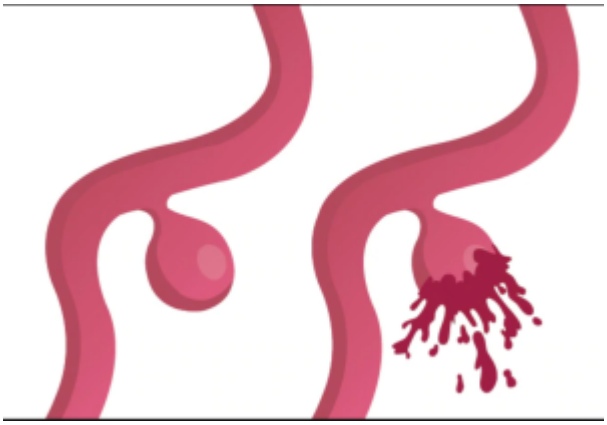
Intracranial aneurysm pathogenesis

- Protective Effect of Resveratrol Against Intracranial Aneurysm Rupture in Mice
- External Validation of the ARISE Prediction Models for Aneurysmal Rebleeding After Aneurysmal Subarachnoid Hemorrhage
- When an aneurysm pretends to be a tumor: thrombosed posterior inferior cerebellar artery aneurysm mimicking a neoplasm in a pediatric patient. Illustrative case
- DWI-based deep learning radiomics nomogram for predicting the impaired quality of life in patients with unruptured intracranial aneurysm developing new iatrogenic cerebral infarcts following stent placement: a multicenter cohort study
- Causal relationships between alterations in shear stress-related genes and aneurysmal subarachnoid hemorrhage
- Circular RNA hsa_circ_0008433 drives vascular smooth muscle cell modulation in intracranial aneurysm pathogenesis
- Incidental aneurysm rupture during endovascular thrombectomy for acute ischaemic stroke
- Factors related to the prognosis of patients with cerebral aneurysms undergoing microsurgical treatment



Most often, aneurysms occur in large blood vessels - the aorta (Thoracic Aortic Aneurysm (TAA) and Abdominal Aortic Aneurysm (AAA) and brain vessels (Intracranial Aneurysm (IA)). Despite the presence of significant differences in the pathogenesis of the development and progression of IA and TAA/AAA, there are also similarities. For instance, both have been shown to be strongly influenced by shear stress, inflammatory processes, and enzymatic destruction of the elastic lamellae and extracellular matrix (ECM) proteins of the vascular wall. Moreover, although IA and TAA are predominantly considered an arteriopaty with different pathological mechanisms, they share risk factors with AAA, such as hypertension and smoking. However, there is a need for a more in- -depth study of the key elements that may influence the formation and progression of a particular aneurysm to find ways of therapeutic intervention or search for a diagnostic tool. Today, it is known that the disruption of gene expression is one of the main mechanisms that contribute to the development of aneurysms. At the same time, growing evidence suggests that aberrant epigenetic regulation of gene function is strongly related to the genesis of aneurysms. Although much has been studied of the known protein-coding genes, circular RNAs (circRNAs), a relatively new and rapidly evolving large family of transcripts, have recently received much scientific attention. CircRNAs regulate gene expression through the sponging of microRNAs (miRNAs) and can also be used as therapeutic targets and biomarkers. Increasing evidence has implicated circRNAs in the pathogenesis of multiple cardiovascular diseases, including the development of aneurysms. However, the mechanism of

dysregulation of certain circRNAs in a particular aneurysm remains to be studied. The discovery of circRNAs has recently advanced our understanding of the latest mode of miRNAs/target genes regulation in the development and progression of IA and TAA/AAA. The aim of this study is to compare the expression profiles of circRNAs to search for similar or different effects of certain circRNAs on the formation and progression of IA and TAA/AAA [1)].

The pathogenesis of intracranial aneurysms and subarachnoid hemorrhage is a multifactorial and complicated process that remains poorly understood. The importance of gut microbiota lies in mediating the immune process in the arterial wall of the forming aneurysm via the gut–brain–microbiota axis. Proinflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin-1, and interleukin-6 are associated with the destabilization of the aneurysmal wall and promote its rupture [2) 3)].

Epigenetic modifications, including DNA methylation, are thought to play a role in the pathogenesis of IAs.

Time-dependent and site-dependent morphological changes and the level of degradation molecules may be indicative of the vulnerability of aneurysm rupture [4)].

Miyata et al. proposed the contribution of a structural change in an adventitia, i.e., vasa vasorum formation, to the rupture of IAs [5)].

Risk Factors

Intracranial aneurysm risk factors.

Aneurysm wall degeneration

Aneurysm wall degeneration.

Genetics

see Intracranial aneurysm genetics.

Pathophysiology

see Intracranial aneurysm pathophysiology.

Hemodynamics

see Intracranial aneurysm hemodynamics.

In addition to ambiental factors (smoking, excessive alcohol consumption and hypertension), epidemiological studies have demonstrated a familiar influence contributing to the pathogenesis of intracranial aneurysms, with increased frequency in first- and second-degree relatives of people with subarachnoid hemorrhage.

Data suggest that macrophage-derived Matrix metalloproteinase 2 and Matrix metalloproteinase 9, may play an important role in the progression of intracranial aneurysms. The findings will shed a new light into the pathogenesis of cerebral aneurysms and highlight the importance of inflammatory response causing the degeneration of extracellular matrix in the process of this disease [6].

Investigations strongly suggest that the pathophysiology is closely associated with chronic inflammation in vascular walls. Nuclear factor kappaB (NF-kappaB) has a key role in the formation and progression.

Children with Sickle Cell Disease (SCD) are at risk for developing multiple intracranial aneurysms, and a high index of suspicion must be maintained during the interpretation of routine magnetic resonance imaging or angiography of the brain [7].

Dental bacterial DNA can be found using a quantitative polymerase chain reaction in both ruptured and unruptured aneurysm walls, suggesting that bacterial DNA plays a role in the pathogenesis of cerebral aneurysms in general, rather than only in ruptured aneurysms [8].

Endothelial cell malfunction

Ono et al. created a 3D-casted mold of the human unruptured intracranial aneurysm lesion and cultured endothelial cells on this model; it was then perfused with culture media to model physiological flow conditions. Gene expression profiles of endothelial cells in each part of the IA lesion were then analyzed. Comprehensive gene expression profile analysis revealed similar gene expression patterns in endothelial cells from each part of the IA lesion but gene ontology analysis revealed endothelial cell malfunction within the IA lesion. Histopathology, electron microscopy, and immunohistochemical analysis indicated that endothelial cells within IA lesions are damaged and dysfunctional. Thus, the findings reveal endothelial cell malfunction in IA lesions and provided new insights into IA pathogenesis [9].

THSD1 in Intracranial aneurysm pathogenesis

Thrombospondin type-1 domain-containing protein 1 is a protein that in humans is encoded by the THSD1 gene.

The protein encoded by this gene contains a type 1 thrombospondin domain, which is found in thrombospondin, a number of proteins involved in the complement pathway, as well as extracellular matrix proteins. Alternatively spliced transcript variants encoding distinct isoforms have been observed.

As illustrated by THSD1 research, cell adhesion may play a significant role in IA [10].

A study discovered that harmful variants in THSD1 (Thrombospondin type-1 domain-containing protein 1) likely cause intracranial aneurysm and subarachnoid hemorrhage in a subset of both familial and sporadic patients with supporting evidence from two vertebrate models [11].

A report identified THSD1 mutations in familial and sporadic IA patients and shows that THSD1 loss results in cerebral bleeding in 2 animal models. This finding provides new insight into IA and subarachnoid hemorrhage pathogenesis and provides new understanding of THSD1 function, which includes endothelial cell to extracellular matrix adhesion [12].

Toll-like receptor

Toll-like receptor (TLR) 2/4 serves an important regulatory role in nerve tissue injury. However, the downstream and potential mechanisms remain to be elucidated. The present study was designed to investigate the roles of the TLR2/4-major myeloid differentiation response gene 88 (MyD88)-NF-κB signaling pathway in the development of an intracranial aneurysm. The expression of TLR2, TLR4, and MyD88 in the blood of normal controls and patients with intracranial aneurysms were detected by quantitative PCR and ELISA. Human brain vascular smooth muscle cells were treated by Angiotensin II (Ang II) to evaluate the involvement of the TLR2/4-MyD88-NF-κB signaling pathway in the process. The in vitro experiment was divided into four groups: The control group, an Ang Ⅱ group, an Ang Ⅱ + small interfering (si)RNA control group, and an Ang Ⅱ + TLR2-group. Cell viability, migration, apoptosis, and expression of TLR2, TLR4, MyD88, NF-κB, and phosphorylated (p-)p65 expression was detected. The results demonstrated that the expression of TLR2, TLR4, MyD88, and NF-κB at mRNA and protein levels in patients with an intracranial aneurysm was significantly higher compared with corresponding protein in normal controls (P<0.05). In vitro experiments demonstrated that Ang Ⅱ treatment increased the cell proliferation and migration rate but reduced the apoptotic rate compared with the control (P<0.05). The expression of TLR2, TLR4, MyD88, NF-κB, and p-p65 was significantly increased in the Ang II group (vs. control; P<0.05). By contrast, TLR2-short interfering RNA reduced the cell proliferation and migration rate and reduced the expression of TLR2, TLR4, MyD88, NF-κB, and p-p65 (vs. Ang Ⅱ + short interfering RNA control; P<0.05). In conclusion, the data of the present study indicated that the TLR2/4-MyD88-NF-κB signaling pathway is involved in the intracranial aneurysm pathogenesis [13].

DNA methylation in intracranial aneurysm pathogenesis

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