

Site Specificity of Aneurysmal Disease

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Aneurysms are localized pathological dilations of any vessel, and in arteries, a diameter of 1.5 times that of the normal artery is a generally accepted definition. Morphologically, aneurysms are usually considered to be either fusiform (Figures 1 and 2) or saccular (Figures 3 and 4). The transition from normal to aneurysmal diameter may be remarkably sudden, particularly in the case of saccular aneurysms. Different sizes and types of arteries may be affected. Although aneurysms are by definition focal, they may be multiple and associated with generalized arteriomegaly in some individuals. This highlights the importance of both systemic and focal factors in their pathogenesis. Only a minority of aneurysms have specific pathological causes, the underlying cause of most aneurysms seen in large to medium-sized arteries being unknown.

The pathological processes involved in the formation of most degenerative aneurysms include upregulation of proteolytic pathways, inflammation, and loss of arterial wall matrix. Similar changes have been reported in cerebral, thoracic aortic, and abdominal aortic aneurysms. The natural history of most aneurysms is gradual expansion with increasing risk of rupture or, in some cases (particularly popliteal aneurysms), thrombosis, distal embolization, or both. Arterial dissection is distinct from true aneurysm formation, although in some animal models and in humans, dissection may progress to aneurysmal change and rupture. The reason that aneurysms are common in some locations and not others is equally unclear. The present review will explore possible explanations for the site specificity of aneurysmal disease, with particular focus on developmental biology, vascular cell lineage, hemodynamic and anatomic factors. The mechanisms and site specificity of dissection and rupture will not be discussed.

Where Do Aneurysms Occur?

Aneurysms are common in some locations, such as the abdominal aorta, and exceedingly rare in other locations, such as the external iliac artery. Prevalence varies greatly with definition of an aneurysm at a given location, detection modality, and population studied. Unfortunately, there are no data comparing the true prevalence of aneurysms at different locations. The best data are for abdominal aortic aneurysms (AAAs), which have been the subject of large-scale population screening studies. For those older than 65 years of age, the prevalence of AAA is approximately 5% to 6% in men

and 1% to 2% in women.¹ In 25% of these cases, the aneurysmal process extends into 1 or both common iliac arteries, and in 7% of these, into the internal iliac arteries (Figure 2).² Aneurysms of the thoracic aorta are \approx 5 times less common than in the abdominal aorta and are most commonly seen in the ascending (40%) or descending (35%) portion.³ Aneurysms in the coronary arteries are relatively common (incidence 1.5% to 5%), with a predilection for the right coronary artery.⁴ Autopsy studies suggest the prevalence of cerebral aneurysms (Figure 3) is \approx 2%.^{5,6}

The coexistence of these aneurysms or their coexistence with the rarer aneurysms in other locations can only be estimated. At autopsy, \approx 40% of men (and \approx 25% of women) with a thoracic aneurysm have coexisting abdominal aortic, iliac, or femoral aneurysms, although only 5% have a thoracoabdominal aneurysm.⁷ Approximately 7% of patients with AAAs and 5% with thoracic aortic aneurysms (TAAs) have a cerebral aneurysm, which suggests only a weak association.^{7,8} Although 30% of patients with popliteal artery aneurysms have an AAA,⁹ relatively few patients (particularly women) with AAA have popliteal aneurysms.¹⁰ Approximately 18% of patients with AAA have evidence of coronary artery ectasia or aneurysm formation.¹¹ Aneurysms in most other arteries are either rare (eg, splenic or pulmonary arteries) or exceedingly rare (eg, upper-limb arteries), with little known about their prevalence, although they do not appear to be associated with the more common aneurysms seen in larger elastic arteries.

Systemic Risk Factors in Aneurysmal Disease

There is some evidence that the entire vascular tree is abnormal in patients with aneurysmal disease, which indicates an important role for systemic factors. AAA, in particular, has been reported to be associated with generalized arteriomegaly.¹² Alterations in matrix composition seen in the walls of AAAs have been detected in both nonaneurysmal aortic segments and the inferior mesenteric vein.^{13,14} There is also evidence of an association between varicose veins and coronary artery ectasia.¹⁵ Carotid arteries in patients with AAA exhibit mild dilation and reduced distensibility compared with controls.^{12,16}

Environmental Factors

The dominant environmental risk factors for most common aneurysms include age, male gender, and smoking, whereas for

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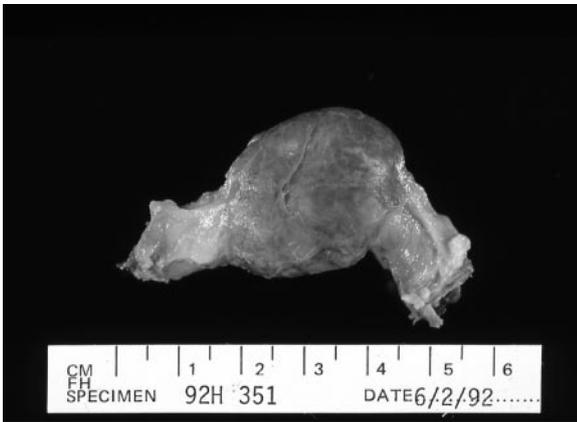


Figure 1. A resected popliteal artery aneurysm demonstrating the focal nature of the pathology.

cerebral aneurysms, they are hypertension, smoking, alcohol, and female gender.^{5,8,17} Some of these factors do have site-specific effects; for example, the abdominal aorta appears to be particularly susceptible to smoking.¹⁸ Atherosclerosis preferentially affects certain arterial locations for complex reasons that have been reviewed elsewhere.¹⁸ The role of atherosclerosis in the causation of aneurysms is debated. Some pathologists argue that aortic and cerebral aneurysms exhibit histological changes of atherosclerosis and that thinning and fragility of the media (a feature of aneurysms) are prominent in atherosclerosis.¹⁹ However, epidemiological studies have identified distinct differences in risk factors for aneurysmal versus atherosclerotic disease, a

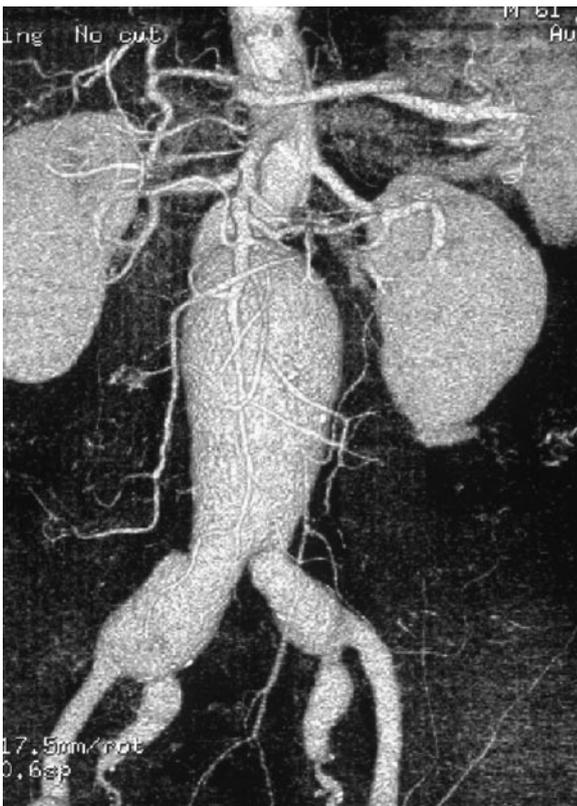


Figure 2. A fusiform AAA with extension into the common (CIA) and internal (IIA) but not external (EIA) iliac arteries.

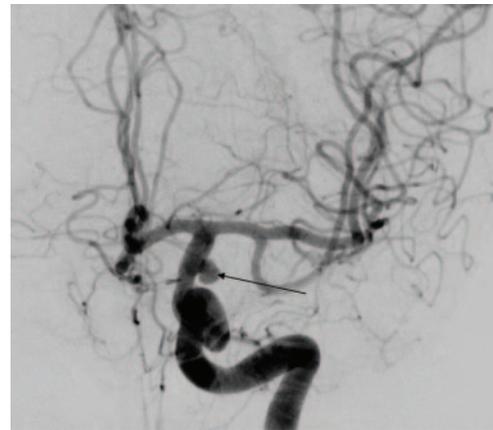


Figure 3. An example of a saccular aneurysm of the posterior communicating artery (arrow).

notable example being the protective effect of diabetes in AAA.²⁰ In addition, aneurysms are very rare in some locations that are particularly prone to atherosclerosis (eg, superficial femoral artery).

Although trauma and chronic injury can result in aneurysm formation, the location of these aneurysms is of little relevance to the site specificity of most aneurysms. Any penetrating arterial injury may result in false aneurysms. Occasionally, chronic trauma due to compression can cause a true aneurysm (eg, of the subclavian artery associated with cervical ribs). There is anecdotal evidence that the tight boots worn by cavalry officers, together with repeated flexion and extension while riding, traumatized the artery in the popliteal fossa to cause an aneurysm, possibly with compression from the arcuate popliteal ligament.²¹

Genetics

The strength of associations between a range of genetic variants and aneurysms in different locations varies considerably. Monogenic mutations associated with aneurysms are discussed fully elsewhere, although it is noted that genes influencing some matrix proteins and microfibrils, the transforming growth factor- β (TGF- β) pathway, and smooth muscle contraction appear to be especially important in humans^{22–24} (Table). Mutations that cause loss of function of the elastin gene are usually associated with stenotic lesions of the aorta and other arteries but may result in AAAs in association with cutis laxa.^{25,26} The importance of single-gene mutations as causes of aneurysms wanes as one passes from the ascending to the descending and abdominal aorta.²⁷ Approximately 20% of TAAs are part of a syndrome often associated with single-gene mutations; examples include Marfan syndrome, Ehlers-Danlos syndrome, bicuspid aortic valve, and some familial TAAs.²⁴ Specific mutations can result in various phenotypes and aneurysms in a variety of locations (Table). The mechanisms that determine the location of these aneurysms are unknown, although TGF- β signaling is often implicated. The early differentiation of aortic smooth muscle cells (SMCs) is known to be dependent on both TGF- β signaling and microfibrils, mechanisms that might contribute to the thoracic aneurysms observed in Loey's-Dietz and Marfan syndromes. Although the biology of the single-gene mutations of matrix proteins and microfibrils often has been elucidated in

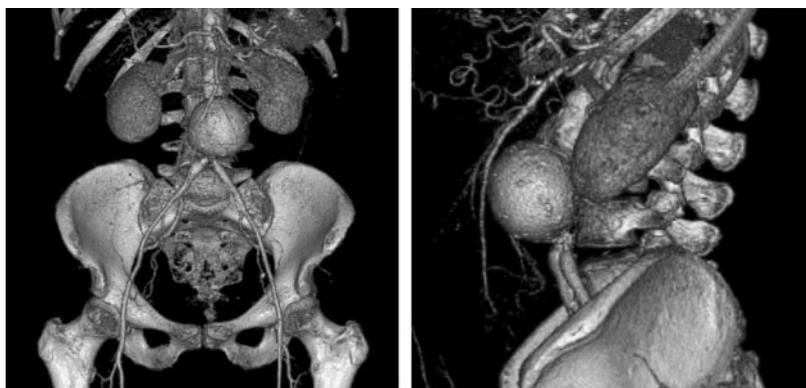


Figure 4. An example of a highly localized sacular AAA.

genetically modified mice, there are differences between mice and humans. In particular, in mice, the aorta is a muscular artery influenced by sympathetic stimulation and endothelium-derived nitric oxide, whereas in humans, the aorta is an elastic artery. Perhaps this is one reason why deficiencies in either the biglycan or the lysyl oxidase gene are associated with aortic rupture in mice but not in humans.²⁸

The association of mutations in genes encoding the contractile apparatus of vascular SMCs with TAAs (Table) and dissections indicates that SMC tonus and function may be an important phenotype that influences site specificity.²⁹ Other evidence for the role of contractile SMC dysfunction comes from polycystic kidney disease, which is associated with cerebral and in some cases aortic aneurysms.⁶ The associated genes, PKD1 and PKD2, encode proteins that appear to regulate SMC contractility through calcium-regulatory mechanisms.³⁰

Susceptibility genes, rather than causal gene mutations, are important in aneurysms, particularly AAAs, which are genetically complex.²² Recently, genome-wide association studies have identified loci on chromosome 9p21 that increase the risk of both AAAs and cerebral aneurysms.^{31,32} Common variations on loci at 2q and 8q also are associated with cerebral aneurysms. Those on 8q may act via SOX17, which is required for endoderm development and probably also for the formation and homeostasis of the endothelium: This implicates endothelial development and repair in the formation of cerebral aneurysms.³² Although 1 study reported no shared gene associations for AAAs and TAAs,²² more recent work has suggested that there may be common susceptibility genes for intracranial aneurysms, thoracic aneurysms, and AAAs, with a region on chromosome 11 being a candidate for shared genetic risk.³³ Susceptibility to aneurysm formation, particularly in Kawasaki disease, also may arise from variations in the immune-response genes.³⁴

Inflammation and Infection

Autoimmune and T-cell responses appear to influence the development of aneurysms at specific anatomic locations. A specific example is Kawasaki disease, an inflammatory vasculitis of unknown origin. Although aneurysmal changes have been reported in various medium-sized to large arteries, for unknown reasons there is a particular predilection for the coronary artery with aneurysms in $\approx 20\%$ of cases of Kawasaki disease.^{34,35}

In the case of the aorta, inflammatory changes tend to be much more florid and diffuse in ascending thoracic aneurysms than in AAAs, which possibly reflects vasa vasorum density and differential immune responsiveness.³⁶ There is evidence from animal models that the media of the thoracic aorta is an immunoprivileged site.³⁷ It has been proposed that impaired T-cell and macrophage access to the elastic media results in chronic inflammation due to persistence of pathogens or antigens.³⁷ The expression of pathogen-sensing Toll-like receptors by resident dendritic cells varies considerably, with each artery having a distinct profile; for example, the pattern seen in iliac arteries is quite different from that of the aorta.³⁸ This results in differential T-cell responses and may form the basis of vessel-specific risk for vasculitides³⁸ but not aneurysmal disease, with the aorta and iliac artery (aneurysm prone) having similar signature patterns to the carotid artery (aneurysm resistant).

Autoimmune disease may be responsible for the inflammation seen in some aneurysms.³⁶ This cause of inflammation is clearly implicated in the pathogenesis, and possibly the location, of the renal and visceral artery aneurysms typically seen in polyarteritis nodosa.³⁹ Patients with giant cell arteritis are 17 times more likely to develop TAA than the age- and sex-matched population, although the risk of developing an AAA is only doubled.⁴⁰ This increased risk of thoracic aneurysm appears to be unrelated to persistent arteritis, although the microanatomy of the thoracic aorta and initial injury may be important factors. Although it has been suggested that AAA is an immune-mediated large-vessel arteritis,⁴¹ this fails to explain the marked propensity for aneurysm formation in this location.

The classic infective cause of aneurysmal disease is syphilis, which results in a lymphoplasmacytic infiltration of the vasa vasorum with endarteritis obliterans.⁴² This may explain the propensity for syphilis to affect the ascending and arch aorta given the paucity of vasa vasorum in the more distal aorta.⁴² The location of some mycotic aneurysms is due to the direct spread from adjacent sepsis, which contributes to degradation or even focal erosion of the arterial wall (for example, aortic or cerebral aneurysms secondary to either tuberculous or other bacterial sepsis).^{43,44} Other mycotic aneurysms, particularly in smaller arteries, arise from hematogenous (sometimes embolic) spread. Although mycotic aneurysm is a well-recognized entity, there is little evidence that latent infection due to organisms such as herpes simplex, cytomegalovirus, or *Chlamydia pneumoniae* causes or influences the location of aneurysms.⁴⁵

Table. Examples of Site Specificity of Aneurysms in Human Monogenic Disorders. Mutations in Genes Denoted in Bold Can Result in Aneurysm as a Principal Phenotype, Mutations in Genes in Italics Can Have Aneurysms as a Secondary Phenotype. Mutations Associated With Arterial Dissections, but Not Aneurysms, Have Not Been Included. See <http://www.ncbi.nlm.nih.gov/omim> for Original Studies and More Detail

Site and Gene	Function	Clinical Manifestation
Cerebral arteries		
<i>PKD1/2</i>	Polycystins, calcium flux in SMC	Polycystic kidney disease (OMIM No. 173900); 5' mutations pre-dispose to cerebral aneurysm
<i>COL4A1</i>	Basement membrane collagen	HANAC syndrome (OMIM No. 611773)
Ascending aorta		
FBN1	Microfibrils, elastogenesis, TGF- β bioavailability & SMC phenotype	Marfan syndrome (OMIM No. 154700)
<i>EFEMP2</i>	Fibulin-4, elastic fibres	Cutis laxa autosomal recessive IIA (OMIM No. 219200)
Thoracic aorta		
<i>FBN1</i>	Microfibrils, elastogenesis, TGF- β bioavailability	Marfan syndrome (OMIM No. 154700)
<i>TGFBR1/2</i>	Signalling domain of TGF- β receptor	Loeys-Dietz syndrome (OMIM No. 609192)
MYH11	SMC tone/contraction	Familial TAA with patent ductus arteriosus (OMIM No. 132900)
ACTA2	SMC tone/contraction	Familial TAA (OMIM No. 611788)
Abdominal aorta		
<i>FBN1</i>	Microfibrils, elastogenesis, TGF- β bioavailability	Marfan syndrome with AAA (OMIM No. 154700)
<i>COL3A1</i>	Type III collagen, altered ECM fibres	Ehlers-Danlos type IV with AAA (OMIM No. 130050)
<i>ELN</i>	Elastin, altered ECM	Cutis laxa autosomal dominant (OMIM No. 123700)
Visceral arteries		
COL3A1	Type III collagen, altered ECM fibres	Ehlers-Danlos type IV (OMIM No. 130050)

Definitions: OMIM, Online Mendelian Inheritance in Man; ECM, Extracellular Matrix. Gene symbols: PKD1/2, polycystic kidney disease 1 & 2; COL4A1, collagen type 4 IV alpha 1; FBN1, fibrillin 1; EFEMP2, EGF-containing fibulin-like extracellular matrix protein 2; TGFBR1/2, transforming growth factor beta receptors 1 & 2; MYH11, Myosin heavy chain 11 for SMC; ACTA2, Actin alpha 2; COL3A1, collagen type III alpha 1.

In summary, systemic factors are important in the pathogenesis of aneurysms and have some influence on site specificity, local anatomic factors (microscopic and gross) must play a decisive role in the location of aneurysms.

Developmental Factors

Cardiac and Outflow Tract Embryogenesis

Complex signaling pathways during embryogenesis influence SMC ontogeny phenotype and response to factors implicated in aneurysm formation, such as TGF- β .⁴⁶ Studies of murine and zebrafish mutants have established that a range of transcriptional factors influence cardiovascular development in an orchestrated segmental fashion.^{47,48} The details of this molecular signaling are beyond the present review but include processes such as arterial and venous differentiation⁴⁹ and segmental aortic development.⁴⁸ The association between various congenital cardiac abnormalities and aneurysms of the proximal aorta suggests that signaling pathways that control the development of the heart and its outflow tracts may influence predisposition to aneurysmal change.⁵⁰ However, apart from some rare syndromic aneurysms (Table), these molecular insights have yet to help explain the site specificity of most aneurysmal disease.⁵⁰

Vascular Elastogenesis

During aortic development, elastin synthesis declines 10-fold between the conus arteriosus and the bifurcation of the iliac arteries.⁵¹ In adults, the thickness and number of elastic lamellae gradually decreases, which results in the wall thickness falling from approximately 1.5 mm at the arch to less than 1 mm in the distal aorta.⁴² The fall in elastin is particularly notable in the aneurysm-prone infrarenal aorta.⁵² In addition to its role as a structural protein, elastin influences arterial morphogenesis by autocrine regulation of SMC behavior. Elastin favors a contractile SMC phenotype with inhibition of SMC migration and proliferation,²⁵ effects that may be regulated in concert with other matrix components, such as versican.⁵³ Elastin, together with its fibrillar components, therefore plays a pivotal role in vessel wall function and structure.

It has been proposed that impaired aortic elastogenesis during fetal life programs an individual for hypertension in adulthood.⁵⁴ This concept could be directly relevant to the pathogenesis of AAA, although only indirectly relevant to cerebral aneurysms. Late gestation is the most important period of elastogenesis in the abdominal aorta, with both elastin deposition and arterial diameter increasing with blood flow.^{55,56} In contrast to the thoracic aorta, elastin synthesis in the abdominal aorta almost ceases at birth; this has been attributed to the sudden cessation of placental blood flow.⁵⁵ Because little elastin is synthesized in adult arteries,⁵⁷ the abdominal aorta has a relatively narrow window of elastin deposition, and any impairment in fetal elastogenesis is likely to have long-term effects. This impairment could be due to placental dysfunction or a micronutritional abnormality.

Intrauterine exposure to a variety of maternal risk factors can result in both congenital heart disease⁵⁸ and increased susceptibility to adult atherosclerotic disease.⁵⁹ The possibility that maternal risk factors play a role in aneurysmal disease has received little attention. In view of evidence that in utero factors can program arterial gene expression in later life, regional differences in hemodynamic conditions could have a similar effect. Therefore, from a developmental perspective, fetal factors could influence arterial diameter and risk of

aneurysmal disease in adulthood. Changes in afterload in early life can alter arterial structure in later life; high placental vascular resistance seen in small-for-gestational age infants has been shown to be associated with greater diastolic abdominal aortic diameters.⁶⁰

Intriguingly, the distribution of iliac aneurysmal disease coincides with those arteries that participate in the placental circulation: AAAs are associated with both common and internal iliac artery aneurysms, but external iliac artery aneurysms are essentially unknown.² There is evidence from human postmortem studies that the increased mechanical load associated with the placental circulation in late gestation causes structural changes such as microcalcification in the aorta and both common and internal, but not external, iliac arteries.⁶¹ Such effects may be synergistic with differences in SMC lineage (see below).

Other Developmental Factors

Dalith⁶² hypothesized an embryological cause for the predisposition of the abdominal (versus thoracic) aorta to atherosclerosis that was related to the involution of abdominal (mesonephric) branches. The contribution of these vestigial branches to aneurysmal disease is unknown, but they are common in arterial segments that are prone to aneurysms and have been implicated in cerebral aneurysm formation.⁵ Sites of arterial fusion during embryogenesis may also be prone to aneurysm formation. The popliteal artery, for instance, has a complex embryology with a tendency for branch variation,⁶³ and aneurysms at this location may have an embryological basis.⁶⁴

Tilson et al⁶⁵ speculated that the external iliac artery is resistant to aneurysm formation because it arises from the extraembryonic anlage, in contrast to the common and internal iliac arteries (which are aneurysm prone), which arise from the somites. In both chick embryos⁶⁵ and humans,⁶⁶ there are differences in the immunohistological characteristics between the internal and external iliac arteries. In keeping with such observations is the occurrence of aneurysms in $\approx 50\%$ of persistent sciatic arteries (a vestigial branch of the internal iliac artery).⁶⁷ These disparate observations suggest that normal and disordered embryogenesis can influence the propensity of an artery to aneurysmal disease.

Hemodynamic and Anatomic Factors: Flow, Shear, and Arterial Enlargement

Endothelial Cell Function and Heterogeneity

Endothelial cell heterogeneity may influence the distribution of atherosclerosis,⁶⁸ although evidence for its role in the site specificity of aneurysms is lacking. However, there are clinical reasons to suggest that endothelial heterogeneity is important to outcomes. For instance, cerebral aneurysms rupture, whereas popliteal aneurysms become occluded by laminated thrombus. The observation that flow in peripheral arterioles is increased in individuals with AAAs, which suggests increased diameter, indicates disturbances in arteriolar wall elastin, endothelial function, or both.⁶⁹

Blood flow is an important modulator of arterial growth. Wall shear stress is tightly regulated, with the normal artery enlarging in response to increases in flow to maintain normal

shear stress.⁷⁰ Endothelial release of nitric oxide is crucial for this response in the short term.⁷⁰ The more substantial structural changes, which occur after 6 months, appear to involve upregulation of matrix metalloproteinase-2 and -9 (both of which are implicated in aneurysmal disease).⁷¹ The expression of TGF- β , which plays an important role in the matrix of the arterial wall, is also shear dependent.⁷²

Studies of cardiac embryogenesis have established that changes in blood flow influence the expression of shear-dependent genes.⁷³ Genes for lung Krüppel-like factor (LKLF) and endothelial cell nitric oxide synthase (eNOS) are expressed at sites of high shear stress, whereas nuclear factor- κ B and endothelin-1 are expressed in areas of low shear stress.^{18,73} These shear-dependent molecules can influence arterial wall structure; for example, the aortic media is poorly organized in LKLF-null mice, although this has not been studied in models of aneurysmal disease.⁷⁴ Similar factors may play a role in poststenotic dilatation⁷⁵ (eg, coronary artery aneurysm formation in Kawasaki disease³⁵).

Role of Bifurcations

A study of war veterans with traumatic above-knee amputations suggested that amputation caused asymmetrical blood flow at the iliac bifurcation and hence an increased risk of AAA.⁷⁶ Hemodynamic disturbances such as low shear stress and turbulent flow, generally associated with branching or high curvature, contribute to some of the localization of atherosclerosis and aneurysms.^{18,77} To optimize blood flow through arterial bifurcations, the branching angle must be very obtuse, and the combined lumen areas of the daughter vessels should be greater than the luminal area of the parent vessel. Variations in the branching structure of muscular arteries appear to influence the site specificity of aneurysms, particularly their location proximal to a sharp-angle bifurcation or proximal to a hypoplastic artery, which gives rise to turbulence and increased wall stress. This has been studied most intensively in the intracranial arteries, where any geometric factor that leads to increased wall shear stress (curvature, bifurcation angle, and limited branch diameter) is thought to predispose to the formation of aneurysms.^{78,79} There is a tendency for the aneurysms in polyarteritis nodosa to occur at arterial branching points, and aneurysms of the coronary artery in Kawasaki disease usually occur immediately proximal to a bifurcation, particularly those in the right coronary artery, with its multiple branches.^{39,80}

Similar observations with respect to branching angles have been made for the aorta, where more acute common iliac branching (higher bifurcation angle) was associated with AAA.⁸¹ There is evidence that branch angles change with age,⁸² with increasing bifurcation angles encouraging aneurysm formation in susceptible arteries (Figure 5). In contrast to the more proximal aorta, the abdominal aorta has fewer lamellar units, a smaller cross-sectional area, and a stiffer wall; is exposed to the reflected pressure wave from the periphery; and has higher systolic and pulse pressures.^{31,83} As the aorta becomes stiffer with advancing age, the pressure increases further.⁸⁴ Compared with the supraceliac aorta, the infrarenal aorta experiences periods of zero (and reverse) flow during diastole and increased oscillatory wall shear stress and peripheral resistance.⁸⁵ These

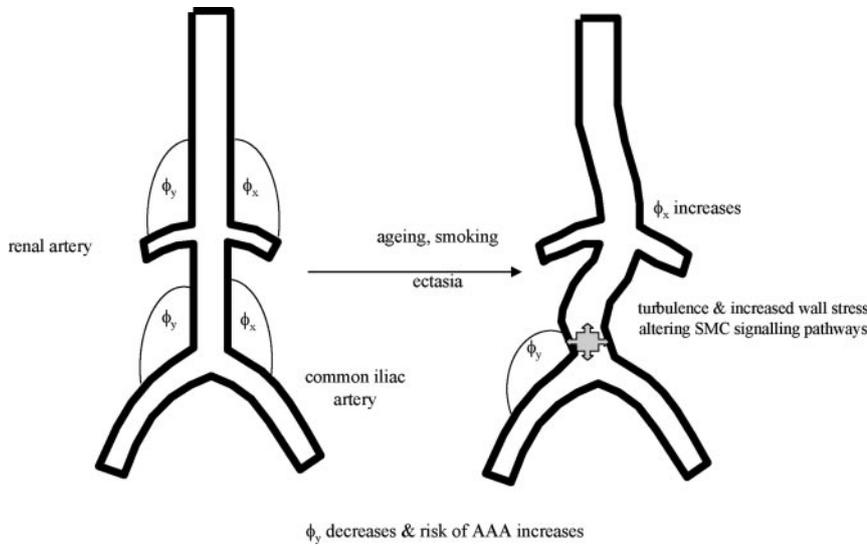


Figure 5. Schematic of the effect of aging and smoking on the common iliac artery branching angle and the predisposition to AAA. The aorta, like other elastic tissues, loses tone with increasing age and becomes ectatic, changes that are exacerbated by smoking. Such changes often lead to decreasing branching angle ϕ_y , with resultant increase in the bifurcation angle, which results in greater disturbances in distal aortic blood flow and susceptibility to aneurysm formation.

“resistive hemodynamic conditions” have the potential to up-regulate inflammatory and proteolytic pathways, predisposing this segment of aorta to both atherosclerotic and aneurysmal disease.¹⁸ For example, in rats, the expression and activity of

matrix metalloproteinase-9 is greater in the abdominal than in the thoracic aorta.⁸⁶ Localized adverse hemodynamic conditions have been implicated in the pathogenesis of cerebral aneurysms.^{19,87}

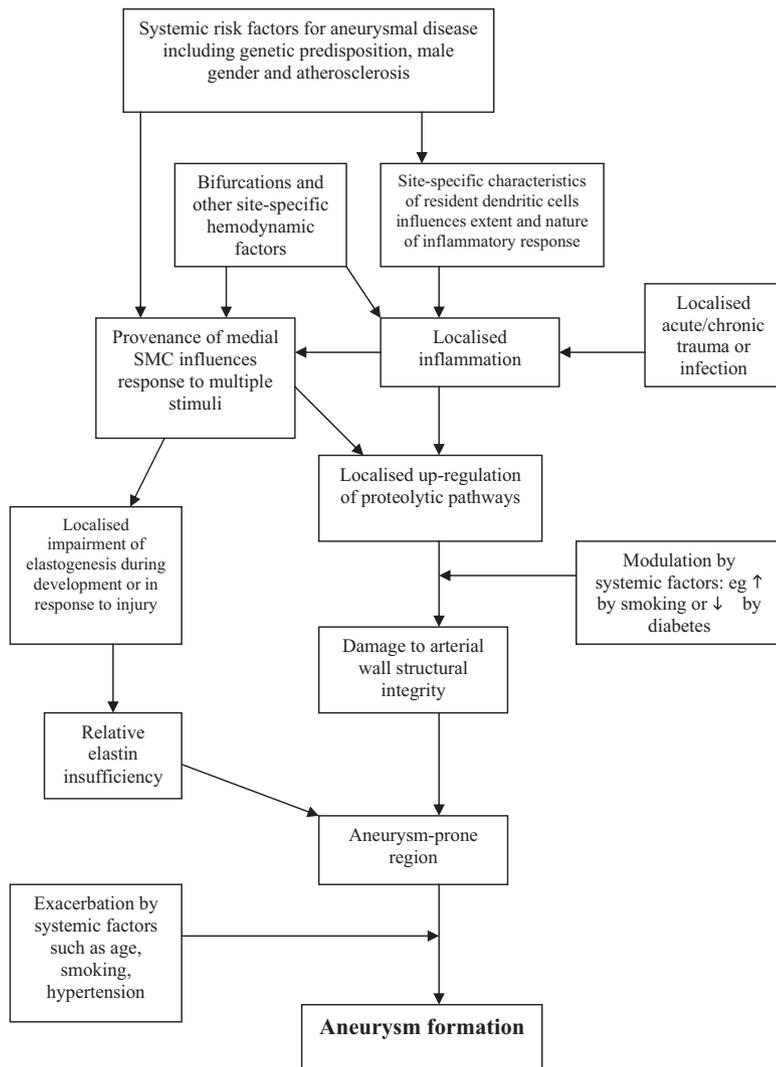


Figure 6. Possible mechanisms underlying the interaction between systemic and local factors that influence the site specificity of aneurysms.

SMC Lineage and Diversity

The diversity and plasticity of vascular SMCs is well recognized.⁸⁸ Arteries grow by the coordinated expansion of SMC clones with little mixing of adjacent clones.⁸⁹ The SMCs that form the aorta and its major branches are derived from multiple embryonic lineages in a discrete segmental fashion. The distal coronary system arises from the proepicardium and is well developed before a proximal connection with the aorta is established.⁹⁰ SMCs of the arch of the aorta are derived from neural crest; those of the thoracic aorta are derived from somite-derived cells; and those of the abdominal aorta are derived from splanchnic mesoderm.⁹⁰

Different parts of the normal and aneurysmal adult aorta appear to have distinct DNA expression profiles,⁹¹ and this may explain the site specificity and prevalence of various aneurysms. In the case of aortic atherosclerosis, there is evidence that susceptibility is governed by intrinsic wall characteristics rather than anatomic location. Abdominal aortas transplanted into the thoracic position in dogs (fed an atherogenic diet) still develop atherosclerotic change, yet placement of the inherently atherosclerosis-resistant thoracic segment in the atherosclerosis-prone abdominal location did not result in atherosclerotic change.⁹² This phenomenon has not been studied in experimental aneurysm formation. However, when Ailawadi et al⁸⁶ transplanted syngeneic thoracic aortic segments into the abdominal aorta, variations in matrix metalloproteinase-9 expression appeared to be related to regional factors and not intrinsic aortic wall factors.

TGF- β Pathways

The relevance of aortic heterogeneity in aneurysmal disease has been reviewed recently, and regional differences in TGF- β signaling appear to be significant.^{24,27} TGF- β is highly pleiotropic, with involvement in both matrix synthesis and degradation.²⁴ Genetic polymorphisms in the receptors for TGF- β have been demonstrated in patients with syndromes associated with aortic dilatation and familial TAA.⁹³ The TGF- β signaling pathway is selectively upregulated in the thoracic aorta; TGF- β induces α -1 procollagen production via c-myc expression in SMCs derived from the neural crest (thoracic aorta) but not from the mesoderm (abdominal aorta).⁹⁴ In addition, innervation by afferent nerves may play an important trophic role, possibly via TGF- β signaling, in the normal development of the aortic arch.⁹⁵ Angiotensin II, which induces TGF- β expression, has a marked vasoconstrictor effect on the mouse abdominal aorta but little effect on the thoracic aorta, a pattern apparently due to differences in angiotensin type 1 receptor levels.⁹⁶ Androgens have been shown to regulate angiotensin type 1a receptor expression in apolipoprotein E^{-/-} mice more strongly in the abdominal than in the thoracic aorta, and this may promote angiotensin II-induced aneurysms in the abdominal aorta.⁹⁷

These studies highlight fundamental differences in the vascular biology of different segments of the aorta. Although much remains to be learned about the boundaries between aortic (and presumably arterial) regions, it appears that embryological provenance may be responsible for regional differences in SMC function and disease susceptibility.

Conclusions

Most aneurysms are a focal manifestation of a systemic condition. Although environmental and genetic factors may determine which individuals develop an aneurysm, regional factors are likely determinants of where an aneurysm occurs (Figure 6). This review has focused on the role of site-specific factors in the most studied and most common aneurysms, those of the aorta and its branches and the cerebral circulation. Similar phenomena may influence aneurysm formation in other locations, and study of the most aneurysm-prone artery, the persistent sciatic artery, is likely to be rewarding. The importance of developmental vascular biology, vessel-specific immune cell profiles, and vascular cell heterogeneity are all attracting considerable attention in research into vasculitis and atherothrombosis and should be considered in the context of the site specificity of aneurysmal disease. Improved understanding of the basis for the site specificity of aneurysmal disease has the potential to yield clues about the cause of aneurysms, and this in turn may identify therapeutic opportunities.

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