Influence of Inflammatory Disease on the Pathophysiology of Moyamoya Disease and Quasi-moyamoya Disease

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Abstract

Moyamoya disease is a unique cerebrovascular disease that is characterized by progressive bilateral stenotic alteration at the terminal portion of the internal carotid arteries. These changes induce the formation of an abnormal vascular network composed of collateral pathways known as moyamoya vessels. In quasi-moyamoya disease, a similar stenotic vascular abnormality is associated with an underlying disease, which is sometimes an inflammatory disease. Recent advances in moyamoya disease research implicate genetic background and immunological mediators, and postulate an association with inflammatory disease as a cause of, or progressive factor in, quasi-moyamoya disease. Although this disease has well-defined clinical and radiological characteristics, the role of inflammation has not been rigorously explored. Herein, we focused on reviewing two main themes: (1) molecular biology of inflammation in moyamoya disease, and (2) clinical significance of inflammation in quasi-moyamoya disease. We have summarized the findings of the former theme according to the following topics: (1) inflammatory biomarkers, (2) genetic background of inflammatory response, (3) endothelial progenitor cells, and (4) noncoding ribonucleic acids. Under the latter theme, we summarized the findings according to the following topics: (1) influence of inflammatory disease, (2) vascular remodeling, and (3) mechanisms gleaned from clinical cases. This review includes articles published up to February 2019 and provides novel insights for the treatment of the moyamoya disease and quasi-moyamoya disease.

Key words: inflammation, moyamoya disease, macrophage

Introduction

Moyamoya disease was defined in 1969 by Suzuki and Takaku1 as a unique cerebrovascular disease characterized by chronic progressive bilateral stenosis of the terminal portion of the internal carotid arteries (ICAs), leading to the formation of an abnormal vascular network composed of collateral pathways at the base of the brain. Although this disease is idiopathic, it is also sometimes associated with an underlying disease. In that case, it is called quasi-moyamoya disease.2,3 Although the epidemiology, clinical features, and genetics of quasi-moyamoya disease have been studied,4 little is known about its etiology and mechanism of progression.

In quasi-moyamoya disease, some of the underlying diseases are associated with acute or chronic inflammation including atherosclerosis, autoimmune disease, meningitis, and irradiation.5,6 These local or systemic inflammatory diseases sometimes precede the clinical progression of quasi-moyamoya disease. Therefore, multiple inflammatory pathways of these inflammatory diseases might promote the onset or progress of moyamoya disease and quasi-moyamoya disease. Recently, chronic inflammation has attracted attention as a common pathological basis of various diseases. Low-level chronic inflammation reaction, called smoldering, is associated with chronic inflammation in the progress of various diseases. The chronic inflammation induces fibrosis or angiogenesis due to the disruption of the adaptive responses, and sometimes leads to organ failure. Current cerebrovascular disease research has adopted a more integrative approach toward inflammatory diseases.7,8 In this review article, the influence of acute or chronic inflammation on the pathophysiology of moyamoya disease and quasi-moyamoya disease is discussed.
Methods

For this review, a systematic search of the English language literature was performed using the PubMed/Medline database with the keywords moyamoya disease and various combinations of words such as pathology, inflammation, genetics, cytokines, and angiogenesis. Considering an association between moyamoya disease or quasi-moyamoya disease and inflammatory disease, this review included two main themes: (1) molecular biology of inflammation in moyamoya disease, and (2) clinical significance of inflammation in quasi-moyamoya disease. We summarized the findings of the former theme according to the following topics: (1) inflammatory biomarkers, (2) genetic background of inflammatory response, (3) endothelial progenitor cells (EPCs), and (4) noncoding ribonucleic acids (RNAs). Under the latter theme, we summarized the findings according to the following topics: (1) influence of inflammatory disease, (2) vascular remodeling, and (3) mechanisms gleaned from clinical cases.

The definitions of moyamoya disease and quasi-moyamoya disease overlap conceptually. Basically, when moyamoya disease is clinically associated with a complicated inflammatory disease, it is defined as quasi-moyamoya disease in this article. Therefore, the association between moyamoya disease (not quasi-moyamoya disease) and an inflammatory disease cannot be explained in a clinical setting. According to this definition, it is transcribed into quasi-moyamoya disease in this article when underlying disease are apparent, and differentiate it from moyamoya disease that is without underlying disease. Atherosclerotic disease is also included in quasi-moyamoya disease. However, when an inflammatory disease was found incidentally, it was transcribed into moyamoya disease. In terms of basic research, we transcribed all it into moyamoya disease.

Molecular biology of inflammation in moyamoya disease

Inflammatory biomarkers Inflammatory response ultimately leads to the hyperplasia of intimal vascular smooth muscle cells and neovascularization by proliferation of endothelial cells, that causes lumen stenosis and collateral formation. The two major pathways conceptualized to be influential in the inflammatory response for the initiation or progression of moyamoya disease are: (1) anti-inflammatory cytokine pathway, and (2) pro-inflammatory cytokine pathway activating the ring finger protein 213 (RNF213) (Fig. 1). The immune responses associated with angiogenesis are promoted by M2 macrophages that are induced by anti-inflammatory cytokines including Interleukin (IL)-4, IL-10, IL-13, interferon (IFN)-α, and transforming growth factor (TGF)-β. Fujimura et al.⁹ reported that serum CD163 and CXCL5 levels of moyamoya disease patients were significantly higher than those of controls, suggesting that moyamoya disease pathology was associated with M2 macrophages. Angiogenetic mediators are activated through these anti-inflammatory cytokines. TGF β from Treg/Th17 cells with unique CD4+
T-helper cell subsets has been recently shown to contribute to abnormal angiogenesis in moyamoya disease through regulation of vascular endothelial growth factor (VEGF) signaling. Elevation of numerous angiogenetic mediators such as VEGF, basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), matrix metalloproteinases (MMPs), hypoxia-inducible factor 1 (HIF-1) and cellular retinoic acid-binding protein-1 (CRABP-1) has been reported in moyamoya disease. These are postulated to play a crucial role in angiogenesis and intimal proliferation by reciprocally influencing endothelial cells, and perhaps causing the initiation or progression of moyamoya disease. The pro-inflammatory cytokines such as IFN-β, IFN-γ, tumor necrosis factor (TNF)-α, IL-1, and IL-6 activating the RNF213-dependent pathway work differently from the anti-inflammatory cytokine pathways.

Genetic background of inflammatory response
In 2011, the RNF213 gene variant, c.14576G>A (p.R4810K, rs112735431), was identified as the susceptibility gene for moyamoya disease in East Asian populations. The p.R4810K variant exists in 0.5–2.0% of the general population in East Asia. Liu et al. screened for the p.R4810K variant and reported that the frequency differed depending on the country; this variant was estimated to exist in approximately 16.16 million people in the East Asian countries. However, the actual number of patients exhibiting these symptoms is much less, indicating that other factors such as inflammatory and immune response might play an indirect role in the onset of moyamoya disease. Interestingly, the frequency of p.R4810K carriers was significantly higher in quasi-moyamoya disease than in controls, supporting the role of the gene variant RNF213 p.R4810K in quasi-moyamoya disease. On the other hand, Miyawaki et al. reported that RNF213 c.14576G>A variant is not associated with quasi-moyamoya disease, although it could be due to a small sample size.

Pro-inflammatory cytokines including IFN-β, IFN-γ, and TNF-α synergistically activated the transcription of RNF213 both in vitro and in vivo. Although these pro-inflammatory cytokines are anti-angiogenic, they have an suppressive effect through the induction of RNF213. PI3 kinase-Akt (PI3K/Akt) pathway in endothelial cell contributes to the transcriptional activation of RNF213. The inhibition of the PI3K/Akt pathway has been shown to reduce the severity of inflammation in autoimmune diseases, some types of moyamoya diseases triggered by inflammatory disease might be involved in the PI3K/Akt pathway. β-Catenin is crucial in the vascular endothelial cell proliferation and migration during neovascularization after myocardial infarction. VEGF was identified as a target gene of the β-catenin signaling. This suggests that the Wnt signal pathway is possibly associated with angiogenesis. Recently, Scholz et al. reported that RNF213 in vascular endothelial cells was involved in angiogenesis regulation via the Wnt signaling pathway. Caveolin-1, critical for an inflammatory response, is also a key mediator of moyamoya disease. Levels of caveolin-1 in the serum were lower in moyamoya disease, and were markedly decreased in those with the RNF213 variant. Caveolin-1 is associated with angiogenesis, and there is bidirectional crosstalk between the caveolin-1/ERK and Wnt/β-catenin pathways. HIF-1 plays distinct roles in regulating the inflammatory response along with NF-κB. Expression of HIF-1 is regulated by the PI3K/Akt pathway. Triggered by inflammatory cytokines due to autoimmune diseases or infections, each signal transduction pathway is mutually activated through RNF213.

RNF213 knock-in mice did not induce moyamoya disease spontaneously, and the characteristic angioarchitecture of moyamoya disease as indicated by the

Fig. 2 Schematic of the progression pattern of arterial stenosis in quasi-moyamoya disease. (A) The terminal portion of the ICA in normal artery. (B) The arterial diameter is reduced by constrictive remodeling as shown in moyamoya disease and a majority of quasi-moyamoya diseases. (C) In some types of quasi-moyamoya diseases, the intimal thickening is remarkable with limited vascular constriction.

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magnetic resonance angiography was missing in these mice. Moreover, wild-type mice showed temporary hyperplasia of the intimal and medial layers after common carotid artery ligation; however, RNF213 knock-in mice did not exhibit these changes. On the basis of these findings, Fujimura et al. hypothesized that RNF213 deficiency might cause vascular fragility and hemodynamic stress vulnerability, which consequently leads to the development of moyamoya disease. In other words, the RNF213 gene may not be directly involved in the development of moyamoya disease. However, these studies suggest that inflammation due to the autoimmune response might influence RNF213 and promote the progression of moyamoya disease.

**Endothelial progenitor cells** The circulating EPCs are derived from the bone marrow, and contribute to postnatal physiological and pathological neovascularization. Opposing opinions exist in the moyamoya disease field regarding the EPCs. Rafat et al. first reported an increase of circulating EPCs in adult patients of moyamoya disease. A decrease of EPCs after revascularization surgery was also indicated in moyamoya disease. EPCs secrete angiogenic factors including VEGF, HGF, angiopoietin-1 (Ang-1), insulin-like growth factor-1 (IGF-1), stromal-derived factor-1α (SDF-1α), bFGF, and PDGF factors which were also increased in moyamoya disease in addition to an increase in circulating EPCs. Conversely, Kim et al. reported a decrease in EPCs in pediatric moyamoya disease. The EPC function was also significantly lower in moyamoya disease. Choi et al. also indicated the impaired functional recovery of in vivo EPCs in moyamoya disease compared with control. These two opposing results indicate that angiogenesis is either facilitated or decreased in moyamoya disease. However, they all point to abnormal angiogenesis being associated with the pathogenesis of moyamoya disease. This is supported by the success of revascularization surgery in moyamoya disease in which restoration of blood flow to the brain helps in angiogenesis, and improves collateral circulation.

**Noncoding RNAs** MicroRNAs (miRNAs) are short non-coding RNAs, fewer than 22 nucleotides in length, that regulate gene expression by targeting mRNA for cleavage or translational repression. miRNAs play an essential role in regulating proliferation, survival, differentiation, and aging of cells. They are also involved in inflammation, neurogenesis, and angiogenesis. miRNAs have emerged as important regulators of Toll-like receptor (TLR) signaling in reducing excessive inflammation, increasing tissue repair, and returning to homeostasis after infection and tissue injury. Dai et al. reported that miR-106b and miRNA-126 were upregulated while miRNA-125a-3p was downregulated in moyamoya disease, and the RNF213 and BRCC3-associated miRNA might contribute to the development of moyamoya disease. In addition, an increase in the expression of miRNA-196a2 and miRNA Let-7c was reported, and these might be potential biomarkers for moyamoya disease.

Long noncoding RNAs (lncRNAs) are longer than 200 nucleotides without the protein-coding ability, and play a role in chromatin remodeling, transcriptional control, and post-transcriptional processing. The regulation of lncRNAs might contribute to inflammatory response. The lncRNAs are also associated with moyamoya disease pathology through inflammatory cascade including the mitogen-activated protein kinase (MAPK) signaling pathway.

**Clinical significance of inflammation in quasi-moyamoya disease**

**Influence of inflammatory disease** The frequency with which an inflammatory disease occurs in association with quasi-moyamoya disease is 1.7–4.7% in adults, and 0.54–1.5% in infants. In this study, approximately half of the quasi-moyamoya disease patients had atherosclerosis; therefore, the autoimmune disease cluster has relatively low numerical data. According to the Japanese national survey by Hayashi et al., diseases except for atherosclerosis accounted for 17.2% of inflammatory diseases in quasi-moyamoya disease. Of these, hyperthyroidism was at 7.5%, meningitis at 2.2%, and other autoimmune diseases were at 17.2% of the total. Thus, hyperthyroidism was the most common autoimmune disease associated with the quasi-moyamoya disease. Other than these, systemic lupus erythematosus, antiphospholipid antibodies syndrome, polyarteritis nodosa, Kawasaki disease, Sjogren’s syndrome, Addison’s disease, dermatomyositis, granulomatosis with polyangiitis, multiple sclerosis, myasthenia gravis, polymyositis, primary systemic vasculitis, rheumatoid arthritis, systemic sclerosis, thyroiditis, and acute limbic encephalitis with anti-LGI1 antibody have been reported. The associated mechanisms between quasi-moyamoya disease and each individual autoimmune disease are difficult to discern, because at present it is difficult to distinguish correlation form causation. However, the association between chronic systemic inflammation due to autoimmune response and quasi-moyamoya disease can be established. Compared with moyamoya disease, the clinical characteristics of quasi-moyamoya disease associated with hyperthyroidism are seen primarily in females, involve ischemia, and a relatively higher onset age. Moreover, the disease progresses more rapidly than in quasi-moyamoya disease. Ischemic attacks often
Inflammation in Moyamoya Disease

aggravate the thyroid function. In most cases, the ischemic symptoms induced by thyrotoxicosis were ameliorated after hyperthyroidism was controlled.\cite{71}

High levels of thyroid hormones might lead to the progression of quasi-moyamoya disease by augmenting vascular sensitivity to the sympathetic nervous system.\cite{72}

T-cell-mediated autoimmune response can also accelerate the pathology. Therefore, the treatment of hormonal abnormality and immunosuppressive therapy prior to surgical treatment are reported to be effective in the management of quasi-moyamoya disease associated with autoimmune diseases.\cite{75,76}

Because vascular sensitivity should be improved by suppressing immunological stimulation, then, controlled appearance of symptoms of the quasi-moyamoya disease. Tendler et al.\cite{77} suggested that cellular proliferation and vascular dysregulation in quasi-moyamoya disease and immunological stimulation in hyperthyroidism had a common pathological mechanism involving T-cell dysregulation. This mechanism is associated with not only vascular sensitivity but also vascular morphological alterations in quasi-moyamoya disease with hyperthyroidism,\cite{78} and procedures such as surgical revascularization are recommended in cases with morphological alterations. Hyperthyroidism itself is associated with surgical risk; therefore, for the management of quasi-moyamoya disease, surgical revascularization should be considered after the control of hyperthyroidism.

Quasi-moyamoya disease due to meningitis is rare, and estimated to be 2.2% of all the quasi-moyamoya diseases.\cite{4} The reported causes of infection are as follows; Propionibacterium acnes,\cite{79} Streptococcus pneumoniae,\cite{80,81} $\beta$-hemolytic group A Streptococcus,\cite{82} Mycobacterium tuberculosis,\cite{83–86} Haemophilus influenzae,\cite{87,88} Leptospira,\cite{89} Mycoplasma pneumoniae,\cite{90} Neisseria meningitidis with Cytomegalovirus,\cite{91} human immunodeficiency virus (HIV),\cite{92–94} syphilis with HIV,\cite{95} measles virus,\cite{96} varicella-zoster virus,\cite{97} and Epstein–Barr virus.\cite{98} Vascular events associated with meningitis generally occur within the first 2 weeks after the onset.\cite{98,99} In some cases with quasi-moyamoya disease associates with meningitis, a late-onset morphological alteration of the circle of the Willis after meningitis was observed;\cite{75,80,84,86–88} the elevated autoimmune antibodies indicate an autoimmune trigger for the onset of quasi-moyamoya disease.\cite{75} Liu et al.\cite{100} reported that cerebrospinal fluid in quasi-moyamoya disease had a positive immune response to leptospiriosis, and quasi-moyamoya disease was associated with immune reactive vasculitis. We reported a case of the quasi-moyamoya disease that developed 9 years after non-herpetic acute limbic encephalitis with a familial history of moyamoya disease.\cite{101} It was positive for the anti-LGI1 antibody, and we postulated that inflammation due to the autoimmune process contributed to the progress of quasi-moyamoya disease. Thus, chronic inflammation through the autoimmune process, rather than acute inflammation itself, can be a trigger for quasi-moyamoya disease in acute inflammatory disease. In addition to meningitis, systemic acute inflammatory disease might be associated with the development of moyamoya disease. Suzuki et al.\cite{102} studied the incidence of infections in patients with moyamoya disease; they found 82.6% of the children and 61.6% of the adults with moyamoya disease had head and face infections such as tonsillitis, otitis media, maxillary sinusitis, and infections of unknown origin.

**Vascular remodeling** Pathologically, the vascular lesions in idiopathic moyamoya disease are multi-layered intimal fibrous thickenings with neither significant disruption of the internal elastic lamina nor inflammatory infiltration.\cite{103} No lipid pool, inflammatory cells, or macrophage infiltration to the subintimal layer were found, as typically observed in atherosclerosis.\cite{104} Based on this, moyamoya disease has been defined as non-inflammatory intracranial vascular disease. Contrary to the above, Masuda et al.\cite{105} demonstrated smooth muscle proliferation, macrophage infiltration, and the presence of T-cells in moyamoya vessel walls of autopsy specimens. In the quasi-moyamoya disease associated with von Recklinghausen disease, inflammatory cells infiltrate the region surrounding the disease lesion. This indicates that some types of quasi-moyamoya diseases are associated with an inflammatory disease.

From the view point of radiological aspects, Kaku et al.\cite{106} reported that both outer and inner diameters of the ICAs shrink during the remodeling process in moyamoya disease, which is different from the atherosclerotic disease that shows an outward remodeling pattern. The vascular shrinkage in moyamoya disease is found specifically in the horizontal segment of the middle cerebral artery (M1).\cite{107} In a subgroup of quasi-moyamoya diseases, the arterial shrinkage was not remarkable, and the outer diameter of the circle of Willis was not reduced on 3D constructive interference in steady-state sequence.\cite{108} However, this was not common in quasi-moyamoya disease. Yamamoto et al.\cite{109} suggest that quasi-moyamoya disease includes two different pathological subgroups: the constrictive subgroup and non-constrictive subgroup. Thus, a section of the former subgroup of quasi-moyamoya disease shows limited intimal hyperplasia and strong vascular constrictive changes (Fig. 2). The latter subgroup of quasi-moyamoya disease might show excessive fibrosis.

**Mechanisms gleaned from clinical cases** Two mechanisms have been proposed to be involved...
in the inflammatory diseases associated with the quasi-moyamoya disease (Fig. 3). One of the mechanisms involves the anti-inflammatory mediators in the blood or cerebrospinal fluid which influence the acceleration or acute aggravation of the quasi-moyamoya disease. In this pathway, anti-inflammatory cytokines directly affect the vascular reactivity and autoregulation, leading to progress. From the pathophysiological perspective, remission of the symptoms of moyamoya disease could be achieved by the treatment of the inflammatory disease. Based on this, pro-inflammatory cytokines might influence on fulminant progression partly.\textsuperscript{109} Specifically, this applies to the quasi-moyamoya disease with hyperthyroidism.\textsuperscript{71–74}

The second mechanism involves an increase in the inflammatory cytokines in the inflammatory diseases that influence \textit{RNF213} and lead to the onset of quasi-moyamoya disease. Presence of high frequency of \textit{RNF213} p.R4810K in quasi-moyamoya disease supports this hypothesis. Late-onset cases fall under this type.\textsuperscript{75,80,86,88,101} This pathway might work as an initiator of the disease, and the clinical course is relatively slow after the onset. This mechanism might be applied not only to quasi-moyamoya disease but also to moyamoya disease widely. Although these concepts are estimates from clinical cases, they play important roles in concurrently controlling both quasi-moyamoya disease and associated diseases. Moyamoya disease and quasi-moyamoya disease is a rare disease, and studying additional cases in the future will provide essential insights for its treatment.

### Conclusion

Although inflammation is not a direct cause of quasi-moyamoya disease, it may influence \textit{RNF213}, leading to angiogenesis. It is important to induce curative angiogenesis reflected in the treatment, and increase collateral circulation. To this end, it is essential to increase the expression of the angiogenetic factors, and enhance interaction between vascular cells and neurons; this can pave the way for identifying novel treatments in the future.

### Conflicts of Interest Disclosure

The authors declare no conflict of interest.

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**Fig. 3** Conceptualized schema of the mechanisms involved in the inflammatory diseases associated with the moyamoya disease. One mechanism highlights the initiation pathway in which pro-inflammatory cytokines influence \textit{RNF213}. The other mechanism indicates that anti-inflammatory or pro-inflammatory cytokines influence the angiogenetic mediators for acceleration or acute aggravation of the moyamoya disease.
neurological manifestations and its clinical course. These observations suggest that inflammatory processes play a critical role in the pathogenesis of moyamoya disease. The activation of various inflammatory factors, such as cytokines, chemokines, and matrix metalloproteinases, has been reported in patients with moyamoya disease. The role of inflammation in moyamoya disease, however, remains largely unexplored.

Inflammation is a key component in the pathogenesis of moyamoya disease. Several studies have shown that the expression of pro-inflammatory cytokines, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), is increased in moyamoya disease compared to normal controls. These cytokines can induce endothelial cell dysfunction, vascular remodeling, and progressive stenosis of the intracranial arteries, leading to ischemia and stroke.

The role of inflammation in moyamoya disease has been further supported by the observation that the expression of inflammatory markers, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), is also increased in moyamoya disease patients. These inflammatory markers are often used as markers of systemic inflammation and are associated with an increased risk of stroke in patients with moyamoya disease.

The involvement of inflammation in moyamoya disease has also been demonstrated by several changes in the peripheral blood counts of moyamoya disease patients. An increase in the number of inflammatory cells, such as neutrophils and monocytes, has been observed in moyamoya disease patients, which suggests an active inflammatory response in the peripheral blood. Moreover, an increase in the number of circulating monocytes, which are known to express adhesion molecules and pro-inflammatory cytokines, has also been reported in moyamoya disease patients.

In conclusion, inflammation plays a significant role in the pathogenesis of moyamoya disease. The activation of various inflammatory factors and the changes in peripheral blood counts observed in moyamoya disease patients support the involvement of inflammation in the disease process. Further research is needed to fully understand the role of inflammation in moyamoya disease and to develop effective therapeutic interventions targeting inflammatory processes.
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