MicroRNA AND VASCULAR PATHOLOGY OF THE EYE

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Since the discovery of microRNAs just a few decades ago, our knowledge of these molecules and their potential as diagnostic biomarkers and therapeutic targets has significantly expanded. There is an ongoing discussion in the scientific community about the possibility of using microRNA for the diagnosis of cardiovascular diseases. It has been shown recently that levels of some microRNAs vary in vascular eye disorders, such as age-related macular degeneration and diabetic retinopathy. However, despite serious advances in our understanding of microRNA's role in eye pathology, we still do not know whether it is possible to use microRNA as a biomarker for central retinal vein occlusion. Perhaps, the discovery of such candidate microRNAs will help in making the timely diagnosis and improve the quality of medical care in patients with retinal vein occlusion.

Keywords: retinal vessel occlusion, microRNA, biomarkers, vascular pathology, retinal vessels

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МикроРНК И СОСУДИСТАЯ ПАТОЛОГИЯ ГЛАЗА

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С момента открытия первой микроРНК несколько десятилетий назад представления о данных молекулах как о биомаркерах и потенциальных терапевтических мишенях различных заболеваний значительно расширились. В современном научном обществе активно обсуждают возможность применения микроРНК для диагностики сердечно-сосудистых заболеваний. Более того, ряд недавно проведенных исследований доказывает, что уровни определенных микроРНК варьируют и при сосудистых заболеваниях глаза, включающих возрастную макулярную дегенерацию и диабетическую ретинопатию. Однако, несмотря на прогресс в исследовании роли некоторых микроРНК в диагностике ряда офтальмологических патологий, информации о возможности использования микроРНК в качестве биомаркеров окклюзии центральной вены сетчатки на сегодняшний день нет. Возможно, что поиск и идентификация данных молекул смогут облегчить постановку диагноза и улучшить качество оказываемой медицинской помощи.

Ключевые слова: окклюзия сосудов сетчатки, микроРНК, биомаркеры, сосудистая патология, ретинальные сосуды

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Making a timely and accurate diagnosis is crucial for effective treatment and positive clinical outcomes. This cannot be any truer for vascular disorders. MicroRNAs (miRNAs) were discovered back in 1993 [1]. They are a class of single-stranded non-coding RNAs constituted by 16 to 27 (an average of 22) nucleotides [2]. Transcription of miRNA precursor genes is regulated by genomic DNA methylation and histone modifications, which, in turn, vary across pathologies [3]. All around the globe, research teams are actively exploring the possibility of using miRNA as a diagnostic biomarker for a broad range of health conditions. Although it is not yet common practice to use miRNAs as biomarkers of eye diseases, such as retinal vessel occlusion, the ongoing research into their role in systemic vascular pathology suggests that they are potent diagnostic tools.

MicroRNA and systemic vascular pathology

There is a huge body of evidence that miRNA expression is changed significantly in systemic and localized vascular pathologies; the amassed data suggest tremendous diagnostic potential for miRNA and, specifically, circulating miRNA [4]. Circulating miRNA levels reflect physiological and pathological changes in the body, including cardiovascular and neurodegenerative disorders. For example, miR-1, miR-133b, miR-145, miR-208b, miR-499, miR-133a, and miR-208a are diagnostic biomarkers for coronary artery disease [5].

Patients with atherosclerosis have significantly elevated miR-122, miR-21, miR-130a, miR-211c and low miR92a, miR-222, miR-126 in their blood [6]. In addition to their diagnostic potential, these miRNAs and their inhibitors can be used to treat atherosclerosis [7].

Ischemic stroke and myocardial infarction are the most severe complications of atherosclerosis. Multiple studies conducted on animal models and human patients indicate a link between the levels of circulating and tissue microRNAs and ischemic stroke or its effects. In the acute phase of ischemic stroke, miR-124 and miR-21 are elevated whereas miR-221 concentrations decline; elevated miR-145 and miR-210 are predictors of a more favorable outcome [8]. Changes in miRNA levels are also reported in patients with myocardial infarction; specifically, such patients demonstrate a sharp decrease in miR-375 expression [9].

Hypertension is the most prevalent cardiovascular condition. It is a risk factor for many vascular disorders, including eye disorders. A Russian study investigated the profiles of miR-126, miR-155, miR-221, and miR-222 in hypertensive patients and healthy volunteers. Increased dispersion was observed for all studied miRNA in all hypertensive patients, as compared with healthy individuals. MiR-221 prevailed in hypertensive patients, whereas miR-126, in healthy volunteers [10].

Thus, the levels of some circulating miRNAs change in patients with systemic vascular disorders and therefore might be a potent candidate diagnostic biomarkers. Because systemic vascular disorders and vascular eye disorders have the same pathogenesis, there might be microRNAs that could act as biomarkers for conditions associated with impeded retinal blood flow. So far, no qualitative and quantitative miRNA analysis has been conducted for retinal vessel occlusion but the available data on changes in microRNA profiles accompanying vascular eye disorders suggest this research field holds great promise.

MicroRNA in age-related macular degeneration

Age-related macular degeneration (AMD) is the primary cause of irreversible central vision loss in elderly people. Choroidal neovascularization (CNV) leads to increased vascular permeability, fluid exudation, and irreversible damage to photoreceptor cells, causing vision decline. Being a complex progressive disease, AMD is linked to genetic (including complementary) and environmental factors [11]. Some miRNAs associated with complementary factors were found to change their regulation function in the blood and ocular tissue of patients with AMD. A PCR-based study of 384 miRNAs in the blood plasma of patients with AMD revealed that characteristics of 16 miRNAs were significantly changed in such patients and 10 other microRNAs were expressed only in individuals with exudative AMD [12]. A team of Italian researchers studied the expression profiles of different microRNAs in patients with or without AMD and in rats with experimentally induced retinal pathology. The levels of miR-9, miR-23a, miR-27a, miR-34a, miR-146a, and miR-155 were significantly different between diseased and healthy individuals. The most pronounced differences were observed for miR-27a, miR-146a and miR-155, suggesting they might have potential as biomarkers and therapeutic targets for treating AMD [13].

MicroRNA in diabetic retinopathy

The possibility of using microRNAs as biomarkers is being considered for diabetic retinopathy (DR), another serious visual impairment arising from a vascular disorder. DR is a common microvascular complication of diabetes mellitus (DM), which is currently recognized as a global epidemic. DR results from damage to microvessels following prolonged exposure to hyperglycemia. Progressive retinal ischemia triggers expression of hypoxia-inducible growth factors, including VEGF, which, in turn, stimulate retinal neovascularization [14]. Consequently, the blood-retinal barrier breaks down, leading to vascular leakage and retinal edema [15]. The analysis of circulating miRNAs isolated from serum and plasma samples of patients with and without DR revealed changes in the expression of many miRNAs in patients of different age, with different DM types, different time of onset, etc. [16]. There were reports of quantitative and qualitative changes in the profiles of miR-126 [17–19], miR-150 [20], miR-155 [21], and miR-200b isolated from patients with DR. Of all those miRNAs, miR-155 and miR-126 had the highest clinical relevance [22]. A research group from China compared serum levels of miR-126 in patients with DR and healthy volunteers by means of real-time PCR and found statistically significant differences in miR-126 expression between the two cohorts. According to the analysis of blood serum samples collected from patients with proliferative (PDT) and non-proliferative (NPDT) diabetic retinopathies, miR-126 levels varied across patients with retinal pathology depending on its severity. MiR-126 concentrations were declining as proliferative retinal pathology was progressing. The researchers were able to determine the diagnostic thresholds for miR-126 that could be used to predict the risk of PDT and NPDT and detect borderline conditions at high risk of transformation into PDT. The researchers pointed out that miR-126 could be used as a biomarker of retinal endothelial damage and early stages of PDT [17].

Using this information, we shortlisted a few microRNA candidates that in our opinion have the best diagnostic and prognostic potential as candidate biomarkers of retinal vein occlusion (Table).

miR-126

MiR-126 is one of the key pro-angiogenic microRNAs that regulate expression of some growth factors, including VEGF and FGF [23, 24]. MicroRNA expression profiles were studied on several animal models of human vascular eye disorders, including oxygen-induced retinopathy (DR-type neovascularization) and laser-induced CNV (wet ARMD). MiR-126 concentrations declined in the choroid of mice with laser-induced CNV [25] and also in the retina and choroid of rodents with oxygen-induced retinopathy [26]. Besides, mice with decreased miR-126 concentrations had signs of damage to the peripheral choroid [27]; stimulated elevation of miR-126 was shown to inhibit retinal neovascularization and breakdown of the blood-retinal barrier in mice with oxygen-induced retinopathy [28]. These findings suggest that miR-126 might be an important biomarker mirroring the condition of

Table 1. Expression of candidate microRNAs in different pathologies

	miR-126	miR-155	miR-21
Vascular disorders			
Atherosclerosis	microRNA expression decreases [6]	[6]*	microRNA expression increases [6]
Ischemic stroke	microRNA expression decreases [36]	[36]*	microRNA expression increases [36]
Hypertension	microRNA expression increases [10]	[10]*	microRNA expression increases [38]
Coronary artery disease	microRNA expression increases [10, 24]	[10, 39]*	microRNA expression increases [38]
Eye disorders			
Diabetic retinopathy	microRNA expression decreases [17–19, 22]	microRNA expression increases [31]	microRNA expression increases [40]
Age-related macular degeneration	microRNA expression decreases [23–25]	microRNA expression increases [13]	microRNA expression increases [35]

Note: *— Changes in microRNA expression depend on the character of the pathology.

the choroid in various pathologies and a potential therapeutic target for developing new approaches to the management of eye disorders.

miR-155

MiR-155 is a proinflammatory microRNA that is specifically expressed in atherosclerotic plaques and proinflammatory M1 macrophages [6]. Retinal miR-155 expression undergoes significant changes in wet ARMD, experimental oxygen-induced retinopathy [29], light-induced retinal degeneration [30], and streptozotocin-induced DR [31]. Its deficit leads to the shrinkage of vascular areas and neovascularization in the rodent model of oxygen-induced retinopathy [29]. Besides, miR-155 was proved to regulate the levels of complement factor H in ARMD [32], maintaining its role in the angiogenesis and inflammation in a range of eye disorders. MiR-155 is an important biomarker that reflects the unfolding of the proinflammatory cascades accompanying the progression of vascular disorders. In addition, this miRNA is being investigated as a potential therapeutic target in eye pathology.

miR-21

MiR-21 is known to be linked to tumor formation and neovascularization [33]. Its expression changes in cardiac pathology [34]. MiR-21 plays a crucial role in the pathogenesis of ARMD. It participates in the regulation of retinal vessel growth, which can be inferred from high miR-21 expression in retinal endothelial cells. Increased miR-21 expression was detected in the experimental mouse model of laser-induced CNV. In another study, stimulation of miR-21 expression inhibited proliferation and migration of cultured endothelial cells through targeted inhibition of certain proteins that affect the dynamics of actin networks [35]. This indicates the diagnostic and modulating potential of miR-21.

CONCLUSIONS

There is a paucity of research studies looking at the expression profiles of miRNA genes in eye pathology. Nevertheless, the available data suggests that miRNAs might hold great promise as potent diagnostic markers of eye disorders, such as retinal vein occlusion. The comprehensive analysis of their expression will help to conduct minimally invasive screening, provide adequate treatment and take timely prevention measures. It is important to develop microRNA panels and determine their threshold values that signal the risk of complications in patients during or after therapy.

Further basic and clinical research on complex 3D organoid and spheroid models is needed to better understand the role of individual microRNAs or their clusters and to evaluate their diagnostic and therapeutic potential in retinal vascular pathology.

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