microRNAs Associated with Carotid Plaque Development and Vulnerability

Subjects: Medicine, Research & Experimental

Contributor: Rafał Badacz , Tadeusz Przewłocki , Jacek Legutko , Krzysztof Żmudka , Anna Kabłak-Ziembicka

Ischemic stroke (IS) related to atherosclerosis of large arteries is one of the leading causes of mortality and disability in developed countries. Atherosclerotic internal carotid artery stenosis (ICAS) contributes to 20% of all cerebral ischemia cases. Atherosclerosis prevention and treatment measures aim at controlling the atherosclerosis risk factors, or at the interventional (surgical or endovascular) management of mature occlusive lesions. Studies emphasize that microRNA (miRNA) are the emerging particles that could potentially play a pivotal role in this approach.

atherosclerosis atherosclerotic risk factors carotid artery stenosis carotid plaque cerebrovascular ischemia endothelial cells microRNAs plaque vulnerability platelets vascular smooth muscle cells

1. Introduction

Ischemic stroke (IS) is one of the leading causes of mortality and disability in developed countries [1]. Atherosclerotic internal carotid artery stenosis (ICAS) accounts for about 20% cases of cerebral ischemia [2]. The present diagnostic tools for carotid artery assessment are based on imaging studies, including carotid Doppler ultrasonography, computed tomography, magnetic resonance, or conventional invasive angiography with a use of intravascular ultrasound (IVUS), and optical coherence tomography (OCT) [3][4][5]. They display the degree of ICAS, as well as carotid plaque morphology [6].

The current guidelines position carotid endarterectomy (CEA) and carotid artery stenting (CS) as the established treatment methods for ICAS [7]. In addition to invasive treatment, the optimal medical approach, including cardiovascular risk factor-control, as well as pharmacotherapy (i.e., antiplatelet and antidiabetic agents, lipid and blood pressure lowering medication), should be introduced in order to reduce IS risk [8][9]. The optimal timing for the intervention on carotid artery is controversial [10][11]. According to guidelines, CEA or CS is recommended in recently symptomatic ICAS with stenosis severity above 50% lumen reduction [10][11], whereas the intervention on asymptomatic ICAS is recommended in high-grade stenosis, or in carotid plaques exceeding 60% lumen reduction when features of high-risk plaque for cerebral ischemia are present [10]. As IS can result from a fragmented plaque debris release with a subsequent embolization of cerebral arteries, plaque rupture followed by local carotid artery thrombosis, or hypoperfusion of cerebral structures, the mechanism of cerebral ischemia is complex [12][13][14][15].

Thus, as evidenced, plaque morphology and structure, in addition to the degree of carotid artery stenosis, play the pivotal role in the IS risk assessment and decision on the intervention [16].

The serious drawback of the aforementioned imaging tools is that they do not allow for the assessment of early stages of atherosclerosis, i.e., those that precede intima-media complex thickening and early fatty lesions incidences [17]. Unfortunately, current guidelines miss laboratory biomarkers which could predict the incidence of IS and thus target the high-risk group of patients with preemptive treatment, whereas early intervention upon the initiation of atherosclerosis seems very attractive [18]. Data show the important roles of pro-atherothrombotic and pro-inflammatory biomarkers, including cytokines (IL-1β, IL-6, TNFα), platelets, and macrophages activity [19][20][21].

Recent studies emphasize that microRNA (miRNA) are the emerging particles that could potentially play a pivotal role in this approach [22]. miRNAs are small, non-coding RNA nucleotides, having a length that is typically between 18 and 27 nucleotides that regulate post-transcriptional gene expression, by binding to the 3′- (more often), or to 5′-untranslated regions of mRNA, or exons [23]. The role of the miRNA has already been confirmed in the broad range of both physiological and pathological processes [24]. They are responsible for target gene expression regulation after the transcription process, either by inhibiting the translation or mRNA degradation [25]. The diagnostic and prognostic role of circulating miRNAs in ICAS leading to IS has been studied, however the conclusions remain inconsistent.

2. From Fatty Streaks and Foam Cells to Mature Plaque

Plaque formation initiates from stages that are not detectable by imaging tools [26]. First stages include endothelium dysfunction, accompanied by inflammation and modified low-density lipoprotein (LDL) retention in the intimal layer of the intima-media complex [27]. In the endothelium equilibrium, a great number of miRNAs are involved, including protective ones [28]. Their protective effect is achieved through many signaling pathways, however their major role is to prevent unfavorable lipid metabolism and reduce inflammation [28]. One of these miRNAs, miR-126, protects endothelial cells (ECs) through the suppression of NOTCH-1 inhibitor and activation of the vascular endothelial growth factor (VEGF) signaling (**Table 1**) [29][30]. At the beginning, miR-155 induces the downregulation of mitogen-activated protein 3 kinase 10 (MAP3K10), endothelin-1 (ET-1), and angiotensin II (ANG II) type I receptor [31][32]. The downregulation of ET-1 is important in many cardiovascular settings, as elevated levels of ET-1 are independently associated with increased cardiovascular mortality [33][34]. miR-146a and miR-125a decrease the lipid uptake in macrophages [35][36]. miR-146a also inhibits endothelial activation by increasing nitric oxide synthase (eNOS) expression [35]. miR-125 modulates extracellular vascular endothelial growth factor (VEGF) by manipulating macrophage soluble VEGF receptor-1 (sVEGFR1) production. This mechanism has a therapeutic potential in many diseases [36]. miR-206 and miR-223 regulate cholesterol synthesis through the reverse cholesterol transport from macrophages to the liver for excretion, attenuates pro-inflammatory cytokine production, and has a role in platelet activation [37][38][39][40][41].

Table 1. Critical miRNAs participating in atherosclerotic carotid artery lesions development: from fatty streaks to mature plaque: a therapeutic approach.

Critical Stages in Atherosclerosis	miRNA	Mechanism	Effect of miRNA Action	Therapeutic Approach (HUVEC or Animal Studies)	Ref.
Initiation and early atherosclerosis					
'Brakes' of atherosclerosis					
Promotes ECs proliferation and repair, protects ECs	miR-126-5p	suppression of the Notch1 inhibitor Dlk1	At non-predilection sites, high miR-126-5p levels in ECs confer a proliferative reserve that compensates for the antiproliferative effects of hyperlipidemia	T, injection of miR-126-5p rescued ECs proliferation at predilection sites and limited atherosclerosis	[29]
Decreases atherosclerosis progression	miR-155	downregulation of MAP3K10 downregulation of ET-1 and ANG II type I receptor	Down-modulates inflammatory cytokine production	T, the miR-155 mimic decreased IL-6, MMP-9 and TNF-α secretions of oxLDL-induced macrophages	[31] [32]
Decreases lipid uptake in macrophages, inhibits endothelial activation	miR-146a	regulates TLR4, increases eNOS expression	Inhibits ox-LDL and inflammatory response (decreases IL-6, -8, MMP-9)	Overexpression may be useful	[35]
Macrophage polarization	MiR-125a	downregulation of sVEGFR1	Decreases lipid uptake in macrophages, modulates extracellular VEGF by manipulating sVEGFR1	T, miR-125a-5p inhibition reduces VEGF through the increased sVEGFR1	[36]
Increase reverse cholesterol transport from macrophages to the liver for excretion	miR-206 miR-223	promote efflux promote efflux	crucial for the prevention of lipid accumulation and atherosclerosis	T, these miRs can be efficiently delivered to macrophages via chitosan nanoparticles	[39] [40]
Prevents ECs senescence	miR-let-7g	Stimulates anti-aging gene SIRT1, and IGF 1, inhibits expression of LOX-1	exert anti-aging effects on ECs	T, antagonizing endogenous let-7 has induced cell proliferation	[42]
Prevents ECs senescence	miR-143	targets a network of transcription factors, including KLF4, myocardin, and Elk-1	promotes differentiation and repress proliferation of VSMCs	microvesicles containing miR-143 injected into mice could reduce the formation of	[43] [44]

Critical Stages in Atherosclerosis	miRNA	Mechanism	Effect of miRNA Action	Therapeutic Approach (HUVEC or Animal Studies)	Ref.
				atherosclerotic plaques	
Suppresses atherosclerotic plaque formation	miR-520	targets RelA/p65	regulates VSMCs decreasing migration and proliferation	miR-520c-3p agomir decreased atherosclerotic plaque size	[45]
High expression is needed to maintain a contractile phenotype of VSMCs	miR-22	multiple target genes	induce the phenotypic switch from synthetic to contractile	T, the stent with the miR-22 coating showed significant capability to inhibit in-stent restenosis	[46]
Promotors of atherosclerosis					
Increases endothelial inflammation	miR-92a	regulation of KLF2	markedly enhanced by hypercholesterolemia	T, inhibition of miR-92a reduces endothelial inflammation and atheroma plaque size	[47]
Vascular senescence, vascular calcifications Altered lipid metabolism Increases inflammatory cytokines secretion of macrophages M1	miR-34a	inhibition of SIRT1 and AXL receptor tyrosine kinase targets cholesterol transporters: ABCA1 and ABCG1 through the nuclear hormone LXRα	aggravates and accelerates vascular senescence increase the binding capacity of oxLDL to macrophages stimulate pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-12, IL-23), and chemokines (CCL5, CCL8, CXCL2, CXCL4)	T, inhibition with antago-miR-34a	[48] [49]
Promotes cholesterol accumulation in macrophages, decreases reverse cholesterol transport	miR-33a	Targets hepatic ABCA1	inhibit efflux, increases macrophages ox-LDL uptake, foam cells accumulation	T, inhibition of miR-33a facilitates atherosclerosis regression	[50] [51]
Promotes atherosclerosis	miR-155	repressing Bcl6 in macrophages, suppress eNOS	increases pro-inflammatory NF-κB signaling, down-regulates the expression of eNOS and production of NO	T, inhibition of miR-155 increased eNOS expression and NO production	[32] [52]

Critical Stages in Atherosclerosis	miRNA	Mechanism	Effect of miRNA Action	Therapeutic Approach (HUVEC or Animal Studies)	Ref.
Increases apoptosis in ECs	miR-17-5p	repression of ABCA1 expression through directly binding to its 3′-UTR	rate of apoptosis in ECs	T, inhibition of miR-17 suppresses apoptosis, hence decrease infarct size area, and improves microcirculation of the heart tissue, decreasing heart failure symptoms	[53] [54]
Promotion of monocyte adhesion, proinflammatory Lipid metabolism	miR-21	targets PPAR α targets TLR4 and NF-κB	enhances the expression of VCAM-1 and MCP-1 and the adhesion of monocytes to ECs LPS-induced lipid accumulation and inflammatory response in macrophages	Overexpression of miR-21 up-regulated ATP-1 activation, which was attenuated by exogenous expression of PPARα overexpression of miR-21 significantly decreased the secretion of IL-6 and increased IL-10 levels	[55] [56]
Induces ECs apoptosis, development of atherosclerosis	miR-142-3p	up-regulation of Rictor and the Akt/eNOS	atherosclerosis-associated ECs apoptosis	T, the antagomir-142-3p attenuated endothelial apoptosis and retarded the atherosclerosis progression in the aorta of ApoE-/- mice	[57]
Increase pro-inflammatory cytokines	miR-342-5p	targets Akt1	induces proinflammatory mediators such as NOS2 and IL-6 in macrophages via the upregulation of miR-155	T, the miR-342-5p antagomir upregulated Akt1 expression and suppressed the expression of miR-155 and NOS2	[58]
Mature plaques					
Marker of response to clopidogrel, targets P2Y12 receptor	miR-223-3p	possible P2Y12 site targeting	on-clopidogrel platelet reactivity	decreased miR-223 expression was a predictor of	[41]

Critical Stages in Atherosclerosis	miRNA	Mechanism	Effect of miRNA Action	Therapeutic Approach (HUVEC or Animal Studies)	Ref.
				low responders to clopidogrel	
Plaque stabilization	miR-145	targets KLF4,5	VSMCs contractility, increase fibrous cap area, reduce the necrotic core area	T, delivery of miR-145 may limit atherosclerotic plaque growth, and restore contractile levels in VSMCs	[59] [60]
Macrophage polarization	miR-455	targets SOCS3	decreased expression leads to ECs injury induced by ox-LDL	T, overexpression with miR-455 inhibits apoptosis, migration of VSMCs, and lowers ox-LDL	[61]
Marker of platelet activation, targets COX-1 receptor through the regulation of TXS	miR-34b-3p	targets TBXAS1	miR-34b-3p may regulate the platelet response by suppressing TBXAS1 expression and megakaryocyte proliferation	T, miR-34b-3p may facilitate the antiplatelet efficiency of aspirin through inhibiting TBXAS1	[62]
Responsive to antiplatelet therapy	miR-126-3p	affects ADAM9 and P2Y12 receptor expression	Increases platelets aggregation	T, antagomiR against miR-126-3p reduces platelets aggregation	[63]
Decreases size of atherosclerotic lesions, alleviate ox-LDL-induced ECs injury, angiogenesis and vascular integrity	miR-126-3p	activation of VEGF and NF-kB signaling	decreased expression in advanced carotid plaques with high discriminating value (AUC: 0.998)	patients with severe carotid stenosis demonstrated down-regulation of miR-126	[64]
Plaque stabilization	miR-210	targets the APC gene, affecting Wnt signaling and regulating VSMCs survival	enhances fibrous plaque stability in mature plaques	T, miR-210 mimics prevent carotid plaque rupture; modulating miR-210 improved fibrous cap stability	[65]
Promotes atherosclerosis growth	miR-103-3p	targets KLF4	stimulates inflammatory activation, and uptake of oxidized LDL cholesterol	T, reduction in miR-103 levels results in the reduction of atherosclerosis and endothelial inflammation	[66]

Critical Stages in Atherosclerosis	miRNA	Mechanism	Effect of miRNA Action	Therapeutic Approach (HUVEC or Animal Studies)	Ref.
Decreases ECs regeneration and repair	miR-652-3p	suppression of the endothelial repair gene Ccnd2	inhibits ECs regeneration and repair following mechanical injury	downregulates Ccnd2 in endothelial cells, lowering cell proliferation	[67]
Plaque stabilization	miR-223	targets TLR4	reduces foam cell formation, and production of pro-inflammatory cytokines	Overexpression decreases lipids deposition and inflammation	[68]
Plaque instability	miR-92a-3p	SIRT1, H_2O_2-induced changes in VSMCs	increased apoptosis, oxidative stress, CIMT, and pro-inflammatory MMP-9	miR-92a overexpression regulates the expression levels of MMP-9 and TIMP3	[69] [70]
Plaque instability	miR-133a	Matrix metallopeptidase 9	inhibits the proliferation of VSMCs and induces apoptosis	the miR-133a-3p mimic inhibited proliferation and promoted VSMC cell apoptosis	[71]
Promotes endothelial migration	miR-486	targets HAT1	induces apoptosis and oxidative stress, pro-atherosclerotic, affects endothelial migratory activity	Inhibition of miR-486 limits foam cell formation by increasing cholesterol efflux	[69] [72]
Increases pro-inflammatory cytokines	miR-331	down-regulation of SOCS1	a pro-inflammatory response in atherosclerotic plaques	miR-331 suppression causes up-regulation of SOCS1 and anti-inflammatory mechanism in atherosclerosis	[73] [74]
Plaque stabilization	miR-100	down-regulation of E-selectin and VCAM-1	miR-100 restrains vascular inflammation in vitro and in vivo by suppressing endothelial adhesion molecule expression and thereby attenuating leukocyte–endothelial interaction	Inhibition of miR-100 Stimulates Atherogenesis in Mice	[75]
Plaque instability	miR-105	transported via HDL [42][43][44]	overexpression of miR-105 in patients with	HDL can deliver miRNA-105 to recipient cells,	[76]

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In mice, inhibition of miR-92a reduces endothelial inflammation and atheroma plaque size through the regulation of Kruppel-like factor 2 (KLF2) [47]. Similarly, miR-34a aggravates and accelerates vascular senescence through the downregulation of SIRT1 and AXL Receptor Tyrosine Kinase [48], whereas miR-34a inhibition by anti-miR-34a

Critical Stages in Atherosclerosis	miRNA	Mechanism	Effect of miRNA Action	Therapeutic Approach (HUVEC or Animal Studies)	Ref.
			[49][86]		miR-34a
			[48] familial hypercholesterolemia	contributing to altered gene expression	and ATP-enhanced [48][49]. ECs
Plaque instability [48][50][51][87]	miR-155	Targets the transcription factor HBP1	Increase macrophages, foam cells content, and necrotic core in plaques	T, inhibition of miR-155 reduced necrotic core, apoptosis, and prevented progression of atherosclerosis	[77][78] holesterol n of foam transport etabolism, ein levels nages [88]. transport [87] [88]
Plaque instability	miR-124	Targets P4HA1	Inhibits collagen synthesis in atherosclerotic plaques	Overexpression of miR-[88]124 increased the expression of anti-inflammatory cytokines by binding p38 signaling pathway	[79][80] s in ECs, signaling stimulate [53][54][73][89][90]
Plaque instability	miR-134	[52] ANGTPL4/LPL	associated with chronic inflammation (hs-CRP and TNF-α), cholesterol mass, and plaque vulnerability features on ultrasonography	T, lower LPL activity with inhibitors of miR-134	[81][82][83] NOS, and [91] s-derived
Lipometabolism	miR-122	inhibits AMPK and SIRT1	[92][93] correlated with TC, TG, and LDL-C levels	serum level of miR-122 [91] correlated with atherosclerosis severity	[84] ease, that from the ation and targeting rosis [45].

Moreover, miR-520c-3p mimics may act as a promising therapeutic strategy for atherosclerosis [45]. The VSMCs equilibrium plays a great role in the inhibition of atherosclerosis. The maintenance of contractile phenotype prevents atherosclerosis [45][59][60][91][92][93][94]. Of the miRs capable of the contractile function recovery in VSMCs, miR-22 and miR143/145 are probably the most investigated ones, and are potential therapeutic targets [59][60][91][94]. Intravenous delivery of miR-143/145 extracellular vesicles blocked atherosclerotic lesion progression and exerted protective effects on intima-media complex [59][60], while miR-22 restores contractile phenotype of VSMCs without a negative impact on EC's function [95]. In addition, miR-22 inhibits intima-media hyperplasia, which is important both for inhibition of atherosclerosis plaque growth, as well as in the restenosis following stent implantation [46][95].

Some miRNAs were investigated in the context of carotid plaques, including miR-520, miR-455, and miR-105. Some are common for many arterial territories, including miR-21, miR-27, miR-100, and miR-122 (**Table 1**) [45][95][96][97][98][99][100][101][102].

ABCA1: ATP-binding cassette subfamily A member 1; ABCG1: ATP-binding cassette subfamily G member 1; Akt: protein kinase B; AMPK: Adenosine monophosphate–activated protein kinase; ANG II: angiotensin II; ANGTPL/LPL: Angiopoietin/lipoprotein lipase; Ccnd2: Cyclin D2; CIMT: carotid intima-media thickness; Dlk1: delta-like 1 homolog; eNOS: nitric oxide synthase; ECs: endothelial cells; ET-1: Endothelin 1; H2O2: hydrogen peroxide; HAT1: Histone acetyl-transferase 1; HMG-box transcription factor 1; hs-CRP: high-sensitivity C-Reactive Protein; IGF: insulin growth factor; KLF: Kruppel-like factor; LXRα: Liver X receptor α; LPS: lipopolysaccharide; MAP3K10: mitogen-activated protein 3 kinase 10; MCP-1; monocyte chemotactic protein-1; MMP: metalloproteinase protein; n/d: no data available; NF-κB: nuclear factor-κB; P4HA1: prolyl 4-hydroxylase subunit alpha-1; PPARα: peroxisome proliferators-activated receptor-α, RelA/p65: REL-associated protein involved in NF-κB heterodimer formation p65 subunit; sVEGFR1: soluble VEGF receptor-1; SIRT1: sirtuin 1; SOCS1: suppressor of cytokine signaling 1; T: therapeutic approach; TBXAS1: thromboxane synthase thromboxane A synthase 1; TLR4: toll-like receptor 4; TNF-

α: tumor necrosis factor alpha; VCAM-1: vascular cell adhesion molecule-1; VSMC: vascular smooth muscle cells; VEGF: vascular endothelial growth factor.

When the anti-atherothrombotic miRNAs are overbalanced by the pro-atherothrombotic miRNAs, researchers can steadily observe carotid intima-media complex thickening (CIMT), followed by the occurrence of focal non-calcified lesions [102]. Then, a formation of mature plaques composed of lipid and necrotic cores, fibrotic matrix, and calcifications are observed, accompanied by inflammation and angiogenesis. The first caution that should attract the attention of clinicians is CIMT [103][104][105]. CIMT, in ranges above the 75th percentile for age and gender, can even be observed in teenagers and young adults, particularly if accompanied by atherosclerosis risk factors, such as diabetes or familial hypercholesterolemia [106][107]. This parameter is well correlated with risk of cardiovascular events, such as cardiovascular death (CVD), IS, and myocardial infarction (MI) [103][104][105]. It has also a good predictive value for a presence of significant atherosclerosis in the other territories, e.g., coronary arteries [108][109]. Several miRNAs are associated with CIMT, including miR-22, miR-29a, miR-143/145, and miR-92a [46][70][110][111]. With increasing CIMT, atherosclerotic process accelerates. There is a huge role for metalloproteinases (MMP), such as MMP-2 and MMP-9, as they are associated with a promotion of plaque growth and CIMT increase, rather than a decrease in VSMCs contractility [111]. Interestingly, in advanced carotid plaques, migration and proliferation of VSMCs is beneficial, promoting the stability of the fibrous cap and prevention of plaque rupture [91][102]. This process in stimulated by the expression of miR-145 and miR-210 that drive the increase in plaque collagen content and a fibrous cap area, while at the same time reducing the necrotic core area [46][65][95].

In contrast, plaque instability is associated with increasing levels of MMP-2, MMP-9, the increasing size of plaque and the lipid and necrotic core, particularly when abundant in lipids [111][112][113][114]. MMP-9 is particularly important as it predicts future adverse cardiovascular events [71][111][112][113]. It was observed that MMP-9 is regulated by several miRNAs, including miR-92a, which is a predictor of plaque instability [114]. However, miR-92a is not necessarily always negative [115][116]. The upregulation of MMP-9 and the downregulation of TIMP3 in H_2O_2-induced VSMCs were observed to be reversed by mimicking miR-92a in addition to SIRT1 and siRNA, which may prevent a phenotypic change of VSMCs [115][116]. Other miRNAs associated with serum concentration of MMP-9 include miR-100, miR-155, miR-133a, and miR-223 [111][114]. These miRNAs are also linked to plaque instability and might be used as biomarkers of plaque conversion from a stable state into a vulnerable state [114][115][116][117][118][119].

Thus, it is of the utmost importance to identify carotid plaques that are likely to undergo transformation from the stable ones to vulnerable ones, prone to rupture and cause symptoms of cerebral ischemia. The research is ongoing for the identification of specific microRNAs that could prevent IS through the manipulation of their expression levels.

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