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Special Review

The Pathophysiology of Moyamoya Disease: An Update

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Moyamoya disease (MMD) is a unique cerebrovascular disease characterized by the progressive stenosis of large intracranial arteries and a hazy network of basal collaterals called moyamoya vessels. Because the etiology of MMD is unknown, its diagnosis is based on characteristic angiographic findings. Re-vascularization techniques (e.g., bypass surgery) are used to restore perfusion, and are the primary treatment for MMD. There is no specific treatment to prevent MMD progression. This review summarizes the recent advances in MMD pathophysiology, including the genetic and circulating factors related to disease development. Genetic and environmental factors may play important roles in the development of the vascular stenosis and aberrant angiogenesis in complex ways. These factors include the related changes in circulating endothelial/smooth muscle progenitor cells, cytokines related to vascular remodeling and angiogenesis, and endothelium, such as caveolin which is a plasma membrane protein. With a better understanding of MMD pathophysiology, non-surgical approaches targeting MMD pathogenesis may be available to stop or slow the progression of this disease. The possible strategies include targeting growth factors, retinoic acid, caveolin-1, and stem cells.

Keywords Angiogenesis; Caveolin; Endothelial progenitor cells; Growth factors; Moyamoya disease

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Introduction

Moyamoya disease (MMD) is a unique cerebrovascular disease characterized by the progressive stenosis of the distal internal carotid artery (ICA) and the resulting hazy network of basal collaterals called moyamoya vessels. The etiology of MMD is unknown. As a result, the criteria for the diagnosis of MMD is based on characteristic angiographic findings. However, the angiographic findings may not be sensitive or specific to MMD. The current diagnostic criteria require the presence of prominent basal collaterals for the diagnosis of MMD. However, a decision on the presence of basal collaterals can be subjective. In patients with MMD, the angiographic findings can differ according to the progressive stage and age of presentation, and the characteristic angiographic findings are not consistently observed in all courses of MMD.[1-3] In patients with an early stage of Suzuki's angiographic grading, the abnormal vascular network is not yet evident.[4] Unlike in childhood-onset MMD, the basal collaterals are often not prominent in adult-onset MMD.[3] In addition, the patients may present with unilateral MMD findings. In fact, the diagnostic criteria for definitive MMD was revised to include patients with both a bilateral and unilateral presentation of the terminal ICA stenosis with an abnormal vascular network at the base of

the brain by the Research Committee of MMD of the Japanese Ministry of Health, Labour, and Welfare in 2015.

Owing to the currently limited understanding of MMD, revascularization techniques (e.g., bypass surgery) to restore perfusion are the primary treatment for MMD. There is no specific treatment to prevent MMD progression. The purpose of this review is to summarize the recent advances in MMD pathophysiology, including the genetic and circulating factors related to disease development.

Pathological features of MMD

The main pathological changes of the stenotic segment in MMD are the fibrocelluar thickening of the intima (e.g., the hyper-proliferation of the vessel wall components, active angiogenesis, and matrix accumulation), irregular undulation of the internal elastic laminae, medial thinness (e.g., an attenuation of media), and a decrease in the outer diameter.[5-10]

Recent neuroimaging techniques, such as the three-dimensional (3D) constructive interference in steady-state (CIISS) magnetic resonance imaging (MRI) and high-resolution MRI studies of patients with MMD, have demonstrated a constrictive remodeling (e.g., the narrowing of the arterial outer diameter) in affected segments and a concentric enhancement of the symptomatic segments.[11-14] In our data set from a large cohort of adult-onset MMD, most patients (90.6%) showed a long-segment concentric enhancement of the distal ICA and/or middle cerebral artery on a high-resolution MRI, regardless of symptom presence or acuteness. The high-resolution MRI findings are consistent with the results of previous pathological reports that showed intimal hyperplasia and medial thinness.[6,7]

There is growing evidence that MMD is primarily a proliferative disease of the intima. The smooth muscle proliferation that is associated with an *ACTA2* mutation has been postulated to be the key mechanism of the vascular occlusion in familial MMD.[15] The histopathological findings in the distal ICA have shown a proliferation of the smooth muscle cells or endothelium[8,10,16] and a stenosis or occlusion associated with the fibrocellular thickening of the intima.[5] An enhancement of the stenotic segments may represent either a neo-vascularization or an intimal hyperplasia.

The moyamoya vessels are the dilated perforating arteries that have various histopathological changes, including fibrin deposits in the wall, fragmented elastic laminae, attenuated media, and the formation of microaneurysms.[5] In addition to the moyamoya vessels, cortical microvascularization, which is characterized by a substantially increased microvascular density and diameter, is suggested as a specific finding in MMD.[17] These basal and cortical vessels may represent compensatory mechanisms for the reduced cerebral blood flow or the aberrant active neo-vascularization before the vascular occlusion. An angiographic study of a large cohort of pediatric patients with MMD showed that the cortical neo-vascularization may occur before any significant hemodynamic impairment, suggesting that neo-vascularization is an active process, not a passive compensation for the vascular occlusion.[18]

The complicated pathologic features of the stenotic segments of MMD (e.g., a coexistence of proliferation and shrinkage) and the unknown nature of the neo-vascularization (e.g., an aberrant vs. compensatory process) suggest that MMD pathophysiology is a complex process.

Genetics underlying MMD

Approximately 10% of individuals with MMD exhibit a familial occurrence. Several genetic loci have been identified in familial MMD, including 3p24-26,[19] 6q25,[20] 8q23,[21] 10q23.31,[15] 12p12,[21] and 17q25.[22] In addition, MMD is also associated with many genetically transmitted disorders, including neurofibromatosis, Down syndrome, sickle cell anemia, and collagen vascular disease. These findings suggest the importance of genetic factors.

RNF213 as a susceptible gene for MMD

More recently, the *Ring finger 213* (*RNF213*) gene in the 17q25-ter region was identified as the strongest susceptibility gene for MMD in East Asian people using a genome-wide linkage and exome analysis.[23,24] The p.R4810K (c.14576G > A) variant of the *RNF213* genetic variant was identified in 95% of patients with familial MMD, 80% with sporadic MMD, and 1.8% of control subjects in a Japanese population.[23] The homozygous p.R4810K variant of *RNF213* predicted an early onset and severe form of MMD in both Japanese[25] and Korean[26] patients with MMD. The population that is susceptible to MMD, such as carriers of the *RNF213* p.R4810K variant, is estimated to be 16.16 million people in East Asian countries.[27] The number of patients with MMD, which was conservatively estimated at 1 per 300 carriers of the *RNF213* p.R4810K variant, is considered to be 53,800 in East Asian populations.[27,28]

Further genetic studies for MMD are warranted, particularly in populations outside East Asia, because the single nucleotide polymorphism (SNP) of p.R4828K in *RNF213* is not the susceptibility gene for MMD in Westerners or South Asian individuals. Novel variants in *RNF213* in non-p.R4828K were recently found in Caucasian and Chinese cases with MMD[24] and in the United States.[29] For example, several variants of

RNF213 in non-p.R4810K (i.e., rs148731719, rs397514563) were recently found in Caucasian and East and South Asian patients with MMD.[24,29-31] In addition, the clinical manifestations and possibly angiographic findings may differ between Westerners and East Asians.[32] The p.R4810K *RNF213* variant was reportedly related to the ischemic type of MMD, while the non-p.R4810K *RNF213* variants, particularly A4399T, were associated with the hemorrhagic-type of MMD.[30]

Function of *RNF213* on MMD pathophysiology

The exact function of *RNF213* is unknown. Recent *in vivo* experiments using genetically engineered *RNF213* mice addressed the mechanism underlying the *RNF213* SNPs in the development of MMD pathology. The target disruption of *RNF213* did not induce MMD in the *RNF213*-defcient mice under normal conditions.[33] Kanoke and colleagues alternatively generated *RNF213*-knock-in mice that expressed a missense mutation in the mouse *RNF213*, p.R4828K, on Exon 61, which corresponds to the human *RNF213*, p.R4859K, on Exon 60 in MMD patients; however, these mice did not develop MMD under normal conditions.[34] These negative results could be consistent with the low penetrance rate of the *RNF213* polymorphisms in patients with MMD, and may indicate the importance of environmental factors in addition to the genetic factors.[35] They subjected the *RNF213*-deficient mice to an ischemic insult, and found that the post-ischemic angiogenesis was significantly enhanced in the mice lacking *RNF213* after a chronic hindlimb ischemia.[36] This suggests the potential role of a *RNF213* abnormality in the development of abnormal vascular networks in chronic ischemia.

Hitomi et al. established a model of induced pluripotent stem cells derived from vascular endothelial cells (iPSECs), and showed that the angiogenic activity from patients with MMD and *RNF213* carriers was lower than that of the control subjects. The overexpression of the *RNF213* variant downregulated Securin and inhibited angiogenic activity.[37] They also showed that *RNF213* may be a mediator downstream of the IFN-β signaling pathway in endothelial cells. Carriers of the *RNF213* variant may be susceptible to cerebral hypoxia because of insufficient angiogenesis if inflammation and hypoxia occur simultaneously.[38] Ohkubo and colleagues also showed that pro-inflammatory cytokines activated *RNF213* transcription, and *RNF213* functions as a common downstream effector of the PI3 kinase-AKT pathway in endothelial angiogenesis.[39] These data suggest that although MMD is not an inflammatory disease, inflammation may play an important role in MMD development. *RNF213* plays a unique role in endothelial cells regarding the proper gene expression in response to inflammatory signals from the environment. However, further studies are needed to elucidate the differential pathological processes between the endothelium (e.g., lowered angiogenesis) and smooth muscle cells (e.g., abnormal proliferation that causes moyamoya vessel formation and stenosis of the major intracranial arteries).

In addition to the preclinical data, clinical data has also shown that exposure to environmental factors, such as an autoimmune response and infection/inflammation, in MMD-susceptible subjects may be associated with the angiographic features of MMD.[35] For example, autoimmune thyroid disease has been reported in different MMD populations (i.e., pediatric and adult-onset MMD, East Asians, and Westerners) and may be involved in MMD development.[40-42] In addition, the *RNF213* genetic variant may be associated with vascular risk factors, such as hypertension,[43] and also could lead to vascular fragility, which may make vessels more vulnerable to hemodynamic stress and secondary insults.[35]

Polymorphisms of microRNAs

MicroRNAs (miRs), which are small non-coding RNAs (~23 nucleopeptides), negatively regulate the expression of many proteins by altering their gene expression through post-transcriptional repression or mRNA degradation.[44] miRs may play an essential role in the regulation of proliferation, differentiation, survival, and aging of various tissues and cells, including stem cells. There is increasing evidence that miRs that are altered after focal ischemia have a functional significance in the recovery after stroke as well as ischemic pathophysiology. Preclinical studies of ischemic stroke have demonstrated that miRs protect against focal ischemia and reperfusion injury by inhibiting oxidative stress.[45] They are also involved in inflammation, neurogenesis, and angiogenesis.[46-48]

A genome-wide miR array analysis of the serum from patients with MMD showed elevated serum levels of miRs associated with *RNF213* and BRCC3 (i.e., BRCA1/BRCA2-containing complex, an important angiogenesis-related protein), both of which are involved in MMD pathogenesis.[49] In addition, a SNP of miR-196a was associated with MMD.[50] ANXA1, which is expressed in endothelial and smooth muscle cells,[51] is a gene target of miR196a and mediates the apoptosis and inhibition of cell proliferation.[52]

Biomarkers underlying vascular stenosis and aberrant angiogenesis

In addition to genetic biomarkers, there are circulating factors that may be involved in MMD pathogenesis, including cir-

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culating endothelial progenitor cells (EPCs), cytokines, and caveolin.

Circulating vascular progenitor cells

In patients with acute myocardial infarcts or ischemic stroke, increasing evidence points to a role for circulating EPCs that originate from the bone marrow and help maintain the vasculature and blood flow in an infarcted area.[53] EPCs potentially contribute to the neo-vascularization at the ischemic brain injury site in patients with MMD.[54] Rafat et al. reported the presence of increased levels of circulating EPCs in patients with MMD.[55] In contrast, Kim et al. demonstrated decreased EPC levels and defective angiogenic function in EPCs in pediatric patients with MMD, indicating there is abnormal angiogenesis during MMD pathogenesis.[56] Similarly, impaired EPC function was observed in adult patients with MMD.[57] Recently, Lee et al. reported a downregulation of retinaldehyde dehydrogenase 2 (RALDH2) using the gene expression profiles of EPC in pediatric patients with MMD. The epigenetic suppression of RALDH2 expression contributed to the defective function of MMD endothelial colony-forming cells; this could be rescued by supplying retinoic acid *in vitro* and *in vivo*.[58] Aberrant angiogenesis was an active angiogenetic process that may cause both stenosis through the proliferation of endothelial and/or smooth muscle cells and abnormal collateral formation.[8]

In addition to endothelial cells, the smooth muscle cells are also involved in this disease process. The MMD pathology is characterized by smooth muscle cell hyperplasia in the intima. Mutations in the smooth muscle cells, such as smooth muscle alpha-actin, which is encoded by *ACTA2*, may be involved in the increased proliferation of the smooth muscle cells, contributing to occlusive diseases.[15] Recently, Kang and colleagues cultured and isolated smooth muscle progenitor cells (SPCs) from the peripheral blood of patients with MMD, and showed that the SPCs in the MMD group tended to make more irregularly arranged and thickened tubules, as well as express differential genes compared to that of the healthy controls.[59] These findings suggest a defect in the cell maturation process that might have occurred in the SPCs from the patients with MMD.

Cytokine and their polymorphisms

Various cytokines and their polymorphisms are associated with MMD, including (a) growth factors, such as vascular endothelial growth factor (VEGF), fibroblast growth factor, platelet-derived growth factor (PDGF), and hepatocyte growth factor, (b) cytokines related to vascular remodeling and angiogenesis, such as matrix metalloproteinases (MMPs) and their inhibitors, hypoxia-inducible factor-1α, and cellular retinoic binding protein-1 (CRABP-1), and (c) cytokines related to inflammation.[55,60-64] The investigations regarding the role of these factors have been inconclusive.

A genetic study of familial MMD investigated the balance between MMPs and their inhibitors, and found that the presence of a certain MMP inhibitor genotype may be a predisposing genetic factor for familial MMD.[65] The levels of several trophic factors, such as VEGF, basic fibroblast growth factor, and PDGF-BB, were increased, but the VEGF receptor levels were decreased in MMD compared to that of controls.[60,66,67] In addition, certain VEGF polymorphisms were associated with pediatric MMD and poor collateral vessel formation.[68] However, these findings were not observed in other studies.[69] Using a multifactor dimensionality reduction method, a recent study evaluated the interactions of different loci for MMD, but failed to show any influence of β-type PDGF receptor and MMPs on MMD.[69] Young et al. suggested that the induction of pro-inflammation cascades and VEGF expression is secondary to the infarct rather than part of the primary MMD pathology.[70]

Changes in the levels of these factors may be simply associated with the disease rather than causative, as many of these factors are also increased in patients with stroke. However, Kim and colleagues identified a polypeptide spot, CRABP-1, in cerebrospinal fluid from pediatric patients with MMD using a proteomics analysis.[63] A higher CRABP-1 level in the CSF was associated with a typical bilateral involvement and a decrease in the basal collaterals post-operatively in adult MMD.[71] It has been proposed that the retinoids attenuate growth factor-stimulated smooth muscle cell migration and proliferation, and CRABP-1 can negatively regulate retinoic acid activity.[63] These findings suggest an important role for retinoid signaling in MMD pathogenesis by controlling the growth factor expression.[63] Further studies are needed to determine whether retinoids are efficacious for MMD treatment.

Although pathological analyses have revealed that the affected vessels do not show any inflammatory changes that lead to occlusion,[16] the role of inflammation in the fibrocellular thickening of the intima and the disease pathogenesis are also being investigated. The plasma levels of MMPs, monocyte chemoattractant protein-1, and inflammatory cytokines (interleukin-1b) were higher in patients with MMD compared to those in controls.[60] A previous study,[72] as well as our unpublished data, showed that the levels of E-selectin, which is involved in endothelial progenitor cell recruitment and angiogenesis) were increased in both patients with MMD and those with atherosclerotic stroke.

Endothelial function and nitric oxide metabolites

Endothelial dysfunction is responsible for the dysregulation of vascular tone, cellular adhesion, thrombus formation, smooth muscle cell proliferation, and vessel wall inflammation. MMD may be a condition that is more vulnerable to environmental influences that cause endothelial dysfunction. A previous study of a small cohort showed that the nitric oxide (NO) metabolites (i.e., nitrate and nitrite) were increased in cerebrospinal flow samples of 18 patients with MMD compared to that of controls, which probably reflects the development of abnormal collateral circulation.[73] However, further studies are needed to confirm this result. In our unpublished data, the serum levels of NO metabolites and asymmetric dimethylarginine (ADMA; an endogenous competitive antagonist of NO synthase, a marker of endothelial dysfunction) in patients with MMD did not differ from those of control subjects. In addition, no differences were observed between control and MMD in endothelial NO synthase polymorphisms.[74]

Caveolin and dysfunction in endothelial vesicular trafficking and signal transduction

Caveolae are 50-100 nm cell surface plasma membrane invaginations that are abundant in endothelial cells, and play a major role in the regulation of endothelial vesicular trafficking and signal transduction.[75] Caveolin-1, a scaffolding protein of the caveolae plasma membrane, is involved in the pathogenesis of cancers and vascular diseases.[75] Caveolin-1 overexpression enhanced caveolae generation and accelerated the capillary tube formation by nearly three-fold, while caveolin-1 down-regulation reduced the *in vitro* and *in vivo* capillary formation, and was associated with pathological angiogenesis.[75-77] Both endothelial NO synthase and VEGFR2 co-localized in the caveolae, while caveolin-1 expression was critical for VEGF-induced angiogenesis in an ischemic hind limb model[78] and endothelial NO-related tumor angiogenesis.[79] One study that used an ischemic hind limb model demonstrated that caveolin-1 was also involved in endothelial progenitor cell recruitment from the bone marrow.[80]

Our recent study showed that caveolin-1 is a key mediator for MMD (unpublished data). In this study, the caveolin-1 serum levels decreased in adult patients with MMD and were markedly decreased in those with the *RNF213* variant. Liu and colleagues showed the differential roles of caveolin-1 during the differential phases of angiogenesis, such as caveolin-1 negatively regulating an earlier phase of angiogenesis (i.e., endothelial cell proliferation), but positively regulating a later phase of angiogenesis (i.e., tube formation).[76] Collectively, the decreased caveolin-1 levels and resulting increased prolifera-

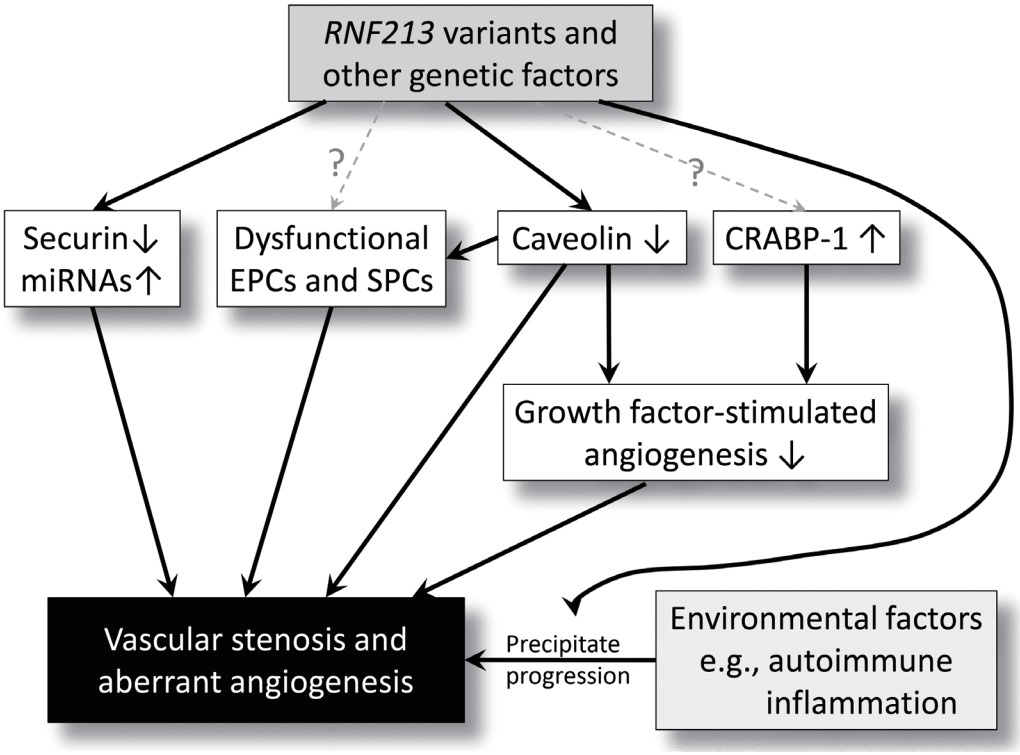

Figure 1. Potential mechanisms of moyamoya disease. The association between genetic, circulating, and environmental factors. *RNF213, Ring finger 213;* EPCs, endothelial progenitor cells; SPCs, smooth muscle progenitor cells; miRNAs, microRNAs; CRABP-1, cellular retinoic acid-binding protein-I.

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tion and decreased stabilization/tube formation in patients with MMD suggests that the nature of neo-vascularization is an aberrant rather than a compensatory process. The elucidation of mechanisms of the caveolin-1-related pathological angiogenesis may pave the way for various therapeutic strategies.[80,81] Caveolin expression could be modulated by genetic regulation targeting caveolin-1, such as antisense/siRNA or microRNA, anti-caveolin-1 antibodies, viral vectors or polymers that target the caveolae. Further studies are needed because most previous studies were performed in ischemic hind limb or cancer models. One study investigated the effects of cerebral ischemia in caveolin-1 knockout mice and demonstrated impaired angiogenesis and increased apoptotic cell death.[82] In addition to angiogenesis, a series of signaling pathways couple caveolae with ischemia (e.g., neuroinflammation, blood-brain barrier permeability, and pre-conditioning), and caveolin was recently suggested as a novel therapeutic target for ischemic stroke.[83]

Conclusion and perspectives

Although the pathogenic mechanisms of MMD are still unknown, there is growing evidence that it is primarily a proliferative disease, such that endothelial and smooth muscle proliferation results in the development of an occlusion, and enhanced, but aberrant, angiogenesis (i.e., moyamoya vessels). Genetic factors and related changes in circulating factors, as well as environmental factors, may play important roles in complex ways (Figure 1).

Further studies are needed because there is no relevant MMD animal model using these factors. In addition, these genetic and related changes in circulating factors would confer pathophysiological effects on the systemic vessels as well as distal ICA/proximal middle cerebral artery. They cannot explain the site specificity with sparing systemic vessels. Moreover, none of the previous reports have studied the levels of circulating biomarkers in relation to the disease stage. The profile of circulating biomarkers may differ according to the disease stage.

At present, surgical re-vascularization is the mainstay MMD treatment. However, surgical treatments pose a possible risk for peri-operative ischemic complications and/or cerebral hyperperfusion syndrome.[84] With a better understanding of MMD pathophysiology, non-surgical approaches targeting MMD pathogenesis may be available to stop or slow the progression of this disease. Non-surgical approaches may include the application of (a) certain trophic factors or chemicals that increase angiogenesis,[85] (b) anti-cancer drugs to decrease the smooth muscle cell proliferation,[15] (c) retinoid to attenuate growth factor-stimulated smooth muscle cell migration and proliferation,[58,63] (d) several strategies to increase caveolin-1 levels,[81] and (e) stem cell therapy to replace or restore function of impaired EPCs or SPCs. Further efforts will benefit from collaborative works between the clinical hospital bed and the laboratory bench.

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