International Journal of
Molecular Sciences

MDPI

Review

A Systematic Review of MicroRNAs in Hemorrhagic Neurovascular Disease: Cerebral Cavernous Malformations as a Paradigm

Roberto J. Alcazar-Felix [1], Aditya Jhaveri [1], Javed Iqbal [1], Abhinav Srinath [1], Carolyn Bennett [1], Akash Bindal [1], Diana Vera Cruz [2], Sharbel Romanos [1], Stephanie Hage [1], Agnieszka Stadnik [1], Justine Lee [1], Rhonda Lightle [1], Robert Shenkar [1], Janne Koskimäki [1], Sean P. Polster [1], Romuald Girard [1,†] and Issam A. Awad [1,*,†]

[1] Neurovascular Surgery Program, Department of Neurological Surgery, University of Chicago Medicine and Biological Sciences, Chicago, IL 60637, USA; justinelee89@bsd.uchicago.edu (J.L.); spolster@uchicago.edu (S.P.P.)
[2] Center for Research Informatics, University of Chicago Medicine and Biological Sciences, Chicago, IL 60637, USA
* Correspondence: iawad@bsd.uchicago.edu; Tel.: +1-773-702-2123; Fax: +773-702-3518
† These authors contributed equally to this work.

Abstract: Hemorrhagic neurovascular diseases, with high mortality and poor outcomes, urge novel biomarker discovery and therapeutic targets. Micro-ribonucleic acids (miRNAs) are potent post-transcriptional regulators of gene expression. They have been studied in association with disease states and implicated in mechanistic gene interactions in various pathologies. Their presence and stability in circulating fluids also suggest a role as biomarkers. This review summarizes the current state of knowledge about miRNAs in the context of cerebral cavernous malformations (CCMs), a disease involving cerebrovascular dysmorphism and hemorrhage, with known genetic underpinnings. We also review common and distinct miRNAs of CCM compared to other diseases with brain vascular dysmorphism and hemorrhage. A systematic search, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline, queried all peer-reviewed articles published in English as of January 2025 and reported miRNAs associated with four hemorrhagic neurovascular diseases: CCM, arteriovenous malformations, moyamoya disease, and intracerebral hemorrhage. The PubMed systematic search retrieved 154 articles that met the inclusion criteria, reporting a total of 267 unique miRNAs identified in the literature on these four hemorrhagic neurovascular diseases. Of these 267 miRNAs, 164 were identified in preclinical studies, while 159 were identified in human subjects. Seventeen miRNAs were common to CCM and other hemorrhagic diseases. Common and unique disease-associated miRNAs in this systematic review motivate novel mechanistic hypotheses and have potential applications in diagnostic, predictive, prognostic, and therapeutic contexts of use. Much of current research can be considered hypothesis-generating, reflecting association rather than causation. Future areas of mechanistic investigation are proposed alongside approaches to analytic and clinical validations of contexts of use for biomarkers.

Keywords: cerebral cavernous malformation; microRNAs; biomarkers; systematic review; hemorrhage; neurovascular diseases

Academic Editor: Leonidas D. Panos

Received: 5 March 2025
Revised: 7 April 2025
Accepted: 16 April 2025
Published: 17 April 2025

Citation: Alcazar-Felix, R.J.; Jhaveri, A.; Iqbal, J.; Srinath, A.; Bennett, C.; Bindal, A.; Vera Cruz, D.; Romanos, S.; Hage, S.; Stadnik, A.; et al. A Systematic Review of MicroRNAs in Hemorrhagic Neurovascular Disease: Cerebral Cavernous Malformations as a Paradigm. *Int. J. Mol. Sci.* **2025**, *26*, 3794. https://doi.org/10.3390/ijms26083794

1. Introduction

Stroke is the second-leading cause of death worldwide, and neurological disorders are the leading cause of disability-adjusted life-years [1,2]. The global economic burden of stroke was estimated at USD 891 billion in 2017 and is predicted to increase to USD 2.31 trillion by 2050 [3]. Hemorrhagic stroke is associated with high mortality rates and worse outcomes than ischemic stroke [4]. Several vascular pathologies can cause brain bleeding, with varying degrees of understanding regarding their pathophysiologic mechanisms [5].

In 1993, Nobel laureates Ambros and Ruvkun first reported micro-ribonucleic acids (miRNAs) in post-transcriptional gene regulation [6,7]. Circulating miRNAs have since emerged as candidate biomarkers of clinical activity in cancer, and more recently in association with neurovascular disorders [8,9]. MiRNAs are small (19–25 bp), non-coding RNAs that regulate post-transcriptional gene expression via mRNA silencing [10]. Their direct relationship with the cellular transcriptome makes them key players in the regulation of intracellular signaling pathways and cell-to-cell communication [10]. Of interest, several studies indicate that miRNAs from pathological tissue are detectable in the blood flow or cerebrospinal fluid (CSF), suggesting their propensity to reflect tissue-specific clinical changes [11]. Furthermore, miRNAs have also been proven to be effective measures of treatment response [12]. MiRNAs can be leveraged as diagnostic and prognostic indicators of disease state and applied as monitoring biomarkers of drug effects; they have even been suggested as gene silencing therapies [8,13,14]. Several miRNA-based diagnostic tools are currently available to clinicians largely focused on cancer, but no miRNAs have been approved as therapies [15,16]. The role of miRNAs in neurovascular disease has only begun to be explored. Several miRNA discoveries have been reported in cerebral cavernous malformations (CCMs), a disease involving vascular dysmorphism and brain bleeding, where substantial progress has been made regarding its genetic underpinnings. Other neurovascular entities such as arteriovenous malformations (AVMs) and moyamoya disease (MMD) involve vascular dysmorphism primarily, with a lesser predisposition to bleeding, and allow the exploration of potentially common and distinct miRNAs. And of course, spontaneous intracerebral hemorrhage (ICH) offers an opportunity to identify miRNAs implicated in brain bleeding per se. We conduct a systematic review of miRNAs implicated in these pathologies. Commonalities may reveal new insights into the mechanisms of vascular dysmorphism and brain bleeding, which will pave the way toward identifying prime miRNA candidates for future study and clinical biomarker development. Distinct miRNAs may reflect unique and different mechanisms. We clarify knowledge gaps, identify cogent hypotheses based on this emerging knowledge, and pro-pose areas of future research.

2. Methods

A comprehensive search through PubMed was conducted in January 2025 using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guidelines (Figure 1) [17]. The search strategy is included in the Supplementary Material.

Clinical and preclinical studies written in English that reported miRNAs associated with CCMs, AVMs, MMD, or ICH were included. Reviews, commentaries, editorials, and studies solely focused on in silico-predicted miRNAs were excluded.

Eight researchers (A.Sr., A.J., C.B., J.K., R.J.A.-F., A.B., S.R., J.I.) first independently screened the abstracts and titles. Three team members (C.B., A.B., A.J.) performed data extraction independently from selected queried articles. Any disagreements between the reviewers were resolved by group consensus of at least three other authors (R.G., J.K., A.Sr., S.R., R.J.A.-F., J.I.).

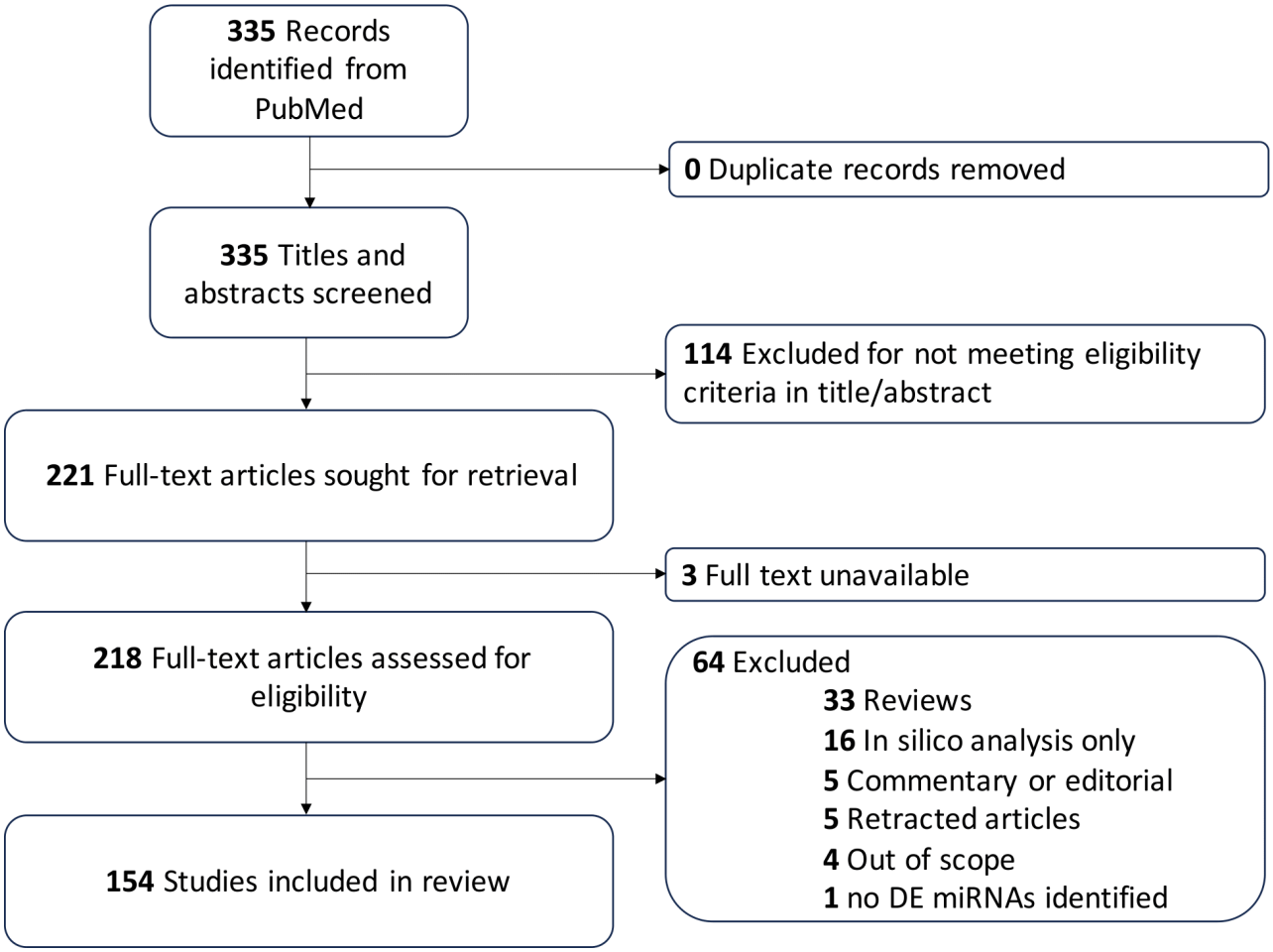

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. Flow of information through the various phases of the systematic review. A comprehensive search on PubMed, following the PRISMA guidelines, queried 335 studies. No duplicate records were found. As they were not in English (n = 4) or not about miRNAs in CCM, AVM, MMD, or ICH (n = 110), 114 articles were excluded. In addition, 3 full texts were not retrievable. From the 218 full-text articles assessed for eligibility, 64 were excluded because they were either reviews (n = 33), in silico analyses (n = 16), commentary or editorial (n = 5), retracted articles (n = 5), or out of scope (n = 4). One article did not find any differentially expressed (DE) miRNAs in a mouse ICH model. Finally, 154 studies were included in this systematic review.

Data extraction was conducted methodically using predefined criteria to ensure precision and consistency, capturing key elements such as miRNAs, the type of experimental model, whether target validation was mechanistic or predictive, the biological processes involved, control cohort in clinical studies, the sample type, and the directionality of miRNA expression. Data synthesis then followed a structured approach that utilized Venn diagrams, narrative synthesis, and thematic analysis to comprehensively integrate and interpret the findings across the included studies. The systematic review was not registered with a public registry.

Ingenuity Pathway Analysis (IPA) was further performed for differentially expressed (DE) miRNAs from various samples in preclinical and clinical studies common between those with CCM and AVM, MMD, or ICH (i.e., unsupervised analysis), limiting the query to only DE genes of lesional CCM tissue (i.e., supervised analysis) [13,18–20]. For more information, refer to the Supplementary Material.

3. Results

The PubMed search retrieved 335 manuscripts. After an initial screening of titles and abstracts, 221 articles met the inclusion criteria. Full-text analysis led to the exclusion of 67 studies, resulting in a final selection of 154 studies (Figure 1).

The studies included five preclinical [18,21–24] (Supplementary File S1) and three clinical studies [23,25,26] (Supplementary File S2) on CCM, three preclinical [27–29] (Supplementary File S3) and six clinical [28–33] (Supplementary File S4) studies on AVM, and four preclinical [34–37] (Supplementary File S5) and fourteen clinical studies [36–49] (Supplementary File S6) for MMD. Finally, 115 preclinical [14,50–163] (Supplementary File S7) and 26 clinical studies [14,148–172] (Supplementary File S8) on ICH were also included. Some studies included both preclinical and clinical components, contributing to the overall count.

The clinical studies reported a total of 1359 patients with CCM (n = 46; age = 29.91 years ± 18.49, range = [24–45]), AVM (n = 15; age = 27.53 years ± 9.82, range = [24–31]), MMD (n = 391; age = 34.18 years ± 16.48, range = [12–53]), or ICH (n = 907; age = 57.62 years ± 9.43, range = [47–68]) pathologies (Supplementary Files S2, S4, S6 and S8).

The systematic search identified a total of 267 unique miRNAs, of which 44 were found in CCM, 9 in AVM, 55 in MMD, and 198 in ICH studies (Figure 2, Supplementary File S9). Of interest, 10 miRNAs identified in preclinical studies on CCM disease were also reported dysregulated in CCM patients. In addition, 3 miRNAs reported in preclinical studies on AVM, 3 in MMD, and 28 in ICH were also dysregulated in patients (Supplementary File S10). Using CCM as a paradigm, six miRNAs overlapped with MMD and seven with ICH, and four were common across CCM, MMD, and ICH (Figure 2). Further comparisons showed that 27 miRNAs identified either in a preclinical context or in patients were only observed in CCM disease (Supplementary File S9). No miRNAs were found to overlap between CCM and AVM (Figure 2).

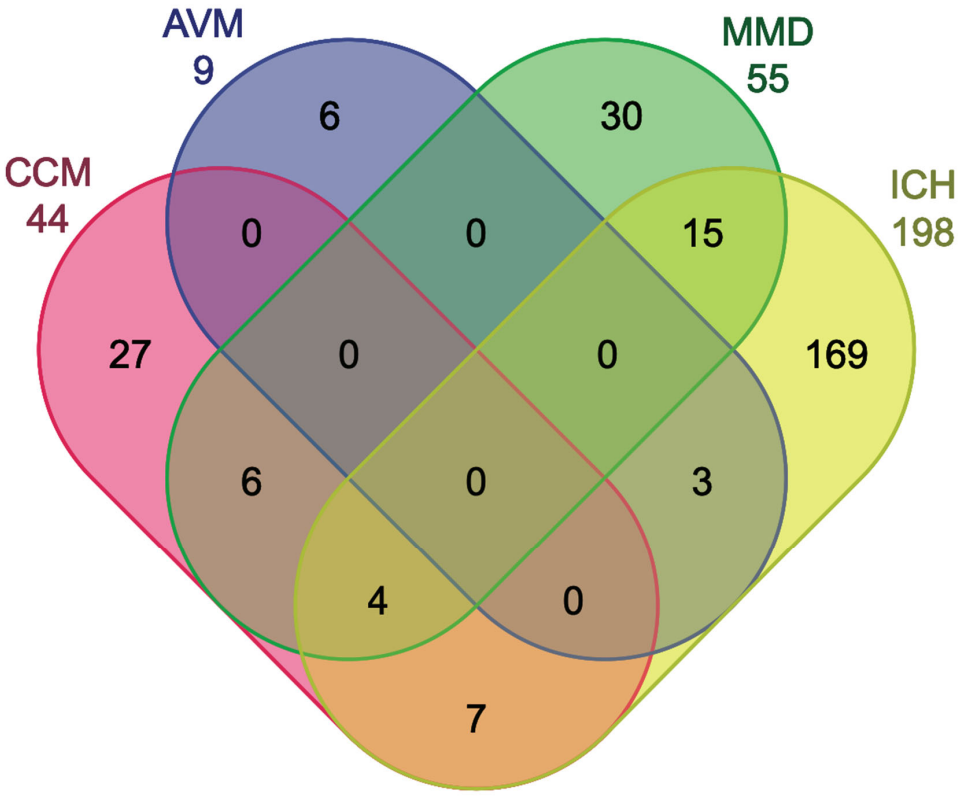

Figure 2. Unique and shared miRNAs across CCM, AVM, MMD, and ICH studies. Venn diagram illustrating the common and distinct miRNAs identified in the four studied pathologies.

3.1. Cerebral Cavernous Malformations

CCMs are vascular lesions characterized by clusters of leaky, immature vessels that predispose patients to a lifetime risk of hemorrhagic stroke, seizures, and focal neurologic deficits [173–175]. CCMs affect approximately 0.5% of the population and occur in either a sporadic or genetically inherited (familial) form [25,176]. CCM pathobiology includes loss of vascular endothelial cell (EC) junctions [177], neuroimmune cell activity [178], increased endothelial-to-mesenchymal stem cell transition [179], and aberrations in apoptosis, cytoskeletal organization, and cell proliferation processes [180,181].

3.1.1. Dysregulated Intracellular miRNAs Are Mechanistically Tied to Vascular Pathobiology

Several studies have reported the mechanistic ties of miRNAs to CCM pathobiology and to clinical course using human plasma. Li et al. (2020) have reported in a cell line of mouse-derived ECs that the levels of *miR-27a* modulate the activity of VE-cadherin, a major endothelial adhesion molecule (Supplementary File S1) [22]. The inhibition of this binding using CD5-2 normalized the vasculature within CCMs [22]. Of interest, *miR-27a* has been previously identified as being upregulated in the brain tissue of CCM patients [25]. Upregulation of *miR-27a* results in loss of vascular integrity at the blood–brain barrier (BBB) [22]. In lesional tissue, upregulation of *miR-27a* may be related to altered redox homeostasis and oxidative stress conditions implicated in CCM pathogenesis (Supplementary File S1) [182–187]. A similar binding between *miR-425-5p* and the 3′ UTR of *CCM3* was identified in human ECs (Supplementary File S1) [21]. This binding was further tied to downstream inhibition of Notch signaling and activation of p38/VEGF signaling [21].

3.1.2. CCM miRNAs Are Differentially Expressed in Mouse and Human Tissue

A preclinical study in murine models sought to identify circulating miRNAs reflecting the *Ccm3* genotype [18]. Koskimaki et al. (2019) showed lower plasma levels of *miR-3472a*, which targets *Cand2* (Supplementary File S1) [18]. Several other reports have queried CCM-relevant miRNAs using DE analysis in surgically resected human tissue [24,25]. Kar et al. (2017) identified five additional miRNAs as being downregulated in the brain tissue of CCM patients compared to healthy controls (Supplementary File S2) [25]. In a similar study, Schwefel et al. (2019) later investigated the DE of intracellular miRNAs in ECs resected from *CCM3* patients [24]. This study identified seven dysregulated miRNAs, with follow-up gene ontology analyses showing enriched pathways related to vascular development and aging (Supplementary File S1) [24]. Further analyses showed that three of these five miRNAs targeted genes such as *VEGF*, *MAPK1*, *RHOA*, *and ENG* [25].

While these intracellular miRNAs show putative association with CCM pathways and genotypes, they failed to appear as in vivo markers in analyses of CCM patient plasma [23].

3.1.3. Circulating miRNAs as Clinical Markers of CCM and Symptomatic Hemorrhage

Several plasma miRNAs have been shown to be up- or downregulated when compared between CCM patients and healthy controls (Supplementary File S2) [13,23,25]. Analyses of the differential plasma miRNome identified nine homologous DE common miRNAs between mouse models of *Ccm1/3* and neurovascular units (NVUs) resected from patients with similar genotypes (Supplementary Files S1 and S2) [23]. The targets of these DE miRNAs included major CCM-associated pathways, including PI3K-Akt signaling, focal adhesion, HIF-1, cell adhesion molecules, and Rap1 signaling [23]. This reverse-translational finding not only suggested the ability of circulating miRNA to signal disease states but also generated viable targets for future investigations into preclinical models of CCM gene restoration therapy [23]. Additionally, this same study showed that circulating

miRNAs were able to predict new lesion formation in CCM patients, further iterating the potential for plasma miRNAs to act as markers of disease progression [23].

Having established the biomarker viability of circulating miRNAs, the plasma miRNome of CCM patients has been integrated with additional circulating molecules to achieve higher specificity and selectivity models [26]. One such integrative study found that the ability of a diagnostic association model to distinguish patients who had sustained a symptomatic bleed from those who had not was improved by more than 20% after adding the plasma levels of DE miRNAs compared to a model with only plasma proteins [26]. Of interest, *miR-20a-5p*, *miR-25-3p*, and *miR-486-5p* showed mechanistic links to CCM pathways such as HIF-1, MAPK, PI3K-Akt, Rap1, and VEGF signaling (Supplementary File S2) [26]. Furthermore, recent evidence suggests that polymorphic variations in genetic modifiers (e.g., polymorphic cytochrome P450 enzymes) observed in CCM patients may be used for personalized medicine strategies and to improve hemorrhage risk stratification [188].

3.2. Arteriovenous Malformations

AVMs are abnormal connections between arteries and veins, predisposing patients to a lifetime risk of hemorrhagic stroke and seizures [175]. The mechanisms of AVM pathogenesis are poorly understood beyond vascular wall remodeling changes and feeding artery flow rates [28]. A stronger understanding of these mechanisms could improve clinical care, as current treatments rely on surgical resection or radiation therapy.

In in vitro assays of EC lines, *miR-18a* was found to protect against aberrant angiogenic processes by increasing thrombospondin-1 and decreasing VEGF (Supplementary File S3) [29,31,32]. In addition, increased activity of *miR-18a* was associated with decreased extracellular matrix disruption by decreasing matrix metalloproteinases activity, preventing vascular breakdown [29]. Of interest, several experiments have further shown that Argonaute-2 promotes the entry of this *miR-18a* into brain tissue (Supplementary File S4) [31]. Other studies have also shown that KRAS mutant ECs of AVMs increased exosomal *miR-3131* levels, which promoted endothelial–mesenchymal transition via PICK1 (Supplementary File S4) [33]. In addition, Chen et al. (2022) studied altered blood flow within AVMs using an arteriovenous high-blood-flow shunt rat model [27]. The results showed the upregulation of *miR-134-5p* and downregulation of *miR-204-3p* in the vascular wall remodeling process (Supplementary File S3) [27].

Several studies in patients have suggested the role of miRNAs in the pathophysiology and clinical course of AVM. Huang et al. (2017) showed decreased levels of *miR-137* and *miR-195* in the smooth muscle cells of human AVMs, which are important for cell survival and protecting the NVU from hemorrhage (Supplementary File S4) [28]. Finally, studies with the plasma of AVM patients have identified *miR-7-5p*, *miR-199a-5p*, and *miR-200b-3p* as central in VEGF signaling (Supplementary File S4) [30].

3.3. Moyamoya Disease

MMD is characterized by stenosis and occlusion of blood vessels within the circle of Willis, namely the intracranial internal carotid artery, and the middle and anterior cerebral arteries [189]. In response to occlusive arteriopathy, abnormal small vessel networks form near the base of the brain [189], which can cause ischemia and hemorrhage.

3.3.1. MiRNAs Are Mechanistically Associated with MMD

Two miRNAs, *miR-125a-3p* and *let-7c*, have been shown to regulate the "synthetic" phenotype in vascular smooth muscle cells (VSMCs), which can lead to fibrocellular hyperplasia and intimal thickening [35,36]. Such fibrocellular hyperplasia and intimal thickening were accompanied by increased cell migration, proliferation, and extracellular matrix deposition [35,36]. In addition, Liu et al. (2022) showed in an in vitro ischemic MMD

model that circZXDC sponges *miR-125a-3p*, increasing VSMC transition to the synthetic state (Supplementary File S5) [35]. Finally, this miRNA was also shown to regulate VSMC transdifferentiation by targeting *ABCC6*, a gene that induces ER stress and is highly expressed in MMD vessels (Supplementary File S5) [35]. Ma et al. (2023) showed that the levels of *let-7c* were elevated in the plasma of MMD patients when compared to controls [36]. This miRNA has also been upregulated in human ECs under hypoxic conditions (Supplementary File S5) [36]. In both in vitro and in vivo models, *let-7c* activation of TLR7 was shown to induce VSMC transition into the synthetic phenotype through Akt/mTOR signaling, ultimately leading to MMD-related vascular wall remodeling and intimal hyperplasia [36]. In addition, *let-7c* has been shown to target *RNF213*, a gene implicated in MMD pathogenesis [49]. Dysregulation of *RNF213* affects wall formation and vessel growth (Supplementary File S6) [49]. An *Rnf213* deficiency in mice led to thinner vessel walls after carotid artery ligation [49]. This result suggests that *RNF213* may be associated with angiogenesis [49]. Finally, *RNF213* has also been associated with MMD risk in human genome studies [49].

3.3.2. Circulating miRNAs Are Differentially Expressed in MMD Patients

Of interest, *let-7c* was also found to be DE in both MMD patient plasma and serum when compared to controls (Supplementary File S6) [36,49]. Dai et al. (2014) also identified DE miRNAs in the serum of MMD patients, four of which were validated and found to have mechanistic implications in MMD pathogenesis [38].

Additional analysis of the circulating miRNAs identified by Dai et al. (2014) with DE lncRNA and mRNA data from another cohort of MMD patients revealed *miR-107* and *miR-423-5p* to be core regulators of vascular remodeling and cell proliferation under hypoxic conditions (Supplementary File S6) [38,39]. Several other studies identified DE miRNAs as potential MMD biomarkers (Supplementary File S6) [40,45,46]. Of interest, Uchino et al. (2018) reported that *miR-6722-3p* and *miR-328-3p* differentiated MMD from non-MMD cases in a study of MMD-discordant monozygotic twins (Supplementary File S6) [45]. Finally, Wang et al. (2021) developed a prognostic model with four miRNAs, upregulated in the CSF of MMD patients, which were able to predict neoangiogenic collateral vessel formation after indirect bypass surgery [46].

3.4. Intracerebral Hemorrhage

Non-traumatic ICH is the second most common type of stroke, representing 15% of cases and showing the highest mortality [190]. Primary ICH constitutes 85% of cases and typically results from the rupture of arteries and arterioles due to chronic hypertension or cerebral amyloid angiopathy [85,190,191]. Secondary ICH may arise from an underlying vascular malformation [192]. Evidence suggests that miRNAs modulate genes related to ICH pathological processes such as vascular integrity, oxidative stress, and neurodegeneration [85].

3.4.1. MiRNAs Are Shown to Modulate Brain Vascular Integrity and Adhesion

In rat ICH models, *miR-18* and *miR-124* have been shown to affect bleeding and neurological outcomes by regulating the production of tight junction proteins (Supplementary File S7) [85,90]. Furthermore, *miR-24-1-5p* and *miR-126* have been shown to act as crucial regulators of HIF-1α and VEGFA in ECs within the PI3K/Akt signaling pathway (Supplementary File S7) [56,59]. Their dysregulation has been implicated in the breakdown of tight junction protein expression, cellular viability, and angiogenesis [56,59]. In in vitro and in vivo murine models of ICH, overexpression of *miR-6838-5p* and *miR-126* (Supplementary File S7) has also been shown to reduce apoptosis and neuroinflammation while enhancing tight junction expression [75,153]. This modulation improves BBB integrity

by inhibiting VEGFA [153], which, if increased, leads to EC apoptosis and exacerbates ICH pathology [75].

Liu et al. (2022) recently reported in rat models that an in situ upregulation of *miR-126* following ICH decreased glial fibrillary acidic protein expression, neuroinflammation, and brain edema by downregulating ZEB1 (Supplementary File S7) [82]. Of interest, in ICH, *miR-126a-3p* promoted bone marrow mesenchymal stem cell differentiation into vascular ECs in vivo and in vitro (Supplementary File S7) [106]. This in turn produced a decrease in brain edema and BBB permeability via enhanced expression of tight junction proteins [106]. Precise therapeutic miRNA delivery may modulate ICH permeability across various pathways, cell types, and developmental stages [193].

3.4.2. MiRNAs Are Shown to Modulate Apoptosis/Ferroptosis

Two in vitro studies have demonstrated that targeting acyl-CoA synthetase long-chain family member 4 using *miR-29a-3p* and *miR-106b-5p* reduced oxidative stress and ferroptosis (i.e., iron-dependent cell death) in hippocampal neurons and increased capillary EC survival (Supplementary File S7) [52,53]. Kong et al. (2021) showed that administering *antagomiR-23a-3p* in vivo reduced ferroptosis in rat ICH models by activating NRF2 signaling, which mitigated neuroinflammation (Supplementary File S7) [76]. In addition, oxidative stress, inflammation, and apoptosis have also been linked to *miR-93-5p* [158]. Upregulating NRF2, an important antioxidant response regulator, reduced apoptosis in vitro via transforming growth factor-β1, which acts as a competitive endogenous RNA of *miR-93-5p* (Supplementary File S7) [158]. In a rat ICH model, monomethyl fumarate pretreatment increased *miR-139* expression and led to upregulation of NRF2 and downregulation of NF-κB pathways (Supplementary File S7) [95].

Inhibition of the TRAF6/NF-κB axis by *miR-194-5p* and *miR-150-3p* has also been shown to reduce inflammasome activation and apoptosis in mouse ICH models (Supplementary File S7) [97,102]. Inhibiting NLRP3 inflammasomes using *miR-194-5p* and *miR-223* improved brain edema and neurological outcomes (Supplementary File S7) [102,131]. Additionally, inhibition of *let-7c* in the insulin-like growth factor receptor 1 pathway decreased cell death, neuroinflammation, and brain edema, ultimately improving neurological outcomes (Supplementary File S7) [74].

3.4.3. MiRNAs Are Shown to Modulate Neuroinflammation After ICH in Microglia

An upregulation of *miR-7* and *miR-140-5p* mitigated secondary ICH inflammation through inhibition of the TLR4 pathway (Supplementary File S7) [110,143]. Secondary neuroinflammation and gliosis in perihematomal tissue are important mediators of neurological outcomes following ICH [194]. Microglial infiltration and neuroinflammation correlate with endoplasmic reticulum (ER) stress markers like HSPA5, which have been shown to be mitigated by overexpression of *miR-181b* (Supplementary File S7) [116]. In addition, an *miR-124* mimic has been reported to promote in vitro and in vivo microglia M2 polarization in perihematomal tissue, attenuating neuron apoptosis and neuroinflammation (Supplementary File S7) [133]. The importance of C/EBP-α in perihematomal tissue was further highlighted in an in vitro study with microglial cells isolated from ICH patients, showing that *miR-367* overexpression promoted microglia M2 polarization and decreased neuroinflammation (Supplementary File S7) [157]. Similarly, increased microglia M2 polarization has also been observed following *let-7a* overexpression through decreasing protein levels of CKIP-1 (Supplementary File S7) [130]. Upregulation of *miR-183-5p* and *miR-590-5p* decreased microglial-mediated inflammation and attenuated brain injury in ICH by inhibiting heme oxygenase and Pellino-1, respectively (Supplementary File S7) [65,112]. Additionally, the knockdown of lncRNA metastasis suppressor-1 upregulated *miR-709* and

decreased secondary brain injury in both in vitro and in vivo mouse ICH models by decreasing microglial activation and proinflammatory cytokines (Supplementary File S7) [54].

In the lesional bed, blood degradation products cause microglia-mediated metabolic and oxidative stress in neurons through exosome transfer of *miR-383-3p* (Supplementary File S7) [118]. Of interest, hemoglobin-induced autophagy of microglia was attenuated with *miR-144* inhibitors in vivo by upregulating the mTOR pathway (Supplementary File S7) [117]. The Akt/mTOR pathway has been implicated in ICH as *miR-23b* upregulation increased both p-Akt and p-mTOR expression, resulting in negative regulation of inositol polyphosphate multikinase-mediated autophagy (Supplementary File S7) [69]. Paradoxically, Nie et al. (2020) showed that hemoglobin degradation products can decrease inflammatory signaling in microglia by downregulating *miR-331-3p* (Supplementary File S7) [86].

3.4.4. MiRNAs Are Shown to Modulate Neuroinflammation After ICH in Neurons

Several studies have demonstrated that PTEN inhibition with upregulation of the PI3K signaling pathway has neurological benefits [61,81,145]. For instance, an overexpression of *miR-29a* promoted axonal regeneration and enhanced neurological outcomes in a rat ICH model by targeting *Pten* (Supplementary File S7) [145]. PTEN downregulation via L-lysine-induced overexpression of *miR-575* was also shown to be neuroprotective in mouse ICH models (Supplementary File S7) [55]. Liu et al. (2021) reported that an upregulation of the PI3K pathway with hypoxia-induced *miR-326* overexpression enhanced stem cell therapy in ICH by increasing autophagy and improving neuronal survival (Supplementary File S7) [81]. Conversely, downregulating the PI3K/AKT pathway increased neuroinflammation, neuronal apoptosis, BBB permeability, and microglial activation [61,136].

Neurodegeneration following ICH has been associated with multiple pathways and miRNAs [71,93,125]. In a rat model, *miR-146a* overexpression decreased neuroinflammation, brain edema, neuronal cell death, and oxidative stress, by modulating NF-κB signaling (Supplementary File S7) [71,125]. Early after ICH, intracellular levels of Ca^{2+} increase dramatically, causing ER stress and decreasing anti-apoptotic proteins [93]. Shen et al. (2021) reported that *miR-124* overexpression in a rodent ICH model reduced Ca^{2+} overload in neurons, mitigating neurodegeneration by targeting calmodulin-dependent protein kinase II (Supplementary File S7) [93]. Upregulating *Bcl-2* via *miR-133b* modified mesenchymal stromal cell-derived exosomes, reduced neuronal apoptosis by suppressing RHOA, and activated the ERK1/2/CREB pathway (Supplementary File S7) [94]. Similarly, sevoflurane decreased neuronal apoptosis in a mouse ICH model by enhancing *miR-133b* expression, which targets *FOXO4*, which increased BCL2 expression (Supplementary File S7) [78]. Anti-apoptotic pathway-targeting miRNA therapies could thus potentially be leveraged to prevent neurodegeneration in ICH.

3.4.5. MiRNAs Are Shown to Modulate Neuroinflammation After ICH in Immune Cells

In a mouse ICH model, upregulation of *miR-125b-2-3p* decreased neuroinflammation by attenuating mast cell degranulation (Supplementary File S7) [129]. In addition, decreased expression of *miR-181a* in peripheral blood mononuclear cells (PBMCs) of a swine ICH model was shown to correlate with increased neuroinflammation via an interconnected network of monocytes and IL-8 (Supplementary File S7) [101]. Higher PBMC counts, particularly monocytes, are associated with increased 30-day fatality in ICH patients [195].

3.4.6. Circulating miRNAs Are Dysregulated in ICH Patients

In ICH patients, various circulating miRNAs have been found dysregulated compared to control subjects (Supplementary File S8) [109,149,152,165,167,170,172]. Notably, *miR-124* serum levels correlate with neurological severity and functional outcomes (Supplementary File S7) [149]. Of interest, *miR-21-5p* has shown contradictory roles in studies reporting both upregulation and downregulation in cerebral hematoma samples as well as in peripheral blood and hematoma samples (Supplementary File S8) [87,170]. In a case–control study of 106 ICH cases, plasma levels of *miR-223*, *miR-155*, and *miR-145* were increased while *miR-181b* was decreased compared to healthy subjects (Supplementary File S8) [165]. Serum levels of *miR-23a-3p* and *miR-130a* have been found upregulated in ICH patients, while most DE miRNAs are downregulated in ICH patients (Supplementary File S8) [109,152]. Yang et al. (2021) suggest that ICH severity could be rather explained by single-nucleotide polymorphisms, as decreased serum and CSF levels of *miR-143* in patients with rs41291957 genotype were associated with poor neurological outcomes and increased proinflammatory factors (Supplementary File S8) [14]. Finally, Zheng et al. (2012) found that hematoma expansion or stability after ICH can be classified with 100% accuracy using 10 DE plasma miRNAs (Supplementary File S8) [171].

4. Discussion

4.1. MiRNA Commonalities of CCM and AVM

This systematic review did not identify any documented dysregulated miRNAs common to both CCMs and AVMs. Since these two neurovascular diseases have different genetic and molecular origins, the miRNA regulatory networks may therefore not overlap. In addition, these two vascular malformations have phenotypic differences [28,176]. CCMs typically represent low-flow lesions that can leak or bleed at low pressure [176]. On the contrary, AVMs are high-flow lesions characterized by direct arteriovenous shunting that may modulate different endothelial remodeling processes geared toward coping with excessive shear and hemodynamic stress [27]. Of interest, Lee et al. (2024) showed an upregulation of *miR-135b-5p*, under hypoxic conditions within the ECs, suggesting a role of this miRNA during the physiopathogenesis of AVMs [196]. In addition, there are a limited number of preclinical and human CCM and AVM studies reporting DE miRNAs. These studies show heterogeneity in inclusion criteria that introduce variability in miRNA findings and complicate cross-study comparisons. Finally, the documented studies have a small sample size that can result in underpowered analyses, making it difficult to detect subtle differences in miRNA expression.

4.2. MiRNA Commonalities Between CCM and MMD

This review identified a total of ten DE miRNAs in both CCM and MMD. Six of them, *miR-139-5p*, *miR-361-5p*, *miR-486-3p*, *miR-486-5p*, *miR-501-3p*, and *miR-92a*-3p, were only DE in CCM and MMD, while four (discussed separately) were also commonly DE between CCM, MMD, and ICH (Figure 3). Schwefel et al. (2019) demonstrated that *miR-139-5p* targets CXCR4, which has been shown to activate the PI3K/Akt, PLC, and ERK1/2 signaling pathways, all of which contribute to cell migration and proliferation [24,197]. Although *miR-139-5p* was upregulated in *CCM3*$^{-/-}$ endothelium, its inhibition did not restore *CXCR4* expression or reverse endothelial dysmorphism [24].

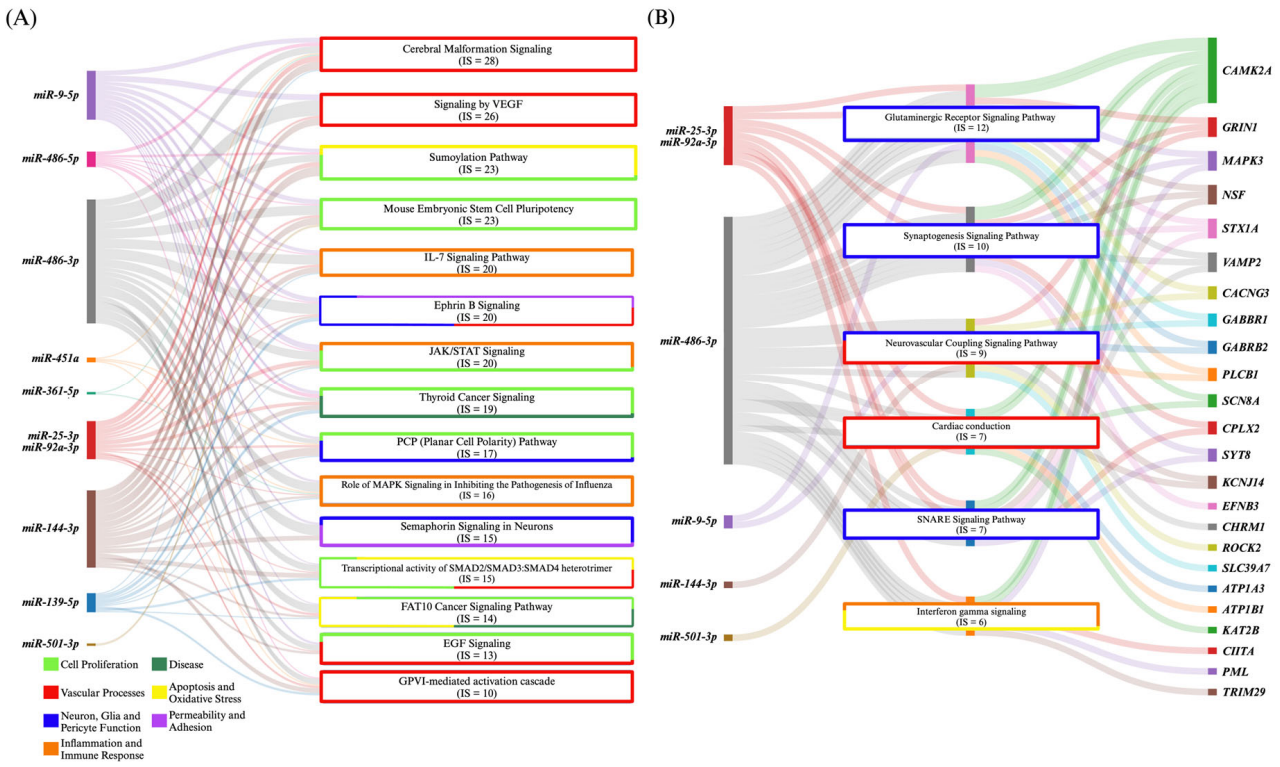

Figure 3. Ingenuity Pathway Analysis (IPA) of differentially expressed (DE) miRNAs common between cerebral cavernous malformation (CCM) and moyamoya disease. The IPA analyses of the gene targets and their associated pathways of *miR-9-5p*, *miR-486-5p*, *miR-486-3p*, *miR-451a*, *miR-361-5p*, *miR-25-3p*, *miR-92a-3p*, *miR-144-3p*, *miR-139-5p*, and *miR-501-3p* common between cerebral cavernous malformation (CCM) and moyamoya disease (**A**) identified 360 pathways ($p < 0.01$, false discovery rate [FDR] corrected) related to vascular, cell proliferation, and inflammation and immune response processes. Only pathways with an interaction score (IS) of 10 and a gene ratio of 0.265 are displayed. (**B**) Further analyses identified 201 enriched pathways ($p < 0.01$, FDR corrected) with gene targets (i.e., of the miRNAs mentioned above) that have been shown to be dysregulated in the transcriptome of neurovascular units of surgically resected CCMs. This result suggests common pathogenic processes between the CCM and moyamoya diseases. Only pathways with an IS of 6 and a gene ratio of 0.2 are displayed. IPA considered *miR-25-3p* and *miR-92a-3p* as the same entities as they harbor the same seed sequence.

While the majority of these miRNAs were upregulated in MMD [40,42,43,46], they were predominantly downregulated in CCM [25,26], suggesting fundamental differences in their underlying molecular mechanisms. Huang et al. (2023) observed that elevated plasma levels of 10 miRNAs, including *miR-501-3p*, had a high accuracy for diagnosing MMD [40]. This miRNA has been associated with actin cytoskeleton modulation via MAPK signaling, and increased levels have been shown to promote vascular sclerosis through tight junction protein-1 disruption [40,198]. Wang et al. (2021) showed that increased CSF levels of *miR-486-3p* and *miR-92a-3p* were able to predict angiogenesis in MMD patients with high accuracy [46]. In MMD, stenosis of large arteries causes collateral vessel formation through aberrant VEGF-mediated angiogenesis, induced by ischemia [199]. In CCM, increased VEGF similarly causes dysmorphic angiogenesis with high permeability [20]. However, decreased plasma levels of VEGF have been observed to predispose patients to cavernous angioma with symptomatic hemorrhage (CASH) or lesion growth [200]. Of interest, *miR-486-3p*, *miR-486-5p*, and *miR-92a-3p* together with *miR-501-3p* were found to be downregulated in the plasma of CASH patients [26]. Taken together, these results suggest that cytoskeletal, junctional, and angiogenic factors regulated by miRNAs may

influence bleeding risk and serve as potential clinical biomarkers. Although mechanistic and predictive studies of *these miRNAs* are lacking in CCM and MMD research, common DE miRNAs identified in clinical studies between CCM and MMD may underscore a common pathological angiogenic process in both, inherent to vascular dysmorphism.

4.3. MiRNA Commonalities of CCM and ICH

CCM and ICH are both characterized by a failure of the NVU, with disruption of the vascular wall and blood extravasation occurring in small vessels [190,201]. In addition to the four common miRNAs in MMD, ICH, and CCM, this review identified *let-7b-5p*, *miR-128-3p*, *miR-183-5p*, *miR-20a-5p*, *miR-27a*, *miR-375-3p*, *and miR-93-5p* as commonly dysregulated in CCM and ICH, reflecting potential common molecular underpinnings and therapeutic targets for both diseases (Figure 4).

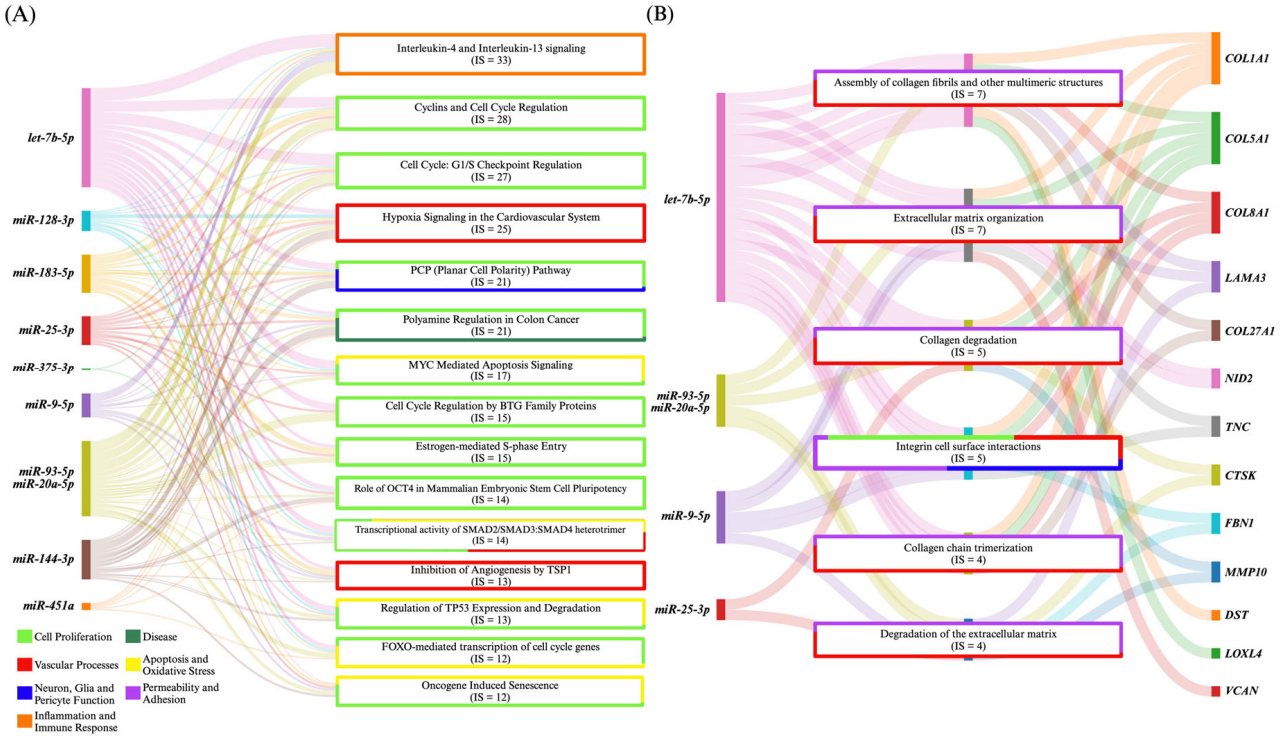

Figure 4. Ingenuity Pathway Analysis (IPA) of differentially expressed (DE) miRNAs common between cerebral cavernous malformation (CCM) and intracerebral hemorrhage. The IPA analyses of the gene targets and their associated pathways of *let-7b-5p*, *miR-128-3p*, *miR-183-5p*, *miR-25-3p*, *miR-375-3p*, *miR-9-5p*, *miR-93-5p*, *miR-20a-5p*, *miR-144-3p*, *miR-451a*, and *miR-27a*, commonly differently expressed between cerebral cavernous malformation (CCM) and intracerebral hemorrhage, (**A**) identified 450 pathways ($p < 0.05$, false discovery rate [FDR] corrected) related to cell proliferation and vascular processes. Only pathways showing an interaction score (IS) of 12 and a gene ratio of 0.29 are displayed. (**B**) Further analyses identified 190 enriched pathways ($p < 0.01$, FDR corrected) with gene targets (i.e., of the miRNAs mentioned above) that have been shown to be dysregulated in the transcriptome of neurovascular units of surgically resected CCMs. This result suggests common pathogenic processes between the CCM disease and intracerebral hemorrhage. Only pathways with an IS of 4 and a gene ratio of 0.29 are displayed. IPA considered *miR-93-5p* and *miR-20a-5p* as the same entities due to the same seed sequence, while *miR-27a* was unmapped.

Vascular processes and permeability and adhesion pathways such as extracellular matrix organization and collagen degradation pathways emerged with IPA of ICH and CCM miRNAs and the CCM transcriptome (Figure 4). Although its exact role remains unclear, *let-7b-5p* targets *MLLT4* and may influence vascular integrity [25]. By contrast, *miR-128-3p* has shown therapeutic promise in ICH models, where its administration dampens

microglial inflammatory response by repressing TXNIP expression [62]. Yet in CCM, *miR-128-3p* is paradoxically upregulated in a *Ccm1* mouse model and downregulated in the plasma of *CCM3* patients [23]. This duality highlights how the same miRNA can differentially regulate vascular stability and inflammation depending on lesion subtype or stage. Notably, *miR-128-3p* also targets *IGF1* and *NRXN1,* which have been linked to PI3K–Akt, HIF-1 signaling, and cell adhesion [23]. In addition, *miR-183-5p* has been shown to be downregulated in the brain tissue of ICH murine models as well as in the plasma of CCM CASH patients. Exogenous delivery of *miR-183-5p* reduced neuroinflammation, oxidative stress, and functional deficits in mouse ICH models via modulation of Nrf2 and NLRP3 pathways [26,58,112].

MiR-20a-5p, *miR-27a*, and *miR-93-5p* have been shown to modulate endothelial proliferation and vessel stability [22,162]. *MiR-20a-5p* and *miR-93-5p* have been found downregulated both in the plasma of CCM and blood of ICH patients [23,26,162], while *miR-27a* was upregulated in the plasma of ICH patients and in an in vivo CCM model [22,167]. In a mouse ICH model, *miR-20a-5p* overexpression attenuated hemorrhagic injury by regulating the HIF1α/VEGFA signaling pathway [162]. Meanwhile, *miR-27a* and *miR-93-5p* are downstream modulators of two important CCM transcription factors, KLF2 and KLF4 [22,167,202]. Alterations in these pathways have been shown to decrease intracellular levels of VE-cadherin and disrupt vascular integrity [22]. In fact, inhibition of the *miR-27a*/VE-cadherin interaction rescues CCM lesion development [22]. In addition, *miR-93-5p* targets VEGFA, ADAMTS5, ROCK2, and MAP3K14 and may affect both angiogenesis and lesion stability [23]. A downregulation of *miR-93-5p* has been shown in in vitro ICH models to decrease apoptosis via upregulation of NRF2, an important regulator of antioxidant response [158]. Of interest, KRIT1 loss of function is known to cause increased oxidative stress with responsive upregulation of NRF2 [203,204]. However, chronic upregulation of this antioxidant pathway predisposes CCM patients to additional oxidative insults via an increase in reactive oxygen species, as well as aberrant cell death [203,204]. These shared miRNAs highlight overlapping pathways of endothelial dysfunction, inflammation, and oxidative injury in ICH and cavernous malformations. Future investigations will clarify their mechanistic roles and therapeutic value in stabilizing the NVU across diverse cerebrovascular diseases.

4.4. MiRNA Commonalities of MMD, ICH, and CCM

This review also showed that *miR-9-5p*, *miR-144-3p*, *miR-25-3p*, and *miR-451a* were identified as commonly dysregulated across CCM, MMD, and ICH. Recent studies show that 13.5% of *miR-9-5p* gene targets appear in the human CCM lesional transcriptome and are tied to cell adhesion molecules and focal adhesion (including TNC, VAV3, and VCAN) [23]. Endothelial secretion of ADAMTS5, together with the cleavage of versican (i.e., encoded by *Vcan*), has been identified as a downstream mechanism in CCM pathogenesis [205]. In addition, increased ADAMTS5 expression in endothelial cells appears to act with CCM1 loss of function, resulting in larger vascular malformations [23].

For instance, *miR-144-3p* and *miR-25-3p* have been linked to apoptotic and oxidative stress pathways, processes central to hemorrhagic injury [61,79]. In a rat ICH model, *miR-144-3p* overexpression aggravated brain edema and neurobehavioral disorders by targeting *Fpr2*, associated with the PI3K/AKT pathway [61]. In a mouse ICH model, lower levels of *miR-25-3p* induced upregulation of NOX4 and the production of hydrogen peroxide and ER stress [79]. The increased expression observed in ICH models might reflect a compensatory or pathogenic response to acute hemorrhage and oxidative damage.

A consistent, albeit opposite, expression pattern in MMD/CCM versus ICH models points to a shared molecular framework with disease-specific contexts that modulate miRNA activity and downstream vascular responses. Overall, data suggests that targeting these miRNAs may hold therapeutic promise, but clinical translation requires a nuanced understanding of when and how each miRNA exerts its functions. Further studies are needed to validate these regulatory roles in larger patient cohorts with more comparable control groups, elucidate cell-type-specific mechanisms, and explore the potential for miRNA-based interventions to improve outcomes.

4.5. Distinct miRNAs in CCM, AVM, MMD, and ICH and Their Implications

Preclinical mouse models and clinical plasma samples suggest that *miR-20b-5p*, *miR-323-3p*, *miR-369-5p*, *miR-410-3p*, and *miR-487b-3p* were only upregulated in CCM disease [23]. These miRNAs appear to converge on pathways critical for vascular homeostasis and inflammation, including Rap1 and NF-κB signaling [23,206,207]. For example, *miR-20b-5p* targets *VEGFA* and *ADAMTS5*, impacting Rap1 signaling, which is integral to EC migration, proliferation, and membrane localization of *CCM1/KRIT1* [23]. *MiR-323-3p and miR-410-3p* have been linked to elevated EC apoptosis or inflammatory cascades in vascular diseases, underscoring their broader involvement in pathological vascular remodeling [206,207]. Taken together, these findings suggest that the upregulated miRNAs in CCM may serve both as biomarkers of disease progression and as potential targets for therapeutic intervention.

Clinical and preclinical findings reported that *miR-137* and *miR-195** are downregulated in AVM tissue [28]. In vivo mouse models further show that mimics of these miRNAs suppress aberrant VSMC migration and tube formation [28]. Notably, *miR-137* and *miR-195** modulate key signaling pathways such as including VEGF, PI3K/Akt, and MAPK/ERK that are essential for normal vascular development [28]. Therapeutic strategies aimed at restoring *miR-137* and *miR-195** may help promote proper vasculogenesis, inhibit aberrant vascular growth, and ultimately protect against the occurrence or progression of AVMs [28].

Among the miRNAs uniquely associated with MMD, *miR-125a-3p* and *miR-6760-5p* each show consistent differential expression across at least two independent studies [35,37,38,47]. *MiR-125a-3p* is downregulated in both in vitro and clinical samples, and mechanistic data suggest that this decrease leads to ABCC6 overexpression, which correlates with intimal thickening and ER stress [35,38]. In contrast, *miR-6760-5p*—which antagonizes the angiogenic activity of YAP1 through the Hippo signaling pathway—is upregulated in both preclinical and clinical MMD samples, where it reduces cell proliferation, movement, and tube formation [37,47]. Notably, *miR-6760-5p* also exhibits strong diagnostic potential, with an area under the curve of 0.918 in distinguishing MMD patients from healthy controls [47]. Together, these findings highlight *miR-125a-3p* and *miR-6760-5p* as critical molecular players in MMD pathogenesis and potential biomarkers or therapeutic targets.

In addition, *miR-124*, *miR-124-3p*, *miR-155*, *miR-181b*, and *miR-195-5p* were reported in both preclinical and clinical ICH studies, appearing in at least three distinct investigations [63,64,83,85,91,93,99,100,107,116,122,123,133,142,149,150,154,159,165,166,169]. Consistent with clinical observations, *miR-124* circulating plasma level appears to exhibit a biphasic pattern [159]. In acute ICH murine models, an upregulation of *miR-124* suppresses AGO2 [159] and C/EBP-α and fosters an M2-dominant microglial phenotype that lessens inflammatory damage [133]. Conversely, in later phases, the downregulation of *miR-124* beneficially increases ferroportin levels, thereby reducing iron overload and related injury [149]. Although *miR-124* and *miR-124-3p* represent different strand maturation stages, the 3p strand has been reported to target distinct genes, including *TRAF6* and

MTF1 [107,150]. Overexpression of *miR-124-3p* has been shown to attenuate oxidative stress as well as proinflammatory responses in microglia and astrocytes [107,150,154]. Notably, clinical data indicate that serum levels of *miR-124* rise sharply after ICH onset, followed by a decline as recovery ensues—an expression trajectory that may reflect ongoing tissue repair mechanisms [159].

Beyond the *miR-124* family, additional miRNAs consistently display impactful roles in ICH outcomes. *MiR-155* is predominantly upregulated across multiple models, potentiating inflammatory mediators such as IL-1β, IL-6, and TNF-α, whereas inhibiting this pathway reduces oxidative stress and improves neurological function [63,123,142,165]. Conversely, *miR-181b* and *miR-195-5p* exhibit more protective profiles [83,99,100,122,169]. An increase in *miR-181b* levels counteracts inflammation and edema [122,169]. Similarly, *miR-195-5p* upregulation mitigates apoptosis, dampens oxidative stress, and decreases MMP-2/9 activity to preserve the BBB [83,99,100]. Collectively, these findings underscore the therapeutic potential of miRNA modulation for regulating iron metabolism, neuronal survival, inflammatory cascades, and vascular integrity in ICH.

5. Limitations

Several limitations must be acknowledged while interpreting the results. Most of the papers do not consider different disease phenotypes, genetic modifiers, and environmental or therapeutic factors. The majority of the studies are retrospective, with suboptimal controls, and subject to selection and interpretation biases. Secondly, animal models do not always accurately mimic human conditions. However, homologous miRNAs have been shown in preclinical models of CCM and patients [23]. Furthermore, the difference in tissue sampling and the comparison of their miRNome can lead to the identification of miRNAs that may not be shared across all three diseases. Finally, many of the associations do not prove causality, nor do they implicate specific mechanisms of miRNAs in disease pathogenesis.

6. Conclusions and Future Directions

MiRNAs have risen to the forefront of neurovascular biomarker research and hold the potential to become powerful tools in diagnostic and prognostic evaluations. Common miRNAs may reflect shared pathogenic mechanisms between hemorrhagic neurovascular disorders occurring during their natural history. Different vascular dysmorphisms predisposing patients to brain bleeding reflect unique and common molecular aberrations, and these are reflected in the associated miRNAs. Brain bleeding proper, regardless of vascular pathology, involves molecular cascades that reflect miRNA interactions and associations.

Much of the research herein can be considered hypothesis-generating and compels future mechanistic studies of individual miRNAs in tissue and fluids, and in relation to disease gene aberrations. These studies will clarify the biologic plausibility of miRNA associations and identify the potential roles of miRNAs as gene silencing therapies.

Biomarker associations require analytic validations to confirm molecular sensitivity and specificity related to miRNA levels and not mere differential expression. Research should address the stability of these molecules, their potential association with sex, age, and co-morbidities, and their change in different disease states. Finally, clinical validations of biomarker contexts of use require well-designed prospective studies with rigorous controls.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijms26083794/s1.

Funding: This study was supported by the National Institutes of Health (NIH) P01NS092521 and R01NS114552 to I.A.A.

Conflicts of Interest: I.A.A. is a consultant to Neurelis and Ovid. All other authors declare no conflicts of interest.

References

1. Feigin, V.L.; Vos, T.; Nichols, E.; Owolabi, M.O.; Carroll, W.M.; Dichgans, M.; Deuschl, G.; Parmar, P.; Brainin, M.; Murray, C. The global burden of neurological disorders: Translating evidence into policy. *Lancet Neurol.* **2020**, *19*, 255–265. [CrossRef] [PubMed]
2. Katan, M.; Luft, A. Global Burden of Stroke. *Semin. Neurol.* **2018**, *38*, 208–211. [CrossRef] [PubMed]
3. Feigin, V.L.; Owolabi, M.O. Pragmatic solutions to reduce the global burden of stroke: A World Stroke Organization-Lancet Neurology Commission. *Lancet Neurol.* **2023**, *22*, 1160–1206. [CrossRef] [PubMed]
4. Salvadori, E.; Papi, G.; Insalata, G.; Rinnoci, V.; Donnini, I.; Martini, M.; Falsini, C.; Hakiki, B.; Romoli, A.; Barbato, C.; et al. Comparison between Ischemic and Hemorrhagic Strokes in Functional Outcome at Discharge from an Intensive Rehabilitation Hospital. *Diagnostics* **2020**, *11*, 38. [CrossRef]
5. Magid-Bernstein, J.; Girard, R.; Polster, S.; Srinath, A.; Romanos, S.; Awad, I.A.; Sansing, L.H. Cerebral Hemorrhage: Pathophysiology, Treatment, and Future Directions. *Circ. Res.* **2022**, *130*, 1204–1229. [CrossRef]
6. Wightman, B.; Ha, I.; Ruvkun, G. Posttranscriptional regulation of the heterochronic gene lin-14 by lin-4 mediates temporal pattern formation in *C. elegans*. *Cell* **1993**, *75*, 855–862. [CrossRef]
7. Lee, R.C.; Feinbaum, R.L.; Ambros, V. The *C. elegans* heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. *Cell* **1993**, *75*, 843–854. [CrossRef]
8. Takasaki, S. Roles of microRNAs in cancers and development. *Methods Mol. Biol.* **2015**, *1218*, 375–413. [CrossRef]
9. Tsai, P.C.; Liao, Y.C.; Wang, Y.S.; Lin, H.F.; Lin, R.T.; Juo, S.H. Serum microRNA-21 and microRNA-221 as potential biomarkers for cerebrovascular disease. *J. Vasc. Res.* **2013**, *50*, 346–354. [CrossRef]
10. Kala, R.; Peek, G.W.; Hardy, T.M.; Tollefsbol, T.O. MicroRNAs: An emerging science in cancer epigenetics. *J. Clin. Bioinform.* **2013**, *3*, 6. [CrossRef]
11. Fellizar, A.; Refuerzo, V.; Ramos, J.D.; Albano, P.M. Expression of specific microRNAs in tissue and plasma in colorectal cancer. *J. Pathol. Transl. Med.* **2023**, *57*, 147–157. [CrossRef] [PubMed]
12. Acunzo, M.; Romano, G.; Wernicke, D.; Croce, C.M. MicroRNA and cancer—A brief overview. *Adv. Biol. Regul.* **2015**, *57*, 1–9. [CrossRef] [PubMed]
13. Lyne, S.B.; Girard, R.; Koskimaki, J.; Zeineddine, H.A.; Zhang, D.; Cao, Y.; Li, Y.; Stadnik, A.; Moore, T.; Lightle, R.; et al. Biomarkers of cavernous angioma with symptomatic hemorrhage. *JCI Insight* **2019**, *4*, e128577. [CrossRef] [PubMed]
14. Yang, X.; Guo, Z.; Cao, F.; Teng, Z.; Huang, Z.; Sun, X. Rs41291957 polymorphism in the promoter region of microRNA-143 serves as a prognostic biomarker for patients with intracranial hemorrhage. *Mol. Med. Rep.* **2021**, *23*, 295. [CrossRef]
15. Ho, P.T.B.; Clark, I.M.; Le, L.T.T. MicroRNA-Based Diagnosis and Therapy. *Int. J. Mol. Sci.* **2022**, *23*, 7167. [CrossRef]
16. What will it take to get miRNA therapies to market? *Nat. Biotechnol.* **2024**, *42*, 1623–1624. [CrossRef]
17. Tricco, A.C.; Lillie, E.; Zarin, W.; O'Brien, K.K.; Colquhoun, H.; Levac, D.; Moher, D.; Peters, M.D.J.; Horsley, T.; Weeks, L.; et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann. Intern. Med.* **2018**, *169*, 467–473. [CrossRef]
18. Koskimaki, J.; Zhang, D.; Li, Y.; Saadat, L.; Moore, T.; Lightle, R.; Polster, S.P.; Carrion-Penagos, J.; Lyne, S.B.; Zeineddine, H.A.; et al. Transcriptome clarifies mechanisms of lesion genesis versus progression in models of Ccm3 cerebral cavernous malformations. *Acta Neuropathol. Commun.* **2019**, *7*, 132. [CrossRef]
19. Kramer, A.; Green, J.; Pollard, J., Jr.; Tugendreich, S. Causal analysis approaches in Ingenuity Pathway Analysis. *Bioinformatics* **2014**, *30*, 523–530. [CrossRef]
20. Li, Y.; Girard, R.; Srinath, A.; Cruz, D.V.; Ciszewski, C.; Chen, C.; Lightle, R.; Romanos, S.; Sone, J.Y.; Moore, T.; et al. Transcriptomic signatures of individual cell types in cerebral cavernous malformation. *Cell Commun. Signal.* **2024**, *22*, 23. [CrossRef]
21. Gao, Y.; Yin, Y.; Xing, X.; Zhao, Z.; Lu, Y.; Sun, Y.; Zhuang, Z.; Wang, M.; Ji, W.; He, Y. Arsenic-induced anti-angiogenesis via miR-425-5p-regulated CCM3. *Toxicol. Lett.* **2016**, *254*, 22–31. [CrossRef] [PubMed]
22. Li, J.; Zhao, Y.; Choi, J.; Ting, K.K.; Coleman, P.; Chen, J.; Cogger, V.C.; Wan, L.; Shi, Z.; Moller, T.; et al. Targeting miR-27a/VE-cadherin interactions rescues cerebral cavernous malformations in mice. *PLoS Biol.* **2020**, *18*, e3000734. [CrossRef] [PubMed]

23. Romanos, S.G.; Srinath, A.; Li, Y.; Xie, B.; Chen, C.; Li, Y.; Moore, T.; Bi, D.; Sone, J.Y.; Lightle, R.; et al. Circulating Plasma miRNA Homologs in Mice and Humans Reflect Familial Cerebral Cavernous Malformation Disease. *Transl. Stroke Res.* **2023**, *14*, 513–529. [CrossRef]
24. Schwefel, K.; Spiegler, S.; Ameling, S.; Much, C.D.; Pilz, R.A.; Otto, O.; Volker, U.; Felbor, U.; Rath, M. Biallelic CCM3 mutations cause a clonogenic survival advantage and endothelial cell stiffening. *J. Cell. Mol. Med.* **2019**, *23*, 1771–1783. [CrossRef] [PubMed]
25. Kar, S.; Bali, K.K.; Baisantry, A.; Geffers, R.; Samii, A.; Bertalanffy, H. Genome-Wide Sequencing Reveals MicroRNAs Downregulated in Cerebral Cavernous Malformations. *J. Mol. Neurosci.* **2017**, *61*, 178–188. [CrossRef]
26. Srinath, A.; Xie, B.; Li, Y.; Sone, J.Y.; Romanos, S.; Chen, C.; Sharma, A.; Polster, S.; Dorrestein, P.C.; Weldon, K.C.; et al. Plasma metabolites with mechanistic and clinical links to the neurovascular disease cavernous angioma. *Commun. Med.* **2023**, *3*, 35. [CrossRef]
27. Chen, B.; Tao, W.; Yan, L.; Zeng, M.; Song, L.; Huang, Z.; Chen, F. Molecular feature of arterial remodeling in the brain arteriovenous malformation revealed by arteriovenous shunt rat model and RNA sequencing. *Int. Immunopharmacol.* **2022**, *107*, 108653. [CrossRef]
28. Huang, J.; Song, J.; Qu, M.; Wang, Y.; An, Q.; Song, Y.; Yan, W.; Wang, B.; Wang, X.; Zhang, S.; et al. MicroRNA-137 and microRNA-195* inhibit vasculogenesis in brain arteriovenous malformations. *Ann. Neurol.* **2017**, *82*, 371–384. [CrossRef]
29. Marin-Ramos, N.I.; Thein, T.Z.; Ghaghada, K.B.; Chen, T.C.; Giannotta, S.L.; Hofman, F.M. miR-18a Inhibits BMP4 and HIF-1alpha Normalizing Brain Arteriovenous Malformations. *Circ. Res.* **2020**, *127*, e210–e231. [CrossRef]
30. Chen, Y.; Li, Z.; Shi, Y.; Huang, G.; Chen, L.; Tan, H.; Wang, Z.; Yin, C.; Hu, J. Deep Sequencing of Small RNAs in Blood of Patients with Brain Arteriovenous Malformations. *World Neurosurg.* **2018**, *115*, e570–e579. [CrossRef]
31. Ferreira, R.; Santos, T.; Amar, A.; Gong, A.; Chen, T.C.; Tahara, S.M.; Giannotta, S.L.; Hofman, F.M. Argonaute-2 promotes miR-18a entry in human brain endothelial cells. *J. Am. Heart Assoc.* **2014**, *3*, e000968. [CrossRef] [PubMed]
32. Ferreira, R.; Santos, T.; Amar, A.; Tahara, S.M.; Chen, T.C.; Giannotta, S.L.; Hofman, F.M. MicroRNA-18a improves human cerebral arteriovenous malformation endothelial cell function. *Stroke* **2014**, *45*, 293–297. [CrossRef] [PubMed]
33. He, Q.; Huo, R.; Wang, J.; Xu, H.; Zhao, S.; Zhang, J.; Sun, Y.; Jiao, Y.; Weng, J.; Zhao, J.; et al. Exosomal miR-3131 derived from endothelial cells with KRAS mutation promotes EndMT by targeting PICK1 in brain arteriovenous malformations. *CNS Neurosci. Ther.* **2023**, *29*, 1312–1324. [CrossRef] [PubMed]
34. Liu, J.; Chen, C.; Qin, X.; Wang, J.; Zhang, B.; Jin, F. Plasma-derived exosomes contributes to endothelial-to-mesenchymal transition in Moyamoya disease. *Heliyon* **2024**, *10*, e26748. [CrossRef]
35. Liu, Y.; Huang, Y.; Zhang, X.; Ma, X.; He, X.; Gan, C.; Zou, X.; Wang, S.; Shu, K.; Lei, T.; et al. CircZXDC Promotes Vascular Smooth Muscle Cell Transdifferentiation via Regulating miRNA-125a-3p/ABCC6 in Moyamoya Disease. *Cells* **2022**, *11*, 3792. [CrossRef]
36. Ma, X.; Huang, Y.; He, X.; Zhang, X.; Liu, Y.; Yang, Y.; Yue, P.; Liu, Y.; Gan, C.; Shu, K.; et al. Endothelial Cell-Derived Let-7c-Induced TLR7 Activation on Smooth Muscle Cell Mediate Vascular Wall Remodeling in Moyamoya Disease. *Transl. Stroke Res.* **2023**, *14*, 608–623. [CrossRef]
37. Wen, Y.; Chen, J.; Long, T.; Chen, F.; Wang, Z.; Chen, S.; Zhang, G.; Li, M.; Zhang, S.; Kang, H.; et al. miR-6760-5p suppresses neoangiogenesis by targeting Yes-associated protein 1 in patients with moyamoya disease undergoing indirect revascularization. *Gene* **2025**, *937*, 149152. [CrossRef]
38. Dai, D.; Lu, Q.; Huang, Q.; Yang, P.; Hong, B.; Xu, Y.; Zhao, W.; Liu, J.; Li, Q. Serum miRNA signature in Moyamoya disease. *PLoS ONE* **2014**, *9*, e102382. [CrossRef]
39. Gu, X.; Jiang, D.; Yang, Y.; Zhang, P.; Wan, G.; Gu, W.; Shi, J.; Jiang, L.; Chen, B.; Zheng, Y.; et al. Construction and Comprehensive Analysis of Dysregulated Long Noncoding RNA-Associated Competing Endogenous RNA Network in Moyamoya Disease. *Comput. Math. Methods Med.* **2020**, *2020*, 2018214. [CrossRef]
40. Huang, D.; Qi, H.; Yang, H.; Chen, M. Plasma exosomal microRNAs are non-invasive biomarkers of moyamoya disease: A pilot study. *Clinics* **2023**, *78*, 100247. [CrossRef]
41. Kang, K.; Shen, Y.; Zhang, Q.; Lu, J.; Ju, Y.; Ji, R.; Li, N.; Wu, J.; Yang, B.; Lin, J.; et al. MicroRNA Expression in Circulating Leukocytes and Bioinformatic Analysis of Patients With Moyamoya Disease. *Front. Genet.* **2022**, *13*, 816919. [CrossRef] [PubMed]
42. Lee, M.J.; Fallen, S.; Zhou, Y.; Baxter, D.; Scherler, K.; Kuo, M.F.; Wang, K. The Impact of Moyamoya Disease and RNF213 Mutations on the Spectrum of Plasma Protein and MicroRNA. *J. Clin. Med.* **2019**, *8*, 1648. [CrossRef] [PubMed]
43. Ota, S.; Yokoyama, K.; Kanamori, F.; Mamiya, T.; Uda, K.; Araki, Y.; Wakabayashi, T.; Yoshikawa, K.; Saito, R. Moyamoya disease-specific extracellular vesicle-derived microRNAs in the cerebrospinal fluid revealed by comprehensive expression analysis through microRNA sequencing. *Acta Neurochir.* **2023**, *165*, 2045–2055. [CrossRef]
44. Park, Y.S.; Jeon, Y.J.; Lee, B.E.; Kim, T.G.; Choi, J.U.; Kim, D.S.; Kim, N.K. Association of the miR-146aC>G, miR-196a2C>T, and miR-499A>G polymorphisms with moyamoya disease in the Korean population. *Neurosci. Lett.* **2012**, *521*, 71–75. [CrossRef]

45. Uchino, H.; Ito, M.; Kazumata, K.; Hama, Y.; Hamauchi, S.; Terasaka, S.; Sasaki, H.; Houkin, K. Circulating miRNome profiling in Moyamoya disease-discordant monozygotic twins and endothelial microRNA expression analysis using iPS cell line. *BMC Med. Genom.* **2018**, *11*, 72. [CrossRef]
46. Wang, G.; Wen, Y.; Chen, S.; Zhang, G.; Li, M.; Zhang, S.; Qi, S.; Feng, W. Use of a panel of four microRNAs in CSF as a predicted biomarker for postoperative neoangiogenesis in moyamoya disease. *CNS Neurosci. Ther.* **2021**, *27*, 908–918. [CrossRef]
47. Wang, G.; Wen, Y.; Faleti, O.D.; Zhao, Q.; Liu, J.; Zhang, G.; Li, M.; Qi, S.; Feng, W.; Lyu, X. A Panel of Exosome-Derived miRNAs of Cerebrospinal Fluid for the Diagnosis of Moyamoya Disease. *Front. Neurosci.* **2020**, *14*, 548278. [CrossRef]
48. Wang, M.; Zhang, B.; Jin, F.; Li, G.; Cui, C.; Feng, S. Exosomal MicroRNAs: Biomarkers of moyamoya disease and involvement in vascular cytoskeleton reconstruction. *Heliyon* **2024**, *10*, e32022. [CrossRef]
49. Zhao, S.; Gong, Z.; Zhang, J.; Xu, X.; Liu, P.; Guan, W.; Jing, L.; Peng, T.; Teng, J.; Jia, Y. Elevated Serum MicroRNA Let-7c in Moyamoya Disease. *J. Stroke Cerebrovasc. Dis.* **2015**, *24*, 1709–1714. [CrossRef]
50. Bai, Y.Y.; Niu, J.Z. miR-222 regulates brain injury and inflammation following intracerebral hemorrhage by targeting ITGB8. *Mol. Med. Rep.* **2020**, *21*, 1145–1153. [CrossRef]
51. Cepparulo, P.; Cuomo, O.; Vinciguerra, A.; Torelli, M.; Annunziato, L.; Pignataro, G. Hemorrhagic Stroke Induces a Time-Dependent Upregulation of miR-150-5p and miR-181b-5p in the Bloodstream. *Front. Neurol.* **2021**, *12*, 736474. [CrossRef] [PubMed]
52. Chen, B.; Wang, H.; Lv, C.; Mao, C.; Cui, Y. Long non-coding RNA H19 protects against intracerebral hemorrhage injuries via regulating microRNA-106b-5p/acyl-CoA synthetase long chain family member 4 axis. *Bioengineered* **2021**, *12*, 4004–4015. [CrossRef] [PubMed]
53. Chen, H.; Ren, L.; Ma, W. Mechanism of SOX10 in ferroptosis of hippocampal neurons after intracerebral hemorrhage via the miR-29a-3p/ACSL4 axis. *J. Neurophysiol.* **2023**, *129*, 862–871. [CrossRef] [PubMed]
54. Chen, J.X.; Wang, Y.P.; Zhang, X.; Li, G.X.; Zheng, K.; Duan, C.Z. lncRNA Mtss1 promotes inflammatory responses and secondary brain injury after intracerebral hemorrhage by targeting miR-709 in mice. *Brain Res. Bull.* **2020**, *162*, 20–29. [CrossRef]
55. Cheng, J.; Tang, J.C.; Pan, M.X.; Chen, S.F.; Zhao, D.; Zhang, Y.; Liao, H.B.; Zhuang, Y.; Lei, R.X.; Wang, S.; et al. l-lysine confers neuroprotection by suppressing inflammatory response via microRNA-575/PTEN signaling after mouse intracerebral hemorrhage injury. *Exp. Neurol.* **2020**, *327*, 113214. [CrossRef]
56. Cui, H.; Yang, A.; Zhou, H.; Wang, Y.; Luo, J.; Zhou, J.; Liu, T.; Li, P.; Zhou, J.; Hu, E.; et al. Thrombin-induced miRNA-24-1-5p upregulation promotes angiogenesis by targeting prolyl hydroxylase domain 1 in intracerebral hemorrhagic rats. *J. Neurosurg.* **2020**, *134*, 1515–1526. [CrossRef]
57. Di, Y.L.; Yu, Y.; Zhao, S.J.; Huang, N.; Fei, X.C.; Yao, D.D.; Ai, L.; Lyu, J.H.; He, R.Q.; Li, J.J.; et al. Formic acid induces hypertension-related hemorrhage in hSSAO(TG) in mice and human. *Exp. Neurol.* **2022**, *358*, 114208. [CrossRef]
58. Ding, H.; Jia, Y.; Lv, H.; Chang, W.; Liu, F.; Wang, D. Extracellular vesicles derived from bone marrow mesenchymal stem cells alleviate neuroinflammation after diabetic intracerebral hemorrhage via the miR-183-5p/PDCD4/NLRP3 pathway. *J. Endocrinol. Investig.* **2021**, *44*, 2685–2698. [CrossRef]
59. Dong, B.; Zhou, B.; Sun, Z.; Huang, S.; Han, L.; Nie, H.; Chen, G.; Liu, S.; Zhang, Y.; Bao, N.; et al. LncRNA-FENDRR mediates VEGFA to promote the apoptosis of brain microvascular endothelial cells via regulating miR-126 in mice with hypertensive intracerebral hemorrhage. *Microcirculation* **2018**, *25*, e12499. [CrossRef]
60. Duan, S.; Wang, F.; Cao, J.; Wang, C. Exosomes Derived from MicroRNA-146a-5p-Enriched Bone Marrow Mesenchymal Stem Cells Alleviate Intracerebral Hemorrhage by Inhibiting Neuronal Apoptosis and Microglial M1 Polarization. *Drug Des. Dev. Ther.* **2020**, *14*, 3143–3158. [CrossRef]
61. Fan, W.; Li, X.; Zhang, D.; Li, H.; Shen, H.; Liu, Y.; Chen, G. Detrimental Role of miRNA-144-3p in Intracerebral Hemorrhage Induced Secondary Brain Injury is Mediated by Formyl Peptide Receptor 2 Downregulation Both In Vivo and In Vitro. *Cell Transplant.* **2019**, *28*, 723–738. [CrossRef] [PubMed]
62. Gong, F.; Wei, Y. LncRNA PVT1 promotes neuroinflammation after intracerebral hemorrhage by regulating the miR-128-3p/TXNIP axis. *Int. J. Neurosci.* **2024**, 1–15, *Online ahead of print*. [CrossRef] [PubMed]
63. Gong, Y.; Zhang, G.; Li, B.; Cao, C.; Cao, D.; Li, X.; Li, H.; Ye, M.; Shen, H.; Chen, G. BMAL1 attenuates intracerebral hemorrhage-induced secondary brain injury in rats by regulating the Nrf2 signaling pathway. *Ann. Transl. Med.* **2021**, *9*, 1617. [CrossRef] [PubMed]
64. Guo, M.; Ge, X.; Wang, C.; Yin, Z.; Jia, Z.; Hu, T.; Li, M.; Wang, D.; Han, Z.; Wang, L.; et al. Intranasal Delivery of Gene-Edited Microglial Exosomes Improves Neurological Outcomes after Intracerebral Hemorrhage by Regulating Neuroinflammation. *Brain Sci.* **2023**, *13*, 639. [CrossRef]
65. Guo, Q.; Su, H.; He, J.B.; Li, H.Q.; Sha, J.J. MiR-590-5p alleviates intracerebral hemorrhage-induced brain injury through targeting Peli1 gene expression. *Biochem. Biophys. Res. Commun.* **2018**, *504*, 61–67. [CrossRef]
66. Han, J.; Zhang, J.; Yao, X.; Meng, M.; Wan, Y.; Cheng, Y. Mechanism of HDAC1 Regulating Iron Overload-Induced Neuronal Oxidative Damage After Cerebral Hemorrhage. *Mol. Neurobiol.* **2024**, *61*, 7549–7566. [CrossRef]

67. Hou, Y.; Xie, Y.; Liu, X.; Chen, Y.; Zhou, F.; Yang, B. Oxygen glucose deprivation-pretreated astrocyte-derived exosomes attenuates intracerebral hemorrhage (ICH)-induced BBB disruption through miR-27a-3p/ARHGAP25/Wnt/beta-catenin axis. *Fluids Barriers CNS* **2024**, *21*, 8. [CrossRef]
68. Hu, L.; Zhang, H.; Wang, B.; Ao, Q.; He, Z. MicroRNA-152 attenuates neuroinflammation in intracerebral hemorrhage by inhibiting thioredoxin interacting protein (TXNIP)-mediated NLRP3 inflammasome activation. *Int. Immunopharmacol.* **2020**, *80*, 106141. [CrossRef]
69. Hu, L.; Zhang, H.; Wang, B.; Ao, Q.; Shi, J.; He, Z. MicroRNA-23b alleviates neuroinflammation and brain injury in intracerebral hemorrhage by targeting inositol polyphosphate multikinase. *Int. Immunopharmacol.* **2019**, *76*, 105887. [CrossRef]
70. Hu, L.T.; Wang, B.Y.; Fan, Y.H.; He, Z.Y.; Zheng, W.X. Exosomal miR-23b from bone marrow mesenchymal stem cells alleviates oxidative stress and pyroptosis after intracerebral hemorrhage. *Neural Regen. Res.* **2023**, *18*, 560–567. [CrossRef]
71. Huan, S.; Jin, J.; Shi, C.X.; Li, T.; Dai, Z.; Fu, X.J. Overexpression of miR-146a inhibits the apoptosis of hippocampal neurons of rats with cerebral hemorrhage by regulating autophagy. *Hum. Exp. Toxicol.* **2020**, *39*, 1178–1189. [CrossRef] [PubMed]
72. Jin, J.; Zhou, F.; Zhu, J.; Zeng, W.; Liu, Y. MiR-26a inhibits the inflammatory response of microglia by targeting HMGA2 in intracerebral hemorrhage. *J. Int. Med. Res.* **2020**, *48*, 300060520929615. [CrossRef] [PubMed]
73. Jin, S.; Meng, J.; Zhang, C.; Qi, J.; Wu, H. Consistency of mouse models with human intracerebral hemorrhage: Core targets and non-coding RNA regulatory axis. *Aging* **2024**, *16*, 1952–1967. [CrossRef] [PubMed]
74. Kim, J.M.; Lee, S.T.; Chu, K.; Jung, K.H.; Kim, J.H.; Yu, J.S.; Kim, S.; Kim, S.H.; Park, D.K.; Moon, J.; et al. Inhibition of Let7c microRNA is neuroprotective in a rat intracerebral hemorrhage model. *PLoS ONE* **2014**, *9*, e97946. [CrossRef]
75. Kong, F.; Zhou, J.; Zhou, W.; Guo, Y.; Li, G.; Yang, L. Protective role of microRNA-126 in intracerebral hemorrhage. *Mol. Med. Rep.* **2017**, *15*, 1419–1425. [CrossRef]
76. Kong, Y.; Li, S.; Zhang, M.; Xu, W.; Chen, Q.; Zheng, L.; Liu, P.; Zou, W. Acupuncture Ameliorates Neuronal Cell Death, Inflammation, and Ferroptosis and Downregulated miR-23a-3p After Intracerebral Hemorrhage in Rats. *J. Mol. Neurosci.* **2021**, *71*, 1863–1875. [CrossRef]
77. Li, D.; Wang, L.; Shi, S.; Deng, X.; Zeng, X.; Li, Y.; Li, S.; Bai, P. Ubiquitin-like 4A alleviates the progression of intracerebral hemorrhage by regulating oxidative stress and mitochondrial damage. *Exp. Anim.* **2024**, *73*, 421–432. [CrossRef]
78. Li, L.; Zhan, Y.; Xia, H.; Wu, Y.; Wu, X.; Chen, S. Sevoflurane protects against intracerebral hemorrhage via microRNA-133b/FOXO4/BCL2 axis. *Int. Immunopharmacol.* **2023**, *114*, 109453. [CrossRef]
79. Liao, Y.; Huang, J.; Wang, Z.; Yang, Z.; Shu, Y.; Gan, S.; Wang, Z.; Lu, W. The phosphokinase activity of IRE1a prevents the oxidative stress injury through miR-25/Nox4 pathway after ICH. *CNS Neurosci. Ther.* **2024**, *30*, e14537. [CrossRef]
80. Liu, D.Z.; Tian, Y.; Ander, B.P.; Xu, H.; Stamova, B.S.; Zhan, X.; Turner, R.J.; Jickling, G.; Sharp, F.R. Brain and blood microRNA expression profiling of ischemic stroke, intracerebral hemorrhage, and kainate seizures. *J. Cereb. Blood Flow Metab.* **2010**, *30*, 92–101. [CrossRef]
81. Liu, J.; He, J.; Ge, L.; Xiao, H.; Huang, Y.; Zeng, L.; Jiang, Z.; Lu, M.; Hu, Z. Hypoxic preconditioning rejuvenates mesenchymal stem cells and enhances neuroprotection following intracerebral hemorrhage via the miR-326-mediated autophagy. *Stem Cell Res. Ther.* **2021**, *12*, 413. [CrossRef] [PubMed]
82. Liu, Y.; Mo, C.; Mao, X.; Lu, M.; Xu, L. Increasing miR-126 Can Prevent Brain Injury after Intracerebral Hemorrhage in Rats by Regulating ZEB1. *Contrast Media Mol. Imaging* **2022**, *2022*, 2698773. [CrossRef] [PubMed]
83. Lu, Z.; Huang, K. Protective effect of silencing lncRNA HCP5 against brain injury after intracerebral hemorrhage by targeting miR-195-5p. *BMC Neurosci.* **2025**, *26*, 2. [CrossRef] [PubMed]
84. Luo, B.; Li, L.; Song, X.D.; Chen, H.X.; Yun, D.B.; Wang, L.; Zhang, Y. MicroRNA-7 attenuates secondary brain injury following experimental intracerebral hemorrhage via inhibition of NLRP3. *J. Stroke Cerebrovasc. Dis.* **2024**, *33*, 107670. [CrossRef]
85. Matsuoka, H.; Tamura, A.; Kinehara, M.; Shima, A.; Uda, A.; Tahara, H.; Michihara, A. Levels of tight junction protein CLDND1 are regulated by microRNA-124 in the cerebellum of stroke-prone spontaneously hypertensive rats. *Biochem. Biophys. Res. Commun.* **2018**, *498*, 817–823. [CrossRef]
86. Nie, H.; Hu, Y.; Guo, W.; Wang, W.; Yang, Q.; Dong, Q.; Tang, Y.; Li, Q.; Tang, Z. miR-331-3p Inhibits Inflammatory Response after Intracerebral Hemorrhage by Directly Targeting NLRP6. *Biomed. Res. Int.* **2020**, *2020*, 6182464. [CrossRef]
87. Ouyang, Y.; Li, D.; Wang, H.; Wan, Z.; Luo, Q.; Zhong, Y.; Yin, M.; Qing, Z.; Li, Z.; Bao, B.; et al. MiR-21-5p/dual-specificity phosphatase 8 signalling mediates the anti-inflammatory effect of haem oxygenase-1 in aged intracerebral haemorrhage rats. *Aging Cell* **2019**, *18*, e13022. [CrossRef]
88. Qi, J.; Meng, C.; Mo, J.; Shou, T.; Ding, L.; Zhi, T. CircAFF2 Promotes Neuronal Cell Injury in Intracerebral Hemorrhage by Regulating the miR-488/CLSTN3 Axis. *Neuroscience* **2023**, *535*, 75–87. [CrossRef]
89. Qu, X.; Wang, N.; Cheng, W.; Xue, Y.; Chen, W.; Qi, M. MicroRNA-146a protects against intracerebral hemorrhage by inhibiting inflammation and oxidative stress. *Exp. Ther. Med.* **2019**, *18*, 3920–3928. [CrossRef]
90. Ren, S.; Wu, G.; Huang, Y.; Wang, L.; Li, Y.; Zhang, Y. MiR-18a Aggravates Intracranial Hemorrhage by Regulating RUNX1-Occludin/ZO-1 Axis to Increase BBB Permeability. *J. Stroke Cerebrovasc. Dis.* **2021**, *30*, 105878. [CrossRef]

91. Robles, D.; Guo, D.H.; Watson, N.; Asante, D.; Sukumari-Ramesh, S. Dysregulation of Serum MicroRNA after Intracerebral Hemorrhage in Aged Mice. *Biomedicines* **2023**, *11*, 822. [CrossRef] [PubMed]
92. Shao, G.; Zhou, C.; Ma, K.; Zhao, W.; Xiong, Q.; Yang, L.; Huang, Z.; Yang, Z. MiRNA-494 enhances M1 macrophage polarization via Nrdp1 in ICH mice model. *J. Inflamm.* **2020**, *17*, 17. [CrossRef] [PubMed]
93. Shen, F.; Xu, X.; Yu, Z.; Li, H.; Shen, H.; Li, X.; Shen, M.; Chen, G. Rbfox-1 contributes to CaMKIIalpha expression and intracerebral hemorrhage-induced secondary brain injury via blocking micro-RNA-124. *J. Cereb. Blood Flow Metab.* **2021**, *41*, 530–545. [CrossRef] [PubMed]
94. Shen, H.; Yao, X.; Li, H.; Li, X.; Zhang, T.; Sun, Q.; Ji, C.; Chen, G. Role of Exosomes Derived from miR-133b Modified MSCs in an Experimental Rat Model of Intracerebral Hemorrhage. *J. Mol. Neurosci.* **2018**, *64*, 421–430. [CrossRef]
95. Shi, Y.Y.; Cui, H.F.; Qin, B.J. Monomethyl fumarate protects cerebral hemorrhage injury in rats via activating microRNA-139/Nrf2 axis. *Eur. Rev. Med. Pharmacol. Sci.* **2019**, *23*, 5012–5019. [CrossRef]
96. Song, H.; Xu, N.; Jin, S. miR-30e-5p attenuates neuronal deficit and inflammation of rats with intracerebral hemorrhage by regulating TLR4. *Exp. Ther. Med.* **2022**, *24*, 492. [CrossRef]
97. Sun, J.; Xu, G. Mesenchymal Stem Cell-Derived Exosomal miR-150-3p Affects Intracerebral Hemorrhage By Regulating TRAF6/NF-kappaB Axis, Gut Microbiota and Metabolism. *Stem Cell Rev. Rep.* **2023**, *19*, 1907–1921. [CrossRef]
98. Tang, J.; Yan, B.; Tang, Y.; Zhou, X.; Ji, Z.; Xu, F. Baicalein ameliorates oxidative stress and brain injury after intracerebral hemorrhage by activating the Nrf2/ARE pathway via miR-106a-5p/PHLPP2 axis. *Int. J. Neurosci.* **2023**, *133*, 1380–1393. [CrossRef]
99. Tsai, Y.C.; Chang, C.H.; Chong, Y.B.; Wu, C.H.; Tsai, H.P.; Cheng, T.L.; Lin, C.L. MicroRNA-195-5p Inhibits Intracerebral Hemorrhage-Induced Inflammatory Response and Neuron Cell Apoptosis. *Int. J. Mol. Sci.* **2024**, *25*, 10321. [CrossRef]
100. Tsai, Y.C.; Chang, C.H.; Chong, Y.B.; Wu, C.H.; Tsai, H.P.; Cheng, T.L.; Lin, C.L. MicroRNA-195-5p Attenuates Intracerebral-Hemorrhage-Induced Brain Damage by Inhibiting MMP-9/MMP-2 Expression. *Biomedicines* **2024**, *12*, 1373. [CrossRef]
101. Walsh, K.B.; Zimmerman, K.D.; Zhang, X.; Demel, S.L.; Luo, Y.; Langefeld, C.D.; Wohleb, E.; Schulert, G.; Woo, D.; Adeoye, O. miR-181a Mediates Inflammatory Gene Expression After Intracerebral Hemorrhage: An Integrated Analysis of miRNA-seq and mRNA-seq in a Swine ICH Model. *J. Mol. Neurosci.* **2021**, *71*, 1802–1814. [CrossRef] [PubMed]
102. Wan, S.Y.; Li, G.S.; Tu, C.; Chen, W.L.; Wang, X.W.; Wang, Y.N.; Peng, L.B.; Tan, F. MicroNAR-194-5p hinders the activation of NLRP3 inflammasomes and alleviates neuroinflammation during intracerebral hemorrhage by blocking the interaction between TRAF6 and NLRP3. *Brain Res.* **2021**, *1752*, 147228. [CrossRef] [PubMed]
103. Wang, B.; Tian, L.; Zhang, Z.; Liu, Z.; Li, K.; Zhang, Q.; Song, Y.; Qi, J. CircTrim37 Ameliorates Intracerebral Hemorrhage Outcomes by Modulating Microglial Polarization via the miR-30c-5p/SOCS3 Axis. *Mol. Neurobiol.* **2024**, *61*, 4038–4054. [CrossRef] [PubMed]
104. Wang, B.; Zhao, X.; Xiao, L.; Chen, Y. FoxO1 Silencing Facilitates Neurological Function Recovery in Intracerebral Hemorrhage Mice via the lncRNA GAS5/miR-378a-5p/Hspa5 Axis. *J. Stroke Cerebrovasc. Dis.* **2022**, *31*, 106443. [CrossRef]
105. Wang, B.Q.; He, M.; Wang, Y.; Liu, S.; Guo, Z.W.; Liu, Z.L. Hyperbaric oxygen ameliorates neuronal injury and neurological function recovery in rats with intracerebral hemorrhage by silencing microRNA-204-5p-targeted chloride channel protein 3. *J. Physiol. Pharmacol.* **2023**, *74*, 347–354. [CrossRef]
106. Wang, C.; Cao, J.; Duan, S.; Xu, R.; Yu, H.; Huo, X.; Qian, Y. Effect of MicroRNA-126a-3p on Bone Marrow Mesenchymal Stem Cells Repairing Blood-brain Barrier and Nerve Injury after Intracerebral Hemorrhage. *J. Stroke Cerebrovasc. Dis.* **2020**, *29*, 104748. [CrossRef]
107. Wang, J.; Teng, F.; Liu, S.; Pan, X.; Yang, B.; Wu, W. lncRNA SND1-IT1 delivered via intracerebral hemorrhage-derived exosomes affect the growth of human microglia by regulating the miR-124-3p/MTF1 axis. *J. Cell. Physiol.* **2023**, *238*, 366–378. [CrossRef]
108. Wang, M.; Mungur, R.; Lan, P.; Wang, P.; Wan, S. MicroRNA-21 and microRNA-146a negatively regulate the secondary inflammatory response of microglia after intracerebral hemorrhage. *Int. J. Clin. Exp. Pathol.* **2018**, *11*, 3348–3356.
109. Wang, M.D.; Wang, Y.; Xia, Y.P.; Dai, J.W.; Gao, L.; Wang, S.Q.; Wang, H.J.; Mao, L.; Li, M.; Yu, S.M.; et al. High Serum MiR-130a Levels Are Associated with Severe Perihematomal Edema and Predict Adverse Outcome in Acute ICH. *Mol. Neurobiol.* **2016**, *53*, 1310–1321. [CrossRef]
110. Wang, S.; Cui, Y.; Xu, J.; Gao, H. miR-140-5p Attenuates Neuroinflammation and Brain Injury in Rats Following Intracerebral Hemorrhage by Targeting TLR4. *Inflammation* **2019**, *42*, 1869–1877. [CrossRef]
111. Wang, X.; Hong, Y.; Wu, L.; Duan, X.; Hu, Y.; Sun, Y.; Wei, Y.; Dong, Z.; Wu, C.; Yu, D.; et al. Deletion of MicroRNA-144/451 Cluster Aggravated Brain Injury in Intracerebral Hemorrhage Mice by Targeting 14-3-3zeta. *Front. Neurol.* **2020**, *11*, 551411. [CrossRef]
112. Wang, Y.; Song, Y.; Pang, Y.; Yu, Z.; Hua, W.; Gu, Y.; Qi, J.; Wu, H. miR-183-5p alleviates early injury after intracerebral hemorrhage by inhibiting heme oxygenase-1 expression. *Aging* **2020**, *12*, 12869–12895. [CrossRef] [PubMed]

113. Wang, Y.; Yu, Z.; Cheng, M.; Hu, E.; Yan, Q.; Zheng, F.; Guo, X.; Zhang, W.; Li, H.; Li, Z.; et al. Buyang huanwu decoction promotes remyelination via miR-760-3p/GPR17 axis after intracerebral hemorrhage. *J. Ethnopharmacol.* **2024**, *328*, 118126. [CrossRef] [PubMed]
114. Wang, Y.; Zhang, H.; Hao, Y.; Jin, F.; Tang, L.; Xu, X.; He, Z.; Wang, Y. Expression profile of circular RNAs in blood samples of Northern Chinese males with intracerebral hemorrhage shows downregulation of hsa-circ-0090829. *Heliyon* **2024**, *10*, e35864. [CrossRef]
115. Wang, Y.Y.; Li, K.; Wang, J.J.; Hua, W.; Liu, Q.; Sun, Y.L.; Qi, J.P.; Song, Y.J. Bone marrow-derived mesenchymal stem cell-derived exosome-loaded miR-129-5p targets high-mobility group box 1 attenuates neurological-impairment after diabetic cerebral hemorrhage. *World J. Diabetes* **2024**, *15*, 1979–2001. [CrossRef]
116. Wang, Z.; Fang, L.; Shi, H.; Yang, Z. miR-181b regulates ER stress induced neuron death through targeting Heat Shock Protein A5 following intracerebral haemorrhage. *Immunol. Lett.* **2019**, *206*, 1–10. [CrossRef]
117. Wang, Z.; Yuan, B.; Fu, F.; Huang, S.; Yang, Z. Hemoglobin enhances miRNA-144 expression and autophagic activation mediated inflammation of microglia via mTOR pathway. *Sci. Rep.* **2017**, *7*, 11861. [CrossRef]
118. Wei, M.; Li, C.; Yan, Z.; Hu, Z.; Dong, L.; Zhang, J.; Wang, X.; Li, Y.; Zhang, H. Activated Microglia Exosomes Mediated miR-383-3p Promotes Neuronal Necroptosis Through Inhibiting ATF4 Expression in Intracerebral Hemorrhage. *Neurochem. Res.* **2021**, *46*, 1337–1349. [CrossRef]
119. Wu, T.S.; Lin, Y.T.; Huang, Y.T.; Yu, F.Y.; Liu, B.H. Ochratoxin A triggered intracerebral hemorrhage in embryonic zebrafish: Involvement of microRNA-731 and prolactin receptor. *Chemosphere* **2020**, *242*, 125143. [CrossRef]
120. Xi, T.; Jin, F.; Zhu, Y.; Wang, J.; Tang, L.; Wang, Y.; Liebeskind, D.S.; He, Z. MicroRNA-126-3p attenuates blood-brain barrier disruption, cerebral edema and neuronal injury following intracerebral hemorrhage by regulating PIK3R2 and Akt. *Biochem. Biophys. Res. Commun.* **2017**, *494*, 144–151. [CrossRef]
121. Xiao, W.; Jiang, Z.; Wan, W.; Pan, W.; Xu, J. miR-145-5p targets MMP2 to protect brain injury in hypertensive intracerebral hemorrhage via inactivation of the Wnt/beta-catenin signaling pathway. *Ann. Transl. Med.* **2022**, *10*, 571. [CrossRef] [PubMed]
122. Xie, B.; Qiao, M.; Xuan, J. lncRNA MEG3 Downregulation Relieves Intracerebral Hemorrhage by Inhibiting Oxidative Stress and Inflammation in an miR-181b-Dependent Manner. *Med. Sci. Monit.* **2021**, *27*, e929435. [CrossRef] [PubMed]
123. Xu, H.F.; Fang, X.Y.; Zhu, S.H.; Xu, X.H.; Zhang, Z.X.; Wang, Z.F.; Zhao, Z.Q.; Ding, Y.J.; Tao, L.Y. Glucocorticoid treatment inhibits intracerebral hemorrhage-induced inflammation by targeting the microRNA-155/SOCS-1 signaling pathway. *Mol. Med. Rep.* **2016**, *14*, 3798–3804. [CrossRef]
124. Xu, W.; Li, F.; Liu, Z.; Xu, Z.; Sun, B.; Cao, J.; Liu, Y. MicroRNA-27b inhibition promotes Nrf2/ARE pathway activation and alleviates intracerebral hemorrhage-induced brain injury. *Oncotarget* **2017**, *8*, 70669–70684. [CrossRef]
125. Xu, Z.; Zhao, B.; Mao, J.; Sun, Z. Knockdown of long noncoding RNA metastasis-associated lung adenocarcinoma transcript 1 protects against intracerebral hemorrhage through microRNA-146a-mediated inhibition of inflammation and oxidative stress. *Bioengineered* **2022**, *13*, 3969–3980. [CrossRef]
126. Yang, W.; Ding, N.; Luo, R.; Zhang, Q.; Li, Z.; Zhao, F.; Zhang, S.; Zhang, X.; Zhou, T.; Wang, H.; et al. Exosomes from young healthy human plasma promote functional recovery from intracerebral hemorrhage via counteracting ferroptotic injury. *Bioact. Mater.* **2023**, *27*, 1–14. [CrossRef]
127. Yang, W.S.; Shen, Y.Q.; Yang, X.; Li, X.H.; Xu, S.H.; Zhao, L.B.; Li, R.; Xiong, X.; Bai, S.J.; Wu, Q.Y.; et al. MicroRNA Transcriptomics Analysis Identifies Dysregulated Hedgehog Signaling Pathway in a Mouse Model of Acute Intracerebral Hemorrhage Exposed to Hyperglycemia. *J. Stroke Cerebrovasc. Dis.* **2022**, *31*, 106281. [CrossRef]
128. Yang, Y.; Gao, L.; Xi, J.; Liu, X.; Yang, H.; Luo, Q.; Xie, F.; Niu, J.; Meng, P.; Tian, X.; et al. Mesenchymal stem cell-derived extracellular vesicles mitigate neuronal damage from intracerebral hemorrhage by modulating ferroptosis. *Stem Cell Res. Ther.* **2024**, *15*, 255. [CrossRef]
129. Yang, Z.; Huang, J.; Liao, Y.; Gan, S.; Zhu, S.; Xu, S.; Shu, Y.; Lu, W. ER Stress is Involved in Mast Cells Degranulation via IRE1alpha/miR-125/Lyn Pathway in an Experimental Intracerebral Hemorrhage Mouse Model. *Neurochem. Res.* **2022**, *47*, 1598–1609. [CrossRef]
130. Yang, Z.; Jiang, X.; Zhang, J.; Huang, X.; Zhang, X.; Wang, J.; Shi, H.; Yu, A. Let-7a promotes microglia M2 polarization by targeting CKIP-1 following ICH. *Immunol. Lett.* **2018**, *202*, 1–7. [CrossRef]
131. Yang, Z.; Zhong, L.; Xian, R.; Yuan, B. MicroRNA-223 regulates inflammation and brain injury via feedback to NLRP3 inflammasome after intracerebral hemorrhage. *Mol. Immunol.* **2015**, *65*, 267–276. [CrossRef] [PubMed]
132. Yin, M.; Chen, Z.; Ouyang, Y.; Zhang, H.; Wan, Z.; Wang, H.; Wu, W.; Yin, X. Thrombin-induced, TNFR-dependent miR-181c downregulation promotes MLL1 and NF-kappaB target gene expression in human microglia. *J. Neuroinflamm.* **2017**, *14*, 132. [CrossRef] [PubMed]
133. Yu, A.; Zhang, T.; Duan, H.; Pan, Y.; Zhang, X.; Yang, G.; Wang, J.; Deng, Y.; Yang, Z. MiR-124 contributes to M2 polarization of microglia and confers brain inflammatory protection via the C/EBP-alpha pathway in intracerebral hemorrhage. *Immunol. Lett.* **2017**, *182*, 1–11. [CrossRef] [PubMed]

134. Yu, A.; Zhang, T.; Zhong, W.; Duan, H.; Wang, S.; Ye, P.; Wang, J.; Zhong, S.; Yang, Z. miRNA-144 induces microglial autophagy and inflammation following intracerebral hemorrhage. *Immunol. Lett.* **2017**, *182*, 18–23. [CrossRef]
135. Yu, M.; Tian, T.; Zhang, J.; Hu, T. miR-141-3p protects against blood-brain barrier disruption and brain injury after intracerebral hemorrhage by targeting ZEB2. *J. Clin. Neurosci.* **2022**, *99*, 253–260. [CrossRef]
136. Yu, N.; Tian, W.; Liu, C.; Zhang, P.; Zhao, Y.; Nan, C.; Jin, Q.; Li, X.; Liu, Y. miR-122-5p Promotes Peripheral and Central Nervous System Inflammation in a Mouse Model of Intracerebral Hemorrhage via Disruption of the MLLT1/PI3K/AKT Signaling. *Neurochem. Res.* **2023**, *48*, 3665–3682. [CrossRef]
137. Yuan, B.; Shen, H.; Lin, L.; Su, T.; Zhong, L.; Yang, Z. MicroRNA367 negatively regulates the inflammatory response of microglia by targeting IRAK4 in intracerebral hemorrhage. *J. Neuroinflamm.* **2015**, *12*, 206. [CrossRef]
138. Zhang, C.Y.; Ren, X.M.; Li, H.B.; Wei, W.; Wang, K.X.; Li, Y.M.; Hu, J.L.; Li, X. Effect of miR-130a on neuronal injury in rats with intracranial hemorrhage through PTEN/PI3K/AKT signaling pathway. *Eur. Rev. Med. Pharmacol. Sci.* **2019**, *23*, 4890–4897. [CrossRef]
139. Zhang, H.; Lu, X.; Hao, Y.; Tang, L.; He, Z. MicroRNA-26a-5p alleviates neuronal apoptosis and brain injury in intracerebral hemorrhage by targeting RAN binding protein 9. *Acta Histochem.* **2020**, *122*, 151571. [CrossRef]
140. Zhang, H.; Wang, Y.; Lian, L.; Zhang, C.; He, Z. Glycine-Histidine-Lysine (GHK) Alleviates Astrocytes Injury of Intracerebral Hemorrhage via the Akt/miR-146a-3p/AQP4 Pathway. *Front. Neurosci.* **2020**, *14*, 576389. [CrossRef]
141. Zhang, H.; Wang, Y.; Lv, Q.; Gao, J.; Hu, L.; He, Z. MicroRNA-21 Overexpression Promotes the Neuroprotective Efficacy of Mesenchymal Stem Cells for Treatment of Intracerebral Hemorrhage. *Front. Neurol.* **2018**, *9*, 931. [CrossRef] [PubMed]
142. Zhang, W.; Wang, L.; Wang, R.; Duan, Z.; Wang, H. A blockade of microRNA-155 signal pathway has a beneficial effect on neural injury after intracerebral haemorrhage via reduction in neuroinflammation and oxidative stress. *Arch. Physiol. Biochem.* **2022**, *128*, 1235–1241. [CrossRef] [PubMed]
143. Zhang, X.D.; Fan, Q.Y.; Qiu, Z.; Chen, S. MiR-7 alleviates secondary inflammatory response of microglia caused by cerebral hemorrhage through inhibiting TLR4 expression. *Eur. Rev. Med. Pharmacol. Sci.* **2018**, *22*, 5597–5604. [CrossRef]
144. Zhang, Y.; Han, B.; He, Y.; Li, D.; Ma, X.; Liu, Q.; Hao, J. MicroRNA-132 attenuates neurobehavioral and neuropathological changes associated with intracerebral hemorrhage in mice. *Neurochem. Int.* **2017**, *107*, 182–190. [CrossRef]
145. Zhao, M.; Gao, J.; Zhang, Y.; Jiang, X.; Tian, Y.; Zheng, X.; Wang, K.; Cui, J. Elevated miR-29a Contributes to Axonal Outgrowth and Neurological Recovery After Intracerebral Hemorrhage via Targeting PTEN/PI3K/Akt Pathway. *Cell. Mol. Neurobiol.* **2021**, *41*, 1759–1772. [CrossRef]
146. Zheng, Z.Q.; Yuan, G.Q.; Zhang, G.G.; Chen, Y.T.; Nie, Q.Q.; Wang, Z. Identification of CCL20 as a Key Biomarker of Inflammatory Responses in the Pathogenesis of Intracerebral Hemorrhage. *Inflammation* **2023**, *46*, 1290–1304. [CrossRef]
147. Zhu, Z.; Mo, S.; Wang, X.; Meng, M.; Qiao, L. Circ-AGTPBP1 promotes white matter injury through miR-140-3p/Pcdh17 axis role of Circ-AGTPBP1 in white matter injury. *J. Bioenerg. Biomembr.* **2024**, *56*, 1–14. [CrossRef]
148. Bai, S.; Zhang, G.; Chen, S.; Wu, X.; Li, J.; Wang, J.; Chen, D.; Liu, X.; Wang, J.; Li, Y.; et al. MicroRNA-451 Regulates Angiogenesis in Intracerebral Hemorrhage by Targeting Macrophage Migration Inhibitory Factor. *Mol. Neurobiol.* **2024**, *61*, 10481–10499. [CrossRef]
149. Bao, W.D.; Zhou, X.T.; Zhou, L.T.; Wang, F.; Yin, X.; Lu, Y.; Zhu, L.Q.; Liu, D. Targeting miR-124/Ferroportin signaling ameliorated neuronal cell death through inhibiting apoptosis and ferroptosis in aged intracerebral hemorrhage murine model. *Aging Cell* **2020**, *19*, e13235. [CrossRef]
150. Fang, Y.; Hong, X. miR-124-3p Inhibits Microglial Secondary Inflammation After Basal Ganglia Hemorrhage by Targeting TRAF6 and Repressing the Activation of NLRP3 Inflammasome. *Front. Neurol.* **2021**, *12*, 653321. [CrossRef]
151. Fu, X.; Niu, T.; Li, X. MicroRNA-126-3p Attenuates Intracerebral Hemorrhage-Induced Blood-Brain Barrier Disruption by Regulating VCAM-1 Expression. *Front. Neurosci.* **2019**, *13*, 866. [CrossRef] [PubMed]
152. Hu, Y.L.; Wang, H.; Huang, Q.; Wang, G.; Zhang, H.B. MicroRNA-23a-3p promotes the perihematomal edema formation after intracerebral hemorrhage via ZO-1. *Eur. Rev. Med. Pharmacol. Sci.* **2018**, *22*, 2809–2816. [CrossRef] [PubMed]
153. Jiang, F.; Liu, X.; Wang, X.; Hu, J.; Chang, S.; Cui, X. LncRNA FGD5-AS1 accelerates intracerebral hemorrhage injury in mice by adsorbing miR-6838-5p to target VEGFA. *Brain Res.* **2022**, *1776*, 147751. [CrossRef] [PubMed]
154. Li, T.; Zhang, L.; Wang, P.; Yu, J.; Zhong, J.; Tang, Q.; Zhu, T.; Chen, K.; Li, F.; Hong, P.; et al. Extracellular vesicles from neural stem cells safeguard neurons in intracerebral hemorrhage by suppressing reactive astrocyte neurotoxicity. *Cell Rep.* **2024**, *43*, 114854. [CrossRef]
155. Liang, T.; Liu, R.; Liu, J.; Hong, J.; Gong, F.; Yang, X. miRNA506 Activates Sphk1 Binding with Sirt1 to Inhibit Brain Injury After Intracerebral Hemorrhage via PI3K/AKT Signaling Pathway. *Mol. Neurobiol.* **2025**, *62*, 4093–4114. [CrossRef]
156. Lu, X.; Zhang, H.Y.; He, Z.Y. MicroRNA-181c provides neuroprotection in an intracerebral hemorrhage model. *Neural Regen. Res.* **2020**, *15*, 1274–1282. [CrossRef]
157. Pei, H.; Peng, Q.; Guo, S.; Gu, Y.; Sun, T.; Xu, D.; Jiang, Y.; Xie, J.; Zhang, L.; Zhu, Z. MiR-367 alleviates inflammatory injury of microglia by promoting M2 polarization via targeting CEBPA. *Vitr. Cell. Dev. Biol. Anim.* **2020**, *56*, 878–887. [CrossRef]

158. Wang, H.; Cao, X.; Wen, X.; Li, D.; Ouyang, Y.; Bao, B.; Zhong, Y.; Qin, Z.; Yin, M.; Chen, Z.; et al. Transforming growth factor-beta1 functions as a competitive endogenous RNA that ameliorates intracranial hemorrhage injury by sponging microRNA-93-5p. *Mol. Med. Rep.* **2021**, *24*, 499. [CrossRef]
159. Wang, Z.; Lu, G.; Sze, J.; Liu, Y.; Lin, S.; Yao, H.; Zhang, J.; Xie, D.; Liu, Q.; Kung, H.F.; et al. Plasma miR-124 Is a Promising Candidate Biomarker for Human Intracerebral Hemorrhage Stroke. *Mol. Neurobiol.* **2018**, *55*, 5879–5888. [CrossRef]
160. Wu, X.; Liu, H.; Hu, Q.; Wang, J.; Zhang, S.; Cui, W.; Shi, Y.; Bai, H.; Zhou, J.; Han, L.; et al. Astrocyte-Derived Extracellular Vesicular miR-143-3p Dampens Autophagic Degradation of Endothelial Adhesion Molecules and Promotes Neutrophil Transendothelial Migration after Acute Brain Injury. *Adv. Sci.* **2024**, *11*, e2305339. [CrossRef]
161. Xi, T.; Jin, F.; Zhu, Y.; Wang, J.; Tang, L.; Wang, Y.; Liebeskind, D.S.; Scalzo, F.; He, Z. miR-27a-3p protects against blood-brain barrier disruption and brain injury after intracerebral hemorrhage by targeting endothelial aquaporin-11. *J. Biol. Chem.* **2018**, *293*, 20041–20050. [CrossRef]
162. Xu, L.; Mo, C.; Lu, M.; Wang, P.; Liu, Y. MiR-20a-5p targets RBM24 and alleviates hypertensive intracerebral hemorrhage. *Cell. Mol. Biol.* **2023**, *69*, 134–141. [CrossRef] [PubMed]
163. Zhou, W.; Huang, G.; Ye, J.; Jiang, J.; Xu, Q. Protective Effect of miR-340-5p against Brain Injury after Intracerebral Hemorrhage by Targeting PDCD4. *Cerebrovasc. Dis.* **2020**, *49*, 593–600. [CrossRef] [PubMed]
164. Cheng, X.; Ander, B.P.; Jickling, G.C.; Zhan, X.; Hull, H.; Sharp, F.R.; Stamova, B. MicroRNA and their target mRNAs change expression in whole blood of patients after intracerebral hemorrhage. *J. Cereb. Blood Flow Metab.* **2020**, *40*, 775–786. [CrossRef]
165. Gareev, I.; Yang, G.; Sun, J.; Beylerli, O.; Chen, X.; Zhang, D.; Zhao, B.; Zhang, R.; Sun, Z.; Yang, Q.; et al. Circulating MicroRNAs as Potential Noninvasive Biomarkers of Spontaneous Intracerebral Hemorrhage. *World Neurosurg.* **2020**, *133*, e369–e375. [CrossRef]
166. Giordano, M.; Trotta, M.C.; Ciarambino, T.; D'Amico, M.; Schettini, F.; Sisto, A.D.; D'Auria, V.; Voza, A.; Malatino, L.S.; Biolo, G.; et al. Circulating miRNA-195-5p and -451a in Patients with Acute Hemorrhagic Stroke in Emergency Department. *Life* **2022**, *12*, 763. [CrossRef]
167. Guo, D.; Liu, J.; Wang, W.; Hao, F.; Sun, X.; Wu, X.; Bu, P.; Zhang, Y.; Liu, Y.; Liu, F.; et al. Alteration in abundance and compartmentalization of inflammation-related miRNAs in plasma after intracerebral hemorrhage. *Stroke* **2013**, *44*, 1739–1742. [CrossRef]
168. Kalani, M.Y.S.; Alsop, E.; Meechoovet, B.; Beecroft, T.; Agrawal, K.; Whitsett, T.G.; Huentelman, M.J.; Spetzler, R.F.; Nakaji, P.; Kim, S.; et al. Extracellular microRNAs in blood differentiate between ischaemic and haemorrhagic stroke subtypes. *J. Extracell. Vesicles* **2020**, *9*, 1713540. [CrossRef]
169. Wang, H.; Wang, L.; Shi, Q. Changes in Serum LncRNA MEG3/miR-181b and UCH-L1 Levels in Patients with Moderate and Severe Intracerebral Hemorrhage. *Turk. Neurosurg.* **2024**, *34*, 20–27. [CrossRef]
170. Wang, J.; Zhu, Y.; Jin, F.; Tang, L.; He, Z.; He, Z. Differential expression of circulating microRNAs in blood and haematoma samples from patients with intracerebral haemorrhage. *J. Int. Med. Res.* **2016**, *44*, 419–432. [CrossRef]
171. Zheng, H.W.; Wang, Y.L.; Lin, J.X.; Li, N.; Zhao, X.Q.; Liu, G.F.; Liu, L.P.; Jiao, Y.; Gu, W.K.; Wang, D.Z.; et al. Circulating MicroRNAs as potential risk biomarkers for hematoma enlargement after intracerebral hemorrhage. *CNS Neurosci. Ther.* **2012**, *18*, 1003–1011. [CrossRef] [PubMed]
172. Zhu, Y.; Wang, J.L.; He, Z.Y.; Jin, F.; Tang, L. Association of Altered Serum MicroRNAs with Perihematomal Edema after Acute Intracerebral Hemorrhage. *PLoS ONE* **2015**, *10*, e0133783. [CrossRef] [PubMed]
173. Kurata, A.; Miyasaka, Y.; Kitahara, T.; Kan, S.; Takagi, H. Subcortical cerebral hemorrhage with reference to vascular malformations and hypertension as causes of hemorrhage. *Neurosurgery* **1993**, *32*, 505–511. [CrossRef] [PubMed]
174. Margolis, G.; Odom, G.L.; Woodhall, B.; Bloor, B.M. The role of small angiomatous malformations in the production of intracerebral hematomas. *J. Neurosurg.* **1951**, *8*, 564–575. [CrossRef]
175. Jellinger, K. Vascular malformations of the central nervous system: A morphological overview. *Neurosurg. Rev.* **1986**, *9*, 177–216. [CrossRef]
176. Fischer, A.; Zalvide, J.; Faurobert, E.; Albiges-Rizo, C.; Tournier-Lasserve, E. Cerebral cavernous malformations: From CCM genes to endothelial cell homeostasis. *Trends Mol. Med.* **2013**, *19*, 302–308. [CrossRef]
177. Glading, A.; Han, J.; Stockton, R.A.; Ginsberg, M.H. KRIT-1/CCM1 is a Rap1 effector that regulates endothelial cell–cell junctions. *J. Cell Biol.* **2007**, *179*, 247–254. [CrossRef]
178. Lai, C.C.; Nelsen, B.; Frias-Anaya, E.; Gallego-Gutierrez, H.; Orecchioni, M.; Herrera, V.; Ortiz, E.; Sun, H.; Mesarwi, O.A.; Ley, K.; et al. Neuroinflammation Plays a Critical Role in Cerebral Cavernous Malformation Disease. *Circ. Res.* **2022**, *131*, 909–925. [CrossRef]
179. Maddaluno, L.; Rudini, N.; Cuttano, R.; Bravi, L.; Giampietro, C.; Corada, M.; Ferrarini, L.; Orsenigo, F.; Papa, E.; Boulday, G.; et al. EndMT contributes to the onset and progression of cerebral cavernous malformations. *Nature* **2013**, *498*, 492–496. [CrossRef]
180. Rath, M.; Schwefel, K.; Malinverno, M.; Skowronek, D.; Leopoldi, A.; Pilz, R.A.; Biedenweg, D.; Bekeschus, S.; Penninger, J.M.; Dejana, E.; et al. Contact-dependent signaling triggers tumor-like proliferation of CCM3 knockout endothelial cells in co-culture with wild-type cells. *Cell. Mol. Life Sci.* **2022**, *79*, 340. [CrossRef]

181. Valentino, M.; Dejana, E.; Malinverno, M. The multifaceted PDCD10/CCM3 gene. *Genes Dis.* **2021**, *8*, 798–813. [CrossRef] [PubMed]
182. Ou, Y.; An, R.; Wang, H.; Chen, L.; Shen, Y.; Cai, W.; Zhu, W. Oxidative stress-related circulating miRNA-27a is a potential biomarker for diagnosis and prognosis in patients with sepsis. *BMC Immunol.* **2022**, *23*, 14. [CrossRef] [PubMed]
183. Perrelli, A.; Ferraris, C.; Berni, E.; Glading, A.J.; Retta, S.F. KRIT1: A Traffic Warden at the Busy Crossroads Between Redox Signaling and the Pathogenesis of Cerebral Cavernous Malformation Disease. *Antioxid. Redox Signal* **2023**, *38*, 496–528. [CrossRef]
184. Retta, S.F.; Glading, A.J. Oxidative stress and inflammation in cerebral cavernous malformation disease pathogenesis: Two sides of the same coin. *Int. J. Biochem. Cell Biol.* **2016**, *81*, 254–270. [CrossRef]
185. Ruiz, G.P.; Camara, H.; Fazolini, N.P.B.; Mori, M.A. Extracellular miRNAs in redox signaling: Health, disease and potential therapies. *Free Radic. Biol. Med.* **2021**, *173*, 170–187. [CrossRef]
186. Wang, L.; Bayanbold, K.; Zhao, L.; Wang, Y.; Adamcakova-Dodd, A.; Thorne, P.S.; Yang, H.; Jiang, B.H.; Liu, L.Z. Redox sensitive miR-27a/b/Nrf2 signaling in Cr(VI)-induced carcinogenesis. *Sci. Total Environ.* **2022**, *809*, 151118. [CrossRef]
187. Zhao, Y.; Dong, D.; Reece, E.A.; Wang, A.R.; Yang, P. Oxidative stress-induced miR-27a targets the redox gene nuclear factor erythroid 2-related factor 2 in diabetic embryopathy. *Am. J. Obstet. Gynecol.* **2018**, *218*, 136e1–136e10. [CrossRef]
188. Perrelli, A.; Retta, S.F. Polymorphisms in genes related to oxidative stress and inflammation: Emerging links with the pathogenesis and severity of Cerebral Cavernous Malformation disease. *Free Radic. Biol. Med.* **2021**, *172*, 403–417. [CrossRef]
189. Suzuki, J.; Takaku, A. Cerebrovascular "moyamoya" disease. Disease showing abnormal net-like vessels in base of brain. *Arch. Neurol.* **1969**, *20*, 288–299. [CrossRef]
190. Elijovich, L.; Patel, P.V.; Hemphill, J.C., 3rd. Intracerebral hemorrhage. *Semin. Neurol.* **2008**, *28*, 657–667. [CrossRef]
191. Haseeb, A.; Shafique, M.A.; Mustafa, M.S.; Singh, A.; Iftikhar, S.; Rangwala, B.S.; Waggan, A.I.; Fadlalla Ahmad, T.K.; Raja, S.; Raja, A. Neuroendoscopic versus Craniotomy Approach in Supratentorial Hypertensive Intracerebral Hemorrhage: An Updated Meta-Analysis. *World Neurosurg.* **2024**, *190*, e721–e747. [CrossRef] [PubMed]
192. Rajashekar, D.; Liang, J.W. Intracerebral Hemorrhage. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2025.
193. Zolboot, N.; Du, J.X.; Zampa, F.; Lippi, G. MicroRNAs Instruct and Maintain Cell Type Diversity in the Nervous System. *Front. Mol. Neurosci.* **2021**, *14*, 646072. [CrossRef] [PubMed]
194. Flower, O.; Smith, M. The acute management of intracerebral hemorrhage. *Curr. Opin. Crit. Care* **2011**, *17*, 106–114. [CrossRef] [PubMed]
195. Adeoye, O.; Walsh, K.; Woo, J.G.; Haverbusch, M.; Moomaw, C.J.; Broderick, J.P.; Kissela, B.M.; Kleindorfer, D.; Flaherty, M.L.; Woo, D. Peripheral monocyte count is associated with case fatality after intracerebral hemorrhage. *J. Stroke Cerebrovasc. Dis.* **2014**, *23*, e107–e111. [CrossRef]
196. Lee, J.S.; Kim, G.; Lee, J.H.; Ryu, J.Y.; Oh, E.J.; Kim, H.M.; Kwak, S.; Hur, K.; Chung, H.Y. MicroRNA-135b-5p Is a Pathologic Biomarker in the Endothelial Cells of Arteriovenous Malformations. *Int. J. Mol. Sci.* **2024**, *25*, 4888. [CrossRef]
197. Bianchi, M.E.; Mezzapelle, R. The Chemokine Receptor CXCR4 in Cell Proliferation and Tissue Regeneration. *Front. Immunol.* **2020**, *11*, 2109. [CrossRef]
198. Toyama, K.; Igase, M.; Spin, J.M.; Abe, Y.; Javkhlant, A.; Okada, Y.; Wagenhauser, M.U.; Schelzig, H.; Tsao, P.S.; Mogi, M. Exosome miR-501-3p Elevation Contributes to Progression of Vascular Stiffness. *Circ. Rep.* **2021**, *3*, 170–177. [CrossRef]
199. Chen, Y.; Tang, M.; Li, H.; Liu, H.; Wang, J.; Huang, J. TGFbeta1 as a Predictive Biomarker for Collateral Formation Within Ischemic Moyamoya Disease. *Front. Neurol.* **2022**, *13*, 899470. [CrossRef]
200. Girard, R.; Zeineddine, H.A.; Koskimaki, J.; Fam, M.D.; Cao, Y.; Shi, C.; Moore, T.; Lightle, R.; Stadnik, A.; Chaudagar, K.; et al. Plasma Biomarkers of Inflammation and Angiogenesis Predict Cerebral Cavernous Malformation Symptomatic Hemorrhage or Lesional Growth. *Circ. Res.* **2018**, *122*, 1716–1721. [CrossRef]
201. Li, Y.; Srinath, A.; Alcazar-Felix, R.J.; Hage, S.; Bindal, A.; Lightle, R.; Shenkar, R.; Shi, C.; Girard, R.; Awad, I.A. Inflammatory Mechanisms in a Neurovascular Disease: Cerebral Cavernous Malformation. *Brain Sci.* **2023**, *13*, 1336. [CrossRef]
202. Kuosmanen, S.M.; Kansanen, E.; Kaikkonen, M.U.; Sihvola, V.; Pulkkinen, K.; Jyrkkanen, H.K.; Tuoresmaki, P.; Hartikainen, J.; Hippelainen, M.; Kokki, H.; et al. NRF2 regulates endothelial glycolysis and proliferation with miR-93 and mediates the effects of oxidized phospholipids on endothelial activation. *Nucleic Acids Res.* **2018**, *46*, 1124–1138. [CrossRef] [PubMed]
203. Antognelli, C.; Trapani, E.; Delle Monache, S.; Perrelli, A.; Daga, M.; Pizzimenti, S.; Barrera, G.; Cassoni, P.; Angelucci, A.; Trabalzini, L.; et al. KRIT1 loss-of-function induces a chronic Nrf2-mediated adaptive homeostasis that sensitizes cells to oxidative stress: Implication for Cerebral Cavernous Malformation disease. *Free Radic. Biol. Med.* **2018**, *115*, 202–218. [CrossRef] [PubMed]
204. Padarti, A.; Zhang, J. Recent advances in cerebral cavernous malformation research. *Vessel Plus* **2018**, *2*, 21. [CrossRef]
205. Hong, C.C.; Tang, A.T.; Detter, M.R.; Choi, J.P.; Wang, R.; Yang, X.; Guerrero, A.A.; Wittig, C.F.; Hobson, N.; Girard, R.; et al. Cerebral cavernous malformations are driven by ADAMTS5 proteolysis of versican. *J. Exp. Med.* **2020**, *217*, e20200140. [CrossRef]

206. Du, S.; Shen, S.; Ding, S.; Wang, L. Suppression of microRNA-323-3p restrains vascular endothelial cell apoptosis via promoting sirtuin-1 expression in coronary heart disease. *Life Sci.* **2021**, *270*, 119065. [CrossRef]
207. Nan, S.; Wang, Y.; Xu, C.; Wang, H. Interfering microRNA-410 attenuates atherosclerosis via the HDAC1/KLF5/IKBalpha/NF-kappaB axis. *Mol. Ther. Nucleic Acids* **2021**, *24*, 646–657. [CrossRef]