Age	60	65	50	45	40	<40	40
Male sex (%)	65	70	70	60	50	70	25
Bilateral cases (%)	–	–	10–15	10–15	15	10–30	30

ICA internal carotid artery, ren. A. renal artery, VA vertebral artery

**Table 2** Symptoms and complications

Artery	Ascending aorta	Descending aorta	Ren. A.	ICA	VA	Intracran. Aa.	Coron. Aa.
Symptoms	Pain	Pain	Pain	Pain	Pain	Headache pain	Pain
Complications	Aortic rupture	Aortic rupture	HTN	Horner syndrome	Brain ischemia	Brain ischemia	MI
	MI	Organ/leg ischemia		Brain ischemia		SAH	Acute coronary syndrome
	Neurological complications						

ICA internal carotid artery, ren. A. renal artery, VA vertebral artery, MI myocardial infarction, HTN hypertension, SAH subarachnoid hemorrhage

### Risk factors

Controlled studies of risk factors for AD have rarely been performed. Hypertension seems to be a common risk factor for AD [8, 26, 28, 29], but patients might also present with hypertension as a reaction on the acute event (Table 3). The association between arterial dissection and smoking is less well investigated. More consistent is the finding of mild trauma, mechanical stress and severe physical exercise as risk factors for acute AD [12, 15, 30, 31]. The role of mechanical injury was analyzed in detail for vertebral AD. Chiropractic treatment of the cervical region might be responsible for some reported dissections. However, some of the patients presenting with ischemic stroke after a chiropractic treatment may have suffered from neck pain due to an unrecognized, but already pre-existing AD. In those cases, the chiropractic maneuver might not have caused the dissection event itself, but might have induced its ischemic complication which is thrombo-embolic in most cases [13, 32]. The association with pregnancy and childbearing [33–36] is not sufficiently explained by the mere physical effort of parturition and the association with coronary or cervical AD seems to be particularly strong during the first weeks post partum. Some case reports suggest that oral contraceptives and hormone replacement therapy increase the risk for coronary AD [37]. A number of patients suffered dissections of different arteries after cocaine consumption [38–42]. Cocaine abuse was found to be a major risk factor for aortic dissections in a series of young patients from San Francisco [43], but in the large International Registry of Acute Aortic Dissection (IRAD) the number of events following cocaine abuse is low [20, 44].

Several studies suggest that infectious diseases, in particular recent upper respiratory infections, increase the risk for carotid AD [45–49]. Imaging techniques using positron emission tomography (PET) to detect  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) visualize the uptake of FDG which reflects the presence of metabolically active cells. PET studies

revealed also signs of perivascular inflammation in arteries with a spontaneous but not with a traumatic cervical AD [50]. In those patients with spontaneous cervical AD inflammatory signals were also observed along the contralateral non-affected artery, which indicates that FDG uptake along the affected artery is not caused by reactive inflammation after the dissection event. Several PET studies were performed with patients with aortic disease [51–53]. These studies revealed vessel wall inflammation in one-third of the patients with acute aortic syndrome and this patient group seemed to have a high risk for disease progression [54].

### Cellular and molecular phenotypes

#### Histopathology

Pathologic alterations are a common finding in biopsies from dissected arteries (Fig. 2). The observed pathologic alterations are (1) chronic and preceding the acute dissection event for a long time, (2) characterized by fragmentation and rarefaction of elastic components, (3) involving the medial layer of the arterial wall, (4) focal and (5) not strongly associated with traditional vascular risk factors like hypertension, smoking, obesity, age or diabetes mellitus. Importantly, these findings are not specific for spontaneous AD but were also observed in arteries with aneurysms and—at a low degree—even in arteries from healthy individuals of high age [55]. The histopathology of affected arteries in patients with AD is not uniform and a variety of degenerative abnormalities were defined.

The most common histopathological alterations were initially described as “cystic medial necrosis” or “muroid (or myxoid) medial degeneration”. They are defined as a non-inflammatory process in the medial layer of arterial walls with focal loss of smooth muscle cells (SMC), fibrosis, accumulation of basophilic ground substance and fragmentation of elastic laminae [56].

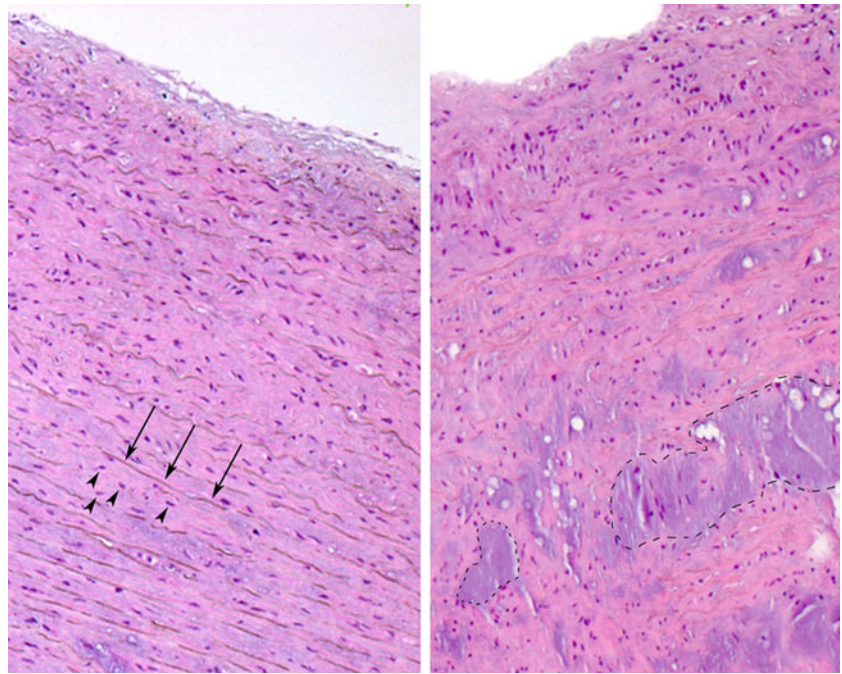
**Table 3** Risk factors

Artery	Ascending aorta	descending aorta	Ren. A.	ICA	VA	Intracran. Aa.	Coron. Aa.
Hypertension	+	++	+	+	+	+	+
Smoking	+	+	–	+	+	+	–
Mild trauma	+	+	+	+	+	+	+
Severe exercise	+	+	+	+	+	+	+
Pregnancy/puerperium	+	+	+	+	+	(+)	++
Oral contraceptive	(+)	(+)	(+)	(+)	(+)	(+)	+
Cocaine	+	+	(+)	(+)	(+)	(+)	+

ICA internal carotid artery, ren. A. renal artery, VA vertebral artery, + = significant association with risk factor, (+) = association with risk factor is weak or not documented



**Fig. 2** Histology of aortic medial degeneration. Normal aorta (*left side*) and aorta with medial degeneration stained with Hematoxylin and eosin (*right side*). *Thin arrows* point to elastic fibers, *arrowheads* point to SMC nuclei. Note areas with pronounced focal fibrosis, loss of SMC, loss of elastic fibers and accumulation of eosinophilic ground substance in aorta with medial degeneration (*encircled areas*)



Fibromuscular dysplasia is another disease of the vessel wall that was associated with AD, mainly in the renal and the cervical arteries. It is a non-inflammatory, non-atherosclerotic disease that has been reported in almost every arterial bed and primarily affects women aged 15–50 years [57, 58].

Intimal thickening resulting in stenosis is another vascular pathology that is associated with aortic dissection as well as with atherosclerosis. It was recently described in more detail in patients with familial TAAD and mutations in the alpha-actin-2 (ACTA2) gene that codes for SMC specific actin (see below). It is unclear, whether these various pathologies are to be considered as different diseases or as variable signs of a same underlying disease. More important, the connections between these different pathologies and atherosclerosis are complex and to a large extent unknown.

Atherosclerosis is a risk factor for aortic disease, in particular for the abdominal part, and might thus be involved in the associated vascular morphology. The risk profiles of cervical AD or coronary AD or renal AD do not indicate a significant association between these diseases and atherosclerosis. Inflammation, however, seems to accompany both atherosclerosis and the various degenerative diseases of the vessel wall that predispose to AD.

Histopathological studies of the aorta identified signs of SMC apoptosis within areas of medial degeneration in the absence of inflammation [59]. Other studies claim that T-Lymphocytes (CD3+) and macrophages (CD68+) accumulate upon medial degeneration and that the focal loss of SMCs is attributable to the local expression of death-promoting mediators by these immune infiltrates

[60]. Eosinophilic infiltrations were found in the adventitial layer of dissected coronary arteries [61] which suggested that isolated eosinophilic arteritis can entail coronary AD. The contradictory results are difficult to explain [62]. Anatomical and physiological differences along the arterial tree play probably a role. Not all studies perceived that the nature of the SMCs varies along the arterial tree: neural crest derived SMCs prevail in the ascending aorta and its proximal branches, whereas other SMCs are of mesodermal origin. This is of importance, because the ontogenetic origin of the SMC is associated with opposite responses to TGF-beta stimulation [56].

#### Proteases involved in matrix degradation

Proteases, including matrix metalloproteinases (MMPs), cathepsins, chymase, tryptase, neutrophil derived serine elastase, tissue type plasminogen activator (tPA), urokinase type plasminogen activator (uPA) and plasmin are found in excess in aortic aneurysms and dissections. The main sources of proteases in the arterial wall are macrophages, neutrophils, fibroblasts and vascular smooth muscle cells. Furthermore, the mural thrombus, frequently observed by atherosclerotic aneurysms and in the false lumen of chronic dissections, tends to trap leucocytes and absorb plasma components, thus might act as a source of proteases in arterial diseases. [63] Numerous proteases have been implicated to cause ECM-destruction in aortic diseases and might account for the expansion of areas with medial degeneration, most prominent among which are the members of the matrix metalloproteinase (MMP) family.

MMPs are a family of structurally-related, zinc-dependent endopeptidases. The members of the MMP family are collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs. Collectively they are capable of degrading all kinds of extracellular matrix proteins. MMPs are synthesized as inactive zymogens with a pro-peptide domain that must be removed before the enzyme becomes active. Under physiological conditions, the activity of MMPs is regulated at the level of transcription, activation of the precursor zymogens and interaction with specific ECM components [64]. With their proteolytic activity MMPs play an important role in vascular remodeling and cellular migration. Gelatinases—MMP2 and MMP9—are the most intensively studied MMPs, which are involved in the development of aortic diseases. They share substrate affinity to short collagens, degradation products of interstitial collagen and elastin. TIMPs—tissue inhibitors of MMPs—have inhibitory effects on the proteolytic activity of MMPs. The role of extracellular matrix proteolytic systems in AD [64, 65, 68] and aneurysm formation and progression [56, 66] was extensively studied. The imbalance between the activity of MMPs and their tissue inhibitors (TIMPs), low TIMP2/MMP2 and low TIMP2/MMP9 ratios respectively, might play an important role in ECM destruction and aortic dissections [67]. MMP3 and MMP7 have high affinities for sulphated residues and are able to degrade numerous adhesive glycoproteins. High concentrations of these MMPs were recently found in the proteoglycan-rich mucoid depositions within the medial degeneration areas of ascending aortic aneurysms and dissections [68]. It is also suggested that MMPs have direct or indirect effects on ion channels in the endothelium and SMCs and take part on the regulation of vascular contraction or relaxation. MMPs can also act as regulatory molecules controlling cellular interactions, both by functioning in enzyme cascades and by processing matrix proteins and adhesion molecules. MMPs and its inhibitors will also be discussed in relation with TGF-beta signaling.

#### Whole genome expression studies

Gene expression profiling studies were performed to characterize the vascular phenotype of dissected arteries in molecular terms. Gene expression profiling involves quantifying mRNA levels by probing the total mRNA (= transcriptome) with specific sequences that are fixed on a slide. Thousands of transcripts in a biological sample can thus be analyzed simultaneously. Gene expression profiles of arterial biopsies from patients were compared with non-affected arterial segments or with material from healthy control persons. Differences in signal intensity does not necessarily indicate differential gene expression but might reflect any difference between the compared tissue biopsies

including inequalities in cellular composition or imperfect matching of the study samples. Various array systems with different numbers of targeted transcripts are currently used and evaluated with a growing number of statistical tools.

The expression profile of acute dissections of the ascending aorta [69, 70] showed increased signals for interleukin 8 (IL8), interleukin 6 (IL6) and some further genes involved in chronic inflammation. The signal intensities of transcripts which play a role in SMC contraction like myosin regulatory light chain 2 and actin alpha 2 were lower in dissected aortic biopsies than in control material. Hierarchical clustering of the expression profiles revealed perfect separation of control tissue and patients. Most interestingly, tissue samples taken from dissected aortic wall and from macroscopic intact aortic wall from the same patient showed highly similar expression profiles. In all cases, samples taken from the same aorta (dissected and unaffected parts) were more similar to each other than to any of the other samples. The increased level of IL6 and IL8 transcripts, together with significant up-regulation of transcripts of CD25 (found on activated B-cells and T-cells), CD53 (leukocyte surface antigen) and of MNDA (myeloid cell nuclear differentiation antigen) indicated that medial degeneration was accompanied by immune cell infiltration. Increased expression of IL6 and IL8 was also found in whole genome expression profiling studies of abdominal aortic aneurysms (AAAs) [71, 72]. A recent gene expression profiling study of the intracranial aneurysm wall also supported the involvement of the inflammatory response pathway, but the expression of IL6 and IL8 was reduced in the aneurysm wall [73, 74]. However, in this study the material of the aneurysm wall was not compared with tissue from healthy control individuals but with the superficial temporal artery from the same patient. The choice this control material explain some of the discrepancies between this study and earlier gene expression profiling studies on aortic disease. The superficial temporal artery from patients with cervical AD showed significant signs of an inflammatory systemic vasculopathy with adventitial infiltrates [75]. In this latter study the authors even assumed that the pathologic changes in the temporal and cervical arteries are similar.

In summary, gene expression profiling as well as other studies show that inflammation plays a role in medial degeneration, but there some inconsistencies between the different findings that might be partially explained by the local diversity of the SMC population and by focal differences between analyzed biopsies [56, 76].

Several other functional pathways are involved in the molecular phenotype of AD. The most impacted pathways in medial degeneration of the intracranial aneurysm wall were focal adhesion, extracellular matrix receptor interaction, cell communication, inflammatory response and

apoptosis [73]. In acute Stanford A dissection genes involved in inflammation, extracellular matrix proteolysis, proliferation, hemostasis, SMC proteins and focal adhesion were differentially expressed [69, 70]. Similar alterations were found in other arterial diseases. Thoracic aortic aneurysms were found strongly associated with differential regulation of genes involved in cell proliferation and apoptosis, whereas genes involved in atherosclerosis and chronic inflammation were increasingly expressed in AAAs. The most common alteration in both thoracic and abdominal aortic aneurysms was the marked increase in expression of MMP9 [72]. MMP9 is thought to contribute to elastin degradation in aneurysmal disease as it exhibits enzymatic activity against elastic fibers and other extracellular matrix proteins and it is produced by medial SMCs and aneurysm-infiltrating macrophages. Transcripts of SMC-specific genes were generally down-regulated upon medial degeneration [69, 73]. This might indicate loss of SMCs, but the low expression of SMC-specific actin, myosin or other genes involved in contractile function might also indicate the activation of SMCs upon vessel wall injury and their transition from the contractile into a proliferating, synthetic or apoptotic stage [77].

### Predisposing genetic variants

Genetic syndromes with an increased risk for arterial dissections

Three well known inherited connective tissue disorders are associated with AD: Marfan syndrome, the vascular type of Ehlers Danlos syndrome (vEDS) and Loeys-Dietz syndrome. Turner Syndrome is a fourth condition with increased risk for arterial dissections.

#### *Marfan syndrome*

Marfan syndrome is an autosomal dominant inherited disorder with a prevalence of about 1:10,000. Typical signs of Marfan syndrome are chest deformities and disproportionate long limbs caused by long bone overgrowth, dislocation of the ocular lenses, dural ectasia and aortic dilatation and dissection, predominantly at the aortic root. Heterozygous mutations in the fibrillin-1 (FBN1) gene were identified as the cause of Marfan syndrome [78, 79]. Since mutation search in FBN1 is expensive and time consuming, the diagnosis of Marfan syndrome is not always confirmed by molecular techniques. Moreover, the mutation detection rate in FBN1 is incomplete and Marfan-like phenotypes can be caused by mutations in other candidate genes like TGFBR2 (transforming growth factor, beta receptor 2). In a large ( $n > 1,000$ ) series of patients

with confirmed molecular diagnosis 15% of the patients had a dissection of the ascending aorta in, 4% of the descending aorta and 3% had dissection of the abdominal aorta. No dissections in other arteries were reported [80]. Medial degeneration is a typical finding in aortic biopsies [81].

#### *Ehlers Danlos syndrome*

Ehlers Danlos syndrome (EDS) is a clinically and genetically heterogeneous connective tissue disorder, caused by genetic defects in collagen biosynthesis. Arterial involvement is mainly observed in the vascular type of EDS, formerly designed as EDS type IV [82]. Additional subtypes of EDS that predispose to AD were recently defined as the “vascular-like EDS subtype” and the “EDS/OI (Osteogenesis imperfecta) overlap syndrome” [79]. Vascular EDS is a rare autosomal dominant disorder (estimated prevalence below 1:100,000) caused by mutations in the gene that codes for type III procollagen (COL3A1). The clinical phenotype seems mild, but vascular EDS is a life threatening disorder due to the high risk of organ rupture (intestine, uterus, or aorta). About 40% of patients presents with vascular events by 40 years of age, typically aortic rupture and in a minority of cases carotid artery dissections. Arterial complications are slightly more frequent among male patients.

#### *Loeys-Dietz syndrome*

Loeys-Dietz syndrome, a rare autosomal dominant genetic disorder with clinical similarities to vascular EDS, was recently identified in patients with mutations in the transforming growth factor beta receptors 1 and 2 (TGFBR1 and TGFBR2) [83]. Two subtypes of the disorder are recognized. Patients with Loeys-Dietz syndrome type 1 present with aneurysms and dissections of the thoracic aorta as well as in other arteries. Additional symptoms of this syndrome are hypertelorism, cleft palate/bifid uvula, craniosynostosis, mental retardation, patent ductus arteriosus and arterial tortuosity. Patients with Loeys-Dietz syndrome type 2 resemble patients with vascular EDS. They do not show craniofacial abnormalities, but develop arterial aneurysms and dissections together with joint laxity, easy bruising, translucent skin and atrophic scars. Histopathological findings in the aorta show medial degeneration with pronounced fibrosis and elastic fiber fragmentation [84].

#### *Turner syndrome*

Turner syndrome is a developmental disorder caused by partial or complete monosomy of the X chromosome. The prevalence of Turner syndrome is about 1 in 2,500 live

births. Turner syndrome is a common cause of aortic dissection in young women [85, 86], but the pathogenesis of aortic dissection is unclear. The risk for fatal aortic events was particularly high in pregnant Turner women (via egg donation). In patients with Turner syndrome, dissections are predominantly located in the ascending aorta. Medial degeneration was observed in biopsies from the majority of Turner patients with aortic dissection [87, 88].

#### Mutations in patients with familial AD

Familial clustering is reported for patients with AD but without additional signs of a known inherited disorder. Familial clustering of thoracic aortic aneurysms and dissections was found in 15–20% of all cases [89–91] and is also evident for intracranial aneurysms and subarachnoid hemorrhage [92]. On the contrary, familial cervical AD is very rare [93]. These observations suggest a different impact of genetic factors in the pathogenesis of these diseases.

Recent developments in the elucidation of familial ADs are mainly based on the study of familial aortic dissection. Linkage and mutation analysis in patients with familial thoracic aortic aneurysms and dissections (TAAD) identified mutations in *FBN1*, *TGFBR1*, *TGFBR2* in patients without other symptoms of the Marfan, Loeys Dietz or Ehlers Danlos syndromes. The co-segregation of the identified familial mutations with the disease phenotype strongly suggests a causative role for the mutations in the pathogenesis of AD. Disease-causing mutations were also identified in *ACTA2* (encoding smooth muscle alpha-actin) and *MYH11* (encoding smooth muscle beta-myosin heavy chain). In most families the mutations in *FBN1*, *TGFBR1*, *TGFBR2*, *ACTA2* and *MYH11* affect the aorta, but some relatives with *TGFBR1* and *ACTA2* mutations suffered dissections in other arteries (Table 4). The penetrance of *ACTA2* mutations is only about 50%, i.e. only half of the family members carry a mutation present with arterial disease. As a consequence *ACTA2* mutations might also be detected in sporadic patients. Mutations in several other

genes (*COL3A1*, *COL1A1*, *COL5A2*) were found in some rare sporadic or familial cases with arterial disease [93–95], but their importance in the pathogenesis of AD without other signs of a known connective tissue disorder is less well established. The spectrum of mutations identified in familial TAAD points to three biological systems involved in the pathogenesis of AD: 1 connective tissue structure, 2 TGF-beta signaling and 3 SMC function and proliferation.

#### Connective tissue defects

The association of AD with known inherited connective tissue syndromes and the observation of morphologic alterations in the dermal connective tissue of patients with cervical AD [96, 97] and intracranial aneurysms [98] supported the hypothesis of a generalized structural connective tissue defect predisposing for AD [2, 99] even in sporadic patients without evident signs of a connective tissue disorder [11]. Mutations in *COL3A1*, *COL5A2*, *COL1A1* and *ACTA2* were found in sporadic patients with cervical AD without further signs of a connective tissue syndrome [100, 141]. Arterial complications as major or isolated sign were also found in part of the large series of patients with *COL3A1* mutations [82]. Carriers of *FBN1* mutations may present with isolated ascending aortic dilatation [101].

Based on a static concept it was initially assumed that the reduced or altered biosynthesis of mutated components of the ECM lead to structural weakness of the vessel wall which explained the increased risk for AD. However, inflammatory and degenerative processes accompany the structural defects of the vascular ECM and are crucial for the vascular phenotype.

Several studies suggested a crucial role for fibrillin, elastin, and collagen fragments in SMC signaling [102]. Elastin is one of the dominant ECM proteins in the arterial wall. It is deposited and cross-lined in the elastic fibers along the fibrillin containing microfibrils. Collagen might play an important role in matrix signaling, too. Collagens are recognized by two major classes of receptors: the beta1 family of integrins ( $\alpha1\beta1$ ,  $\alpha2\beta1$ ,  $\alpha10\beta1$ ,  $\alpha10\beta1$ ) and DDR1

**Table 4** Genes involved in the pathogenesis of AD

Gene	Locus	Involved arterial component	Syndrome	Arterial phenotype
<i>COL3A1</i> [82]	2q31	Collagen biosynthesis	Vascular EDS	Aortic rupture cervical AD
<i>FBN1</i> [78]	15q21	Elastic fiber biosynthesis/TGF-beta signaling	MS	TAAD
<i>TGFBR1</i> [83]	9q22	TGF-beta signaling	LDS	TAAD/AD in other locations
<i>TGFBR2</i> [83]	3p22	TGF-beta signaling	LDS/MS	TAAD
<i>ACTA2</i> [118]	10q23	SMC function	No	TAAD/PAOD AD in other locations
<i>MYH11</i> [119]	16p13	SMC function	No	TAAD/PDA
<i>CDKN2A/B</i> [127]	9p21	SMC senescence	No	IA, Aortic dissection

*EDS* Ehlers Danlos syndrome, *IA* intracranial aneurysm, *LDS* Loeys-Dietz syndrome, *MS* Marfan syndrome, *TAAD* thoracic aortic aneurysms and dissections, *PAOD* premature arterial occlusive disease, *PDA* patent ductus arteriosus

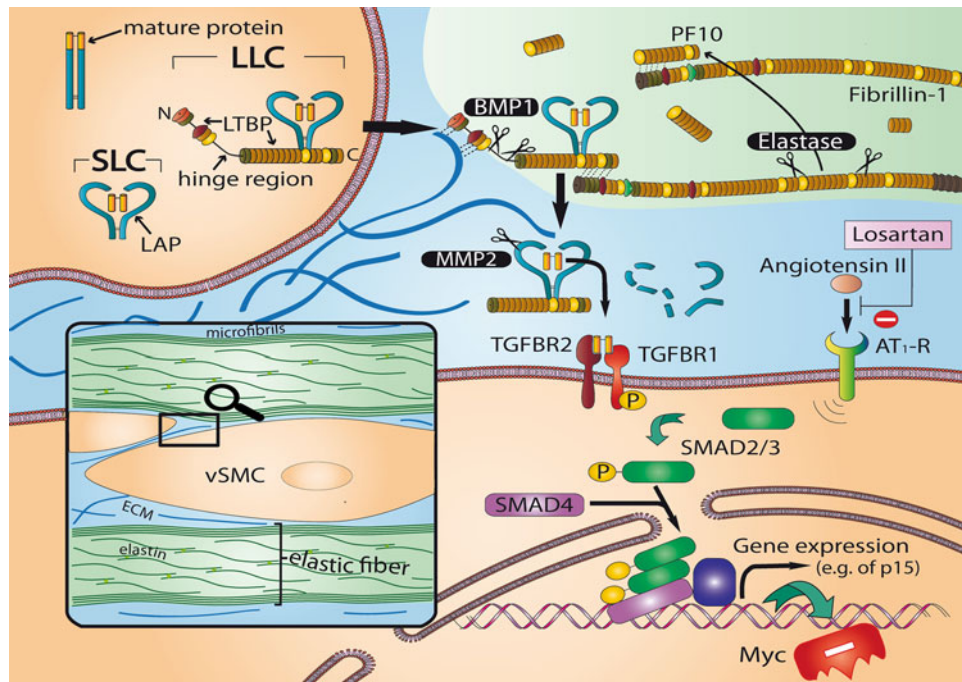


and DDR2, two members of the discoidin-domain receptor family. Both of these receptor groups are produced by SMCs and are thought to mediate cellular migration, adhesion and proliferation. However, mice lacking some of these receptors failed to reveal significant vascular defects. Therefore, the contribution of collagen signaling to vascular diseases remains unclear at present [102].

A pathogenic frameshift mutation in the filamin A encoding *FLNA* gene was found in a patient who died of a subarachnoid hemorrhage [103]. Filamin A is the non-muscle isoform of filamin. It has an important function in the formation of intercellular junctions and the anchoring of the cell to the ECM. *FLNA* knockout mice show cardiac and vascular developmental abnormalities [104]. Proteomic analysis in aortic media of patients with Marfan syndrome revealed upregulation of the C-terminal fragment of filamin A in aortic aneurysms from patients with Marfan syndrome [105] and hypertensive rats [106].

### Mutations affecting TGF-beta signaling

The discovery that mutations in the *TGFBR2* gene cause Marfan syndrome type 2 as well as the finding of mutations in *TGFBR1* and *TGFBR2* in patients with Loeys-Dietz syndrome [78] or in families with TAAD and dissections in other arteries [107] revealed the prominent role of TGF-beta signaling in the pathogenesis of arterial disease. TGF-beta signaling is regulated at multiple levels in a highly complex manner. TGF-beta signaling appears to be decisive for the vascular phenotype of classic Marfan syndrome with mutations in *FBN1*. In mouse models of Marfan syndrome fibrillin deficiency leads to elevated TGF-beta levels. TGF-beta remains inactive as long as it is captured by latent TGF-beta binding protein (LTBP). Increased amounts of fibrillin fragments which show structural homology with LTBP lead to release and proteolytic activation of TGF-beta [108, 109] (Fig. 3). Interestingly, the



**Fig. 3** TGF-beta signaling in the arterial wall. In most cells including SMCs TGF-beta binds to TGFBR2 (type II receptor) and ALK5 (type I receptor, also known as TGFBR1). The inactivation of TGF-beta by latent TGF-beta binding protein (LTBP) is an important mechanism regulating TGF-beta activity within the extracellular compartment and plays a prominent role in the vascular pathology of Marfan and Loeys-Dietz syndromes. The C-terminal domain of LTBP interacts with the N-terminal domain of Fibrillin-1, the major component of elastin-associated microfibrils [152, 153]. Elastase and other proteolytic enzymes release fibrillin fragments by disintegration of microfibrils. Subsequently internal fibrillin fragments bind with high affinity to the N-terminal region of fibrillin-1, the former binding site of LTBP which releases TGF-beta. TGF-beta induces a large set of cytostatic gene responses. TGF-beta stimulates among others

$p15^{INK4b}$  (p15) both by direct Smad-mediated transactivation and by the simultaneous downregulation of the Myc transcription factor, which leads to a rapid cellular depletion of Myc and to relief of p15 transcriptional repression [154, 155]. AT1-R, Angiotensin-II type I receptor; BMP, bone morphogenetic protein; LCC, large latent complexes, consisting of SCL complexed with latent TGF-beta binding protein (LTBP); PF-10, recombinant human fibrillin-1 fragment encoded by exons 41–52 of the *FBN1* gene, interacting strongly and specifically with the N-terminal region of fibrillin-1; SLC (small latent complex) consisting of mature TGF-beta and latency associated peptide (LAP); SMAD, signal transducer and transcriptional modulator that mediate multiple signaling pathways; vSMC, vascular smooth muscle cell

aorta of Marfan mice was normal at birth but developed medial degeneration during early life, which was accompanied by inflammatory infiltration. Fibrillin fragments appear to be potent attractants for macrophage chemotaxis in *in vitro* experiments [110, 111].

It is well established that Marfan syndrome and Loeys-Dietz syndrome are associated with increased TGF- $\beta$  signaling, but the relationship between aberrant TGF- $\beta$  signaling and the histopathological changes in the arterial wall remain to be elucidated. TGF- $\beta$  stimulates the synthesis of procollagens and fibronectin and thus leads to ECM deposition and fibrosis. Accordingly, accumulation of collagen is considered to be an indirect marker of increased TGF- $\beta$  signaling. Indeed mice with fibrillin deficiencies show thickening of the aortic media with accumulation of ECM and fragmentation of elastic fibers. MMP2 and MMP9 were up-regulated in Marfan syndrome during the progression of thoracic aortic aneurysms [112] and it is suggested that these MMPs are at least in part responsible for the extensive degeneration of elastic fibres, the endothelium dysfunction and the reduction of smooth muscle contractility. Doxycycline—a tetracycline antibiotic—is a nonspecific inhibitor of MMPs, acting by binding to the zinc–calcium at their catalytic sites. In a mouse-model of Marfan syndrome doxycycline was effective in preventing thoracic aortic aneurysms by preserving elastic fibre integrity, normalizing vasomotor function and suppressing TGF- $\beta$  activation, with mechanisms which are at least in part attributable to its inhibitory effects on MMP2 and MMP9 [113]. Since TGF- $\beta$  can stimulate the expression of several MMPs the production of fibrillin fragments may increase due to fibrillin cleavage. This increase leads to a vicious circle because more fibrillin fragments enhance the TGF- $\beta$  activation [114].

Antihypertensive treatment may effectively prevent the development of the progression of aneurysmal growth. Genetic studies of the TGF- $\beta$  and angiotensin-II type 1 (AT1) receptor pathways revealed that this preventive effect might be partially independent of the blood pressure lowering. A short introduction of this work intends to illustrate the value of genetic research as a tool to unravel complex biological systems. Perfusion with the hypertensive agent angiotensin-II (Ang-II) in mice induced the following vascular alterations: (1) sustained blood pressure elevations; (2) increase in the thickness of the aortic media through mechanisms including smooth muscle hyperplasia, smooth muscle proliferation, and accumulation of ECM proteins; (3) signs of inflammation, including oxidative damage to the vascular tissue, infiltration of monocytes/macrophages, and activation of MMPs. Not surprisingly, Ang-II treatment induced aortic dissections 6 out of 26 wild-type mice. Animals deficient for NOX1 (NADPH oxidase, a crucial component of the response to Ang-II)

had lower blood pressure elevation and only one of 25 developed AD [115]. However, blood pressure elevation by norepinephrine did not lead to aortic dissection in wild type mice, suggesting that hypertension is not sufficient to cause aortic dissection. In fact, Ang-II induces—independent from blood pressure elevations—a multitude of other alterations in the arterial wall, amongst them an altered protease/inhibitor balance. NOX1 was shown to suppress the activity of TIMP1 and it was suggested that NOX1 attenuates the Ang-II-induced TIMP1 gene expression. The effect of losartan might be similarly complex. Losartan, an AT1 1 receptor antagonist, is a widely used medication to decrease blood pressure. A careful comparison of two anti-hypertensive drugs, losartan and propranolol, in FBN1-deficient mice revealed that the beta blocker propranolol may diminish the aortic root growth but cannot prevent progressive deterioration of the aortic wall. However, losartan maintained the aortic wall structure in Fibrillin-1-deficient mice and fully prevented aortic root dilatation [116]. The beneficial effect of Losartan is in part independent of its anti-hypertensive effects, like antagonizing TGF- $\beta$ . A clinical trial is currently being performed to evaluate the effects of losartan on the progression of aortic root growth rate [117].

#### *Vascular smooth muscle cells*

The finding of disease-causing mutations in ACTA2 and MYH11 in large families with TAAD suggests that dysfunction of SMCs results in medial degeneration leading to AD. The major function of vascular SMCs is to contract in response to the stretch resulting from the blood flow pulses. This contraction is dependent on the interaction between thin filaments, composed of SMC-specific  $\alpha$ -actin (encoded by ACTA2) and thick filaments, composed of SMC-specific  $\beta$  myosin (encoded by MYH11). The identification of mutations in specific contractile components of SMCs suggested a causal relation between SMC contractile function and degenerative arterial diseases. Increased amounts of SMCs were found in the medial arterial layer of patients with heterozygous ACTA2 mutations. Cell-proliferation essays of cultured SMCs demonstrated that these arterial cells from patients with ACTA2 mutations proliferated more rapidly than control cells. The increased cell-proliferation correlates with a thickening of the medial arterial layer, leading to stenosis. Premature vascular occlusive disease was diagnosed in about one-third of the carriers of ACTA2 mutations, with ischemic stroke as a possible complication [118]. Moreover, occlusion of vasa vasorum might entail focal arterial ischemic injury and predispose to medial degeneration or to increased arterial vulnerability for atherosclerotic or other lesions.

Mutations in MYH11 were found in a few families with familial TAAD, associated with patent ductus arteriosus. Patients with MYH11 mutations show a distinctive occlusive arterial pathology [119]. Histological inspection of aortic biopsies revealed specific alterations with areas of focal medial degeneration, increased proteoglycans and loss of elastic fibers and SMCs, as well as areas with SMCs proliferation in a disorganized pattern, resembling the phenotype of fibromuscular dysplasia.

During the formation of aneurysms and dissections of the thoracic aorta the transition of SMCs from the contractile to the synthetic type is accompanied by elevated concentrations of matrix metalloproteinases [120, 121]. It is conceivable that increased MMP concentrations enable SMC migration. Genetic deficiency of MMP2 and MMP9 decreases the *in vitro* migration ability of SMCs significantly. SMCs express constitutively MMP2 but other MMPs including MMP9 only after stimulation by cytokines. MMP9 is secreted primarily by inflammatory cells, including neutrophils and macrophages. MMP2 and MMP9 can enhance the contractile function of vascular SMCs by inhibiting the  $\text{Ca}^{2+}$  entry into the cells from the extracellular space [122]. Interestingly, circulating smooth muscle myosin and circulating MMP9 were also analyzed as possible plasma markers for the diagnosis of aortic dissection and aneurysm [123, 124].

#### Genetic association studies

Genetic association studies are case–control studies (or cohort studies) that analyze the prevalence of common genetic variants, usually single nucleotide polymorphisms—SNPs, in diseases. Most genetic association studies analyzed the genetic variation in a single candidate gene, but recent technical developments currently permit the simultaneous analysis of hundred thousands of SNPs. Such genome wide association studies (GWAS) require a rigorous design and a careful statistical evaluation [125, 126].

A genetic variant on chromosome 9p21.3 was found to be involved in different vascular diseases, including coronary artery disease, abdominal aortic aneurysms, intracranial aneurysms [127, 128] and arterial stiffness [129]. Interestingly, the identified locus harbors the CDKN2A (cyclin dependent kinase inhibitor 2A) and CDKN2B genes that code for the senescence markers p16 and p15. Both genes are known to play an important role in cell cycle regulation and belong to a family of genes that have been implicated in the pathogenesis of atherosclerosis through their role in TGF- $\beta$ -induced growth inhibition. The most strongly associated SNPs in the 9p21.3 locus lie close to the CDKN2B gene [130]. Recent data indicated that the genetic variation in the CDKN2B/CDKN2A locus was associated with transcription activity of CDKN2B but not of

neighboring genes including CDKN2A, MTAP (encoding methylthioadenosine phosphorylase), or ANRIL (a non-coding antisense RNA in the INK4 locus) [131]. Therefore, both p15 and p16 are interesting candidates with a possible role in dissection and aneurysm formation. Suppression of the cyclin dependent kinase inhibitor and tumor suppressor p16 resulted in an enhanced SMC proliferation underlying intimal hyperplasia in a carotid arterial injury mouse model [132]. Elevated blood pressure markedly induced p16 expression in rat kidneys and hearts as well as in human kidneys [133]. The tumor suppressor p15, the gene product of CDKN2B, is a potential effector of TGF- $\beta$ -induced cell cycle arrest [134]. It is interesting that some of the involved candidate genes were originally identified in tumor biology.

The TAAD phenotype was analyzed in several candidate gene association studies. TAAD was associated with genetic variants in MMP9 [135] and VKORC1 (encoding the vitamin K epoxide reductase complex, subunit 1) [136], but these results require validation in independent populations. Several candidate gene studies of patients with AAA were recently performed [137–139], but confirmation of the results is warranted. GWAS with large series of patients with TAAD or AAA were not yet published. Genetic association studies of cervical AD revealed that carriers of the T-allele of the MTHFR gene might have an increased risk, but the evidence is weak and the finding needs confirmation in a large and independent population [140]. No other genetic variants were found to be associated with cervical AD [141, 142]. The results of a large multicenter GWAS of cervical AD are to be expected in the near future [143].

#### Concluding remarks

The notion of AD refers to various arterial pathologies including mural hematoma with and without intimal tear, double lumen or pseudo-aneurysm in different arteries. All AD phenotypes have several risk factors in common and are associated with medial degeneration. The association with genetic syndromes like Marfan syndrome, Loeys-Dietz syndrome or Ehlers-Danlos syndrome and the finding of electron microscopic alterations in skin biopsies from patients with cervical AD and intracranial aneurysms [99] indicate that AD may be a symptom of a systemic disease.

However, patients rarely show multiple AD in different arteries [144–147], whereas the occurrence of bilateral dissections in the carotid, vertebral, renal or coronary arteries is frequent. Moreover, patients with genetic syndromes and familial forms of AD typically suffer dissections in specific arterial segments (ascending aorta in patients with Marfan syndrome, carotid AD in patients with

vascular EDS). Therefore, we can conclude that some risk factors are specific for a particular arterial segment: genetic as well as environmental risk factors indicate differences between aortic regions and within the cervical arteries.

In this review we brought all forms and stages of AD together and searched for general and specific pathogenetic factors. Notwithstanding the striking similarities in epidemiology, risk profile and histopathology of most ADs important differences may be masked by not sufficiently differentiated terminology. For instance, the very notion of AD does not have the exact same meaning when applied to the aorta or to the cervical arteries. Cervical AD is usually characterized by a mural hematoma without intimal tear, whereas such mural hematoma without open communication with the arterial lumen is not common in the aorta. This intimal tear allows free access of thrombolytic agents into the false lumen of the dissected aorta. This may explain why thrombolysis is considered to be safe in patients with cervical AD and stroke, but potential harmful in patients with aortic dissection [148]. Moreover, the hematoma of a cervical AD is usually older at diagnosis, whereas the arterial hemorrhage in patients with acute aortic dissection is fresh. Other notions with ambivalent sense are pseudo-aneurysm [149, 150] and dissecting aneurysm [151].

Imaging studies of dissected arteries reveal a variety of vascular abnormalities such as fibromuscular dysplasia, arterial tortuosity, aneurysmal dilatation and arterial stiffness. These different vascular abnormalities are all associated with medial degeneration. The complex molecular signature of medial degeneration has been characterized by independent techniques. Medial degeneration can be accompanied by inflammation, cell proliferation or apoptosis, senescence and increased proteolytic activity. Metalloproteinases and their inhibitors play a prominent role in these pathological alterations. Some studies suggest that medial degeneration is a systemic disease, affecting the whole arterial system [75], whereas others underline the focal nature of medial degeneration, which means that highly affected areas and less affected areas can be found within the same arterial segment [118].

The research in the molecular pathogenesis of AD is rapidly evolving. The identification of several disease causing mutations by genetic linkage analysis and DNA sequencing showed that ECM structure, TGF- $\beta$  signaling and SMC contraction are involved in the pathogenesis of AD. Since SMC contraction requires a functional connective tissue structure and since TGF- $\beta$  signaling is important for SMC proliferation, all affected biological systems are related to SMC functioning. Several additional genetic loci for familial AD and aneurysms are currently being studied and it is expected that additional disease-causing genes will be discovered soon.

First results of genome wide association studies (GWAS) convincingly showed that the CDKN2A/CDKN2B locus on chromosome 9p21.3 is involved in the pathogenesis of AD and other arterial diseases. Large study samples are required for GWAS with high power. This research method is suitable for the study of aortic dissections and first results of a large GWAS of cervical AD are to be expected in the near future [143]. Due to their low incidence, it will be difficult to analyze renal or coronary AD by the GWAS technology.

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