Biomedical Research 2017; 28 (22): 9739-9744

ISSN 0970-938X
www.biomedres.info

MicroRNA-148a regulates inflammation in microglia induced by oxygen-glucose deprivation via MAPK pathways.

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Abstract

Inflammation and immune response occupy an important place in the progress of acute ischemic stroke. Microglia are a kind of resident immune cells in the central nervous system (CNS), play a vital regulatory role in the neuroinflammatory processes. Nowadays, miRNAs have been shown to play significant roles in the inflammatory response. MiR-148a was reported to be related in acute ischemic stroke. However, the specific connection between miR-148a and acute cerebral ischemia is still awaited to be studied, as well as the involved mechanisms. Here, we aimed to figure out the role of miR-148a played in the inflammatory activation of microglial cells. We found that miR-148a was downregulated in activated microglia induced by Oxygen-Glucose Deprivation/Reoxygenation (OGD/R). Subsequently, microglial cells were transfected with miR-148a mimic or inhibitor to alter the expression of miR-148a. Results showed that upregulation of miR-148a in primary microglial cells suppressed the secretion of inflammatory mediators such as TNF-α, IL-1β, and IL-10. On the contrary, downregulation of miR-148a in microglia promoted the expression of the inflammatory mediators, indicating that miR-148a might play a justicial role in regulating the neuroinflammation. Further, we discovered that transfection of primary microglial cells with miR-148a mimic observably inhibited the activation of p38MAPK, ERK, and JNK. All the results demonstrated that miR-148a could protect OGD/R injury by inhibiting the microglial activation thus attenuating neuroinflammation *via* p38MAPK, ERK, and JNK pathways.

Keywords: MiR-148a, OGD/R, Activated microglia, MAPK pathways

Accepted on September 27, 2017

Introduction

Ischemic stroke is one of the major public health problems, characterized by a high morbidity, mortality and disability [1]. Due to its sudden onset and rapid progression, there is still lacking of effective therapeutics for acute cerebral ischemic injury; the development of novel treatments for acute ischemic stroke is urgently needed. MicroRNAs (miRNAs) are ribonucleic acids with short (17-25 nucleotides long) non-protein coding [2], they are important regulators of gene expression and play important roles in the initiation and progression of several diseases [3]. It has been estimated through bioinformatic approaches that 30% to 80% of protein-coding genes may be under the regulation of miRNAs [4], with each miRNA targeting up to several hundred genes [5,6]. Related reports have shown that miRNAs, such as miRNA-126, -146a, -27b, -17-5p, and -424 play significant roles in the inflammatory responses, and have a profound impact on neuroprotection after cerebral ischemia [7]. Studies have demonstrated an association between miR-148a and ischemic stroke, with a decreased miR-148a level in the blood of patients suffering from acute ischemic stroke compared to normal people [8]. However, the function of miR-148a in acute cerebral ischemia has not been elucidated.

Researches have revealed that post-stroke neuroinflammation is a key determinant of acute outcomes and long-term prognoses [9,10]. After the occurrence of ischemic stroke, the ensuing neuronal cell death triggers a cascade of inflammatory responses contributing to secondary brain damage [11]. Microglia, the major source of cytokines and other immune molecules, will be activated and play a vital role in regulating inflammatory reactions by releasing diverse inflammatory cytokines such as interleukin-1 beta (IL-1β), necrosis factor-α (TNF-α) and interleukin-10 (IL-10) [12,13]. The suppression of microglial activation following stroke can prevent brain injury and represent an attractive therapeutic strategy for stroke [14].

The Mitogen-activated protein kinase (MAPK) signaling pathway is involved in directing cellular response to oxidative stresses, cellular apoptosis, as well as inflammation and cytokine stimulations [15,16]. Previous research reported that overexpression of miR-148a significantly inhibited cutaneous squamous cell proliferation and metastasis via down-regulation of MAPK pathways [17]. In this study, we aimed to figure out