Moyamoya Disease Pathogenesis

- Long-Term Outcomes in Patients With Hemorrhagic Moyamoya Disease Combined With Hypertension After Encephaloduroarteriosynangiosis
- Blurred by a "Puff of Smoke"-A Case-Based Review on the Challenging Recognition of Coexisting CNS Demyelinating Disease and Moyamoya Angiopathy
- Recent Advances in Genetics of Moyamoya Disease: Insights into the Different Pathogenic Pathways
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Despite decades of research, the mechanisms underlying Moyamoya Disease remain poorly clarified, and current gaps in the understanding of pathogenesis have hampered the development of suitable preventive strategies and therapeutic options.

Several factors are thought to contribute to its pathogenesis:

Genetic Factors

There is a strong genetic component to Moyamoya disease. It can run in families, and specific genetic mutations have been associated with the condition. Mutations in certain genes, such as the RNF213 gene, are more prevalent in individuals with Moyamoya disease. These genetic factors can contribute to the development of the abnormal blood vessels characteristic of the disease.

see RNF213 in Moyamoya Disease Pathogenesis.

An HLA imputation was conducted to explore the relationship between HLA and patients with moyamoya disease (MMD) in the Chinese Han population.

In this study, Wan et al. performed an association analysis of the major histocompatibility complex region in 2,786 individuals of Chinese Han ancestry (2,031 controls and 755 patients with MMD), through a widely used HLA imputation method.

They identified that the variant rs3129731 (odds ratio [OR] = 1.79, p = 3.69 × 10-16) located between the MTCO3P1 and HLA-DQA2 is a major genetic risk factor for MMD. In addition to this variant, found in the conditional association analysis, we also detected another independent signal, rs1071817 (OR = 0.62, p = 1.20 × 10-11), in HLA-B.

This research suggests that the genetic polymorphism of HLA-DQA2 and HLA-B could be a genetic predisposing factor for MMD in Chinese Han. This may provide some evidence for further HLA-related

studies of patients with MMD of Chinese Han ethnicity and indicates that MMD is an autoimmune disease [1].

Abnormal Blood Vessel Development

One of the hallmarks of Moyamoya disease is the development of small, fragile blood vessels (called “moyamoya vessels”) to compensate for the lack of blood flow through the narrowed or blocked arteries. These new blood vessels are often disorganized and prone to bleeding, which can lead to the symptoms and complications of Moyamoya disease.

Angiogenic factors associated with Moyamoya disease (MMD) are overexpressed in M2 polarized microglia in ischemic stroke, suggesting that microglia may be involved in the pathophysiology of MMD; however, existing approaches are not applicable to explore this hypothesis. Herein we applied blood-induced microglial-like (iMG) cells. We recruited 25 adult patients with MMD and 24 healthy volunteers. Patients with MMD were subdivided into progressive (N = 7) or stable (N = 18) groups whether novel symptoms or radiographic advancement of the Suzuki stage within 1 year was observed or not. We produced 3 types of iMG cells; resting, M1-, and M2-induced cells from monocytes, then RNA sequencing followed by GO and KEGG pathway enrichment analysis and qPCR assay was performed. RNA sequencing of M2-induced iMG cells revealed that 600 genes were significantly upregulated (338) or downregulated (262) in patients with MMD. Inflammation immune-related factors and angiogenesis-related factors were specifically associated with MMD in GO analysis. qPCR for MMP9, VEGFA, and TGFB1 expression validated these findings. This study is the first to demonstrate that M2 microglia may be involved in the angiogenic process of MMD. The iMG technique provides a promising approach to exploring the bioactivity of microglia in cerebrovascular diseases [2]

Environmental Factors

While genetic factors play a significant role, environmental factors may also contribute to the development of Moyamoya disease. Some studies suggest that certain environmental factors, such as viral infections or radiation exposure, may trigger or exacerbate the condition in genetically susceptible individuals.

Autoimmune and Inflammatory Processes

Some researchers believe that an autoimmune or inflammatory component may be involved in the pathogenesis of Moyamoya disease. Autoimmune reactions or chronic inflammation could contribute to the narrowing of blood vessels and the formation of moyamoya vessels.

Potenza et al. observed a significant increase of sphingolipids ($p < 0.05$) and phospholipids ($p < 0.05$) in MA CSF. A partial least squares discriminant analysis separated MA and CTRL by 64% on Principal Component 1. We identified lipid classes (n = 12) with a Variance Importance in Projection score ≥

1.5, within which lipids were highly correlated with MA (n = 70). A significant increase in acylcarnitines, sphingolipids (sphingomyelins and ceramides), phospholipids (lysophosphatidylcholines; phosphatidylcholines; phosphatidylethanolamines; ether-phosphatidylcholines; ether-phosphatidylcholines), and cholesterol esters was found by multivariate and univariate analyses. Monoacylglycerols were the only lipid class displaying a markedly significant ($p < 0.001$) decrease in CSF of MA patients as compared to CTRL subjects. The ROC curve and simple linear regression analysis identified 10 out of 12 lipid classes as reliable MA biomarkers, mainly dealing with phospholipids. We then compared current and previous data on the plasma lipidomic profile. The discriminant analysis returned n = 175 (in plasma) and n = 70 (in CSF) simultaneously altered lipids, respectively, and phosphatidylcholines (n = 10) resulted as commonly decreased in plasma and increased in CSF.

The findings highlighted a strong pro-inflammatory environment in MA CSF. These preliminary hallmarks could be helpful to decipher the complex MA pathogenesis by supplying candidate biomarkers for patient stratification [3].

Abhinavet al. investigated 62 secreted factors in both MMD subtypes (ischemic and hemorrhagic) and examined their relationship with preoperative perfusion status, the extent of postoperative angiographic revascularization, and functional outcomes. Intraoperative CSF was collected from 32 control and 71 MMD patients (37 ischemic and 34 hemorrhagic). Multiplex Luminex assay analysis showed that 41 molecules were significantly elevated in both MMD subtypes when compared to controls, including platelet-derived growth factor-BB (PDGF-BB), plasminogen activator inhibitor 1 (PAI-1), and intercellular adhesion molecule 1 (ICAM1) ($p < 0.001$). Many of these secreted proteins have not been previously reported in MMD, including interleukins (IL-2, IL-4, IL-5, IL-7, IL-8, IL-9, IL-17, IL-18, IL-22, and IL-23) and C-X-C motif chemokines (CXCL1 and CXCL9). Pathway analysis indicated that both MMD subtypes exhibited similar cellular/molecular functions and pathways, including cellular activation, migration, and inflammatory response. While neuroinflammation and dendritic cell pathways were activated in MMD patients, lipid signaling pathways involving nuclear receptors, peroxisome proliferator-activated receptor (PPAR), and liver X receptors (LXR)/retinoid X receptors (RXR) signaling were inhibited. IL-13 and IL-2 were negatively correlated with preoperative cerebral perfusion status, while 7 factors were positively correlated with the extent of postoperative revascularization. These elevated cytokines, chemokines, and growth factors in CSF may contribute to the pathogenesis of MMD and represent potential future therapeutic targets [4].

Endothelial Dysfunction

Endothelial cells lining the blood vessels play a crucial role in regulating blood flow and vessel health. Dysfunction of these cells can contribute to the narrowing of arteries and the development of Moyamoya disease.

In cases of endothelial dysfunction, the endothelium may produce less nitric oxide, a molecule that helps relax blood vessels and regulate blood flow. Reduced nitric oxide production can lead to vasoconstriction, or the narrowing of blood vessels, contributing to reduced blood flow in the affected arteries.

FLNA (filamin A) and ZYX (zyxin) proteins were significantly higher in Moyamoya Disease serum compared with those in health controls (Log2FC >2.9 and >2.8, respectively). Immunofluorescence revealed an intimal hyperplasia in the superficial temporal artery and middle cerebral artery specimens of MMD. FLNA and ZYX proteins increased the proportion of endothelial cells in the S phase and promoted their proliferation, angiogenesis, and cytoskeleton enlargement. Mechanistic studies revealed that AKT (serine/threonine kinase)/GSK-3β (glycogen synthase kinase 3β)/β-catenin signaling pathway plays a major role in these FLNA- and ZYX-induced changes in endothelial cells.

This study provides proteomic data on a large sample size of Moyamoya Disease. The differential expression of FLNA and ZYX in patients with MMD and following in vitro experiments suggest that these upregulated proteins are related to the pathology of cerebrovascular intimal hyperplasia in MMD and are involved in Moyamoya Disease pathogenesis, with diagnostic and therapeutic ramifications [5].

Hemodynamic Stress

Abnormal blood flow patterns in the brain, such as increased turbulence or changes in blood pressure, may contribute to the development of Moyamoya disease. Hemodynamic stress can lead to vascular remodeling and the formation of moyamoya vessels.

The precise interplay of these factors and the underlying mechanisms leading to Moyamoya disease are still the subject of ongoing research. While genetic factors are clearly involved, the condition is likely to result from a complex interplay of genetic and environmental factors. Treatment for Moyamoya disease often involves surgical procedures to improve blood flow to the brain, such as indirect bypass surgeries or direct revascularization procedures. Early diagnosis and intervention are crucial to prevent severe complications like strokes.

References

1)
Wan J, Ling W, Zhengshan Z, Xianbo Z, Lian D, Kai W. Association of HLA-DQA2 and HLA-B With Moyamoya Disease in the Chinese Han Population. Neurol Genet. 2021 Jun 2;7(3):e592. doi: 10.1212/NXG.0000000000000592. PMID: 34095496; PMCID: PMC8176556.
2)
Shirozu N, Ohgidani M, Hata N, Tanaka S, Inamine S, Sagata N, Kimura T, Inoue I, Arimura K, Nakamizo A, Nishimura A, Maehara N, Takagishi S, Iwaki K, Nakao T, Masuda K, Sakai Y, Mizoguchi M, Yoshimoto K, Kato TA. Angiogenic and inflammatory responses in human induced microglia-like (iMG) cells from patients with Moyamoya disease. Sci Rep. 2023 Sep 8;13(1):14842. doi: 10.1038/s41598-023-41456-z. PMID: 37684266; PMCID: PMC10491754.
3)
Potenza A, Gorla G, Carrozzini T, Pollaci G, Dei Cas M, Acerbi F, Vetrano IG, Ferroli P, Canavero I, Paroni R, Rifino N, Bersano A, Gatti L. Lipidomic profiling of the cerebrospinal fluid in moyamoya angiopathy patients. Orphanet J Rare Dis. 2025 May 23;20(1):243. doi: 10.1186/s13023-025-03782-5. PMID: 40410905.
4)
Abhinav K, Lee AG, Pendharkar AV, Bigder M, Bet A, Rosenberg-Hasson Y, Cheng MY, Steinberg GK.

Comprehensive Profiling of Secreted Factors in the Cerebrospinal Fluid of Moyamoya Disease Patients. Transl Stroke Res. 2023 Feb 6. doi: 10.1007/s12975-023-01135-7. Epub ahead of print. PMID: 36745304.
[5]
He S, Zhang J, Liu Z, Wang Y, Hao X, Wang X, Zhou Z, Ye X, Zhao Y, Zhao Y, Wang R. Upregulated Cytoskeletal Proteins Promote Pathological Angiogenesis in Moyamoya Disease. Stroke. 2023 Oct 27. doi: 10.1161/STROKEAHA.123.044476. Epub ahead of print. PMID: 37886851.