

A Role of MicroRNA in the Pathogenesis of Ischemic Stroke

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Abstract

Ischemic stroke (IS) is one of the leading causes of death and disability worldwide. Among all the causes of IS, cardioembolic stroke (CES) accounts for up to 40%. Based on the literature data, modern ideas about the role and location of cardiac diseases in the pathogenesis of CES are presented. The leading cause of CES is non-rheumatic atrial fibrillation. Numerous attempts to study and prove the genetic nature of the development of IS led to the discovery of new markers-microribonucleic acids (microRNAs), the regulators of gene expression, that inhibit mRNA translation and play a key role in the pathogenesis of IS. This review summarizes the current knowledge of microRNAs, their ability to simultaneously regulate several target genes and their significance as potential diagnostic and prognostic biomarkers in IS.

Keywords: *Ischemic Stroke; Cardioembolic Stroke; MicroRNA; Biomarkers*

Introduction

One of the most important medical and social problems health care are vascular diseases of the brain, the importance of which is determined by their high share in the structure of morbidity and mortality, as well as significant indicators of labor losses and disability in stroke [1]. The annual death rate from strokes in Russia is one of the highest in the world (175 cases per 100 thousand population per year). Stroke is the leading cause of disability of the population. Patients who have suffered stroke, impose special obligations on family members, significantly reducing their labor potential and lay a heavy socio-economic burden on society as a whole [2]. All this causes interest in the problem of stroke, the search for ways of prevention and effective treatment [3].

In Russia, among the diseases of the circulatory system, the first place is occupied by arterial hypertension: 7801.4 cases per 100 thousand adults population [4-6]. Reducing elevated blood pressure reduces absolute risk development of stroke by 1.04% over 5 years and relative-by 38.0% [7,8]. As part of the development of the concept of heterogeneity of ischemic strokes (IS) a significant place is occupied by the study of cardioembolism that comprise 22 - 40% of all IS [9-11].

75% of patients with IS have different cardiac pathology, including chronic heart failure (CHF), coronary heart disease (CHD), arrhythmias, heart defects, cardiomyopathy, congenital anomalies, tumors [12]. Cardioembolic stroke (CES) is associated with severe residual disorders of motor, speech, coordination functions, high risk of recurrence, which significantly reduces the quality of life of patients [10,13]. In this regard, timely recognition of the cardiac cause of stroke and determining the optimal strategy for its secondary prevention is relevant.

So far, more than 20 causes of cardioembolism have identified, the most significant among them is non-valvular atrial fibrillation (AF), which accounts for 40 - 50% of all cases of CES [14]. CES associated with AF is characterized by a more severe course, a worse prognosis and a high risk of recurrence [15]. The introduction of neuroimaging and ultrasound methods into clinical practice made it possible to more accurately and early to diagnose IS, to establish etiopathogenetic connections of cardiac and cerebral pathology, to carry out pathogenetically reasonable tactics of management of the patient. It is important to study the genetic causes and their role in the pathogenesis of the disease. Among them, non-coding ribonucleic acids (RNA) attract great attention [16].

MicroRNAs-new regulators of gene expression

According to the results obtained in the course of research on the program ENCODE [17,18], at least 75% of the human genome is capable of transcribing and more than half of it is associated with non-coding RNA (ncRNA) that do not contain open reading frames for protein translation. They are divided into two large groups: "long" ncRNA (from 200 nucleotides to 10 tons of nucleotides) and "small" ncRNA (less than 200 nucleotides). Among the latter, the most studied class of microRNAs that perform important regulatory functions in the life of normal cells and play an important role in the regulation of translation and degradation of matrix RNA (mRNA).

MicroRNAs - ncRNA, comprising 19 to 24 nucleotides, are formed from longer RNA precursors and have a specific spire structure [19,20]. MicroRNAs are effective post-transcriptional regulators of gene expression [21-24]. Regulation is carried out by complementary binding of microRNAs to partially complementary sites in 3' - untranslated sites of mRNA targets [18].

MicroRNAs were first discovered in 1993 in the study of retroviruses [25]. To date, microRNAs have been identified in all multicellular organisms, including plants, worms, insects and vertebrates, indicating an early evolutionary origin this mechanism of gene expression regulation [26,27]. It is established that microRNAs play a key role in both normal development processes both in the organism and in pathology, they take part in the implementation of the inflammatory reaction, cell proliferation, differentiation, apoptosis and oncogenesis [28-33]. *In vivo* and *in vitro* experiments have shown the role of microRNAs in IS pathogenesis by regulating oxidant stress, inflammation, apoptosis and endothelial dysfunction [34,35]. Few clinical and genetic studies have also shown that circulating microRNAs are potential biomarkers, which can be used to diagnose IS and predict its outcome [36,37].

The severity and reversibility of ischemic damage depends on degree of decrease in blood flow. So, the area of the brain with the most pronounced reduced blood flow is damaged within 2 minutes with the moment of ischemia development [38]. This nuclear zone of ischemia is surrounded for several hours by ischemic, but still living tissue-the zone of ischemic half-shade (penumbra). It is assumed that the latter can be a target for therapeutic effects [39,40]. Cerebral ischemia also causes a number of pathological processes (excitotoxicity, oxidative stress, inflammation and apoptosis) in the penumbra zone, which can lead to neuronal death (see picture). As can be seen in the picture, ischemia, due to a decrease in cerebral blood flow of any genesis, leads to a deficiency of oxygen and glucose in the brain, which causes loss of ATP and disruption of the Na⁺/K⁺-pump. The loss of the ion concentration gradient causes cytotoxic edema and the release of inhibitory amino acids. After lowering glucose levels, the availability of aerobic cell metabolism switches to anaerobic, leading to metabolic acidosis. These processes lead to cell death. Ischemia also causes activation of a number of early response genes that lead to inflammatory reactions, apoptosis and activation of matrix metalloproteinases, which can lead to brain edema or hemorrhage. After ischemia, kinase activation and enhancement of trophic factors are observed, which determine the recovery processes, including neurogenesis, synaptogenesis and angiogenesis [34].

An important pathogenetic link in the development of IS is hypoxia. Low RCO₂ is known to induce various microRNAs, including miR-210, miR-103, miR-181c, miR-373, miR-26b and miR-26a-2 [41-44]. Among them, miR-210, which is specifically sensitive to hypoxic stimuli, is the most studied [35]. It is shown [45] that miR-210 is induced by hypoxia in almost all cells and tissues. In addition, its blood level correlates with the course and outcome of acute IS. Compared to healthy patients, miR-210 expression was significantly reduced in patients with IS 7 and 14 days after the onset of the disease. MiR-210 levels in patients with favorable IS were significantly higher than in severe IS [35].

A number of studies (Y Chen., *et al.* 2017; S Yao., *et al.* 2016; X Zhou., *et al.* 2016; JR Tan., *et al.* 2017 and others) are devoted to studying the level of microRNA expression in patients with IS. So, Y Chen., *et al.* [36] determined the level of exosomal expression of microRNA-223 (miR-223) in patients with IS. They conducted a retrospective case-control study to determine the level of exosomal expression of miR-223 in IS patients and in healthy and compared this indicator in patients with different subtypes of IS. The authors showed that miR-223 levels in circulating exosomes are elevated in the debut of acute IS and tend to increase over time. Exosomal expression of miR-223 was positively correlated with the NIHSS score. It turned out that patients with KES had a higher level of exosomal miR-223 and patients with severe IS had a higher level of exosomal miR-223 expression. However, these studies were conducted on a small number of material without taking into account other subtypes of IS.

In IS, miR-223 performs the function of controlling the induced N-methyl-D-aspartate - receptor, which in turn weakens the flow of CA⁺⁺ into neurons [46], suppresses the level of glutamate receptor-2, thereby protecting ischemic tissue [47]. S. Yao., *et al.* [37] the role

of microRNA-455 (miR-455) in IS *in vitro* and *in vivo* was studied. The authors determined the level of miR-455 expression and its effect on the protection of neural cells from deaths. It turned out that miR-455 protects neurons from death after oxygen-glucose deprivation, suppressing TRAF3 expression and reducing the volume of mouse brain infarction after brain damage, due to occlusion of the middle cerebral artery.

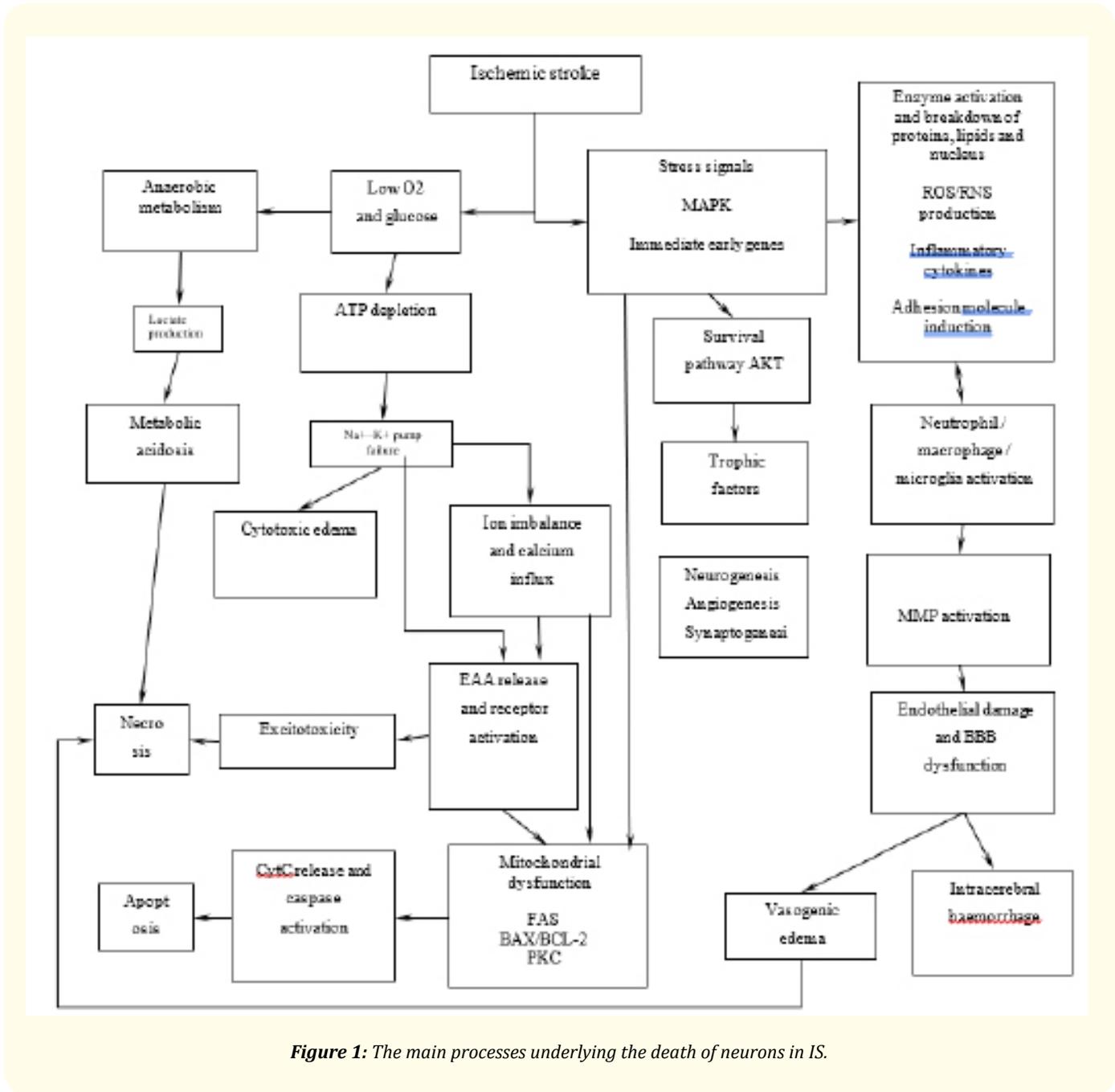


Figure 1: The main processes underlying the death of neurons in IS.

Expression levels of miR-185, miR-146a and miR-145 were determined in patients in acute and subacute stages of IS [48]. It turned out that miR-145 levels were comparable in patients and in healthy individuals, whereas miR-146a and miR-185 were present in small amounts in the blood in the acute phase of IS. Moreover, miR-146a levels were reduced in the acute phase of IS but increased significantly later. Subsequently, an increase in miR-146a activity in the subacute stage of IS was confirmed [49]. It was found that in IS miR-145

increases the volume of oxidant damage by suppressing the activity of the antioxidant enzyme superoxide dismutase, which plays an important role in the recovery of ischemic cells [50] and miR-146a suppresses the expression of cyclooxygenase type 2, which produces reactive oxygen, preventing the development of oxidant stress [51].

A study of the Association of microRNAs polymorphisms (miR-34a rs6577555C>A, miR-130a rs731384C>T, miR-150 rs73056059G>A and miR-155 rs767649T>A) with the risk of IS among members of the Korean population showed that miR-150G > A polymorphism may be associated with a predisposition to atherothrombotic IS and CES [52].

In experiments on mice found that overexpression microRNA let-7c-5p promotes inhibition of microglia activation and it has a neuroprotective effect, prevents neuronal apoptosis, which leads to a decrease in the volume of infarction and improvement of neurological deficit [52,53]. The results of recent studies have broadened the understanding of the important role of CD46 expression level and microRNAs inhibiting it in the development of CES. CD46 is a complement cascade inhibitor, its function is to protect autolytic cells against attack by foreign agents by the complement system. It is expressed by all cells except red blood cells; registered high expression of CD46 in blood cells and endothelial cells. CD46 is known to bind to CD9, which in turn is responsible for the activation and aggregation of platelets, which play an important role in the pathogenetic cascade of IS.

The results of the study [53] showed that CD46 expression levels were lower in patients with CES than in patients with non-cardioembolic IS. In addition, the authors revealed the maximum inhibitory activity against CD46 mRNA in 4x microRNAs (miR-19a, -20a, -185, -374b) in patients with CES. However, this study had too small a sample (13 patients with CES).

Conclusion

The foregoing indicates the undoubted importance of obtaining new data, expanding modern ideas about the importance of gene polymorphisms in the genetic control of the development of common diseases of the cardiovascular system. Thus, the diagnostic and prognostic significance of microRNAs determination in IS is not in doubt. MicroRNAs have high potential because they are endogenous molecules that are able to control the expression of genes involved in the pathogenesis of IS. Moreover, microRNAs can regulate genes that contribute to neuroprotection, neurogenesis and angiogenesis, leading to activation of repair mechanisms in IS [34]. However, the number and results of studies on the genetic aspects of cardiovascular disease do not yet correspond to the scientific and practical significance of the existing problem. In particular, many aspects of the unconditional role of both miRNAs and genes involved in miRNA biogenesis in the development of AI and its complications in humans remain unexplored. There are few domestic publications on the role of microRNAs in AI and studies conducted abroad are mainly experimental in nature. In aggregate, the data presented indicate that further study of the basic mechanisms of the pathogenesis of ischemic strokes and the search for new biomarkers for the development of AI is of both theoretical and practical interest to the clinician.

Thus, the genetic aspects of AI, in particular the role of miRNAs in the pathogenesis of stroke, are an urgent little-studied scientific problem with many unresolved issues.

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