Review

Inflammation-Regulatory MicroRNAs: Valuable Targets for Intracranial Atherosclerosis

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Abstract: Intracranial atherosclerosis (ICAS) is the most common etiology of ischemic stroke with the highest rate of stroke recurrence. Little is currently known of the association of circulating inflammation-regulatory microRNAs (miRNAs) with ICAS. In this review, we briefly discuss that ICAS is characterized as a dynamic and unstable inflammatory process within intracranial arteries. Then, as a topic of discussion, we mainly concentrate on the following crucial miRNAs (miR-155, miR-27a/b, miR-342-5p, miR-21, miR-124 and miR-223) by virtue of their multiple roles in regulating the progression of atherosclerosis involved with systemic and local inflammatory activities in cerebral arteries. Clinical perspectives of other miRNAs (miR-146a, miR-181b, miR-126, miR-143 and let-7b) in ICAS are also mentioned. In relevance to the inflammatory mechanisms of ICAS, the in-depth knowledge of miRNAs engaged in the progression of intracranial atherosclerotic plaques may provide an approach to a more precise exploration of diagnostic and therapeutic targets for ICAS.

Keywords: MicroRNA; Inflammation; Mechanism; Intracranial atherosclerosis

1. Introduction

Ischemic stroke (IS) is a major cause of death and permanent disability worldwide (Hankey, 2017). During the past twenty years, the numbers of incidence, disability-adjusted life-years lost and death caused by IS were still ascending (Feigin et al., 2014; Hankey, 2017). Even worse, in the low-income and middle-income countries, the rate of IS incidence was increased by 6% (Feigin et al., 2014; Hankey, 2017). The prevalence of IS due to intracranial atherosclerosis (ICAS) among Asians is nearly 40%, which is larger than that among African-Americans (29%) and Caucasians (15%) (Holmstedt, Turan, & Chimowitz, 2013; Suri & Johnston, 2009). ICAS remains the most common etiology of IS with the highest rate of recurrent stroke (Lange et al., 2018; Y. Wang et al., 2014).

ICAS entails a dynamic and unstable process in relation to chronic systemic and local inflammation (Arenillas et al., 2008; Fadini et al., 2014; R. Jin, Liu, Zhang, Nanda, & Li, 2013), primarily complicated by the formation and rupture of vulnerable intracranial atherosclerotic plaques (Arenillas, Lopez-Cancio, & Wong, 2016). Even though atherosclerosis within intracranial arteries possesses distinct features by virtue of unique anatomy and haemodynamics in the intracranial vascular system, the course of atherogenesis may be based on the general mechanism (D'Armiento et al., 2001; Elkind, 2006; Kiechl & Willeit, 1999). Normally,

atherogenesis in intracranial arteries engages with a series of systemic and local lipid-driven inflammatory activities (Wong, Caplan, & Kim, 2016; Wu, Li, Hou, & Chu, 2017). Chronic systemic inflammation may exacerbate the progression of ICAS via the activation of endothelial injury and inflammatory cells within cerebral arteries (X. Y. Chen & Fisher, 2016; Wong et al., 2016). Additionally, local inflammatory infiltration evolving a fate of macrophages may increase the vulnerability of atherosclerotic plaques, which results in the rupture of plaques and subsequent thrombotic events (Hilgendorf, Swirski, & Robbins, 2015; Moore, Sheedy, & Fisher, 2013; Wong et al., 2016). Accordingly, several studies indicated that circulating blood inflammatory biomarkers were found to have predictive values on the ICAS progression (Ridker et al., 2005; Shimizu et al., 2013; Virani & Nambi, 2007).

microRNAs (miRNAs) are short, single-stranded and non-protein coding RNAs, post-transcriptionally decreasing the expressions of genes via targeting the 3' untranslated regions in mRNAs (Stefani & Slack, 2008). It was reported that a wide variety of pro-inflammatory and anti-inflammatory miRNAs could play distinct roles in the pathogenesis of IS in relevance to neuro-inflammation (Gaudet, Fonken, Watkins, Nelson, & Popovich, 2018), as well as in the pathobiology of atherosclerosis (Feinberg & Moore, 2016; Laffont & Rayner, 2017). Consequently, similar to the conventional inflammatory biomarkers, miRNAs were also identified as potential diagnostic or prognostic targets for IS (Badacz et al., 2018; Gacon et al., 2018; W. A. Li, Efendizade, & Ding, 2017; Shekhar et al., 2018; W. Xu et al., 2018). A recent study further demonstrated that circulating miRNAs in human blood serum might be used to differentiate the IS etiological subtypes (Gui et al., 2018). Among these miRNAs, miR-7-2-3p and miR-1908 were significantly associated with ICAS and lacunar infarct, but not with other IS etiologies (Gui et al., 2018). Yet, the underlying mechanisms in correlation of pro- and anti-inflammatory miRNAs with ICAS were not fully elucidated.

In this review, we first consider that chronic systemic and local inflammation within the cerebral arteries primarily engages in the progression of ICAS plaques. Then, the following key miRNAs (miR-155, miR-27a/b, miR-342-5p, miR-21, miR-124 and miR-223) are specifically discussed, because of their inflammation-regulatory roles in atherosclerotic plaques involved with systemic and local inflammatory activities [Table 1]. Furthermore, other miRNAs (miR-146a, miR-181b, miR-126, miR-143 and let-7b) are also stated for their clinical perspectives in ICAS. Hence, the in-depth knowledge in this inflammation-regulatory miRNA-related field is essential for elucidating the underlying pathophysiology of ICAS and establishing potential diagnostic and therapeutic targets for ICAS.

Table 1. The potential regulatory roles of pro- and anti-inflammatory miRNAs in intracranial atherosclerosis.

miRNA	Key miRNA targets in intracranial atherosclerosis	Relevant atherosclerotic events in intracranial atherosclerosis	Dominant effects of miRNA on relevant events
miR-155	endothelial tight junction proteins	endothelial damage	pro-inflammatory
	Bcl6	monocyte activation	pro-inflammatory
	HBP1	foam cell formation	pro-inflammatory
	CEH, CARHSP1	foam cell formation	anti-inflammatory
	SOCS1, p-STAT3, PDCD4	plaque rupture	pro-inflammatory
miR-27a/b	NF-κBs	oxidative stress	anti-inflammatory

	SEMA6A	endothelial damage	pro-inflammatory (miR-27a/b suppression)
	ABCA1	macrophage cholesterol efflux	pro-inflammatory
	CD36, LPL	macrophage cholesterol uptake	pro-inflammatory
	ACAT1	macrophage cholesterol esterification	pro-inflammatory
miR-342-5p	AKT1, miR-155, NO, TNFA, IL-6	macrophage activation	pro-inflammatory
miR-21	PTEN	endothelial damage	anti-inflammatory
	IL-6, IL-10	foam cell formation	anti-inflammatory
	MKK3	plaque rupture	pro-inflammatory (miR-21 absence)
	MPRIP, TIMP3, JAG1	plaque rupture	anti-inflammatory
miR-124	MMP-2, MMP-9, Sp1	VSMC function	anti-inflammatory
	P4Hα1	plaque rupture	pro-inflammatory (high glucose)
miR-223	ICAM-1, NF-κBs, TF	endothelial damage	anti-inflammatory
	IGF-1R	endothelial damage	pro-inflammatory
	ABCA1	macrophage cholesterol efflux	anti-inflammatory
	NF-κBs	foam cell formation	anti-inflammatory

2. Inflammation in ICAS

2.1. Systemic inflammation in ICAS

At the beginning of atherogenesis, systemic inflammatory status, such as hyperlipidemia, hypertension, diabetes and smoking, can stimulate a cumulative effect of advanced glycation end products (AGEs), contributing to the activation of reactive oxygen species (ROS) and the preservation of oxidized low-density lipoprotein (ox-LDL) (Barlovic, Soro-Paavonen, & Jandeleit-Dahm, 2011; Perrotta & Aquila, 2015). This process of oxidative stress can result in a damage to releasing nitric oxide (NO), but an increased expression level of endothelin-1 (ET-1) within endothelial cells (Gonzalez, Valls, Brito, & Rodrigo, 2014). The dysfunctional endothelium may express adhesion molecules induced by ET-1, including intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), which enhance the adhesion between leukocyte and endothelial cells (Zhou et al., 2016). Besides, within atherosclerotic lesions, endothelial dysfunction may also lead to the overexpression of monocyte chemoattractant protein 1 (MCP-1) via ET-1, activating and recruiting monocytes (Sheikine & Hansson, 2004; Shi et al., 2005). These accumulated immune and inflammatory cells in the atherosclerotic arterial lesions can further secrete inflammatory cytokines that may cause the proliferation of smooth muscle cells (SMCs), thereby having a pro-thrombotic influence on the endothelium (McColl, Allan, & Rothwell, 2009). Accordingly, growing evidence demonstrated that systemic inflammation throughout the whole period of ICAS dramatically affects the susceptibility to ICAS, as well as the outcomes (Anrather & Iadecola, 2016; Burrows et al., 2016; Murray et al., 2014).

2.2. Local inflammation in ICAS

With the advanced atherosclerotic lesions formed, the differentiation of activated and accumulative monocytes into lesional macrophages is induced by granulocyte macrophage-colony stimulating factor (GM-CSF) and interleukin-3 (IL-3) (Robbins et al., 2012; M. Wang et al., 2014). The lesional macrophages are observed to accumulate locally in the developing atherosclerotic plaques where these macrophages also proliferate into pro-inflammatory and anti-inflammatory macrophages (known as M1 and M2 phenotype, respectively) (Adamson & Leitinger, 2011; Robbins et al., 2013). The polarization to pro-inflammatory and anti-inflammatory macrophages may be balanced by macrophage-polarizing factors (MPFs) secreted from T helper (Th)-1 and Th-2 cells (Hansson & Hermansson, 2011). Pro-inflammatory macrophages are abundant in the plaque lipid and far from anti-inflammatory macrophages (Chinetti-Gbaguidi et al., 2011). Pro-inflammatory macrophages can enhance the inflammatory activities in the atherosclerotic plagues by the release of IL-6, IL-12 and ROS (Adamson & Leitinger, 2011), while anti-inflammatory macrophages can inhibit the inflammation in the plaques via efferocytosis (Alberts-Grill, Denning, Rezvan, & Jo, 2013). Cholesterol accumulation is accelerated by CCAAT/enhancer-binding protein delta (CEBPD) only within pro-inflammatory macrophages of atherosclerotic lesions (Lai et al., 2017). Once the disruption in macrophage cholesterol homeostasis persists, the generation of macrophage-derived foam cells is unavoidable (Yu, Fu, Zhang, Yin, & Tang, 2013). These foam cells play a pivotal role in forming advanced atherosclerotic plaques, the vulnerability of which is characterized by a thin fibrous cap, a lipid core with necrotic cells and dense infiltrating inflammatory cells (Lee, Lindsay, Kylintireas, & Choudhury, 2008). Atherosclerotic plaque rupture eventually activates and aggregates a mass of platelets within the atherosclerotic arterial lesions, contributing to subsequent thrombotic events (X. R. Xu et al., 2016) [Figure 1].

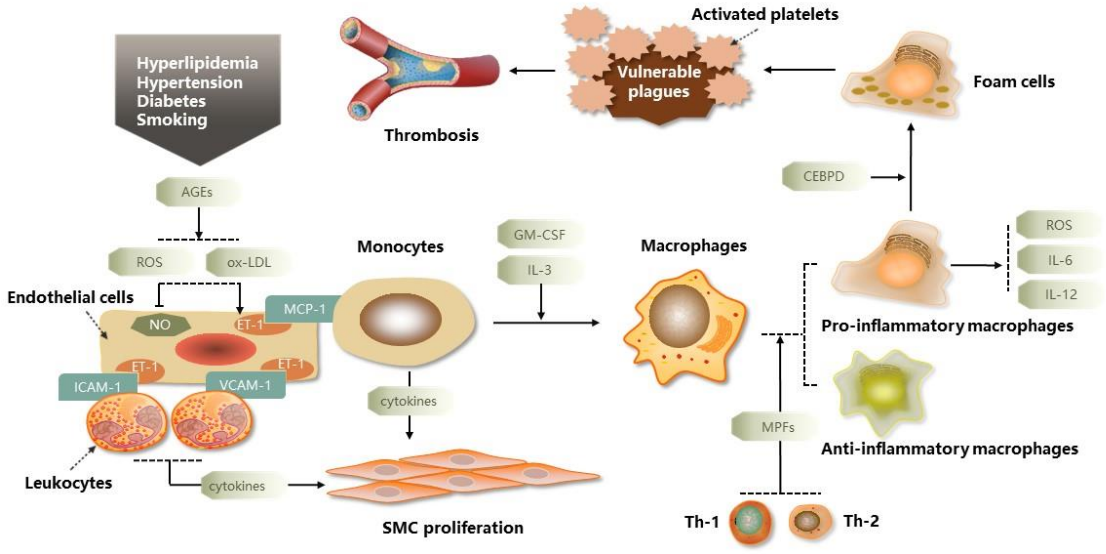

Figure 1. This figure summarizes the molecular and cellular actions within the cerebral arteries in the progression of intracranial atherosclerosis. Arrow (→) indicates a role of promotion and line (⊣) indicates a role of inhibition .

2.3. Circulating inflammatory biomarkers in ICAS

Based on the interaction between systemic and local inflammation in ICAS, many studies revealed a feasible function of circulating blood inflammatory biomarkers on predicting the progression of ICAS (Dziedzic, 2015; R. Jin et al., 2013; Shimizu et al., 2013). Serum levels of high-sensitivity C-reactive protein (CRP), highly suggestive of chronic systemic inflammation (Ridker et al., 2005), may be utilized as a valuable predictor of any further ischemic stroke events in patients with ICAS (Arenillas et al., 2003). IL-6 serves as a soluble regulator to chronic inflammation and can induce host defense against inflammatory responses (Tanaka, Narazaki, & Kishimoto, 2014). Serum IL-6 concentrations detected after the onset of IS were reported to be significantly correlated with subsequent ICAS progression (Shimizu et al., 2013). Asymmetric dimethylarginine (ADMA) can adversely affect the endothelial function in vascular atherosclerotic disorders mainly via inhibiting endogenous nitric oxide synthase (Cooke, 2004). Elevated serum ADAM levels were found in a significant association with the early stage of ICAS (Lopez-Cancio et al., 2012). Lipoprotein-associated phospholipase A2 (Lp-PLA2) can impair biological activity of LDL, thus stimulating the adhesion of monocytes to endothelial cells (Zalewski & Macphee, 2005). Higher plasma expression levels of Lp-PLA2 were related to more intracranial arterial atherosclerotic lesions, as well as severer ICAS (Y. Wang et al., 2015). Matrix metalloproteinases (MMPs) can play pleiotropic roles in the pathogenic events of atherosclerosis, especially the plaque vulnerability and rupture (Heo et al., 2011). Decreased plasma concentrations of MMP-2 were shown in relevance to the location of ICAS (Jeon et al., 2012). These findings suggest that the prediction of ICAS progression may benefit from measuring circulating blood inflammatory biomarkers. However, further investigations with higher precision are also needed to elevate the sensitivity and specificity of circulating blood inflammatory biomarkers in diagnosing and evaluating ICAS.

3. miRNAs in Inflammation of ICAS

3.1. miRNA-155 directly participates in the multiple events of ICAS.

Well-studied miR-155 was reported to enrich in endothelial cells and lesional macrophages (Nazari-Jahantigh et al., 2012; Zheng et al., 2017). Other research demonstrated that in the mouse model of IS, suppressing miR-155 expression could attenuate the pro-inflammatory courses, thereby contributing to a neuro-protective regulation and an improvement of functional recovery (Caballero-Garrido et al., 2015; Pena-Philippides, Caballero-Garrido, Lordkipanidze, & Roitbak, 2016).

miR-155 may take direct participation in the multiple atherosclerotic events in the intracranial vessels through various inflammatory signaling pathways, particularly endothelial damage, monocyte/macrophage activation, foam cell formation and plaque rupture (Feinberg & Moore, 2016; Gaudet et al., 2018; Laffont & Rayner, 2017; Shekhar et al., 2018; W. Xu et al., 2018). miR-155 induced by the overexpression of Krüppel-like factor 5 (KLF5) within vascular smooth muscle cells (VSMCs) could be transferred from SMCs to endothelial cells by exosomes in VSMCs (Zheng et al., 2017). In this process, miR-155 could affect the response of endothelial cells to accumulative ox-LDL and reduce the expression levels of endothelial tight junction proteins, thus aggravating vascular endothelial permeability and promoting atherogenesis (Zheng et al., 2017). Upregulation in this miRNA could directly inhibit B-cell lymphoma 6 (Bcl6)

expression, and then promoted C-C motif chemokine ligand 2 (Ccl2) transcription, which induced monocytes to recruit in the atherosclerotic plaques and thus accelerated the atherosclerotic progression (Nazari-Jahantigh et al., 2012). Besides, miR-155 upregulation stimulated by ox-LDL could also directly suppress the expression of HMG box-transcription protein1 (HBP1), which enhanced the accumulation of lipid and the generation of ROS in macrophages, resulting in the formation of foam cells (Tian et al., 2014). However, recent studies indicated that miR-155 could play inhibitory roles on foam cell formation through different pathways, such as upregulating cholesterol ester hydrolase (CEH) expression (F. Zhang, Zhao, Sun, & Wei, 2018) or downregulating calcium-regulated heat stable protein 1 (CARHSP1) expression levels (X. Li et al., 2016), eventually repressing atherosclerotic lesion development. As for plaque rupture, miR-155 could directly reduce the expression of suppressor of cytokine signaling 1 (SOCS1) and upregulate the expression levels of phospho-signal transducer and activator of transcription 3 (p-STAT3) and programmed cell death protein 4 (PDCD4), thus enhancing inflammatory reactions in macrophages and accelerating atherosclerotic plaque formation and rupture (Ye et al., 2016).

3.2. miRNA-27a/b maintains endothelial and macrophage functions in ICAS.

The abundance of miR-27 family (miR-27a and -27b) was found in human endothelial cells and macrophages of atherosclerotic lesions (W. J. Chen, Yin, Zhao, Fu, & Tang, 2012). Yet, decreased expressions of miR-27a/b could be induced by ROS within macrophages (Thulasingam et al., 2011).

The regulatory roles of miR-27a/b in maintaining endothelial and macrophage functions may provide a deep insight into the inflammatory modulation of ICAS (A et al., 2017; W. J. Chen et al., 2012; Fernandez-Hernando, 2013; Novak, Olejnickova, Tkacova, & Santulli, 2015). In endothelial cells, miR-27a/b suppression could elevate the expression of semaphorin 6A (SEMA6A) and thus damage the formation of endothelial cell sprouting, suggesting that miR-27a/b could affect the vascular integrity through regulating the endothelial function (Urbich et al., 2012). Meanwhile, miR-27b upregulation could inhibit nuclear factor (NF)-κB signaling pathway in macrophages, indicating that miR-27 family could also have an effect on the function of macrophages in response to oxidative stress via inflammatory pathway (Thulasingam et al., 2011). Moreover, miR-27a/b could directly downregulate the expression levels of ATP binding cassette transporter A1 (ABCA1) and attenuate cholesterol efflux from macrophages modulated by apolipoprotein A1 (apoA1) (M. Zhang et al., 2014). miR-27a/b could also inhibit scavenger receptor CD36 (CD36) and lipoprotein lipase (LPL) expressions, impairing the adhesion of DiI-oxLDL in Th-1 macrophages and thereby disturbing cholesterol uptake (M. Zhang et al., 2014). miR-27a/b could decrease the expression of Acyl-CoA:cholesterol acyltransferase-1 (ACAT1), resulting in the reduction of macrophage cholesterol esterification (M. Zhang et al., 2014). All these findings demonstrated that miR-27a/b could serve as a crucial regulator in sustaining macrophage cholesterol homeostasis and a possible therapeutic target for atherosclerosis (M. Zhang et al., 2014).

3.3. miRNA-342-5p interacts with miRNA-155 in ICAS.

In the early stage of atherosclerosis, the expression of miR-342-5p was prominent within lesional macrophages (Laffont & Rayner, 2017; Natarelli & Schober, 2015). With the

development of atherogenesis, however, the levels of miR-342-5p descended in the advanced atherosclerotic lesions (Wei et al., 2013).

The interaction between miR-342-5p and miR-155 may promote pro-inflammatory activities in macrophages of early atherosclerosis (Wei et al., 2013). miR-342-5p could directly inhibit the expression levels of bone morphogenetic protein receptor type 2 (BMPR2) and AKT serine/threonine kinase 1 (AKT1), while upregulated miR-342-5p could increase miR-155 levels only by repressing AKT1 expression (Wei et al., 2013). Then, miR-342-5p could stimulate the generation of NO and the release of tumor necrosis factor a (TNFA) and IL-6, further activating the pro-inflammatory reactions in macrophages (Wei et al., 2013). Accordingly, miR-342-5p could induce macrophage and SMC accumulation within the early atherosclerotic lesions and accelerate atherogenesis (Wei et al., 2013). Nevertheless, direct evidence is required to illustrate the regulatory influence of miR-342-5p on the progression of ICAS.

3.4. miRNA-21 enhances plaque stability of ICAS.

Serum miR-21 expression levels were measured to significantly upregulate in patients with IS and atherosclerosis, and this miRNA could act as an independent predictive factor of IS and atherosclerosis (Tsai et al., 2013). Interestingly, decreased expressions of miR-21 along with more arterial infiltrating macrophages and foam cells were later detected in the instable atherosclerotic lesions, whereas overexpressed miR-21 levels could increase the stability of atherosclerotic plaques (H. Jin et al., 2018).

The essential effects of miR-21 on IS and atherosclerosis may lead to an access to elucidating the underlying mechanisms of ICAS (Koroleva, Nazarenko, & Kucher, 2017; Rink & Khanna, 2011; Volny, Kasickova, Coufalova, Cimflova, & Novak, 2015). Upregulation of miR-21 stimulated by unidirectional shear stress in human endothelial cells could attenuate endothelial cell apoptosis and promote NO generation via directly downregulating the expression of phosphatase and tensin homolog (PTEN), suggesting that miR-21 could affect the endothelial function (Weber, Baker, Moore, & Searles, 2010). In macrophages, moreover, miR-21 upregulation could inhibit the release of IL-6 and promote the expression of IL-10, thereby diminishing the accumulation of lipid and the formation of foam cells (Feng et al., 2014). This reversely regulative role of miR-21 in the progression of atherosclerosis may indicate a potential treatment of ICAS (Feng et al., 2014). On the other hand, miR-21 absence within macrophages could activate the p38 MAP Kinase-C/EBP homologous protein (p38-CHOP) and c-Jun N-terminal kinase (JNK) signaling pathway through the direct upregulation of mitogen-activated protein kinase kinase 3 (MKK3) (Canfran-Duque et al., 2017). This process could further promote macrophage apoptosis, vascular inflammatory activities and plaque necrosis, thus accelerating atherosclerosis progression (Canfran-Duque et al., 2017). Not coincidentally, various decreased relevant targets of upregulated miR-21 within human atherosclerotic plaques were also observed in these atherosclerotic arteries, including myosin phosphatase Rho interacting protein (MPRIP), TIMP metallopeptidase inhibitor 3 (TIMP3) and jagged 1 (JAG1) (Raitoharju et al., 2011).

3.5. miRNA-124 is correlated with plaque vulnerability of ICAS.

Serum concentrations of miR-124 were revealed to increase in patients with acute ischemic stroke (AIS), which were significantly associated with serum IL-6 levels, infarction volumes and

National Institutes of Health Stroke Scale (NIHSS) scores (Ji et al., 2016). miR-124 in human serum could be used as an emerging biomarker to predict the incidence and severity of AIS (Ji et al., 2016).

Other studies put emphasis on the pivotal functions of miR-124 on the atherosclerotic plaque progression, implying the possible mechanisms that miR-124 may target the pathogenesis of atherosclerosis in cerebral arteries (Volny et al., 2015). Upregulated miR-124 induced by high glucose could directly suppress the expressions of prolyl-4-hydroxylase alpha 1 (P4Hα1) within VSMCs, while overexpressed AMP-activated protein kinase alpha (AMPKα) levels stimulated by metformin could promote activator protein 2 alpha (AP-2α) phosphorylation and thus decrease miR-124 levels (Liang et al., 2018). In this process of miR-124 downregulation, atherosclerotic plaques could be stabilized (Liang et al., 2018). Nonetheless, upregulation of miR-124 could dramatically repress MMP-2 and MMP-9 expressions, thus inhibiting the proliferation and migration of VSMCs (Y. Tang et al., 2017). This upregulation could directly inhibit the expression levels of specificity protein 1 (Sp1) within human VSMCs as well, which could influence the function and phenotypic switch of human VSMCs (Y. Tang et al., 2017).

3.6. miRNA-223 influences inflammatory thrombosis of ICAS.

The levels of miR-223 were shown to overexpress in the circulating blood leukocytes of patients with atherosclerotic cerebral infarction, while miR-223 gene promoter methylation levels were declined in these patients (Z. Li et al., 2017). Upregulated miR-223 expressions were also detected in the platelet exosomes activated by thrombin (J. Li, Tan, Xiang, Zhou, & Yan, 2017).

Circulating miR-223 biomarker attracts so much attention in virtue of the importance in regulating ICAS pathology by different potential pathways **(Novak et al., 2015; Shan et al., 2015)**. miR-223 could directly suppress the expression levels of ICAM-1 in vascular endothelial cells via blocking NF-κB signaling pathway **(J. Li et al., 2017)**, and this miRNA could further impair the accumulation of lipid and the formation of foam cells through impacting NF-κB pathway in macrophages **(J. Wang et al., 2015)**. Upregulation of miR-223 could also directly inhibit tissue factor (TF) expressions in vascular endothelial cells and repress the pro-coagulant activation of TF (S. Li et al., 2014). Unlike miR-27a/b, miR-223 could indirectly enhance ABCA1 expression levels and accelerate cholesterol efflux, which could sustain cellular cholesterol homeostasis (Vickers et al., 2014). These results identified a reverse role of miR-223 in dominating the atherosclerosis progression by affecting inflammatory thrombosis process (J. Li et al., 2017; S. Li et al., 2014; Vickers et al., 2014; J. Wang et al., 2015). However, miR-223 released from platelet microvesicles could directly downregulate the expressions of insulin-like growth factor 1 receptor (IGF-1R) within vascular endothelial cells as well, thereby facilitating endothelial cell apoptosis stimulated by AGEs (Pan et al., 2014).

4. Other miRNAs in ICAS and Clinical Perspectives

As was mentioned above that miR-27a/b and miR-21 may possibly function as emerging therapeutic targets for ICAS, these miRNA-based drug targets have been long discussed in the field of atherosclerotic diseases (Araldi, Chamorro-Jorganes, van Solingen, Fernandez-Hernando, & Suarez, 2015; Loyer, Mallat, Boulanger, & Tedgui, 2015; Rocic, 2017; Wei, Zhu,

& Schober, 2018), especially when miRNA mimics and inhibitors may be utilized in the therapeutic strategy to modulate atherosclerotic progression (Laffont & Rayner, 2017). miR-146a was one of the promising anti-inflammatory regulators in monocytes and macrophages to attenuate atherosclerosis (K. Li, Ching, Luk, & Raffai, 2015). After systemically delivering miR-146a mimetics, miR-146a levels were upregulated in *Apoe*$^{-/-}$*Ldlr*$^{-/-}$ and *Ldlr*$^{-/-}$ mice (K. Li et al., 2015). This process could inhibit atherosclerosis via inactivating monocytes and macrophages in the experimental models (K. Li et al., 2015). miR-181b could facilitate atherosclerotic plaque rupture by the direct downregulation of tissue inhibitor of metalloproteinase-3 (TIMP-3) in macrophages and elastin in VSMCs (Di Gregoli et al., 2017). After administrating miR-181b inhibitor in *Apoe*$^{-/-}$ and *Ldlr*$^{-/-}$ mice, atherosclerotic plaque development and progression were repressed in vivo (Di Gregoli et al., 2017). With the help of nanomedicine technology, in addition, local specific delivery of miRNAs may be oriented towards an accurate way to treat ICAS (X. Y. Chen, Tang, & Wong, 2014; Gadde & Rayner, 2016). Although these pre-clinical studies gained some insight into the treatment of ICAS, further clinical trials are eagerly needed to bring miRNA-based therapies into practice.

Considering that circulatory miRNAs have distinct features of being stable and highly detectable in human body fluids (Laffont & Rayner, 2017), growing research highlighted the enormous potential of these regulatory non-coding RNAs as circulating biomarkers for ICAS. miR-126 could figure prominently as a direct regulator in the inflammatory mechanism of atherosclerosis by specific targets (Hao & Fan, 2017; Tang, Wang, Shao, Wang, & Zhu, 2017), and miR-143 could directly regulate the functions of endothelial cells and VSMCs via different pathways and take part in the development of atherosclerosis (R. H. Xu, Liu, Wu, Yan, & Wang, 2016; H. P. Zhang et al., 2016). Levels of both the miRNAs in human plasma were further reported in correlation with the disease severity of ICAS (Gao et al., 2019). miR-126 and miR-143 showed high specificity and sensitivity in distinguishing patients with atherosclerosis from healthy individuals, suggesting the possible use as circulating biomarkers for ICAS (Gao et al., 2019). Upregulated let-7b that repressed endothelial dysfunction could have a protective influence on atherosclerotic progression (Bao, Zhang, Lou, Cheng, & Zhou, 2014), while this miRNA was downregulated in lesional macrophages of the *M-Dicer*$^{-/-}$ mice atherosclerotic artery (Wei, Corbalan-Campos, et al., 2018). Plasma let-7b expressions were also found to decrease in patients with ICAS at each time point after the symptom onset (24h, 1w, 4w and 24w), but increase in other IS etiologies, when compared with healthy subjects (Long et al., 2013). In the future, numerous studies are approaching that a huge range of miRNAs may be precisely identified as sensitive and specific post-ICAS biomarkers.

5. Conclusions

ICAS is considered as a dynamic and unstable disease affected by the interaction between systemic and local inflammation in cerebral arteries. Endothelial injury, monocyte/macrophage activation, foam cell formation and plaque rupture normally get involved in the acceleration of ICAS process. Inflammation-regulatory miRNAs are believed to have a marked impact on the inflammatory activities related to atherosclerotic pathogenesis, and thus participate in the progression of ICAS. Yet, the multiple roles of miRNAs in modulating ICAS progression may make it difficult to illuminate the exact mechanisms [Figure 2]. Besides, consideration of other factors that control miRNA regulation in ICAS, such as single nucleotide polymorphisms (Zhong et al., 2016) and lncRNAs (Huang, Wang, Mao, & Nan, 2019), may spread wider net of miRNA-

inflammation-ICAS pathways. Future clinical researches with a larger scale and a higher power are still required to improve the precision of exploring miRNAs in patients with ICAS, so as to gain a better understanding of ICAS pathophysiology. In conclusion, the establishment of diagnostic and therapeutic targets for ICAS may give priority to this in-depth knowledge in association of miRNAs with the inflammatory mechanisms of ICAS.

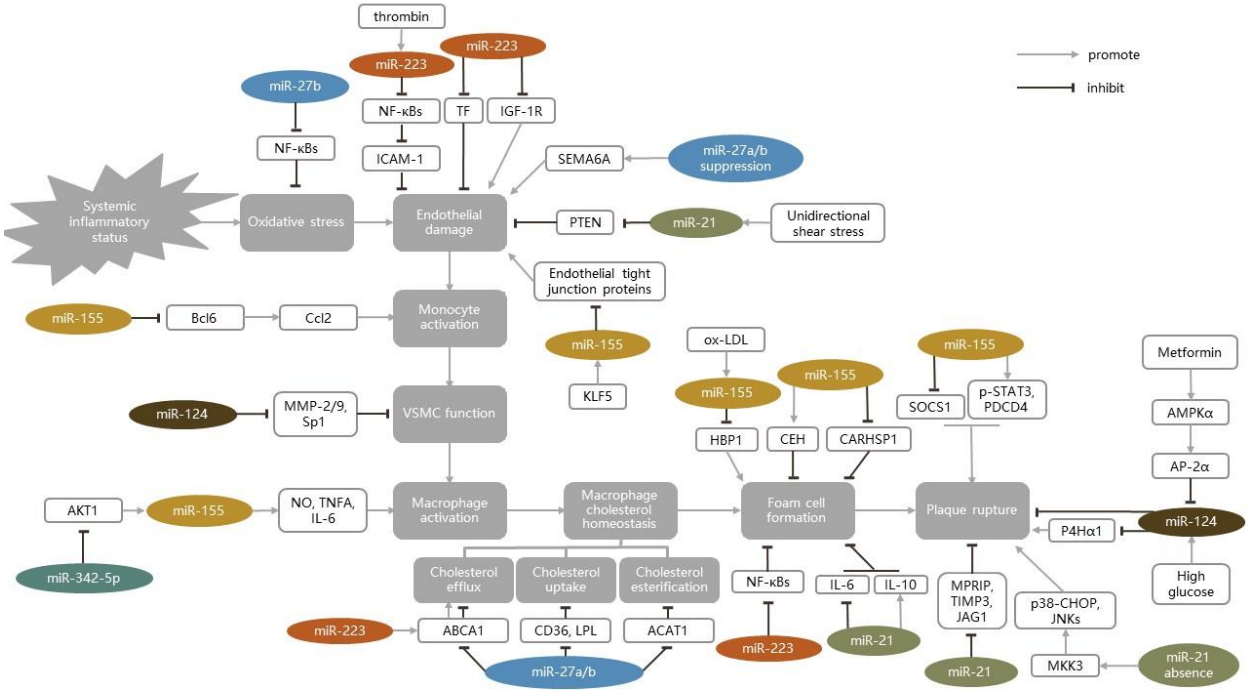

Figure 2. This figure illustrates the multi-functions of miRNAs in modulating the progression of ICAS plaques. Systemic and local inflammatory activities in cerebral arteries get involved in the acceleration of ICAS process. Inflammation-regulatory miRNAs can participate in the progression of ICAS plaques through various pathways.

Author Contributions: conceptualization, J.L. and X.Y.C.; writing—original draft preparation, J.L.; writing—review and editing, K.S.L. and X.Y.C.; supervision, X.Y.C.

Funding: This study was funded by the Health and Medical Research Fund of Hong Kong (HMRF, Project No. 04152586).

Acknowledgments: Thank Chen GUO for helping with figure design.

Conflict of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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