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α-Smooth Muscle Actin and ACTA2 Gene Expressions in Vasculopathies

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Abstract

α-smooth muscle actin, encoded by ACTA2 gene, is an isoform of the vascular smooth muscle actins, typically expressed in the vascular smooth muscle cells contributing to vascular motility and contraction. ACTA2 gene mutations cause a diversity of diffuse vasculopathies such as thoracic aortic aneurysms and dissections as well as occlusive vascular diseases, including premature coronary artery disease and ischemic stroke. Dynamics of differentiation-specific α-smooth muscle actin in arterial smooth muscle cells and proliferation of the proteins have been well described. Although a variety of research works have been undertaken in terms of modifications of α-smooth muscle actin and mutations of ACTA2 gene and myosin, the underlying mechanisms towards the pathological processes by way of gene mutations are yet to be clarified. The purpose of the present article is to describe the phenotypes of α-smooth muscle actin and implications of ACTA2 mutations in vasculopathies in order to enhance the understanding of potential mechanisms of aortic and coronary disorders.

Keywords: Actins. Aorta, Thoracic. Mutation, Missense.

Abbreviations, acronyms & symbols

ACTA2	= Actin, alpha 2, smooth muscle, aorta
bFGF	= Basic fibroblast growth factor
CAD	= Coronary artery disease
HH	= Hamburger - Hamilton stage
MYH11	= Myosin heavy chain 11
MYLK	= Myosin light chain kinase
PDGF	= Platelet derived growth factor
SMA	= α-smooth muscle actin
SMCs	= Smooth muscle cells
TAAD	= Thoracic aortic aneurysm and dissection
TGF	= Transforming growth factor
TGF-β_1	= Transforming growth factor beta 1
TGFβR1	= Transforming growth factor beta-receptor 1
TGFβR2	= Transforming growth factor beta-receptor 2

INTRODUCTION

The pathogenesis of vasculopathies, including aortic and coronary disorders, are uncertain, even though they have been under constant investigation. The potential roles that α-smooth muscle actin (SMA) might play in the development of vasculopathies have drawn much attention.

SMA, encoded by ACTA2 gene, is an isoform of vascular SMA. The major functions of vascular smooth muscle cells (SMCs) are typically vascular motility and contraction, and the functions of certain non-muscle cells, such as myofibroblasts, are healing wounds, scars and fibrocontractive lesions[1], depending on the cyclic interaction between thin filaments composed of the SMC-specific isoform of α-SMA encoded by ACTA2 and thick filaments composed of SMC-specific β-myosin. α-SMA and the encoding gene ACTA2 mutations have been frequently described in relation to pathogenesis of vasculopathies in clinical settings[2]. Studies on ACTA2 mutations have demonstrated that mutation carriers show various vasculopathies, including premature onset of coronary artery disease (CAD), premature ischemic strokes (including Moyamoya disease), and familial thoracic aortic aneurysms and dissections (TAADs)[2]. Proliferative and secretory activities as well as transition from a contractile to a synthetic phenotype of α-SMA were considered the underlying mechanism of vasculogenesis[3]. Experimental studies with explanted SMCs and myofibroblasts from patients harboring ACTA2 revealed that increased proliferation of SMCs contributed to occlusive diseases. Although a series of research works have been undertaken in terms of α-SMA modifications and ACTA2 gene mutations, the underlying mechanisms of pathological processes by way of mutations remain underestimated. In order to highlight the potential mechanisms of pertinent vasculopathies and to enhance management strategies, the phenotypes of α-SMA and implications of ACTA2 mutations in vasculopathies are described.

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Molecular structure of α-SMA

There are four distinct variants of actins: two vascular SMC (α-SM and γ-SM)-specific, and two cytoplasmic actins (β-NM and γ-NM actins) in eukaryotic cells. α-SMA is located primarily in the microfilament bundles of vascular SMCs and exerts contractile functions. It shows a close relationship with arterial tones and the activation of myofibroblasts[4]. The forceful contractile property of myofibroblasts is attributable to the stress fibers dependant on α-SMA[5]. SMC components and extracellular matrix (collagen and elastin) are determinants of the contractility, distensibility and elasticity of the aortic wall. Extracellular matrix disruption or imbalance of the extracellular matrix components leads to stiffness of the aortic wall and further development of TAAD[6]. In experimental homozygous α-SMA knock-out mice, deficits of vascular contractility and reduced basal blood pressure were noted, implicating the important role of α-SMA in maintaining vascular tone[7].

Clinical investigations

Normal aortic media predominantly contains α-SMA-positive SMCs with homogeneous elastic laminae[8] whereas degeneration is marked by disruptions of α-SMA-positive SMCs[9]. Vascular occlusions are pathologically characterized by medial proliferation of SMCs or enhanced proteoglycan accumulation along with fragmentation and loss of elastic fibers[10]. The α-SMA mutations in TAAD hinder the binding affinity between the monomer and the ligands, thereby generating more unpolymerized monomers[10]. The aortic media of abdominal aortic aneurysm displays fewer α-SMA-positive cells, which are secondary to extensive aortic wall structural damages. Medial SMC density may decrease by 79.1% in abdominal aortic aneurysmal tissue in comparison with that of normal control[8]. Aortic aneurysmal wall shows chronic infiltration of the inflammatory cells, degradation of the extracellular matrix, and apoptosis of SMCs[11]. In addition, macrophages express chemoattractant proteins and matrix metalloproteinases in the atherosclerotic plaques[12] similar to aortic aneurysm, in particular in the aneurysm necks for the stent graft anchoring.

An immunohistological study has shown more α-SMA expressions in coronary erosion lesions than in stable plaques or mildly stenotic plaques[13]. Acute arterial injury was found to be associated with changes in glycosaminoglycans of the extracellular matrix ahead of those of SMC phenotype, whereby matrix glycosaminoglycans are substituted by SMCs rapidly during the modification process where neointima does not generate enough heparin sulphates[14].

Coronary stenting may cause concentric narrowing of the lumen due to neointimal formation, in which the extracellular matrix increases and number of SMCs decreases over time. The neointima is composed of three-layered and circular-arranged α-SMA-positive cells. Immunohistochemical studies of the common carotid artery with stent deployment showed in-stent thrombus around the stent struts with the neointima composed mainly of α-SMA-positive cells within type I collagen-positive matrix[15]. Comparative studies on the abdominal aortopathies revealed that α-SMA-positive SMCs were predominant in the aortic media of the occlusive abdominal aorta and the aneurysmal neck; however, SMCs were disrupted and disarrayed in the aneurysmal body, in which much fewer SMCs were present than in the occlusive aorta and the aneurysmal neck[16].

Transforming growth factor (TGF)-β-antagonist reduces α-SMA expression, and treatment with TGF-β may upregulate α-SMA expression. TGF-β_1-stimulated adventitial fibroblasts in TAAD patients attenuated extracellular matrix production and SMC transformation[6]. In the aneurysmal neck, there was increased TGF-β_1 expression and reduced SMC density, and even more upregulated TGF-β_1 expression and much more reduced SMC density were found in the aneurysmal body in comparison with those of the occlusive aorta. Therefore, a link between TGF-β_1 overexpression and reduced SMC density as a result of SMC apoptosis and attenuated SMC proliferative capability may characterize the aneurysmal formation[16].

Genetic aspects of ACTA2 mutations

ACTA2, the encoding gene of α-SMA, located at 10q22-q24 and composed of eight coding exons, is a major contractile component of the arterial SMCs[2]. ACTA2 gene defects that cause familial TAAD type 6 have been reported[17]. So far, more than 20 different missense mutations of ACTA2 have been found to be associated with aortopathies[18]. ACTA2 mutations may show reduced penetrance and variable expressivity due to a dominant negative mechanism[19]. Heterozygous ACTA2 mutations may lead to impaired SMCs, showing pathological hyperplasia and disarray due to medial degeneration, vascular wall remodeling, increased wall stiffness, and aortic dilation[20,21]. It may indicate a possible increased risk of stroke and CAD rather than hypertrophy[2], and it may be a causative etiology of multiple tiny aneurysms of the cerebral arteries, responsible for pediatric acute ischemic stroke[22]. The relationship among SMA, ACTA2 gene, and contractile property in vasculopathies is listed in Figure 1.

Syndromic aneurysms (Marfan syndrome and other connective tissue diseases including Loeys-Dietz syndrome, Ehlers-Danlos syndrome, and familial TAAD) have been proven to have overlapping clinical features and mutated TGF-β genes[23,24] while familial non-syndromic patients are associated with mutations in MYH11, transforming growth factor beta-receptor 1 (TGFβR1), Transforming growth factor beta-receptor 2 (TGFβR2), myosin light chain kinase (MYLK), and ACTA2 genes in spite of incomplete penetrance and/or locus heterogeneity[24]. Casual mutations of fibrillin-1, TGFβR1, TGFβR2, ACTA2, MYH11, and SMAD3 genes were detected in TAAD patients[23,25,26].

A mutation in a single ACTA2 gene can cause a variety of vascular diseases[2]. Guo et al.[27] reported that mutations in ACTA2 gene are the most common mutations, accounting for 10-15% of familial TAAD mutations. By contrast, only 0.9% of the patients with TAAD had a mutation in the ACTA2 gene according to Lerner-Ellis et al.[28]. The prevalence of ACTA2 mutations was 12-16% in familial TAAD[21,29] as opposed to 0% in sporadic cases[21]. In patients with known TAAD, non-synonymous missense mutations were identified in 3.85% probands[30]. The TAAD family members showed a penetrance as low as 0.48% in heterozygous ACTA2 mutations[31]. TAAD was the primary vascular disease in ACTA2-mutation carriers, some of which also had premature CAD, ischemic strokes and multiple vascular diseases, including Moyamoya disease[2,32,33]. However, none of the family members without ACTA2 mutation

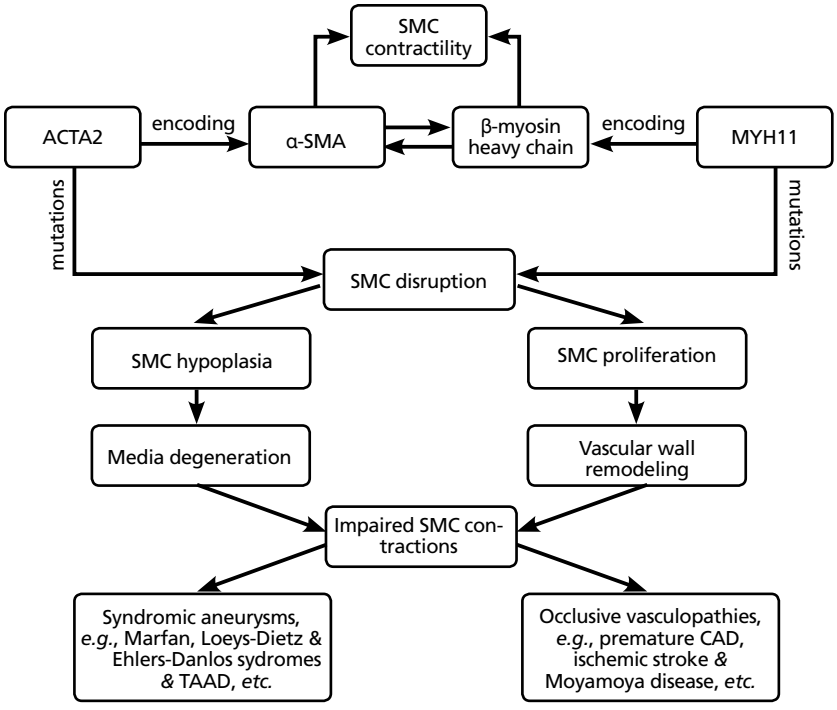

Fig. 1 - The relationship among smooth muscle actin, ACTA2 gene and contractile property in vasculopathies. The contractility of the smooth muscle cells is maintained via cyclic interactions between α-smooth muscle actin (encoded by ACTA2) and the β-myosin heavy chain (encoded by MYH11). Missense mutations in ACTA2 and myosin are responsible for the development of syndromic aneurysms or occlusive vascular disorders, depending on the vascular pathology of either medial smooth muscle cell hypoplasia or medial proliferation.
ACTA2=actin, alpha 2, smooth muscle, aorta; CAD=coronary artery disease; MYH11=myosin heavy chain 11; SMA=smooth muscle actin; SMC=smooth muscle cell; TAAD=thoracic aortic aneurysm and dissection

had TAAD, premature CAD or stroke[2]. Causative gene mutations for TAAD have been identified, including TGFβR2 at the TAAD2 locus, MYH11 at the 16p locus, and ACTA2 at the TAAD4 locus[34]. Causative genes responsible for vasculopathies such as aortic, coronary, peripheral vascular and cerebrovascular disorders were carefully depicted in Table 1[2,20,30,31,34-41].

Heterozygous missense mutations in ACTA2 disrupting Arg179 had persistent ductus arteriosus and congenital mydriasis, variable presentation of pulmonary hypertension, bladder and gastrointestinal disorders, as well as carotid and cerebrovascular abnormalities, including absent basal "Moyamoya" collaterals[42]. MYH11 and ACTA2 missense mutations were associated with upregulation of the TGF-β signaling pathway[29]. Distinct loci for large pedigrees of familial TAAD were on 5q13-q14, 16p13.12-p13.13, 11q23.3-q24, 3p24-p25, 9q22, 10q22-q24, and 15q24-q26 (MIM 607087, 132900, 607086, 6103080, 608967, 611788, and unassigned), with four being identified as ACTA2 (MIM 102620, 10q23), MYH11 (MIM160745, 16p13), TGFβR1 (MIM 190181, 9q22), and TGFβR2 (MIM 190182, 3p22)[43]. Patients presenting with acute ascending or descending aortic dissections have also been found to have ACTA2 mutations[27]. Half of the mutation carriers have no aortic disease, while those with aortic aneurysms usually have missense ACTA2 mutations with fewer deletions and splice-site mutations[19]. Aortic aneurysms pending to rupture may show various aortic dimensions, in particular, patients with aortic aneurysm with ACTA2 mutations have an aortic dimension of <5.0 cm prior to dissection. Therefore, early surgical treatment is recommended in such patients, even with minimal changes to aortic dimensions[2]. Shimojima et al.[44] sequenced the nine exons of ACTA2 in a cohort of 53 patients with Moyamoya disease from 7 familial series without showing any mutations. Similarly, Lee et al.[45] also reported that mutations in human RNF213 were present whereas ACTA2 gene mutations were absent in 36 Taiwanese Moyamoya patients.

Basic Research for Possible Mechanisms

α-SMA is important for contractile functions of the developing heart at an early embryonic stage. Research on avian epimyocardial cells demonstrated α-SMA mRNAs were mainly detected in conus arteriosus and the ventral aorta before Hamburger–Hamilton stage (HH) 12. In subsequent stages, the α-SMA mRNA was apparently confined to SMCs of the vascular system. The contractive properties of SMCs can be suspended while secretory functions prevail by exertions of mitogens, including platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF), and extracellular matrix components such as collagen, elastin and proteoglycans that contribute to SMC differentiation and proliferation[3]. Hence, α-SMA expression inversely correlates with cell proliferation, but directly correlates with contractile efficiency of SMCs[46].

Fibronectin and laminin are expressed typically in the arterial media during fetal and adult life in different forms, and a paradoxical transformation of the proteins from adult to fetal variants takes place during the vascular pathological processes. Vascular SMCs are also implicated in vessel remodeling, in either physiological or pathological conditions, such as pregnancy, exercise, or vascular injury[47]. During the remodeling process after vascular injury, the SMCs resume a contractile phenotype, with a cytoplasm dominated by α-actin filaments until the final extent of neointimal formation. The phenotype of cultured rabbit SMCs can be modified by PDGF-BB, resulting in faster growth, but SMCs preincubated with conditioned medium of macrophages plus anti-PDGF antibody did not grow faster. Human arterial and venous SMCs exhibited very different proliferative responses to PDGF isoforms. Proliferation of arterial

Table 1. Causative ACTA2 gene mutations of vasculopathies.

Causative gene mutation	Typical manifestation	Reference
p.Arg64Lys (c.191G>A) (exon 3), p.Arg179Cys (c.535C>T) (exon 6) & p.Lue244Phe (c.732G>T) (exon 7)	TAAD	[23]
p.Arg179His	TAAD	[23]
G304R (in the vicinity of the ATP-binding site)	TAAD, isolated	[20]
p.G152_T205del (c.616+1G>T), p.R212Q & p.R149C	TAAD, familial	[17]
p.Y145C	TAAD, sporadic & young-onset	[17]
c.76G>T; p.Asp26Tyr	TAAD, non-syndromic familial	[19]
R39C (the DNAse-I-binding loop within subdomain 2 of α-smooth muscle actin)	Aortic aneurysm, recurrent	[20]
M49V (the DNAse-I-binding loop within subdomain 2 of α-smooth muscle actin) R118Q & R149C	Aortic dissection	[20]
R118Q & R149C	Aortic disease, coronary artery disease (early onset)	[15]
R258	Aortic disease, patent ductus arteriosus, cerebrovascular disease (very early onset), including Moyamoya disease	[15]
R179H	Aortic & cerebrovascular disease, fixed dilated pupils, hypotonic bladder, gut malrotation, hypoperistalsis & pulmonary hypertension	[15]
R179H	More severe vasculopathy, thoracic aortic aneurysm & brachial artery occlusion	[16,18]
p.R118Q, p.R149C	Coronary artery disease	
p.R179C amino acid substitution (c.535C>T in exon 6)	Primary pulmonary hypertension, persistent ductus arteriosus, extensive cerebral white matter lesions, fixed dilated pupils, intestinal malrotation & hypotonic bladder	[31]
c.772C/T, p.R258C; c.773 G/A, p.R258H ; R179H, c.536 G/R (Exon 6)	Moyamoya disease	[33]
p.R258C/H	Strokes	
p.R39H (SD2 domain)	Stroke (before the age of 20)	
R179H substitutions	Cerebral developmental defects (underdeveloped corpus callosum & vermis hypoplasia), vascular fragility & ductus arteriosus rupture	[31]
R179H	Neonatal seizures due to multifocal infarcts, asymmetric motor deficits, global developmental delay, spasticity, congenital bilateral mydriasis & patent ductus arteriosus	[30]
p.R149C, p.R118Q & p.T353N (within the hydrophobic cleft of α-smooth muscle actin)	Premature coronary artery disease	
p.R185Q	Perturb adenosine triphosphatase hydrolysis	
R149C	Skin rash caused by dermal capillary and small artery occlusion referring to as livedo reticularis & with iris flocculi, patent ductus arteriosus & bicuspid aortic valve	

ATP=adenosine triphosphate; TAAD=thoracic aortic aneurysm and dissection.

SMCs was strongly stimulated by PDGF-AA, but venous SMCs showed no proliferative response to PDGF-AA, demonstrating instead a significantly greater proliferative response to PDGF-BB than arterial SMCs[48]. In cultured rat aortic SMCs, enhanced proliferation, elongated cellular deformity as well as a fluctuation pattern of growth under the exertion of TGF-β_1 were present[49].

During angiogenesis and vascular remodeling due to restenosis and atherosclerosis, SMCs regulate endothelial cell quiescence and angiogenic responsiveness to cytokines. A series of studies revealed TGF-β stimulates the matrix production of vascular SMCs, including type I collagen. The enhanced α-SMA expression induced by TGF-β_1 increases the contraction of collagen gel mediated by bovine corneal fibroblasts in a dose-dependent manner. Integrin $\alpha_2\beta_1$, one of the collagen-binding receptors, binds fibril-forming collagens, collagens I, II, III and X. It joins the process of TGF-β_1-induced α-SMA production and regulation, capable of generating intracellular tension.

α-SMA disruption results in SMC hyperplasia via certain cellular pathways involving FAK, p53 and PDGF receptor-β, contributing to vascular occlusive disorders in patients with ACTA2 missense mutations. This is supported by the experiments in ACTA2 knockout mice, in which decreased aortic contractility was displayed[50]. The structural heterogeneity of genomic DNA encoding the chicken α-SMA gene in 3' untranslated regions is of alternative polyadenylation signals, but with uncertain functional implications. Moreover, actin isoform synthesis after balloon induced endothelial denudation warrants further investigations in order to be employed early in clinical practice.

CONCLUSION

ACTA2 mutations are associated with structural disruption and functional impairment of contractile proteins, and predispose to a variety of diffuse vascular diseases including TAAD, CAD, ischemic strokes, and Moyamoya disease. Vascular SMCs are also implicated in vascular remodeling in both physiological and pathological conditions. Regulation of differentiation and proliferation of SMCs may control the expression of genes encoding for proteins responsible for the contractile function of the SMCs. In the process of vascular remodeling, contractive properties of SMCs can be suspended while secretory functions prevail by mitogen impacts. Research on α-SMA and ACTA2 mutations is imperative for understanding the pathogenesis and determining the pertinent management strategies of vasculopathies. Further in-depth studies of causative genes of ACTA2 mutations may largely facilitate the diagnosis and treatment of the underlying disorders.

Authors' roles & responsibilities

SMY Study conception and design; analysis and/or interpretation of data; manuscript writing, final approval of the manuscript.

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