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Review Article

Understanding the Role of microRNAs in the Pathogenesis of Intracranial Aneurysms

Wright MC, Medel R, Dumont AS and Amenta PS*
Department of Neurosurgery, Tulane University Medical Center, New Orleans, USA

***Corresponding author:** Amenta PS, Department of Neurosurgery, Tulane University Medical Center, New Orleans, USA

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Abstract

Treatment options for the management of intracranial aneurysms (IA) remain associated with significant morbidity and mortality. As a result, there is a need to identify biochemical markers predictive of the presence of IAs and the risk of rupture. Genetic factors play a key role in IA pathogenesis, as evidenced by the increased susceptibility to IA formation and rupture in the familial form of the disease. microRNAs (miRNAs), which modulate gene expression, have been demonstrated to be differentially expressed in multiple disease states. To date, little data exists pertaining to miRNA expression and IAs. We review the literature examining miRNA expression and IA formation, progression, and rupture. The relationship between miRNA expression profiles and the specific molecular and cellular processes driving IA genesis are examined. The potential clinical relevance of miRNA is also discussed, as it relates to improving the means by which the risk of rupture is estimated.

Keywords: Intracranial aneurysms; microRNA; Genetic markers

Abbreviations

IA: Intracranial Aneurysms; miRNA: microRNA; aSAH: aneurysmal Subarachnoid Hemorrhage; mRNA; messenger RNA; miRISC: RNA-Induced Silencing Complex; UTR: Untranslated Region; ECM: Extracellular Matrix; TGF-β: Tissue Growth Factor-β; VSMC: Vascular Smooth Muscle Cell; NF-κB: Nuclear Factor-kappa B; IL-6: Interleukin 6; IL-8: Interleukin 8; ICAM-1: Intercellular Adhesion Molecule-1; VCAM-1: Vascular Cell Adhesion Molecule; MMPs: Matrix Metalloproteinases; TIMPs: Tissue Inhibitors of Matrix Metalloproteinases; VEGF: Vascular Endothelial Growth Factor; NF-κB: Nuclear Factor kappa-B; TNF-α: Tumor Necrosis Factor-α; IL-1β: Interleukin-1β; MCP-1: Monocyte Chemo Attractant Protein-1; qPCR: Quantitative PCR; AAA: Abdominal Aortic Aneurysms.

Introduction

Intracranial aneurysms (IAs) affect 3-6% of the general population and have an annual rupture rate of 1-3%, resulting in approximately 27,000 aneurysmal subarachnoid hemorrhages (aSAH) in the United States each year [1-3]. The morbidity and mortality of aSAH remains high, with as many as 50% of cases resulting in death, and up to 50% of survivors suffering significant permanent disability [4]. Current microsurgical and endovascular treatment of IAs remains associated with significant risk, which may exceed the annual risk of rupture [5]. Thus, there is a need for both an improved understanding of factors contributing to rupture and the development of noninvasive means by which to identify those aneurysms with a higher risk of rupture.

Currently, establishing the risk of rupture for an individual aneurysm is imprecise and depends on morphologic features of the aneurysm and an assessment of the clinical history of the patient. Aneurysm location, irregularities of the aneurysm dome, and size remain the most relied upon features, with increasing size and posterior circulation location being associated with a higher risk. The clinical picture of the individual patient also contributes to decision making, as a history of hypertension, smoking, alcohol abuse, and positive family history increase the risk of rupture [1].

In an attempt to overcome the limitations of the current methodology, there has been a concerted effort to further delineate the mechanisms of aneurysm formation, growth, and rupture. These investigations have largely focused on the molecular and cellular pathways involved in vascular disease, including, the chronic and pathologic inflammatory response, hemodynamic stress, and the identification of predictive biomarkers. Furthermore, the recognition of genetic markers associated with IAs has played an increasingly important role in the understanding of their pathogenesis. microRNAs (miRNAs) represent one such class of molecular regulating molecules involved in the gene expression underlying aneurysm formation (Table 1).

We review the current data relating to miRNA as it relates to IA progression and rupture. The association between miRNA expression and the specific molecular and cellular processes driving IA formation and rupture are discussed. We conclude by examining the potential utility of miRNAs as clinically relevant biological markers in the management of IAs.

MicroRNA Suppression of mRNA Translation

MicroRNA (miRNA) are small (18-25 nucleotides), highly conserved, non-protein-coding RNAs that play a critical role in the post-transcriptional regulation of gene expression [6-10]. Currently, it is estimated that between 30 – 75 % of human gene expression is regulated by miRNA [7,8]. There are approximately 1,000 miRNAs involved in the regulation of human gene expression, of which 800 have been identified and sequenced [11]. miRNA is expressed in both tissue- and phase-specific patterns that reflect the specific

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Table 1: Summary of miRNA and their associated regulatory function. Upregulation and downregulation in IAs and the role in IA pathogenesis is described.

microRNA	Normal Role	Upregulation/ Downregulation in IA	Role in IA Pathogenesis	Source
miR-1	VSMC differentiation, expression of contractile proteins	Downregulated		[8, 78]
miR-133	Prevents VSMC proliferation, inhibits change from contractile to synthetic VSMC phenotype	Downregulated		[79]
mirR-7	Negative regulator of collagen expression in dermal fibroblasts	Downregulated		[58, 80]
miR-29	Post-transcription suppression of elastin and ECM protein genes; miR-29b suppresses MM2 expression; miR-29a related to immune function	Downregulated in human IA specimens; upregulated in murine cardiac models	Increased levels found in plasma of smokers.	[8-10, 35, 81-87, 100]
miR-34a	Tumor suppressor	Upregulated	Associated with decreased SM22a protein, which normally maintains VSMCs in contractile phenotype	[89-94]
miR-155	Modulates endothelial cell cytoskeletal organization in response to shear stress	Upregulated	Induces expression of pro-inflammatory genes (with macrophage-derived expression of miR-342-5p) during atherosclerosis progression	[53, 110,111]
miR-342-5p	Expressed by activated macrophages as part of inflammatory response	Upregulated	Contributes to atherosclerosis by inducing expression of pro-inflammatory genes (with miR-155) such as NOS2	[109-111]
miR-181b	Systemic administration to mice results in diminished vascular inflammation	Downregulated	Rapidly downregulated in human endothelial cells exposed to TNF-α	[114, 115]
miR-16	Expressed by vascular endothelial cells; associated with angiogenesis	Upregulated	Unclear—*potentially useful marker for assessing IA risk*	[58, 60]
miR-25	Expressed in airway SMCs, possibly in VSMCs	Upregulated	Unclear—*potentially useful marker for assessing IA risk*	[58]
miR-24		Upregulated	Suppresses TGF-β signaling, resulting in VSMC phenotypic switch	[35, 88]

physiological processes they regulate [7,8]. miRNA suppresses messenger RNA (mRNA) translation into protein through low target complementarity and regulates mRNA degradation through high miRNA-mRNA complementarity [12].

A detailed analysis of the pathways involved in miRNA synthesis and mRNA binding are beyond the scope of this review, however, the following provides a short synopsis of the processes. miRNAs are transcribed by RNA polymerase II within the nucleus and miRNA maturation then depends on two RNase III endonucleases, Drosha and Dicer [13-16]. In the nucleus, Drosha processes primary-miRNA into pre-miRNA, while Dicer then cleaves pre-miRNA into 22-nucleotide double-stranded mature miRNA within the cytoplasm [17]. The miRNA guide strand is incorporated into an RNA-induced silencing complex (miRISC), which will direct miRNA to the target mRNA for degradation or translation inhibition [18]. miRNAs may also be relocated to the nucleus or exchanged with other cells via exosomes. miRNA acts on mRNA by binding to the 3'-untranslated region (UTR) of the target mRNA to be suppressed [9,10]. Multiple miRNAs can bind to the same 3'-UTR of a target mRNA in a cooperative fashion, resulting in greater stability or in more effective inhibition of translation. Each miRNA can regulate many different target mRNAs [19].

Changes in miRNA expression in patients with IAs is well-documented, however, the specific cellular functions and pathways influenced are largely unknown [20]. Multiple pathologic processes have been implicated in the formation of IAs, including, activation of the immune/inflammatory response, organization of the extracellular matrix (ECM), endothelial cell dysfunction, tissue growth factor-β (TGF-β) signaling, vascular smooth muscle cell (VSCM) phenotypic changes, and apoptosis [21-25]. Analysis of the miRNAs linked to IAs demonstrates an association between these miRNAs and these cellular and molecular mechanisms [20].

Differential Expression of miRNA in Intracranial Aneurysms

A significant subset of IAs is familial, highlighting the underlying contributions of genetics to their formation, progression, and rupture. Compared to the general population, first-degree relatives of IA patients possess a three- to fivefold higher risk of IA [26,27]. Multiple authors have identified genetic polymorphisms associated with an increased risk of IA rupture [28-31]. Furthermore, there is sufficient evidence to link changes in gene expression to the molecular mechanisms involved in IA pathogenesis, including, endothelial and VSMC dysfunction, ECM remodeling, and inflammation. Chen et al. reported differential expression of 2129 genes in the setting of ruptured IAs [32]. 1062 genes were upregulated and 1057 genes were downregulated. Li et al. demonstrated significant differences in the expression of 1,160 genes in the tissue of unruptured aneurysms compared to normal blood vessels [33]. Among these differentially expressed genes were inflammation-related genes and genes related to the ECM [33].

Examination of IA genetics has identified links between IAs and miRNA expression. Li et al. demonstrated that the CC genotype of miRNA-34b/c rs4938723 was significantly associated with a decreased risk of IA compared to the TT genotype [34]. Lee et al. reported differential expression of miRNAs in aneurysm tissue compared to control arteries in a rat model of IA [35]. IA tissue demonstrated greater than 200% over expression of 14 miRNAs and downregulated expression of greater than 50% for 6 miRNAs compared to controls.

Comparing IAs and control vessels, Liu et al. demonstrated distinct patterns of global expression in 157 miRNAs [20]. IA tissue was associated with upregulation of 72 and downregulation of 85 miRNAs compared to control vessel tissue. Of those miRNAs differentially expressed in the IAs, there were multiple miRNAs associated with endothelial and VSMC function. miRNAs associated with endothelium, including, members of the let-7 family of

miRNAs, miR-17, miR-23b, miR-126, hsa-miR-24-1 and miR-222, were all differentially expressed in IA tissue [36,37]. miR-1, miR-10a, miR-125b, and miR-26a, which are associated with the proliferation, apoptosis, and phenotypic switching of VSMCs, were also found to have altered expression in IAs [20,38,39]. Gene functional annotation analysis was performed to identify a relationship between altered miRNA expression and molecular and cellular processes linked with aneurysm formation and rupture. Identified miRNAs were associated with blood vessel development, smooth muscle cell proliferation, and programmed cell death, response to oxidative stress, ECM organization, TGF-β signaling pathway, innate immune response, and leukocyte activation [20].

Jiang et al. compared the miRNA profiles of normal middle meningeal artery segments against those of wall samples from ruptured IA domes [8]. 30 miRNAs were identified as being differentially expressed between the normal controls and the IA walls. Interestingly, 29 of those miRNAs were upregulated in the microarray analysis, while only one was downregulated. qPCR confirmed significant differences in expression for 18 miRNAs and failed to demonstrate statistically significant differences in the additional 12. Multiple miRNAs within the hsa-mir-1/has-mir-133a, hsa-mir-143/hsa-mir-145, hsa-mir-23b/hsa-mir-24-1, and hsa-mir-29b-2/hsa-mir-29c clusters were downregulated two-fold in the IA specimens compared to normal vessel controls [8]. Additional analysis of differentially expressed miRNAs shed light on the molecular and cellular processes associated with these miRNAs. 11 miRNAs were associated with twelve cellular processes linked to aneurysm formation and rupture, including, inflammatory cell migration, endothelial dysfunction, and changes in VSMCs [8].

miRNA Expression Profiles and the Mechanisms of Intracranial Aneurysm Genesis

Endothelial dysfunction

IAs most commonly arise at vessel branch points, highlighting the role of perturbations of blood flow and shear stress in the pathologic vascular remodeling that is associated with aneurysm formation [40]. Shear stress has been shown to initiate a prolonged inflammatory response, which is particularly intense at vessel bifurcations [41]. The endothelium, the interface between blood flow and the vessel wall, plays a central role in the response to mechanical stress on the vasculature [42-44]. Endothelial cells process the mechanical stimuli of shear, stretch, and flow through mechanotransduction. Multiple mechanical sensors at the endothelial cell apical and basal surfaces allow these cells to alter their physical structure and initiate intracellular cascades that result in a sustained inflammatory response [45-47]. Nuclear factor-kappa B (NF-κB) plays a significant role in endothelial dysfunction and the resultant pro-inflammatory state implicated in multiple vascular pathologies, including, atherosclerosis and IAs [44,48]. The NF-κB pathway initiates a series of events leading to further activation of cellular adhesion molecules (CAMs) and the expression of inflammatory cytokines, including, interleukin 6 (IL-6), IL-8, intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule (VCAM-1), and E-selectin [49-51]. These signaling molecules recruit monocytes, which transmigrate into the sub endothelial space, thereby increasing the permeability of the endothelium [40,52]. There is mounting evidence that miRNAs play critical roles in the processes underlying normal endothelial cell function and dysfunction. miRNA-155 has been demonstrated to modulate endothelial cell cytoskeletal organization in response to shear stress [53]. miRNAs have also been shown to target connexins and vascular endothelial-cadherin, key proteins involved in the maintenance of endothelial permeability [54,55].

Endothelial dysfunction has also been implicated in IA progression through the initiation of pathologic angiogenesis. Proliferation of microvasculature within IA walls is a proposed mechanism by which inflammatory cells access the tunica media and degrades the VSMC layer and ECM [4,56,57]. Li et al. demonstrated altered expression of multiple members of the let-7 family of miRNAs and miRNA-18a in patients with IAs [58]. Endothelial cells strongly express these miRNAs and play a role in endothelial-driven angiogenesis [59]. miRNA-16 is also expressed by endothelial cells and is associated with angiogenesis [58,60].

Vascular smooth muscle cells and the extracellular matrix

VSMCs represent the primary cellular component of the tunica media and maintain vessel wall integrity. Under physiologic conditions, these cells display a contractile phenotype, but maintain the ability to undergo a phenotypic switch to a secretory phenotype when exposed to inflammatory stimuli. The VSMC secretory phenotype is characterized by a loss of the markers of contractility and the expression of pro-inflammatory cytokines and matrix metalloproteinases (MMPs) [61-66]. Endothelial dysfunction, hemodynamic stress, and direct injury have all been identified as stimuli capable of inducing this phenotypic change [67,68]. Secretory VSMCs also become migratory, resulting in a loss of mural cells and weakening of the vessel wall [25]. IA formation is defined by progressive thinning of the tunica media, cellular loss, and erratic VSMC migration and apoptosis [67,69,70]. Ruptured aneurysms more commonly demonstrate hypo cellular and hyalinized walls when compared to unruptured aneurysms [71].

Jiang et al. identified 18 miRNAs within 4 clusters that were significantly downregulated in the IA domes of 14 patients presenting with ruptured aneurysms [8]. These clusters were all found to be associated with varying cellular processes regulating VSMC phenotype and maintenance of the ECM [72-77]. miRNA-1, which is induced during VSMC differentiation and increases the expression of VSMC contractile proteins, was among the downregulated miRNAs [78]. miRNA-133, which prevents VSMC proliferation and inhibits the phenotypic change from contractile to synthetic VSMC phenotype, was also found at significantly diminished levels [79].

Li et al. found a significant upregulation of miRNA-7 in IA patients. miRNA-7 is a negative regulator of collagen expression in dermal fibroblasts [58,80]. The miR-29 family has been implicated in the genesis of IAs due to its role in the post-transcription suppression of the expression of ECM proteins [9,10,81-85]. These miRNAs were identified to suppress elastin and ECM protein genes in mouse models of aortic development [86]. Clinical studies have shown smokers to exhibit higher levels of miRNA-29b in their plasma than nonsmokers [87]. In a rat model of IA, Lee et al. observed over expression of miRNA-24 [35]. miRNA-24 suppresses TGF-β signaling, resulting in the VSCM phenotypic switch [88]. miRNA-

34a is a tumor suppressor miRNA that influences both endothelial cells and VSMCs through its regulation of cell cycle arrest, apoptosis, and senescence in a p53-dependent or independent manner [89-91]. Multiple studies have also implicated miRNA-34a in age-related endothelial cell senescence and dysfunction [92-94]. Badi et al. demonstrated miRNA-34a upregulation in the arteries of aged mice [91]. Increasing levels of miRNA-34a were associated with decreased levels of SM22a, a protein that targets VSMCs and maintains these cells in the contractile phenotype.

Under physiologic conditions, maintenance of the ECM is largely dependent on a balance between the activity of matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMPs) [64]. Perturbations of this balance result in increased breakdown of ECM proteins, including, collagen and elastin, resulting in weakening of the vessel wall and increased susceptibility to hemodynamic stress. As a result, ECM degradation has been identified as a key component of IA formation, progression, and rupture.

Western blot and immunohistochemical analysis of IA walls has identified MMPs within the tissue [23,95]. Elevated MMP-9 levels have been documented in the serum of aneurysmal subarachnoid hemorrhage patients [96,97].

Cigarette smoke, a stimulus of IA growth and rupture, induces the release of MMP-2 and MMP-9 by macrophages [98]. Aoki et al. demonstrated increased levels of MMP-2 and MMP-9 in rat IA walls [63]. Smokers have been demonstrated to have elevated levels of MMPs and diminished levels of TIMPs and elastin within their carotid arteries [99]. TIMP-1 and TIMP-2 have been identified as potentially having a protective role for IA progression due to their ability to limit MMP-related degradation of the ECM [64].

The importance of MMPs and TIMPs in IA growth and rupture can be seen in the analysis of miRNA profiles. miRNA-29b demonstrates anti-angiogenesis properties and works through the suppression of MMP-2 expression [100]. Murine cardiac models identified over expression of miRNA-1, miRNA-26a, miRNA-30d, miRNA-24, miRNA-29a, miRNA223 and miRNA-181c in MMP-9 knockout mice, which resulted in a reduction of cardiac myocyte dysfunction and improved cardiac function [101]. Lee et al. demonstrated over expression of many of these same miRNAs in a rat model of advanced IA formation [35]. The authors hypothesized that upregulation of these miRNAs may represent a protective response aimed at correcting the deleterious imbalance between MMPs and TIMPs in IA walls, thereby preventing further aneurysm progression to rupture [35].

Vascular inflammation and miRNA expression

An abundance of evidence links vascular pathology to chronic inflammation, while the mechanisms of pathologic inflammation have been investigated as causative agents in IA genesis. A pro-inflammatory state has been shown to influence the processes associated with IAs, including, endothelial dysfunction, altered VSMC phenotypes, ECM degeneration, and transmuralinflammatory cell migration. Important inflammatory cytokines have also been linked to IAs, including, nuclear factor kappa-B (NF-κB), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and monocyte chemo attractant protein-1 (MCP-1) [28,67,102-108]. miRNA expression has been shown to play important roles in immunomodulation and the inflammatory response, thereby contributing to multiple disease states [109]. As a result, miRNA-mediated inflammation in vascular disease, particularly in atherosclerosis and abdominal aortic aneurysms (AAAs), has been well-characterized [110-112]. Advances in these areas may be applicable to the understanding of miRNA-driven IA formation and progression.

Upregulation of miRNA-92a and miRNA-712, which participate in the inflammatory response and augment endothelial cell proliferation, have been shown to contribute to atherosclerosis [110]. Macrophage-derived expression of miRNA-342-5p works through miRNA-155 to induce the expression of pro-inflammatory genes during the progression of atherosclerosis [110,111]. Inhibition of miRNA-342-5p in a murine model resulted in a reduction of pro-inflammatory cytokines, such as, nitric oxide synthase 2 (NOS2) and limited the progression of atherosclerosis [109]. Zhang et al. found that inflammation may induce endothelial cells to release pro-angiogenesis-related miRNAs in the setting of atherosclerosis [113]. Although the exact function of miRNA-181b has not been clearly defined, systemic administration to mice results in diminished vascular inflammation [114,115]. Importantly, human endothelial cells exposed to TNF-α demonstrated rapid downregulation of miRNA-181b. Li et al. reported that inflammation in the setting of diabetes and hyperlipidemia alters VSMC function through the selective down-regulation of miR-10a, miR-139b, miR-206, and miR-222 expression, leading to the vascular pathology associated with these disease states [116]. Maegdefessel et al. identified miRNA-24 as a mediator of vascular inflammation in murine models of AAA due to its regulation of macrophage and VSMC cytokine synthesis, stimulation of endothelial adhesion molecule expression, and VSMC migration [117].

miRNAs as Clinically Relevant Biological Markers of IA

At present, no definitive means by which to predict aneurysmal rupture exist. Decision-making is based on acquired clinical acumen, an evaluation of the IA morphology, and the clinical presentation of the patient. As a result, there is a need to identify biochemical markers predictive of the presence of IAs and impending rupture [118]. To date, these efforts have been met with limited success. Phillips et al. found a correlation between elevated serum lipoprotein (a) levels and the presence of IAs [118]. Sandalcioglu et al. found no association between vascular endothelial growth factor (VEGF) and the presence of unruptured IAs [119].

For a molecule to be of clinical utility, it should be reliably detectable, reproducibly measured, and be highly sensitive and specific for the pathologic entity of interest [7]. miRNAs represent a class of potentially clinically relevant biomarkers, in part, due to their presence within the circulation in a relatively stable state [7]. In the plasma and serum, miRNAs are found within microvesicles or in association with RNA-binding proteins or lipoprotein complexes, which protect against enzymatic degradation [120]. There are multiple hypotheses regarding the origins of these circulating miRNAs, including, the cellular secretion of microvesicles and byproducts of dead cells [121,122].

From a practical standpoint, miRNA can be reliably detected in a stable form within the plasma and withstands multiple freezing and thawing cycles [123,124]. There is significant evidence that shows miRNA expression within human plasma changes in the setting of various pathologic conditions, including, myocardial infarction, diabetes mellitus, and hypertension [120,125]. Li et al. demonstrated upregulation of inflammatory-related miRNAs in the plasma of intracerebral hemorrhage patients [125]. Furthermore, miRNA expression is cell-, tissue-, and phase-specific, allowing for localization of the miRNA source and the mapping of the temporal evolution of the pathologic condition [126-128].

Currently, there is limited data identifying miRNAs as clinically relevant biological markers for the identification of IAs and impending rupture. Using microarray analysis, Li et al. detected 223 miRNAs in the plasma of ruptured and unruptured IA patients and in healthy controls [58]. Of these miRNAs, significantly different expression of miRNAs was observed between the serum of IA patients and controls. Importantly, patients with unruptured IAs demonstrated significant changes in 119 miRNAs, while significant alterations in expression were identified in 23 miRNAs in ruptured patients. Further analysis found 20 of these miRNAs to be changed in both ruptured and unruptured patients [58]. Quantitative PCR (qPCR) demonstrated miRNA-16 and miRNA-25 levels to be significantly higher in IA patients. Logistic regression analysis found miRNA-16 and miRNA-25 to be independent factors for IA occurrence. A trend of increased miRNA-let-7g was also observed in IA patients. miRNA-188-5p was found in the plasma in a majority of IA patients, but not detectable in 13 of 15 healthy controls.

Aneurysm morphology, particularly the presence or absence of daughter blebs on the primary aneurysm dome, is used as an indicator of the risk of rupture [129,130]. The presence of these secondary blebs on the primary dome is indicative of progressive growth of the aneurysm, advanced weakening of the aneurysm wall, and a risk factor for impending rupture. Jin et al. studied miRNA expression in the plasma of normal controls, patients with unruptured aneurysms without blebs, patients with unruptured aneurysms with blebs, and aSAH patients [7]. The authors found upregulation of 68 miRNAs and no downregulation of the studied miRNAs in patients harboring an IA with a daughter bleb [7]. Patients with aneurysms lacking a daughter bleb possessed 4 upregulated and 9 downregulated miRNAs. aSAH patients demonstrated upregulation of has-miRNA-3679-5p and hsa-miR-199a-5p and downregulation of 13 miRNAs. miRNA-21, miRNA-22, and miRNA-3665 were upregulated in patients with ruptured and unruptured IAs regardless of whether or not a daughter bleb was present.

There are two particularly important points to be made from this data. First, miRNA expression was significantly altered compared to healthy controls in ruptured and unruptured IA patients. This finding lends support to the proposed utility of miRNAs as biological markers for the identification of IAs. Second, the differential expression of plasma miRNA levels in patients with aneurysms with and without daughter blebs may be evidence of changing miRNA profiles at different time points in aneurysm development and progression. Thus, the cellular and molecular processes underlying aneurysm initiation, growth, and rupture may occur in distinct phases. Further understanding of the miRNA profiles of these phases represents a means by which to better distinguish those aneurysms unlikely to rupture from those unstable aneurysms with advanced dome weakness [7].

Conclusion

Despite significant advances in the endovascular and microsurgical treatment of aneurysms, the associated morbidity and mortality of intervention remains significant. The inherent risk of treatment must be weighed against the risk of rupture and its associated high likelihood of a poor outcome. At present, the ability to identify those aneurysms most likely to rupture remains limited. As a result, an effort to identify reliable biological markers of IA formation and progression is underway.

miRNAs represent an attractive area of study due to their presence in the plasma and their cell- and tissue-specific expression. Their differential expression in multiple disease states has been previously established, however, data pertaining to IA pathogenesis is limited. Currently, there is sufficient data to suggest that alterations in plasma miRNA are indicative of the presence of an IA. Some evidence exists that links miRNA expression to different phases of aneurysm genesis. Furthermore, investigation of miRNA expression profiles has begun to link these miRNAs to the molecular and cellular processes associated with IA formation. Endothelial dysfunction, alterations in VSMC phenotype, and perturbations of the inflammatory response all contribute to IA pathogenesis and appear to be reflected in the presence of specific miRNAs.

Practically, miRNAs exhibit structural and biological properties that render them a potentially useful clinical tool. Further investigation is needed to better understand the relationships between miRNA expression profiles and IAs. Ultimately, knowledge of the downstream effects of miRNA expression is required to better elucidate the functions of these molecules.

References

1. Schnell S, Ansari SA, Vakil P, Wasielewski M, Carr ML, Hurley MC, et al. Three-dimensional hemodynamics in intracranial aneurysms: influence of size and morphology. Journal of magnetic resonance imaging : JMRI. 2014; 39: 120-131.

2. Caranci F, Briganti F, Cirillo L, Leonardi M, Muto M. Epidemiology and genetics of intracranial aneurysms. Eur J Radiol. 2013; 82: 1598-1605.

3. Schievink WI. Intracranial aneurysms. N Engl J Med. 1997; 336: 28-40.

4. Hoh BL, Hosaka K, Downes DP, Nowicki KW, Wilmer EN, Velat GJ, et al. Stromal cell-derived factor-1 promoted angiogenesis and inflammatory cell infiltration in aneurysm walls. J Neurosurg. 2014; 120: 73-86.

5. Starke RM, Chalouhi N, Jabbour PM, Tjoumakaris SI, Gonzalez LF, Rosenwasser RH, et al. Critical role of TNF-Î± in cerebral aneurysm formation and progression to rupture. J Neuroinflammation. 2014; 11: 77.

6. Kroh EM, Parkin RK, Mitchell PS, Tewari M. Analysis of circulating microRNA biomarkers in plasma and serum using quantitative reverse transcription-PCR (qRT-PCR). Methods. 2010; 50: 298-301.

7. Jin H, Li C, Ge H, Jiang Y1, Li Y. Circulating microRNA: a novel potential biomarker for early diagnosis of intracranial aneurysm rupture a case control study. J Transl Med. 2013; 11: 296.

8. Jiang Y, Zhang M, He H, Chen J, Zeng H, Li J, et al. MicroRNA/mRNA profiling and regulatory network of intracranial aneurysm. BMC Med Genomics. 2013; 6: 36.

9. Maegdefessel L, Azuma J, Toh R, Merk DR, Deng A, Chin JT, et al. Inhibition of microRNA-29b reduces murine abdominal aortic aneurysm development. J Clin Invest. 2012; 122: 497-506.

10. Maegdefessel L, Azuma J, Tsao PS. MicroRNA-29b regulation of abdominal aortic aneurysm development. Trends Cardiovasc Med. 2014; 24: 1-6.

11. Ruan W, Xu JM, Li SB, Yuan LQ, Dai RP. Effects of down-regulation of microRNA-23a on TNF-Î±-induced endothelial cell apoptosis through caspase-dependent pathways. Cardiovasc Res. 2012; 93: 623-632.

12. Lewis BP, Shih IH, Jones-Rhoades MW, Bartel DP, Burge CB. Prediction of mammalian microRNA targets. Cell. 2003; 115: 787-798.

13. Lund E, Güttinger S, Calado A, Dahlberg JE, Kutay U. Nuclear export of microRNA precursors. Science. 2004; 303: 95-98.

14. Lee Y, Kim M, Han J, Yeom KH, Lee S, Baek SH, et al. MicroRNA genes are transcribed by RNA polymerase II. EMBO J. 2004; 23: 4051-4060.

15. Lee Y, Ahn C, Han J, Choi H, Kim J, Yim J, et al. The nuclear RNase III Drosha initiates microRNA processing. Nature. 2003; 425: 415-419.

16. Grishok A, Pasquinelli AE, Conte D, Li N, Parrish S, Ha I, et al. Genes and mechanisms related to RNA interference regulate expression of the small temporal RNAs that control C. elegans developmental timing. Cell. 2001; 106: 23-34.

17. Ha M, Kim VN. Regulation of microRNA biogenesis. Nat Rev Mol Cell Biol. 2014; 15: 509-524.

18. Gregory RI, Chendrimada TP, Cooch N, Shiekhattar R. Human RISC couples microRNA biogenesis and posttranscriptional gene silencing. Cell. 2005; 123: 631-640.

19. Baek D, Villén J, Shin C, Camargo FD, Gygi SP, Bartel DP. The impact of microRNAs on protein output. Nature. 2008; 455: 64-71.

20. Liu D, Han L, Wu X, Yang X, Zhang Q1, Jiang F. Genome-wide microRNA changes in human intracranial aneurysms. BMC Neurol. 2014; 14: 188.

21. Reid G, Kirschner MB, van Zandwijk N. Circulating microRNAs: Association with disease and potential use as biomarkers. Crit Rev Oncol Hematol. 2011; 80: 193-208.

22. Penn DL, Witte SR, Komotar RJ, Sander Connolly E, Jr. The role of vascular remodeling and inflammation in the pathogenesis of intracranial aneurysms. Journal of clinical neuroscience: official journal of the Neurosurgical Society of Australasia. 2014; 21: 28-32.

23. Bruno G, Todor R, Lewis I, Chyatte D. Vascular extracellular matrix remodeling in cerebral aneurysms. J Neurosurg. 1998; 89: 431-440.

24. Starke RM, Chalouhi N, Ali MS, Jabbour PM, Tjoumakaris SI, Gonzalez LF, et al. The role of oxidative stress in cerebral aneurysm formation and rupture. Curr Neurovasc Res. 2013; 10: 247-255.

25. Frösen J, Tulamo R, Paetau A, Laaksamo E, Korja M, Laakso A, et al. Saccular intracranial aneurysm: pathology and mechanisms. Acta Neuropathol. 2012; 123: 773-786.

26. Stehbens WE. Familial intracranial aneurysms: an autopsy study. Neurosurgery. 1998; 43: 1258-1259.

27. Ronkainen A, Niskanen M, Piironen R, Hernesniemi J. Familial subarachnoid hemorrhage. Outcome study. Stroke. 1999; 30: 1099-1102.

28. Fontanella M, Rainero I, Gallone S, Rubino E, Fenoglio P, Valfrè W, et al. Tumor necrosis factor-alpha gene and cerebral aneurysms. Neurosurgery. 2007; 60: 668-672.

29. Weinsheimer S, Goddard KA, Parrado AR, Lu Q, Sinha M, Lebedeva ER, et al. Association of kallikrein gene polymorphisms with intracranial aneurysms. Stroke. 2007; 38: 2670-2676.

30. Mineharu Y, Inoue K, Inoue S, Yamada S, Nozaki K, Takenaka K, et al. Association analysis of common variants of ELN, NOS2A, APOE and ACE2 to intracranial aneurysm. Stroke. 2006; 37: 1189-1194.

31. Mc Colgan P, Thant KZ, Sharma P. The genetics of sporadic ruptured and unruptured intracranial aneurysms: a genetic meta-analysis of 8 genes and 13 polymorphisms in approximately 20,000 individuals. Journal of neurosurgery. 2010; 112: 714-721.

32. Chen L, Wan JQ, Zhou JP, Fan YL, Jiang JY. Gene expression analysis of ruptured and un-ruptured saccular intracranial aneurysm. European review for medical and pharmacological sciences. 2013; 17: 1374-1381.

33. Li L, Yang X, Jiang F, Dusting GJ, Wu Z. Transcriptome-wide characterization of gene expression associated with unruptured intracranial aneurysms. Eur Neurol. 2009; 62: 330-337.

34. Li L, Sima X, Bai P, Zhang L, Sun H, Liang W, et al. Interactions of miR-34b/c and TP53 polymorphisms on the risk of intracranial aneurysm. Clinical & developmental immunology. 2012; 2012: 567586.

35. Lee HJ, Yi JS, Lee HJ, Lee IW, Park KC, Yang JH. Dysregulated Expression Profiles of MicroRNAs of Experimentally Induced Cerebral Aneurysms in Rats. Journal of Korean Neurosurgical Society. 2013; 53: 72-76.

36. Kin K, Miyagawa S, Fukushima S, Shirakawa Y, Torikai K, Shimamura K, et al. Tissue- and plasma-specific MicroRNA signatures for atherosclerotic abdominal aortic aneurysm. Journal of the American Heart Association. 2012; 1: e000745.

37. Santoro MM, Nicoli S. miRNAs in endothelial cell signaling: the endomiRNAs. Exp Cell Res. 2013; 319: 1324-1330.

38. Robinson HC, Baker AH. How do microRNAs affect vascular smooth muscle cell biology? Curr Opin Lipidol. 2012; 23: 405-411.

39. Xie C, Zhang J, Chen YE. MicroRNA and vascular smooth muscle cells. Vitam Horm. 2011; 87: 321-339.

40. Marin T, Gongol B, Chen Z, Woo B, Subramaniam S, Chien S, Shyy JY. Mechanosensitive microRNAs-role in endothelial responses to shear stress and redox state. Free Radic Biol Med. 2013; 64: 61-68.

41. Harrison D, Griendling KK, Landmesser U, Hornig B, Drexler H. Role of oxidative stress in atherosclerosis. Am J Cardiol. 2003; 91: 7A-11A.

42. Libby P. Inflammation in atherosclerosis. Nature. 2002; 420: 868-874.

43. Fisher AB, Chien S, Barakat AI, Nerem RM. Endothelial cellular response to altered shear stress. Am J Physiol Lung Cell Mol Physiol. 2001; 281: L529-533.

44. Chiu JJ, Wang DL, Chien S, Skalak R, Usami S. Effects of disturbed flow on endothelial cells. J Biomech Eng. 1998; 120: 2-8.

45. Olesen SP, Clapham DE, Davies PF. Haemodynamic shear stress activates a K+ current in vascular endothelial cells. Nature. 1988; 331: 168-170.

46. Tzima E, del Pozo MA, Shattil SJ, Chien S, Schwartz MA. Activation of integrins in endothelial cells by fluid shear stress mediates Rho-dependent cytoskeletal alignment. The EMBO journal. 2001; 20: 4639-4647.

47. Chachisvilis M, Zhang YL, Frangos JA. G protein-coupled receptors sense fluid shear stress in endothelial cells. Proc Natl Acad Sci U S A. 2006; 103: 15463-15468.

48. Tardy Y, Resnick N, Nagel T, Gimbrone MA, Jr., Dewey CF, Jr. Shear stress gradients remodel endothelial monolayers in vitro via a cell proliferation-migration-loss cycle. Arteriosclerosis, thrombosis, and vascular biology. 1997; 17: 3102-3106.

49. Manning AM, Bell FP, Rosenbloom CL, Chosay JG, Simmons CA, Northrup JL, et al. NF-kappa B is activated during acute inflammation in vivo in association with elevated endothelial cell adhesion molecule gene expression and leukocyte recruitment. J Inflamm. 1995; 45: 283-296.

50. Chiu JJ, Lee PL, Chen CN, Lee CI, Chang SF, Chen LJ, et al. Shear stress increases ICAM-1 and decreases VCAM-1 and E-selectin expressions induced by tumor necrosis factor-[alpha] in endothelial cells. Arteriosclerosis, thrombosis, and vascular biology. 2004; 24: 73-79.

51. Baeuerle PA, Henkel T. Function and activation of NF-kappa B in the immune system. Annu Rev Immunol. 1994; 12: 141-179.

52. Hsiai TK, Cho SK, Wong PK, Ing M, Salazar A, Sevanian A, et al. Monocyte recruitment to endothelial cells in response to oscillatory shear stress. FASEB journal: official publication of the Federation of American Societies for Experimental Biology. 2003; 17: 1648-1657.

53. Kong W, Yang H, He L, Zhao JJ, Coppola D, Dalton WS, et al. MicroRNA-155 is regulated by the transforming growth factor beta/Smad pathway and contributes to epithelial cell plasticity by targeting RhoA. Mol Cell Biol. 2008; 28: 6773-6784.

54. Muramatsu F, Kidoya H, Naito H, Sakimoto S, Takakura N. microRNA-125b inhibits tube formation of blood vessels through translational suppression of VE-cadherin. Oncogene. 2013; 32: 414-421.

55. Li X, Pan JH, Song B, Xiong EQ, Chen ZW, Zhou ZS, et al. Suppression of CX43 expression by miR-20a in the progression of human prostate cancer. Cancer Biol Ther. 2012; 13: 890-898.

56. Numagami Y, Ezura M, Takahashi A, Yoshimoto T. Antegrade recanalization of completely embolized internal carotid artery after treatment of a giant intracavernous aneurysm: a case report. Surgical neurology. 1999; 52: 611-616.

57. Iihara K, Murao K, Sakai N, Soeda A, Ishibashi-Ueda H, Yutani C, et al. Continued growth of and increased symptoms from a thrombosed giant aneurysm of the vertebral artery after complete endovascular occlusion and trapping: the role of vasa vasorum. Case report. J Neurosurg. 2003; 98: 407-413.

58. Li P, Zhang Q, Wu X, Yang X, Zhang Y, Li Y, et al. Circulating microRNAs serve as novel biological markers for intracranial aneurysms. Journal of the American Heart Association. 2014; 3: e000972.

59. Kuehbacher A1, Urbich C, Zeiher AM, Dimmeler S . Role of Dicer and Drosha for endothelial microRNA expression and angiogenesis. Circ Res. 2007; 101: 59-68.

60. Chamorro-Jorganes A, Araldi E, Penalva LO, Sandhu D, Fernandez-Hernando C, Suarez Y. MicroRNA-16 and microRNA-424 regulate cell-autonomous angiogenic functions in endothelial cells via targeting vascular endothelial growth factor receptor-2 and fibroblast growth factor receptor-1. Arteriosclerosis, thrombosis, and vascular biology. 2011; 31: 2595-2606.

61. Turjman AS, Turjman F, Edelman ER. Role of fluid dynamics and inflammation in intracranial aneurysm formation. Circulation. 2014; 129: 373-382.

62. Nakajima N, Nagahiro S, Sano T, Satomi J, Satoh K. Phenotypic modulation of smooth muscle cells in human cerebral aneurysmal walls. Acta Neuropathol. 2000; 100: 475-480.

63. Aoki T, Kataoka H, Morimoto M, Nozaki K, Hashimoto N. Macrophage-derived matrix metalloproteinase-2 and -9 promote the progression of cerebral aneurysms in rats. Stroke. 2007; 38: 162-169.

64. Aoki T, Kataoka H, Moriwaki T, Nozaki K, Hashimoto N. Role of TIMP-1 and TIMP-2 in the progression of cerebral aneurysms. Stroke. 2007; 38: 2337-2345.

65. Kolega J, Gao L, Mandelbaum M, Mocco J, Siddiqui AH, Natarajan SK, et al. Cellular and molecular responses of the basilar terminus to hemodynamics during intracranial aneurysm initiation in a rabbit model. Journal of vascular research. 2011; 48: 429-442.

66. Owens GK, Kumar MS, Wamhoff BR. Molecular regulation of vascular smooth muscle cell differentiation in development and disease. Physiol Rev. 2004; 84: 767-801.

67. Aoki T, Kataoka H, Ishibashi R, Nozaki K, Morishita R, Hashimoto N. Reduced collagen biosynthesis is the hallmark of cerebral aneurysm: contribution of interleukin-1beta and nuclear factor-kappaB. Arteriosclerosis, thrombosis, and vascular biology. 2009; 29: 1080-1086.

68. Chiu JJ, Chen LJ, Chang SF, Lee PL, Lee CI, Tsai MC, et al. Shear stress inhibits smooth muscle cell-induced inflammatory gene expression in endothelial cells: role of NF-kappaB. Arteriosclerosis, thrombosis, and vascular biology. 2005; 25: 963-969.

69. Meng H, Metaxa E, Gao L, Liaw N, Natarajan SK, Swartz DD, et al. Progressive aneurysm development following hemodynamic insult. J Neurosurg. 2011; 114: 1095-1103.

70. Hazama F, Hashimoto N. An animal model of cerebral aneurysms. Neuropathol Appl Neurobiol. 1987; 13: 77-90.

71. Kataoka K, Taneda M, Asai T, Kinoshita A, Ito M, Kuroda R. Structural fragility and inflammatory response of ruptured cerebral aneurysms. A comparative study between ruptured and unruptured cerebral aneurysms. Stroke; a journal of cerebral circulation. 1999; 30: 1396-1401.

72. Carè A, Catalucci D, Felicetti F, Bonci D, Addario A, Gallo P, et al. MicroRNA-133 controls cardiac hypertrophy. Nat Med. 2007; 13: 613-618.

73. Chen J, Yin H, Jiang Y, Radhakrishnan SK, Huang ZP, Li J, et al. Induction of microRNA-1 by myocardin in smooth muscle cells inhibits cell proliferation. Arteriosclerosis, thrombosis, and vascular biology. 2011; 31: 368-375.

74. Bostjancic E, Zidar N, Stajer D, Glavac D. MicroRNAs miR-1, miR-133a, miR-133b and miR-208 are dysregulated in human myocardial infarction. Cardiology. 2010; 115: 163-169.

75. Long X, Miano JM. Transforming growth factor-beta1 (TGF-beta1) utilizes distinct pathways for the transcriptional activation of microRNA 143/145 in human coronary artery smooth muscle cells. J Biol Chem. 2011; 286: 30119-30129.

76. Boucher JM, Peterson SM, Urs S, Zhang C, Liaw L. The miR-143/145 cluster is a novel transcriptional target of Jagged-1/Notch signaling in vascular smooth muscle cells. J Biol Chem. 2011; 286: 28312-28321.

77. Rangrez AY, Massy ZA, Metzinger-Le Meuth V, Metzinger L. miR-143 and miR-145: molecular keys to switch the phenotype of vascular smooth muscle cells. Circ Cardiovasc Genet. 2011; 4: 197-205.

78. Xie C, Huang H, Sun X, Guo Y, Hamblin M, Ritchie RP, et al. MicroRNA-1 regulates smooth muscle cell differentiation by repressing Kruppel-like factor 4. Stem Cells Dev. 2011; 20: 205-210.

79. Liu N, Bezprozvannaya S, Williams AH, Qi X, Richardson JA, Bassel-Duby R, et al. microRNA-133a regulates cardiomyocyte proliferation and suppresses smooth muscle gene expression in the heart. Genes Dev. 2008; 22: 3242-3254.

80. Etoh M, Jinnin M, Makino K, Yamane K, Nakayama W, Aoi J, et al. microRNA-7 down-regulation mediates excessive collagen expression in localized scleroderma. Arch Dermatol Res. 2013; 305: 9-15.

81. Boon RA, Seeger T, Heydt S, Fischer A, Hergenreider E, Horrevoets AJ, et al. MicroRNA-29 in aortic dilation: implications for aneurysm formation. Circ Res. 2011; 109: 1115-1119.

82. Fort A, Borel C, Migliavacca E, Antonarakis SE, Fish RJ, Neerman-Arbez M. Regulation of fibrinogen production by microRNAs. Blood. 2010; 116: 2608-2615.

83. Sinha S, Dutta S, Datta K, Ghosh AK, Mukhopadhyay D. Von Hippel-Lindau gene product modulates TIS11B expression in renal cell carcinoma: impact on vascular endothelial growth factor expression in hypoxia. J Biol Chem. 2009; 284: 32610-32618.

84. Boon RA, Dimmeler S. MicroRNAs and aneurysm formation. Trends Cardiovasc Med. 2011; 21: 172-177.

85. Kriegel AJ, Liu Y, Fang Y, Ding X, Liang M. The miR-29 family: genomics, cell biology, and relevance to renal and cardiovascular injury. Physiol Genomics. 2012; 44: 237-244.

86. Ott CE, Grunhagen J, Jager M, Horbelt D, Schwill S, Kallenbach K, et al. MicroRNAs differentially expressed in postnatal aortic development downregulate elastin via 3' UTR and coding-sequence binding sites. PloS one. 2011; 6: e16250.

87. Corsten MF, Dennert R, Jochems S, Kuznetsova T, Devaux Y, Hofstra L, et al. Circulating MicroRNA-208b and MicroRNA-499 reflect myocardial damage in cardiovascular disease. Circulation Cardiovascular genetics. 2010; 3: 499-506.

88. Chan MC, Hilyard AC, Wu C, Davis BN, Hill NS, Lal A, et al. Molecular basis for antagonism between PDGF and the TGFbeta family of signalling pathways by control of miR-24 expression. EMBO J. 2010; 29: 559-573.

89. Hermeking H. The miR-34 family in cancer and apoptosis. Cell Death Differ. 2010; 17: 193-199.

90. Concepcion CP, Han YC, Mu P, Bonetti C, Yao E, D'Andrea A, et al. Intact p53-dependent responses in miR-34-deficient mice. PLoS Genet. 2012; 8: e1002797.

91. Badi I, Burba I, Ruggeri C, Zeni F, Bertolotti M, Scopece A, et al. MicroRNA-34a Induces Vascular Smooth Muscle Cells Senescence by SIRT1 Downregulation and Promotes the Expression of Age-Associated Pro-inflammatory Secretory Factors. J Gerontol A Biol Sci Med Sci. 2015; 70: 1304-1311.

92. Boon RA, Iekushi K, Lechner S, Seeger T, Fischer A, Heydt S, et al. MicroRNA-34a regulates cardiac ageing and function. Nature. 2013; 495: 107-110.

93. Ito T, Yagi S, Yamakuchi M. MicroRNA-34a regulation of endothelial senescence. Biochem Biophys Res Commun. 2010; 398: 735-740.

94. Xu Q, Seeger FH, Castillo J, Iekushi K, Boon RA, Farcas R, et al. Micro-RNA-34a contributes to the impaired function of bone marrow-derived mononuclear cells from patients with cardiovascular disease. Journal of the American College of Cardiology. 2012; 59: 2107-2117.

95. Kim SC, Singh M, Huang J, Prestigiacomo CJ, Winfree CJ, Solomon RA, et al. Matrix metalloproteinase-9 in cerebral aneurysms. Neurosurgery. 1997; 41: 642-666.

96. Horstmann S, Su Y, Koziol J, Meyding-Lamadé U, Nagel S, Wagner S. MMP-2 and MMP-9 levels in peripheral blood after subarachnoid hemorrhage. J Neurol Sci. 2006; 251: 82-86.

97. Lijnen HR. Metalloproteinases in development and progression of vascular disease. Pathophysiol Haemost Thromb. 2003; 33: 275-281.

98. Hossain M, Sathe T, Fazio V, Mazzone P, Weksler B, Janigro D, et al. Tobacco smoke: a critical etiological factor for vascular impairment at the blood-brain barrier. Brain Res. 2009; 1287: 192-205.

99. Kangavari S, Matetzky S, Shah PK, Yano J, Chyu KY, Fishbein MC, et al. Smoking increases inflammation and metalloproteinase expression in human carotid atherosclerotic plaques. Journal of cardiovascular pharmacology and therapeutics. 2004; 9: 291-298.

100. Fang JH, Zhou HC, Zeng C, Yang J, Liu Y, Huang X, et al. MicroRNA-29b suppresses tumor angiogenesis, invasion, and metastasis by regulating matrix metalloproteinase 2 expression. Hepatology. 2011; 54: 1729-1740.

101. Mishra PK, Metreveli N, Tyagi SC. MMP-9 gene ablation and TIMP-4 mitigate PAR-1-mediated cardiomyocyte dysfunction: a plausible role of dicer and miRNA. Cell Biochem Biophys. 2010; 57: 67-76.

102. Liao JK, Laufs U. Pleiotropic effects of statins. Annu Rev Pharmacol Toxicol. 2005; 45: 89-118.

103. Aoki T, Kataoka H, Ishibashi R, Nozaki K, Hashimoto N. Simvastatin suppresses the progression of experimentally induced cerebral aneurysms in rats. Stroke. 2008; 39: 1276-1285.

104. Aoki T, Kataoka H, Ishibashi R, Nakagami H, Nozaki K, Morishita R, et al. Pitavastatin suppresses formation and progression of cerebral aneurysms through inhibition of the nuclear factor kappaB pathway. Neurosurgery. 2009; 64: 357-365; discussion. 65-66.

105. Zhang HF, Zhao MG, Liang GB, Song ZQ, Li ZQ. Expression of pro-inflammatory cytokines and the risk of intracranial aneurysm. Inflammation. 2013; 36: 1195-1200.

106. Low SK, Zembutsu H, Takahashi A, Kamatani N, Cha PC, Hosono N, et al. Impact of LIMK1, MMP2 and TNF-Î± variations for intracranial aneurysm in Japanese population. J Hum Genet. 2011; 56: 211-216.

107. Moriwaki T, Takagi Y, Sadamasa N, Aoki T, Nozaki K, Hashimoto N. Impaired progression of cerebral aneurysms in interleukin-1beta-deficient mice. Stroke. 2006; 37: 900-905.

108. Kanematsu Y, Kanematsu M, Kurihara C, Tada Y, Tsou TL, van Rooijen N, et al. Critical roles of macrophages in the formation of intracranial aneurysm. Stroke. 2011; 42: 173-178.

109. Fernández-Messina L, Gutiérrez-Vázquez C, Rivas-García E, Sánchez-Madrid F, de la Fuente H. Immunomodulatory role of microRNAs transferred by extracellular vesicles. Biol Cell. 2015; 107: 61-77.

110. Natarelli L, Schober A. MicroRNAs and the response to injury in atherosclerosis. Hamostaseologie. 2015; 35: 142-150.

111. Wei Y, Nazari-Jahantigh M, Chan L, Zhu M, Heyll K, Corbalán-Campos J, et al. The microRNA-342-5p fosters inflammatory macrophage activation through an Akt1- and microRNA-155-dependent pathway during atherosclerosis. Circulation. 2013; 127: 1609-1619.

112. Pahl MC, Derr K, Gäbel G, Hinterseher I, Elmore JR, Schworer CM, et al. MicroRNA expression signature in human abdominal aortic aneurysms. BMC Med Genomics. 2012; 5: 25.

113. Zhang J, Ren J, Chen H, Geng Q. Inflammation induced-endothelial cells release angiogenesis associated-microRNAs into circulation by microparticles. Chinese medical journal. 2014; 127: 2212-2217.

114. Sun X, He S, Wara AK, Icli B, Shvartz E, Tesmenitsky Y, et al. Systemic delivery of microRNA-181b inhibits nuclear factor-Î°B activation, vascular inflammation, and atherosclerosis in apolipoprotein E-deficient mice. Circ Res. 2014; 114: 32-40.

115. Sun X, Icli B, Wara AK, Belkin N, He S, Kobzik L, et al. MicroRNA-181b regulates NF-Î°B-mediated vascular inflammation. J Clin Invest. 2012; 122: 1973-1990.

116. Li T, Yang GM, Zhu Y, Wu Y, Chen XY, Lan D, et al. Diabetes and hyperlipidemia induce dysfunction of VSMCs: contribution of the metabolic inflammation/miRNA pathway. Am J Physiol Endocrinol Metab. 2015; 308: E257-269.

117. Maegdefessel L, Spin JM, Raaz U, Eken SM, Toh R, Azuma J, et al. miR-24 limits aortic vascular inflammation and murine abdominal aneurysm development. Nature communications. 2014; 5: 5214.

118. Phillips J, Roberts G, Bolger C, el Baghdady A, Bouchier-Hayes D, Farrell M, et al. Lipoprotein (a): a potential biological marker for unruptured intracranial aneurysms. Neurosurgery. 1997; 40: 1112-1115.

119. Sandalcioglu IE, Wende D, Eggert A, Regel JP, Stolke D, Wiedemayer H. VEGF plasma levels in non-ruptured intracranial aneurysms. Neurosurg Rev. 2006; 29: 26-29.

120. Creemers EE, Tijsen AJ, Pinto YM. Circulating microRNAs: novel biomarkers and extracellular communicators in cardiovascular disease? Circ Res. 2012; 110: 483-495.

121. Dimmeler S, Zeiher AM. Circulating microRNAs: novel biomarkers for cardiovascular diseases? Eur Heart J. 2010; 31: 2705-2707.

122. Kuwabara Y, Ono K, Horie T, Nishi H, Nagao K, Kinoshita M, et al. Increased microRNA-1 and microRNA-133a levels in serum of patients with cardiovascular disease indicate myocardial damage. Circulation Cardiovascular genetics. 2011; 4: 446-454.

123. Wang K, Zhang S, Marzolf B, Troisch P, Brightman A, Hu Z, et al. Circulating microRNAs, potential biomarkers for drug-induced liver injury. Proc Natl Acad Sci U S A. 2009; 106: 4402-4407.

124. Alevizos I, Illei GG. MicroRNAs as biomarkers in rheumatic diseases. Nat Rev Rheumatol. 2010; 6: 391-398.

125. Guo D, Liu J, Wang W, Hao F, Sun X, Wu X, et al. Alteration in abundance and compartmentalization of inflammation-related miRNAs in plasma after intracerebral hemorrhage. Stroke. 2013; 44: 1739-1742.

126. Ji R, Cheng Y, Yue J, Yang J, Liu X, Chen H, et al. MicroRNA expression signature and antisense-mediated depletion reveal an essential role of MicroRNA in vascular neointimal lesion formation. Circulation research. 2007; 100: 1579-1588.

127. Suzuki HI, Miyazono K. Dynamics of microRNA biogenesis: crosstalk between p53 network and microRNA processing pathway. J Mol Med (Berl). 2010; 88: 1085-1094.

128. Small EM, Frost RJ, Olson EN. MicroRNAs add a new dimension to cardiovascular disease. Circulation. 2010; 121: 1022-1032.

129. Tsukahara T, Murakami N, Sakurai Y, Yonekura M, Takahashi T, Inoue T, et al. Treatment of unruptured cerebral aneurysms; a multi-center study at Japanese national hospitals. Acta Neurochir Suppl. 2005; 94: 77-85.

130. Suga M, Yamamoto Y, Sunami N, Abe T, Kondo A. [Growth of asymptomatic unruptured aneurysms in follow-up study: report of three cases]. No Shinkei Geka. 2003; 31: 303-308.

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