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Review

Dissecting the role of miR-21 in different types of stroke

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ABSTRACT

Stroke is an important neurological disease in which blood flow to the brain is interrupted and it is becoming an increasing non-communicable disease in developing countries. Current treatment options for stroke is modifying lifestyle practice, diabetes treatment, drugs, and other factors management, but yet no cure is available in sight for the disease, despite it requires new insight into the molecular and therapeutic targets. In general, MicroRNAs (miRNAs) are small noncoding RNAs considered as of greater biological importance and controls molecular signaling pathways in diabetic pathogenesis. Among the reported MiRNAs, MIR-21 is considered to be an important MiRNA, which is frequently elevated in many types of types of strokes, suggesting that it plays an important role in cell proliferation, and apoptosis. Until now, there is no research paper that signifying the role of miR-21 in all types of strokes and the number of studies on the different category of strokes is limited, so in this paper, we are highlighting the recent investigations related to the significance of miR-21 in different types of strokes based on the up-to-date reports. It was found that MiR-21 was found to be normally up and down regulated in all types of strokes, however; we summarize the important research findings related to the role of miR-21 in different types of strokes.

1. Introduction

Stroke is a neurological disease in which blood flow to the brain is interrupted and it is becoming an increasing non-communicable disease in developed as well as in developing countries. There are two main types of stroke: ischemic, due to lack of blood flow and hemorrhagic due to bleeding, they result in part of the brain not functioning properly (Martinez and Peplow, 2017a). Recently, diagnosis, treatment, and understanding of stroke syndromes have improved dramatically over the years with the advent of modern imaging, the management of stroke similar to general care as recommended by various guidelines (Balami et al., 2013).

Current treatments for stroke include modified lifestyle practice, diabetes treatment, drugs, and other factors management, yet no cure is available in sight for the disease, despite it requires new insight into the molecular and pathophysiology. It has been known that there is no definitive treatment at reversing stroke syndromes, but it is significant to identify the signs and symptoms for an early diagnosis to rapid treatment of stroke, which can avoid further devastating complications (Balami et al., 2013).

MicroRNAs (miRNAs) are small noncoding RNAs considered as of greater biological importance and controls molecular signaling pathways in stroke pathology (Krishnan et al., 2017; Sekar et al., 2016). MicroRNA 21 has been an important MicroRNA frequently upregulated in all types of diseases, suggesting that it plays an important role in cell proliferation, and apoptosis (Sekar et al., 2017; Shincy et al., 2017). It has been reported that more than 20% of the miRNAs alter in the ischemic brain, demonstrating that miRNAs are promising mediators in the pathogenesis of ischemic stroke (Liu et al., 2016). Among the reported miRNAs, miR-21 is considered to be an important miRNA, which is frequently elevated in many types of types of diseases, suggesting that it plays an important role in cell proliferation and apoptosis (Sekar

Abbreviations: miR-21, microRNA21; miRNAs, microRNAs; mRNAs, messengers RNAs; MEG3, maternally expressed 3; OGD, oxygen-glucose deprivation; PDCD4, programmed cell death protein 4; PTEN, phosphatase and tensin homolog

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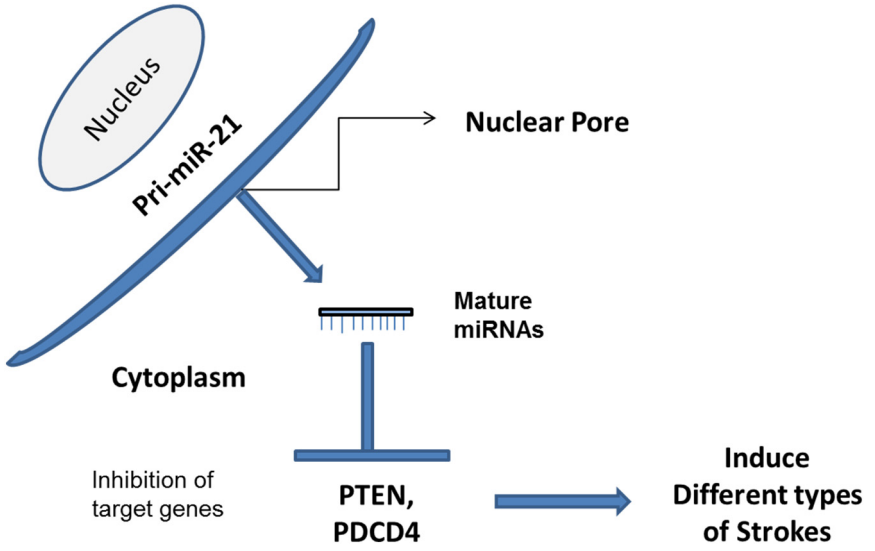

Fig. 1. The schematic representation of miR-21 function to induce different types of strokes in the cells.

et al., 2016; Sekar et al., 2017). It has been studied that the hsa-miR-21 is mapped to chromosome 17q23.2, closely downstream of the vacuole membrane protein 1 (VMP1) gene (Hurst and Lee, 2003) and Phosphatase and tensin homolog (PTEN) is a direct target for miR-21 in many diseases (Sekar et al., 2016; Sekar et al., 2017).

Interestingly, there is no paper that signifying the role of miR-21 in all types of stroke and the number of studies on the different types of stroke is sparse and the number papers related to miR-21 in stroke is very limited, So the present paper highlights the recent investigations related to the importance of miR-21 in different types of strokes based on the up-to-date reports (Fig. 1).

2. Role of miR-21 in ischemic strokes

An ischemic stroke occurs as the result of atherosclerosis, Hyperlipidemia, Hypertension, diabetes, smoking, alcohol consumption and Plaque Rupture (Rink and Khanna, 2011; Goldstein et al., 2001). Approximately 85% of all strokes are ischemic in origin and it has been known that atherosclerosis is a condition where fatty deposits or plaque buildup in the body's blood vessels. Elevated blood pressure, or hypertension, has long been recognized as a significant risk factor for stroke. Rupture of arterial plaque and subsequent embolic occlusion is one of the leading causes of stroke (Rink and Khanna, 2011).

Interestingly, miRNAs have emerged as key mediators of post-transcriptional gene silencing in both pathogenic and pathological aspects of ischemic stroke biology. Recent reports stated that microRNAs represent a strong candidate for the microRNA mediated therapeutic intervention of atherosclerosis (Hurst and Lee, 2003). A recent study stated that both miR-21 and miR-24 could be identified as diagnostic biomarkers in cerebral ischemia and might have potential therapeutic targets for the treatment of post-ischemic injury (Zhou and Zhang, 2014a). Interestingly, one of the studies indicated that miR-21 play roles in the development of ischemic stroke and suggesting that miR-21 might be potential diagnostic biomarkers or therapeutic targets for ischemic stroke (Xiang et al., 2017). Another study data uncover a novel mechanism of lncRNA MEG3 as a ceRNA by targeting miR-21/PDCD4 signaling pathway in regulating ischemic neuronal death, which may help develop new strategies for the therapeutic interventions in cerebral ischemic stroke (Yan et al., 2017).

An investigation revealed that the role of miR-21 in the pathological processes that follow cerebral ischemic injury and examined the potential use of miR-21 in stroke diagnostics as sensitive plasma biomarkers. miR-21 may have an antiapoptotic effect in N2A neuroblastoma cells following oxygen-glucose deprivation (OGD) and reoxygenation (Zhou and Zhang, 2014b). A Study by Yang et al. (2014), miR-21 has been demonstrated to function as protectors against ischemia-reperfusion (I/R) and/or hypoxia-reperfusion (H/R)-induced myocardial injury (Yang et al., 2014). During I/R and H/R, forced expression of miR-21 upregulated the Akt signaling activity via suppressing the expression of phosphatase and tensin homolog (PTEN) which further suppressed the expression of caspase-3 and indicated that miR-21 may be a promising agent for the treatment of I/R and H/R-induced myocardial injury and stroke (Yang et al., 2014).

It has been noted that stroke patients and atherosclerosis subjects show significantly higher miR-21 level and may serve as a novel biomarkers for atherosclerosis and stroke (Tsai et al., 2013). miR-21 levels higher in Middle Cerebral Artery Occlusion (MCAo) male Wister rats (Liu et al., 2013). As we know that miR-21 is a strong antiapoptotic factor in some biological systems. The recent investigation by Buller et al. (2010) suggesting that in situ hybridization revealed that miR-21 expression was upregulated in neurons of the ischemic boundary zone and increased miR-21 levels were observed in neurons isolated from the ischemic boundary zone by laser capture microdissection as compared with homologous contralateral neurons 2 days after stroke. Their data also indicate that overexpression of miR-21 protects against ischemic neuronal death. These findings suggest that miR-21 may be a therapeutic molecule for the treatment of Ischemic stroke (Buller et al., 2010).

In general, myocardial tissue injury caused by ischemia and hypoxia is a major cause of fatal diseases like myocardial infarction and stroke. It has been demonstrated that miR-21 involved trimetazidine (TMZ) induced anti-apoptosis during H/R injury in the H9C2 cell. TMZ increased miR-21 expression which further upregulated the Akt signaling activity via suppressing the expression of phosphatase and tensin homolog (PTEN) in H/R H9C2 cell, suggesting that miR-21 plays a major role in myocardial injury and Ischemic stroke (Yang et al., 2015).

Recently, Circulating miRNAs have emerged as promising biomarkers for ischemic stroke (Wu et al., 2017). Recent qRT-PCR validation confirmed that serum levels of miR-21 were significantly increased in ischemic stroke patients. Up-regulated miR-23b-3p, miR-29b-3p, and miR-21-5p could clearly differentiate between Ischemic Stroke and transient ischemic attack patients, suggesting that miR-21 could be a circulative biomarker for Ischemic Stroke and transient ischemic attack patients (Wu et al., 2017).

miR-21 acting as an anti-inflammatory marker for Ischemic Strokes (Gaudet et al., 2017) and miR-21 correlated with advanced vascular