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Review Article

Circular RNAs in intracranial aneurysms: Emerging roles in pathogenesis, diagnosis and therapeutic intervention

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ABSTRACT

Intracranial aneurysms (IAs) present a substantial health threat, given the potential for catastrophic ruptures and subarachnoid hemorrhages (SAH). Swift and effective measures for diagnosis and treatment are paramount to enhance patient outcomes and alleviate the associated healthcare burden. In this context, circular RNAs (circRNAs) have emerged as an intriguing area of investigation, offering promise as both diagnostic biomarkers and therapeutic targets for IAs. CircRNAs have demonstrated their influence on critical molecular and cellular processes underpinning IAs pathogenesis, revealing their pivotal role in understanding this complex ailment. Beyond their diagnostic potential, circRNAs hold great potential as prognostic markers, providing crucial insights into IAs rupture risk. The unique circular structure and their regulatory functions make circRNAs an enticing avenue for innovative therapeutic approaches. The ongoing study of circRNAs in the context of IAs is an exciting and rapidly evolving field that has the potential to revolutionize approaches to diagnosis, treatment, and prevention of this life-threatening condition. As research continues to unravel the intricate roles of circRNAs, they are poised to become invaluable tools in clinical practice, enhancing patient care and ultimately reducing the impact of cerebral aneurysms on both individuals and healthcare systems. This comprehensive review delves deeply into the world of circRNAs in the realm of IAs, elucidating their multifaceted roles in the onset and progression of this condition. Moreover, this review ventures into the diagnosis and therapeutic potential of circRNAs, exploring their possible applications in gene therapy and as targets for novel treatment modalities.

1. Introduction

Intracranial aneurysms (IAs) are a critical medical condition that involves the abnormal bulging of cerebral arteries, resulting from a complex interplay of multiple factors [1]. The most recent epidemiological data indicates that IAs affect approximately 8 % of the global population, underscoring the significance of this health concern. The rupture of an IA presents a dire threat to human life and well-being, with an alarming mortality rate of nearly 50 % within 30 days of rupture, leaving 30 % of survivors to cope with moderate to severe disabilities [2–5]. The ability to predict and assess the risk of IA rupture is paramount in guiding effective treatment strategies and preventing catastrophic consequences [6]. While traditional risk factors such as smoking, high blood pressure, and genetic predisposition have been recognized, there is still much to uncover about the finer intricacies of IA formation and rupture. Recent years have witnessed a profound exploration of the molecular mechanisms underlying the development and rupture of IAs, shedding light on several factors that may contribute to this critical condition [7–9]. Researchers have increasingly recognized that inflammation, apoptosis, phenotypic changes in vascular smooth muscle cells (VSMCs), cell adhesion, atherosclerosis, and abnormal extracellular matrix (ECM) metabolism may all play significant roles in the mechanisms underlying in development and IA rupture [10,11]. Unraveling these complex processes at the molecular level offers an invaluable opportunity to understand the condition more comprehensively and to identify potential molecular targets that could

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revolutionize the prediction and diagnosis of IA rupture [12]. Adding to the intrigue in this research landscape is the emergence of circular RNAs (circRNAs), a unique subclass of non-coding RNA molecules [13]. Initially regarded as low in abundance due to erroneous exon transcript splicing, circRNAs have gained recognition for their widespread distribution, structural stability, and temporal-spatial specificity in human cells [14,15]. Their diverse functions, including acting as microRNA (miRNA) sponges, interacting with various proteins, and possibly encoding functional peptides or proteins, have ignited research interest [16,17]. While circRNAs have been implicated in a range of diseases such as cerebrovascular diseases (CVDs), their connection to IAs, both in terms of pathogenesis and diagnosis, remains an exciting frontier for investigation [18–20]. This growing field of research not only promises to unravel the molecular underpinnings of IA but also holds the potential to transform diagnostic and therapeutic strategies. The discovery and understanding of circRNAs in the context of IA could provide novel insights into personalized patient care, advanced prognostic tools, and more effective treatment modalities. Intriguingly, some circRNAs have been found to be more abundant in extracellular body fluids like saliva, blood (whole blood or plasma/serum), cerebrospinal fluid (CSF), and urine compared to their canonical linear counterparts, emphasizing their significance [21–24]. As we delve deeper into the intricate molecular aspects of IAs, the prospect of more precise and effective management of this life-threatening condition draws nearer, bringing renewed hope to both patients and healthcare providers. The study of circRNAs in the context of IAs has the potential to revolutionize our understanding and management of this life-threatening condition, offering new avenues for early diagnosis, personalized care, and more effective treatment strategies.

2. CircRNAs biogenesis and functions

CircRNAs are a diverse class of RNAs that encompass several categories, including exon circRNAs (ecircRNAs), circRNAs from introns (ciRNAs), exon-intron circRNAs (EIciRNAs), and intergenic circRNAs [25]. Most ecircRNAs are derived from back-spliced exons and are predominantly located in the cytoplasm, while ciRNAs are primarily found in the nucleus. EIciRNAs represent a distinct type of circRNA that circularizes with both exons and introns, potentially influenced by internal repeat sequences [26]. Recently, intergenic circRNAs have been identified and are characterized by two intronic circRNA fragments flanked by GT-AG splicing signals. The role of circRNAs in physiological processes is substantial, driven by their conservation, abundance, and tissue-specific expression. Notably, circRNAs have emerged as key players in the development of various diseases, with a particular emphasis on cancer [27]. For instance, circ_0000190 has been implicated in myeloma cell proliferation, apoptosis, and cell cycle regulation via the miR-767-5p/mitogen-activated protein kinase 4 (MAPK4) pathway. Additionally, circENO1, along with its host gene enolase 1 (ENO1), plays a role in lung adenocarcinoma by influencing glycolysis and tumor development through the miR-22-3p/ENO1 axis. In the context of non-small cell lung cancer (NSCLC), circABCB10 functions as a tumor promoter by sponging miR-1252 [28]. The discovery of numerous circRNAs across different tissues and cells is just the tip of the iceberg when it comes to understanding their roles in diseases. Different types of circRNAs exhibit diverse properties and functions, participating in regulatory networks as either transcriptional regulators in the nucleus or post-transcriptional regulators in the cytoplasm. Nuclear circRNAs have been found to impact RNA transcription by binding to their cognate DNA locus or RNA polymerase II, leading to transcriptional pausing. In contrast, EIciRNAs positively regulate transcription through specific RNA-RNA (RRIs) interactions with U1 small nuclear RNAs (snRNAs) [29]. Cytoplasmic circRNAs predominantly serve as miRNA sponges, inhibiting miRNA expression and relieving translation suppression on target molecules. Some cytoplasmic circRNAs also act as scaffolds for RNA-binding proteins (RBPs) due to their unique tertiary structures [30]. An intriguing feature of circRNAs is their potential to serve as templates for translation into proteins, a phenomenon observed thus far in the context of the hepatitis delta virus. In summary, circRNAs have transitioned from being an obscure facet of epigenetics to emerging as key regulators in biological processes. As research continues to delve deeper into the mechanisms, circRNAs are unveiled as versatile players capable of acting as miRNA sponges, regulators of splicing and transcription, and modifiers of parental gene expression.

3. CircRNAs as therapeutic targets

IAs are a silent yet potentially catastrophic vascular condition, and understanding their underlying mechanisms is crucial for devising effective therapeutic strategies. The research embarks on a journey into the world of circRNAs, a class of molecules that has proven pivotal in CVDs but has, until now, received limited attention in the context of IAs. The researchers conducted a comprehensive analysis of circRNAs expression profiles in blood samples from both IA patients and control subjects [30]. This approach led to the identification of 235 differentially expressed circRNAs between these two groups. Notably, 150 of these circRNAs were upregulated, while 85 were downregulated in the IA patients. What makes this study particularly intriguing is its exploration of the interplay between circRNAs and miRNAs. The research uncovered five miRNAs that matched the differential expression of circRNAs. These miRNAs play a pivotal role in the regulatory networks associated with IA. The study then delves deeper into the functions of the genes targeted by these miRNAs, using Gene Ontology (GO) analysis. This analysis highlighted specific terms, such as “Homophilic cell adhesion via plasma membrane adhesion molecules” and “Positive regulation of cellular process,” which exhibited significant fold enrichments. These terms shed light on the potential biological processes involved in IA pathogenesis, including cell adhesion and cellular regulation. Perhaps one of the most promising aspects of this research is its implication of the mammalian target of rapamycin (mTOR) pathway as a latent therapeutic strategy for IA. The mTOR pathway is involved in a range of cellular processes, making it an attractive target for further investigation in the context of IA treatment. This study offers valuable insights into the role of circRNAs expression profiling in IA formation. By identifying differentially expressed circRNAs and their potential interactions with miRNAs, the research opens new avenues for understanding the molecular underpinnings of IA. Furthermore, the suggestion of the mTOR pathway as a potential therapeutic target provides hope for future treatment strategies in addressing this life-threatening condition.

By conducting a comprehensive analysis of circRNAs and mRNA expression profiles in human IA walls and STAs, this study uncovers a wealth of information regarding the roles and potential implications of circRNAs in the pathogenesis of IAs [31]. The results are both compelling and enlightening. Numerous differentially expressed circRNAs are unveiled, with close involvement in immune and inflammatory responses, as well as cell adhesion and adherens junctions. Of particular significance are two newly discovered circRNAs, circ_0072309 and circ_0008433 [31]. These circRNAs are shown to regulate key genes, double data rate 2 (DDR2) and matrix metalloproteinase-2 (MMP-2), respectively. DDR2 and MMP-2 are associated with vascular injury. This regulation occurs through a complex ceRNA network, shedding light on their potential impact on IA pathogenesis. The research goes a step further by examining the expression patterns of these two pivotal circRNAs in the peripheral blood of IA patients. Strikingly, the study reveals central and peripheral consistency in the expression pattern of circ_0072309 and circ_0008433, offering a promising avenue for potential IA development. This study is a trailblazing exploration of the epigenetic factors involved in IAs. The discovery of circ_0072309 and circ_0008433 and their implications for IA pathogenesis present exciting opportunities for future research and therapeutic development.

4. Potential circRNAs in IA

Several subtypes of vascular cells including VSMCs, and endothelial cells (ECs) are involved in IA formation and progression. Impaired ECs function (endothelial dysfunction) can cause inflammation of the adventitia and the surrounding environment. The chronic inflammatory response induced by T-cells and macrophages triggers matrix metalloproteinases (MMPs)-mediated proteolytic remodeling of the ECM, ultimately weakening its structure. This process is associated with loss of elasticity of the vascular wall, structural changes in collagen fibers and angiogenesis. Inflammation is a vital factor in the occurrence and development of IA. Transformation of VSMCs from a contractile (differentiated) to a synthetic (dedifferentiated) phenotype correlates with the occurrence of IA and its progression. VSMCs make up the bulk of the cerebral vascular wall. VSMCs proliferate and dedifferentiate, triggering various signaling cascades that, in turn, stimulate proliferation, dedifferentiation, apoptosis, and migration of these cell types. Therefore, these processes are at least regulated in part by circRNAs. We aim to suggest a potential association of circRNAs with ECs and VSMCs in IA.

4.1. CircRNAs and ECs

A series of groundbreaking studies have unveiled an intriguing array of circRNAs that exhibit dysregulation in human ECs and are deemed to play a pivotal role in the pathogenesis of IAs. This discovery builds upon previous reports that have linked myeloperoxidase (MPO) to not only the formation and rupture of IAs but also the predisposition to degenerative remodeling in saccular intracranial aneurysm wall rupture. To uncover the intricate web of molecular interactions at play, a comprehensive microarray screening was conducted, comparing the circRNAs expression profiles in ECs obtained from patients with unruptured intracranial aneurysms (UIAs) and those with ruptured intracranial aneurysms (RIAs). Strikingly, this analysis pinpointed two circRNAs, namely circRNA_0079586 and circRNA_RanGAP1, as being significantly upregulated in ECs from patients with RIAs [32]. Further investigation through luciferase assays shed light on an intricate regulatory network featuring circRNA_0079586, circRNA_RanGAP1, miR-183-5p, miR-877-3p, and MPO. These studies revealed that both miR-183-5p and miR-877-3p exerted their influence by suppressing the expression of circRNA_0079586 and circRNA_RanGAP1 while also reducing MPO expression. The observed differential expression patterns of circRNA_0079586, circRNA_RanGAP1, miR-183-5p, miR-877-3p, and MPO between patients with RIAs and UIAs provided compelling evidence for their intricate involvement in the pathogenesis of IAs. Moreover, conducting experiments in human umbilical vein endothelial cells (HUVECs) to manipulate the expression of circRNA_0079586 and circRNA_RanGAP1 under various conditions consistently demonstrated a significant negative correlation with miR-183-5p and miR-877-3p, and a positive correlation with MPO. The results of this study culminated in the establishment of two distinct but intertwined MPO-modulating signaling pathways, involving circRNA_0079586/miR-183-5p/MPO and circRNA_RanGAP1/miR-877-3p/MPO. Both pathways emerged as vital players in the pathogenesis of IA rupture. Leveraging the power of the Arraystar human circRNAs microarray, differentially expressed circRNAs between patients with UIAs and RIAs were meticulously analyzed. The findings of these studies provide critical insights into the complex molecular landscape underlying IA pathogenesis. The discovery of specific circRNAs, such as circRNA_0079586 and circRNA_RanGAP1, and their roles in modulating miRNA activity and the expression of crucial factors like MPO shed light on the intricate mechanisms governing IA formation and rupture. These insights are a significant step forward in the understanding of this life-threatening condition. By identifying the regulatory networks and signaling pathways involving circRNAs and MPO, researchers and medical professionals gain valuable tools for potentially developing targeted interventions and therapies for IAs. The hope is that by understanding the molecular basis of IAs, it will be possible to diagnose the condition earlier, predict the risk of rupture, and ultimately, prevent or better manage these highly dangerous vascular anomalies.

Multiple intracranial aneurysms (MIAs) present a significant clinical challenge due to the substantial risk associated with vascular rupture and subsequent subarachnoid hemorrhage (SAH) [33]. Understanding the epigenetic regulation underlying MIA is of paramount importance; however, this aspect of the condition has remained relatively unexplored. CircRNAs have been increasingly recognized for their roles in CVDs, yet their connection to MIAs has not undergone extensive investigation. A pioneering study addressed this knowledge gap by conducting circRNAs sequencing in human peripheral blood mononuclear cells (PBMCs), leading to the identification of 60 circRNAs exhibiting significant expression changes in MIA compared to controls. Remarkably, the most prominent Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway associated with these circRNAs was 'leukocyte *trans*-endothelial migration,' suggesting its critical relevance in the pathogenesis of MIAs. This pathway is known to involve the migration of leukocytes through ECs, contributing to the inflammatory processes in vascular diseases. Several of the identified circRNAs were linked to this pathway, indicating their potential roles in the regulation of key molecules involved in this complex process. This groundbreaking study offers novel insights into the regulatory roles of circRNAs in MIAs, highlighting their potential significance in the condition's development [33]. The circRNAs identified, particularly those associated with 'leukocyte *trans*-endothelial migration,' hold promise as targets for further investigation, offering the potential to unveil the intricate mechanisms underpinning MIAs development. Collectively, these studies emphasize the emerging role of circRNAs in the pathogenesis of IAs, whether they occur as single entities or in a multiple MIAs context. While the precise mechanisms and interactions within this network are yet to be fully elucidated, these findings undoubtedly open promising avenues for future research, with the potential to enhance our understanding and management of IAs.

SAH is one of the main causes of death and disability in people. To find effective therapy or diagnostic tools, a deep and comprehensive study of the molecular mechanisms of IA progression is necessary. Healthy endothelium maintains the blood–brain barrier (BBB), controls hemostasis and regulates vascular tone. However, early events after SAH cause EC dysfunction and cell apoptosis, which in turn exacerbates the delayed phase of SAH pathophysiology [34]. Wang et al., demonstrated that circAFF1 was upregulated in ECs that under hypoxic conditions by cobalt chloride (CoCl2) and causes ECs to malfunction [35]. Was demonstrated that upregulation of circAFF1 can suppress the proliferation and tube formation and promote the apoptosis of ECs in vitro. Against, silencing of circAFF1 significantly promoted the proliferation, tube formation, migration and invasion and suppressed the apoptosis of ECs. Besides, through bioinformatics analysis, biotinylated RNA pull-down, and dual-luciferase reporter assays, the authors identified miR-516b as a target of circAFF1. These results suggested that circAFF1 could serve as a miRNA sponge for miR-516b and inhibit the proliferation and tube formation and promote apoptosis of EC. In additionally, Wang et al., analyzed the expression level of serum circAFF1 and found that the expression of circAFF1 was higher in patients older than 45 years old and patients with higher Hunt-Hess levels. In other study, was investigated the regulatory effects of circARF3/miR-31-5p on SAH-induced BBB destruction both in vitro and *in vivo* [36]. Was found that overexpressing circARF3 inhibited miR-31-5p and improved the neurological behaviors of SAH rats via reducing BBB damage and microglial activation. Overexpressing circARF3 significantly attenuated oxygen-glucose deprivation (OGD)-mediated brain microvascular endothelial cells (BMECs) integrity destruction and inflammatory response, while miR-31-5p had the opposite effects in vitro. These results suggest that occurrence of SAH is correlated to the functional injury of ECs and circRNAs may be a potential therapeutic target for relative

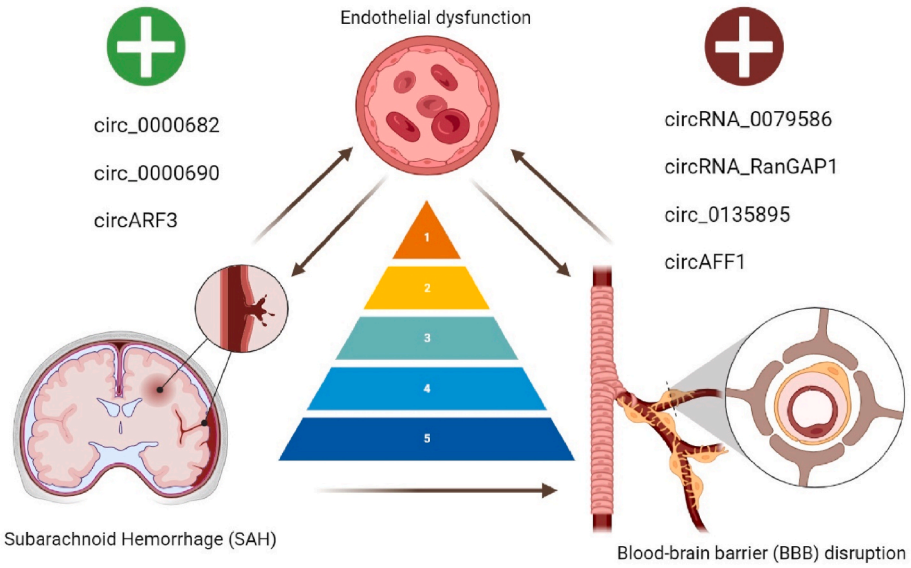

Fig. 1. Schematic illustration of the effect of circular RNAs (circRNAs) on intracranial aneurysm (IA) rupture. Current evidence strongly suggests a central role for endothelial dysfunction in the initiation and progression of IA. Post-subarachnoid hemorrhage (SAH), several early pathophysiological events can be commonly observed in blood-brain barrier (BBB) components, such as the endothelium (endothelial dysfunction). In results, post-*SAH* injuries can *disrupt* the integrity and function of the *BBB*. Both negative (red cross) and positive (green cross) regulation of circRNAs have been observed in this pathological cascade. The role of circRNAs is based on components: 1) strong role in endothelial cells (ECs) homeostasis; 2) regulation of barrier function and vascular tone; 3) associated with SAH and its complications; 4) correlates with clinical outcomes (Glasgow Coma Scale, the volume of SAH, modified Fisher scale, Hunt-Hess levels, and surgical type; 5) regulators of transcription/translation, sequesters of microRNA (miRNA)/RNA-binding proteins (RBPs), and biomarkers of IA.

disease treatment (Fig. 1).

4.2. CircRNAs and VSMCs

Dysfunctional VSMCs are at the heart of IA pathogenesis, and understanding the intricate regulatory mechanisms at play is vital for devising effective interventions. The results presented in this study tackles the critical issue of IAs, a condition with potentially devastating consequences [37]. The study delves into the complexities of IA by exploring the role of circRNA_0020397 in regulating IA progression. By analyzing arterial wall tissues at IA sites from 12 patients, the research uncovers significant changes in circRNA_0020397 and its associated molecules. The findings reveal that circRNA_0020397 is downregulated in artery wall tissues and cells of IA, while miR-138 is upregulated [37]. The research proceeds to investigate the impact of these alterations, shedding light on the regulatory pathway at play. Overexpressing circRNA_0020397 is shown to promote the proliferation of human umbilical artery smooth muscle cells (HUASMCs), indicating its role in enhancing VSMC proliferation. One of the pivotal discoveries in this study is the involvement of miR-138 in the IA pathogenesis. It's revealed that miR-138 exerts its effects by negatively regulating kinase insert domain receptor (KDR) through binding to the 3′ untranslated regions (3′ UTRs) of messenger RNA (mRNA). This finding uncovers an important upstream regulator in IA progression. Additionally, the study highlights the inverse correlation between circRNA_0020397 and miR-138 expression, further underlining the regulatory role of circRNA_0020397 in IA pathogenesis. This research provides significant insights into the molecular mechanisms behind IA development. By demonstrating the decreased expression of circRNA_0020397 and its implications for VSMC proliferation through the miR-138/KDR pathway, the study unveils a complex regulatory network that contributes to IA progression. These findings have the potential to pave the way for novel therapeutic approaches in addressing the challenges posed by intracranial aneurysms, ultimately offering hope for more effective interventions and improved patient outcomes.

The microarray analysis conducted in this study has provided a comprehensive view of the circRNAs landscape, revealing thousands of circRNAs genes, including 63 that were significantly upregulated and 54 that were downregulated in RIAs compared to UIAs cases [38]. Among the upregulated circRNAs, circ_0005505 has emerged as a particularly noteworthy candidate, displaying a substantial increase in RIA tissues. The functional experiments performed in vitro have elucidated the crucial role of circ_0005505 in influencing the proliferation and migration of VSMCs while concurrently suppressing apoptosis. These findings emphasize the significance of hsa_circ_0005505 in the pathophysiological processes that underlie IAs [38]. The recognition of circRNAs emerging role in the pathogenesis of IAs represents a groundbreaking addition to our comprehension of this intricate vascular disorder. Dysregulated circRNAs, exemplified by circ_0005505, appear to exert pivotal influences on IA development and rupture. Furthermore, the elucidation of regulatory networks encompassing miRNAs and target genes provides invaluable insights into the underlying mechanisms. Moreover, circRNAs exhibit the potential to serve as diagnostic biomarkers for IA patients, which positions them as promising candidates for further exploration in the domain of clinical diagnostics and therapeutic approaches. The implications of this research extend to the prospect of opening new avenues for the management and treatment of intracranial aneurysms, addressing a condition known for its substantial morbidity and mortality rates. These findings indeed represent a significant advancement in our quest to better understand and ultimately address IAs.

A significant study in this regard examined human IA lesions obtained during surgical procedures, distinguishing between RIAs and UIAs samples [39]. Using transcriptomic sequencing and qRT-PCR, the study unveiled a distinct set of differentially expressed circRNAs. Among these, circ_0031608 particularly stood out as it exhibited high expression in RIAs and appeared to be associated with a pro-inflammatory transformation of VSMCs. This study extended its investigation to identify a total of 1373 differentially expressed genes between RIAs and UIAs. Additionally, it constructed a comprehensive circRNA-miRNA-mRNA network, providing valuable insights into the complex regulatory landscape that governs IA development. By employing GO and KEGG pathway analyses, the study uncovered several circRNAs that potentially play a role in the inflammatory processes

related to IAs. Among these candidates, hsa_circ_0031608 emerged as a noteworthy participant [39]. It not only influenced the expression of VSMC phenotypic markers but also played a role in promoting the migration and proliferation of VSMCs. The study further emphasized the involvement of key hub genes such as Forkhead Box O3 (FOXO3), DICER1, Cyclin D2 (CCND2), insulin-like growth factor 1 (IGF1), and trinucleotide repeat containing adaptor 6B (TNRC6B), highlighting the intricate nature of the regulatory network that contributes to IA development. Notably, circ_0031608 appeared to be a pivotal regulator of VSMC phenotype and played an indispensable role in the context of RIA. These findings provide valuable insights into the potential mechanism that underlies the development and RIAs. While this study represents a significant step in our understanding of IA pathogenesis, it is essential to recognize that further research will be necessary to confirm the specifics of circ_0031608's function and its role in the broader context of IA.

The research begins by scrutinizing the profiles of differentially expressed circRNAs between superficial temporal arteries (STAs) and IAs, painting a comprehensive picture of these circRNA molecules. This analytical endeavor employs the Arraystar human circRNAs microarray to probe five samples of each tissue type, revealing a plethora of circRNAs that undergo significant upregulation or downregulation in IAs [40]. One circRNAs that takes center stage in this investigation is circDUS2, which exhibits elevated expression in IAs, as validated by qRT-PCR. A critical piece of the puzzle regarding circDUS2's function and role in intracranial aneurysms is provided through fluorescence in situ hybridization (FISH), elucidating its location within the cytoplasm of human brain vascular smooth muscle cells (HBVSMCs). The spotlight on circDUS2 as a potential molecular marker for IAs opens promising avenues for future research, offering a glimpse into the intricate molecular landscape underlying this condition. CircRNAs, with circDUS2 at the forefront, may hold the key to unraveling the mysteries of IAs and ultimately contribute to the development of novel diagnostic and therapeutic strategies.

CircLIFR (circ_0072309) comes under scrutiny as it exhibits crucial roles in HUASMCs and their relationship with IAs [41]. Decreased expression of circLIFR is noted in the artery wall tissues and cells of IA patients, indicating its involvement in the pathogenesis of the condition. CircLIFR, in a fascinating mechanistic twist, engages in a direct interaction with miR-1299. This interaction is pivotal in mediating proliferation, migration, and invasion of HUASMCs. Furthermore, the study identifies the KDR as a direct and functional target of miR-1299. CircLIFR operates as a post-transcriptional regulator, impacting KDR expression via the miR-1299 route.

The emergence of circular RNA circ_FOXO3 as a regulator in the landscape of IA adds a fascinating layer to our understanding of this complex condition [42]. This study ventures into the specific role of circ_FOXO3 in an in vitro model of HBVSMCs in the context of IA induced by H2O2. The research uncovers the multi-faceted impact of circ_FOXO3 on HBVSMCs. It affects critical cellular processes such as proliferation and apoptosis while contributing to regulatory mechanisms within these cells. However, the spotlight shines even brighter as circ_FOXO3's interaction with miR-122-5p comes to the forefront. Circ_FOXO3 is found to bind to miR-122-5p, a pivotal piece in the intricate puzzle of IA regulation. Subsequently, miR-122-5p sets its sights on KLF6, a key player responsible for controlling the progression of IAs. This interplay between circ_FOXO3 and the miR-122-5p/kruppel-like factor 6 (KLF6) axis introduces a novel dimension to our understanding of IA [42]. By delineating the roles of circ_FOXO3, miR-122-5p, and KLF6 within the context of IA, this study paves the way for a more comprehensive comprehension of the underlying mechanisms. The interconnected regulatory network involving these molecules provides fresh insights into the progression of IAs. Ultimately, this research not only sheds light on the molecular intricacies of IA but also offers potential avenues for targeted therapeutic interventions.

The research in question delves into the intriguing role of circular RNA dedicator of cytokinesis 1 (circ_DOCK1) and its influence on the proliferation and apoptosis of HBVSMCs [43]. A notable finding of this investigation is the observation that the expression of circ_DOCK1 is downregulated in HBVSMCs when exposed to H2O2, resulting in a decrease in cell proliferation and an increase in apoptosis. This reduction in circ_DOCK1 levels appears to have a significant impact on cellular behavior, particularly in response to oxidative stress. The study goes on to elucidate the intricate mechanism by which circ_DOCK1 operates. It is revealed that circ_DOCK1 engages with miR-409-3p, a miRNA that is upregulated in hydrogen peroxide (H2O2)-treated HBVSMCs. This interaction between circ_DOCK1 and miR-409-3p uncovers the role of circ_DOCK1 in rescuing cells from the H2O2-induced reduction in proliferation and promotion of apoptosis. This dynamic relationship between circ_DOCK1 and miR-409-3p offers a fresh perspective on the regulatory networks at play in HBVSMCs under oxidative stress conditions [43]. Furthermore, the research sheds light on the control of the anti-apoptotic protein myeloid leukemia 1 (MCL-1) by miR-409-3p. This is a key discovery, as it helps to unravel the molecular mechanisms involved in regulating cell survival and death in response to oxidative stress. This study provides valuable insights into the role of circ_DOCK1 in the regulation of HBVSMC behavior, specifically in the context of oxidative stress. The intricate interplay between circ_DOCK1, miR-409-3p, and MCL1 contributes to our understanding of the molecular processes underlying cell proliferation and apoptosis. These findings offer potential avenues for further research and therapeutic interventions in the field of VSMCs biology.

The intricate interplay of molecular mechanisms underlying IA pathogenesis has a central character in the form of circular RNA ADP ribosylation factor interacting protein 2, also known as circ_ARFIP2 (circ_0021001) [44]. This circRNA stands out as a critical player in the complex landscape of IA progression. A notable feature of circ_ARFIP2 is its reduced expression in IA arterial wall tissues and VSMCs, hinting at its significance in the development and progression of IAs. Its pivotal role becomes even more fascinating when we dive into the intricate web of interactions it orchestrates. Circ_ARFIP2's mechanism hinges on its interaction with miRNA miR-338-3p, a key regulatory molecule. This interaction forms a central axis in the network. Circ-ARFIP2 acts as a sponge or decoy, targeting and sequestering miR-338-3p, which, in turn, plays a significant role in modulating VSMC behaviors [44]. This modulation, orchestrated by miR-338-3p, has far-reaching consequences for IA development. But the complexity doesn't end there. Within this intricate network, another character emerges—KDR. MiR-338-3p directly targets KDR, making it a pivotal player in IA progression. KDR's role as a downstream effector of circ_ARFIP2's function further underscores the multifaceted nature of the regulatory network at play in IA development. Circ_ARFIP2, miR-338-3p, and KDR collectively form a complex and finely tuned network that influences the behavior of VSMCs, which is central to IA pathogenesis. The discoveries made in this study shed light on the multifaceted mechanisms driving IA progression and offer new perspectives for understanding and potentially intervening in this challenging vascular condition.

The dysregulation of circRNA circ_0020397 in VSMCs obtained from IA patients is a striking observation with far-reaching implications [45]. This study delves into the intricate interplay between circ_0020397, Gremlin 1 (GREM1), and miR-502-5p, offering fresh insights into IA pathogenesis and potential therapeutic targets. One of the key findings is the potential of both circ_0020397 and GREM1 to enhance VSMC viability while increasing the expression of proliferating cell nuclear antigen (PCNA), a marker of cellular proliferation. Conversely, inhibiting these molecules leads to the opposite effect, suggesting their significance in IA development. Amid this intricate network, miR-502-5p emerges as a pivotal player, acting as a crucial mediator in these interactions. It forms a critical link between circ_0020397 and GREM1, orchestrating their effects on VSMC viability, apoptosis, and PCNA levels [45]. The study not only highlights the complex regulatory mechanisms involved in IA pathogenesis but also provides new avenues for potential

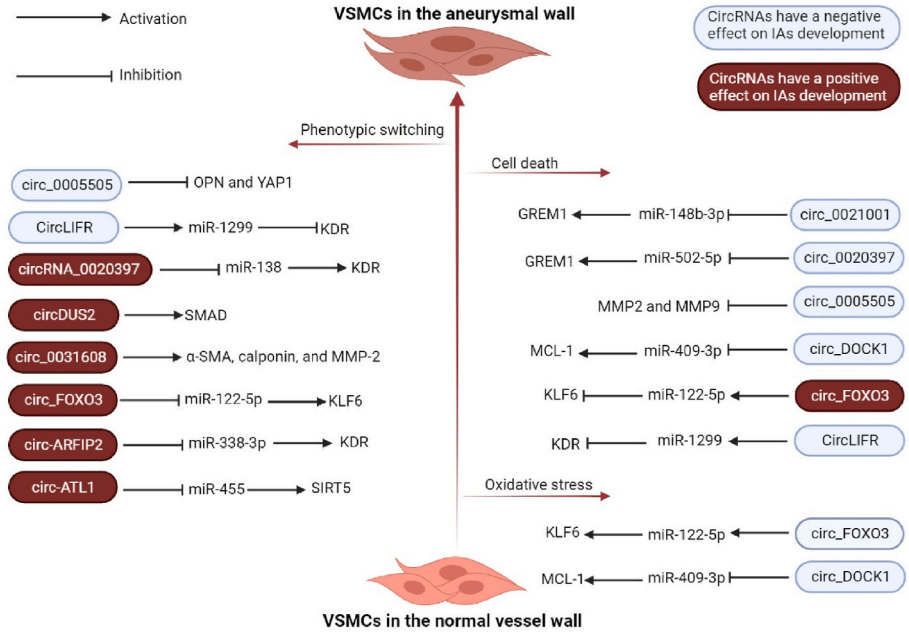

Fig. 2. Schematic illustration of circular RNAs (circRNAs) regulation mechanisms underlying vascular smooth muscle cells (VSMCs) phenotypic modulation, oxidative stress, and cell death in intracranial aneurysms (IAs). As can be seen from the figure, circRNAs play a role both in the development and progression of IA and in the inhibition of IA through the control of VSMC. However, some of them exhibit a double effect as circ_FOXO3 and circ_0020397.

therapeutic interventions. By understanding the roles of circ_0020397, GREM1, and miR-502-5p in VSMC behavior, researchers can explore novel approaches for IA molecular therapy. These findings open up promising possibilities for managing and treating IA, a condition associated with significant morbidity and mortality.

The upregulation of circ_0021001 in IA tissues and HUASMCs is a significant finding, highlighting its potential role in the pathogenesis of IAs [46]. A deeper exploration of its mechanism of action reveals the intriguing role of circ_0021001 as a miR-148b-3p sponge, regulating the expression of GREM1. This discovery sheds light on the critical role played by circ_0021001 in IA progression. It acts as a modulator, influencing cell growth and apoptosis of HUASMCs through its interactions with the miR-148b-3p/GREM1 axis. Understanding these complex interactions provides valuable insights into the molecular mechanisms underpinning IA development and points towards potential therapeutic strategies. The study's findings offer new perspectives for exploring circ_0021001 as a target for IA management and treatment.

Xu et al. demonstrated the intricate interplay between circATL1, miR-455, and SIRT5 in the context of IA is meticulously investigated [47]. The combined use of bioinformatic tools and clinical evaluations highlights the clinical relevance of these molecular players. CircATL1's overexpression, coupled with the downregulation of miR-455, is shown to be a significant contributor to IA development. Silencing circATL1, on the other hand, results in a reduction in VSMC migration, proliferation, and phenotypic modulation, underlining its critical role in IA progression. Furthermore, sirtuin 5 (SIRT5) and miR-455 are identified as downstream targets of circATL1, amplifying its impact on IA pathogenesis. Notably, SIRT5 upregulation and miR-455 inhibition are found to counteract the inhibitory effects induced by circATL1 silencing on VSMC behaviors. These findings shed light on the complex interactions between these molecules and their collective role in IA progression. The study expands our understanding of the molecular mechanisms underlying the development of IA, particularly the influence of circRNAs for VSMCs, and offers potential insight into therapeutic strategies to treat this condition (Fig. 2).

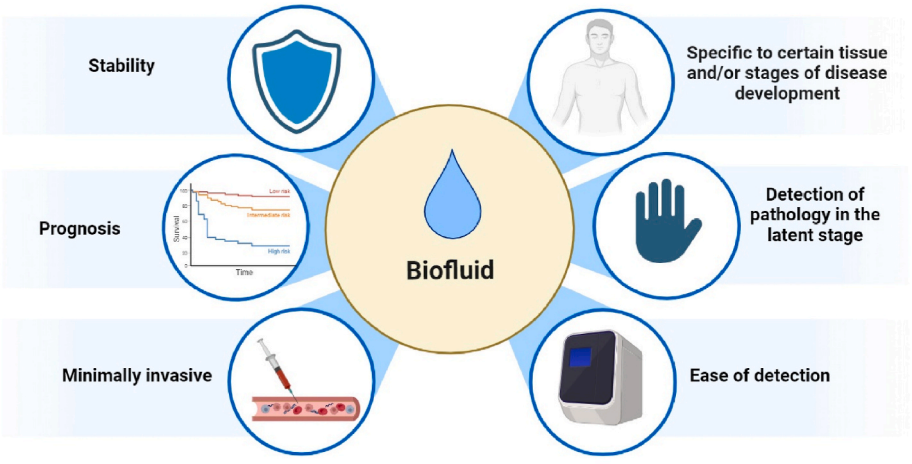

Fig. 3. Benefits of using cell free circular RNAs (circRNAs) as biomarkers.

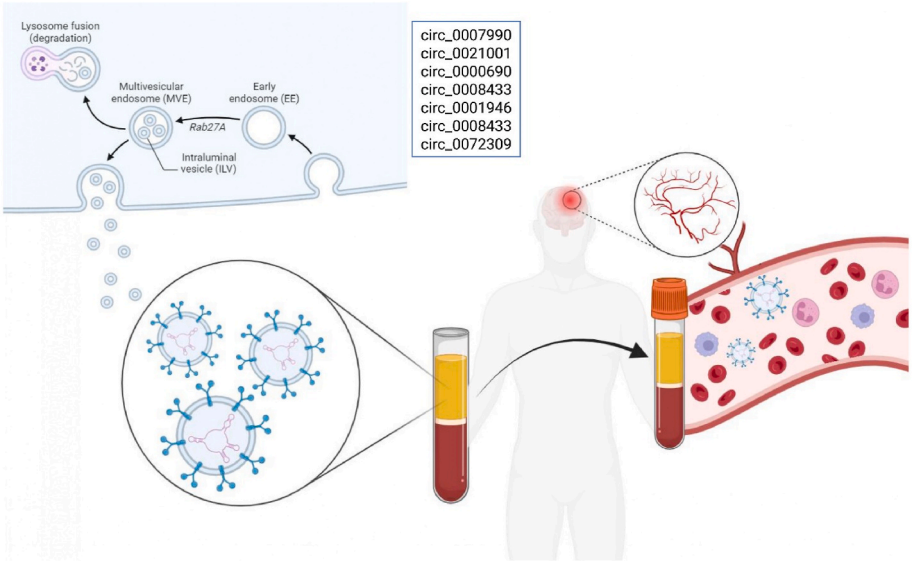

Fig. 4. The studied cell free circular RNAs (circRNAs) are presented as non-invasive biomarkers in intracranial aneurysms (IAs).

5. Cell-free circRNAs as biomarkers

Recent studies have delved into the world of cell free circRNAs, exploring their potential as diagnostic and prognostic biomarkers (Fig. 3).

The research in this review involves analyzing circRNAs expression profiles in peripheral blood samples from UIA patients with aneurysm wall enhancement (AWE), those without AWE, and healthy controls [48]. The circRNAs microarray analysis revealed 412 differentially expressed circRNAs between UIA patients and healthy controls, with 231 circRNAs significantly differentially expressed in UIA patients with AWE compared to those without AWE [45]. Among the upregulated circRNAs associated with AWE, circ_0007990 stood out. The study found that circ_0007990's expression increased progressively from healthy controls to UIA patients without AWE and those with AWE [8]. This suggests its potential as a valuable diagnostic marker for IA patients. The study further predicted that circ_0007990 could interact with various RNA binding proteins and miRNAs. Period circadian regulator 1 was identified as a possible encoding protein with circ_0007990. The circ_0007990-miRNA-mRNA network was constructed, revealing five miRNAs and 97 mRNAs involved in the inflammatory response [48]. Notably, five hub genes, including hypoxia-inducible factor 1 subunit alpha (HIF1A), estrogen receptor 1 (ESR1), forkhead box O1 (FOXO1), insulin-like growth factor 1 (IGF-1), and cyclic AMP response element (CRE)-binding protein (CREB) binding protein, played pivotal roles in this network, potentially influencing the inflammatory processes associated with AWE in UIA. This groundbreaking study highlights the potential of circRNAs as novel inflammatory biomarkers for evaluating UIA patients, particularly those with AWE observed on high-resolution vessel wall imaging (HR-VWI). Among the differentially expressed circRNAs, circ_0007990 emerges as a key player, progressively increasing its expression with the severity of IA. The predicted circRNA-miRNA-mRNA network offers insight into the complex interactions that regulate inflammation in UIA patients. Furthermore, the study underscores the importance of investigating circRNA_0007990's mechanism in IA progression. The results pave the way for further research and the potential development of diagnostic and therapeutic strategies for IAs, focusing on epigenetic regulators like circRNAs. By understanding the inflammatory processes underlying AWE, we take a significant step towards better managing IA patients and improving their outcomes.

Another study investigated the expression of circ_0021001 in the peripheral blood of IA patients, offering an exciting perspective on diagnostic biomarkers [49]. The cohort consisted of 223 IA patients and 131 healthy volunteers. The research found that the expression of hsa_circ_0021001 was significantly lower in IA patients compared to the control group, suggesting its potential as a diagnostic marker. The effectiveness of circ_0021001 in diagnosing IA was assessed using a ROC curve. The high area under the ROC (AUC) value of 0.87 signifies the diagnostic potential of circ_0021001 in identifying IA. Hsa_circ_0021001 expression was further correlated with IA parameters, including aneurysm rupture, Hunt-Hess level, and timing of surgery. Patients with higher circ_0021001 expression exhibited longer disease-free survival (DFS) and overall survival (OS). Differentially expressed circRNAs in blood samples not only provide insights into potential mechanisms underlying IA but also offer promising diagnostic biomarkers, as exemplified by circ_0021001 [49]. As we continue to unravel the intricate biology of IAs, circRNAs stand out as valuable players in improving diagnostics and potentially advancing therapeutic strategies for this challenging vascular condition.

Circ_0000690 emerges as a promising diagnostic biomarker for IA [50]. Through clinical comparisons between IA patients and healthy volunteers, this study highlights the significantly lower levels of circ_0000690 in IA patients, underscoring its diagnostic potential. The diagnostic performance of circ_0000690 is further accentuated by its robust AUC, specificity, and sensitivity. Importantly, the study reveals that hsa_circ_0000690 expression is intricately linked to various clinical factors, including the Glasgow Coma Scale, the volume of SAH, modified Fisher scale, Hunt-Hess levels, and surgical type. While associations with complications like hydrocephalus and delayed cerebral ischemia are observed in univariate analysis, they become nonsignificant in multivariate analysis. However, circ_0000690 demonstrates a significant association with modified Rankin Scales three months after surgery, offering insights into its potential clinical utility for prognosis. Though circ_0000690 may not be directly associated with survival time, these findings pave the way for further exploration of its diagnostic and prognostic value in the context of IA. This circRNA holds promise as a valuable tool for enhancing our understanding of IA and improving patient care.

This comprehensive study delves into the intricate web of factors associated with the RIAs [51]. IAs, often lurking as silent threats, can have devastating consequences when they rupture, making it crucial to identify potential risk factors and diagnostic markers. The research employs a multifaceted approach, encompassing both clinical and

Table 1
Summary information on the role of circular RNAs (circRNAs) in the formation and development of intracranial aneurysms (IAs).

CircRNA	Study model	Regulation	Targets	Important find	References
circRNA_000139, circRNA_101321, circRNA_072697, circRNA_069101, and circRNA_103677	Bioinformatics analysis	Up	mTOR	Involved in the pathogenesis of IA rupture	[30]
circ_0008433 circ_0072309	Human IA walls; bioinformatics analysis	Up Down	MMP2, miR-181c-5p and miR-181b-5p DDR2, SAT2, miR-519e-5p and miR-516b-5p	Involved in the pathogenesis of MIA through the VSMCs function control	[31]
circRNA_0079586 circRNA_RanGAP1	Human ECs and HUVECs	Up Up	miR-183-5p/MPO miR-877-3p/MPO	Involved in the pathogenesis of IA rupture	[32]
circ_0135895 circ_0000682 circ_0000690	Himan PBMCs; bioinformatics analysis	Up Down Down	miR-619-3p, miR-4324, miR-5687, miR-3529-5p, miR-379-5p, PTK2, PRKCB, and ITGAL miR-448, miR-1248, miR-302a-5p, miR-627-3p, miR-1248, PTK2, PRKCB, and ITGAL miR-4726-3p, miR-4520-3p, miR-4514, miR-4692, miR-6842-3p, PTK2, PRKCB, and ITGAL	Involved in the pathogenesis of MIA through the inflammatory link	[33]
circAFF1	Human HUVEC and HBEC-5i (from cerebral microvascular endothelium); human blood samples	Up	miR-516b/SAV1/YAP1 axis	Inhibits the proliferation and tube formation and promote apoptosis of ECs. Progression of SAH	[35]
circARF3	Animal BMECs and human blood and CSF	Down	miR-31-5p/MyD88/NF-κB axis	Neuroprotective effect in the SAH by attenuating BBB destruction and microglia-mediated inflammation	[36]
circ_0020397	Human IA walls and HUASMCs	Up	miR-138/KDR	Promotes VSMCs proliferation and inhibits cell apoptosis	[37]
circ_0005505	HBVSMCs and human IA tissue; bioinformatics analysis	Up	TGF-β, MAPK, melanoma, and Ras signaling pathway	Promotes the proliferation, migration and suppresses the apoptosis of VSMCs vascular smooth muscle cell. Involved in the pathogenesis of IA rupture	[38]
circ_0031608	HBVSMCs and human IA tissue; bioinformatics analysis	Up	TNF-α, α-SMA, calponin, and MMP-2	Promotes phenotypic transformation of VSMCs. Important role in the rupture of IA	[39]
circDUS2	HBVSMC; bioinformatics analysis	Up	SMAD/TGF-β/MAPK signaling pathway	Involved in the pathogenesis of IA rupture	[40]
circLIFR	Human IA walls and HUASMCs	Up	miR-1299/KDR	Enhances VSMCs proliferation, migration, invasion, and impedes apoptosis	[41]
circ_FOXO3	Human IA walls and HUASMCs	Up	miR-122-5p/KLF6	Suppresses H2O2-induced proliferation of VSMCs but promotes apoptosis	[42]
circ_DOCK1	Human IA walls and HBVSMCs	Up	miR-409-3p/MCL1	Suppresses H2O2-induced proliferation of VSMCs and cell apoptosis	[43]
circ_ARFIP2	Human IA walls and HUASMCs	Up	miR-338-3p/KDR	Promotes in VSMCs proliferation, migration, and invasion	[44]
circ_0020397	Human IA walls	Up	miR-502-5p/GREM1	Inhibits VSMC apoptosis	[45]
circ_0021001	Human IA walls and HUASMCs	Up	miR-148b-3p/GREM1	Inhibits VSMC apoptosis	[46]
circATL1	Human IA walls	Down	miR-455/SIRT5	Suppresses of VSMC migration, proliferation, and phenotypic modulation	[47]

molecular perspectives, to unravel the intricacies surrounding this condition. To begin, the study examines a cohort of 347 cases and controls to decipher the main individual environmental factors that contribute to the RIAs. Several key risk factors are identified, including smoking, hair dyeing, extended sitting time, a diet rich in animal fats, and hypertension. Conversely, protective factors are also revealed, such as higher education, longer sleep duration, tea consumption, diabetes, and specific blood parameters like hemoglobin, low-density lipoprotein (LDP), serum calcium, and apolipoprotein-A1. The study goes a step further by exploring the role of circRNAs in RIAs [51]. Two circRNAs, circ_0008433 and circ_0001946, are found to be closely associated with this condition and demonstrate promising clinical diagnostic significance. These circRNAs not only serve as potential markers for RIAs but are also identified as independent epigenetic factors that influence the condition. Moreover, there is evidence of a multiplicative interaction between age and epigenetic score, shedding light on the intricate interplay of these factors in RIAs. Huang et al., demonstrated that the expression pattern of cell free circ_0072309 in blood was consistent with that in tissues, while the expression trend of cell free circ_0008433 in blood differed from that in tissues. AUC of cell free circ_0008433 and cell free circ_0072309 were 0.8022 and 0.7544, respectively [31]. The identification of specific cell free circRNAs as biomarkers adds a valuable dimension to the diagnostic toolkit for IAs (Fig. 4).

6. Conclusion

The emerging research on circRNAs in the context of IAs has brought to light their intricate roles in the pathogenesis of this life-threatening vascular disorder. Once overshadowed in the IA landscape, circRNAs have now stepped into the limelight as pivotal regulators of IA development and progression. A plethora of studies has unveiled numerous circRNAs with differential expression patterns in IA patients, underscoring their significance in IA pathogenesis. These circRNAs have been intricately linked to fundamental cellular processes, including VSMCs dysfunction, inflammation, and phenotypic modulation, all of which play central roles in IA progression. The diagnostic potential of circRNAs is equally compelling. Promising candidates such as circ_0000690 have shown remarkable abilities to distinguish IA patients from healthy

individuals, potentially revolutionizing IA diagnosis [50]. Moreover, their associations with various clinical factors and post-surgical outcomes hint at their utility for prognosis and personalized patient care. The complex interplay of circRNAs, miRNAs, and mRNAs at the heart of IA pathogenesis has expanded our understanding of the disease's intricate nature. While many pieces of this puzzle have been revealed, there is still a vast expanse to explore. The regulatory networks that involve these molecules are continually being unraveled, necessitating further research to confirm and expand upon the specifics of their functions. In summary, circRNAs are emerging as essential players in IA pathogenesis, offering exciting prospects for therapeutic strategies (Table 1) [31–44].

Their multifaceted involvement in the behavior of VSMCs, the regulation of inflammation, and the orchestration of phenotypic changes underscores their significance in IA progression. As research in this field continues to evolve, circRNAs hold great promise for enhancing our understanding of IAs and revolutionizing the way we diagnose and treat this debilitating condition. These novel insights provide renewed hope for both patients and clinicians grappling with the challenges of IA management and care. With each revelation, we move one step closer to unraveling the enigma of IAs.

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CRediT authorship contribution statement

Ilgiz Gareev: Writing – review & editing, Writing – original draft. **Alina Shumadalova:** Formal analysis, Data curation. **Tatiana Ilyasova:** Resources, Investigation, Formal analysis. **Aferin Beilerli:** Data curation, Resources. **Huaizhang Shi:** Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Abbreviations

ECs	Endothelial cells
HUVECs	Human umbilical vein endothelial cells
HBVSMCs	Human brain vascular smooth muscle cells
PBMCs	Human peripheral blood mononuclear cells
HUASMCs	Human umbilical artery smooth muscle cells
MPO	*Myeloperoxidase*
TGF-β	Transforming growth factor beta
MAPK	Mitogen-activated protein kinase
TNF-α	Tumor necrosis factor-alpha
α-SMA	Alpha-smooth muscle actin
MMP-2	Matrix metalloproteinase-2
PTK2	Protein tyrosine kinase 2
PRKCB	Protein kinase Cβ
ITGAL	Integrin subunit αL
SMAD	Mothers against decapentaplegic homolog
MAPK	Mitogen-activated protein kinase
DDR2	Discoidin domain-containing receptor 2
SAT2	Spermidine/spermine N1-acetyltransferase family member 2
KDR	Kinase insert domain receptor
KLF6	Krueppel-like factor 6
MCL1	Myeloid cell leukemia-1
GREM1	Gremlin 1
SIRT5	Sirtuin 5
VSMCs	Vascular smooth muscle cells
MIA	Primary multiple intracranial aneurysm
mTOR	Mammalian target of rapamycin
CSF	Cerebrospinal fluid
MyD88	Myeloid differentiation factor 88
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
SAH	Subarachnoid hemorrhage
BBB	Blood-brain barrier
HBEC-5i	Human brain–derived endothelial cells
SAV1	Salvador homolog-1
YAP1	Yes-associated protein 1

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