Inflammation-related and Brain-enriched MicroRNAs Influence the Activation of Microglia Response to In vitro Oxygen-Glucose Deprivation

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Received: March 17, 2014
Published online: June 14, 2014

Microglia is one of the major resident immunocompetent cells in the central nervous system (CNS) and has become an important cellular component for understanding brain diseases. MicroRNAs (miRNAs) are small, noncoding RNAs molecules that regulate expression of protein-coding mRNAs on the post-transcriptional level; miRNAs plays important roles in microglial activation in response to brain ischemia and other stressors. Through culturing primary rat microglial cells and establishing a microglial activation model by oxygen-glucose deprivation (OGD). We found that the viability of the microglia was time-dependent and expressions of inflammation-related miRNAs (miR-146a, -21, -181a, -221, and -222), and brain-enriched miRNAs (miR-124, -134, -9, -132, and -138) in microglia were modulated in an OGD model of ischemic insult. This research highlight discusses the findings of the recent study and the investigators’ active research endeavors.

Keywords: MicroRNAs; Microglia; Oxygen glucose deprivation; Activation

To cite this article: Huimin Kong, et al. Inflammation-related and Brain-enriched MicroRNAs Influence the Activation of Microglia Response to In vitro Oxygen-Glucose Deprivation. Inflamm Cell Signal 2014; 1: e123. doi: 10.14800/ics.123.

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Microglial cells are the resident macrophages of the brain, which have a very important role in brain surveillance and response to pathological insults [1]. Under physiological conditions, resting microglia play critical roles in brain homeostasis and in supporting neuronal function; in the activated state, they undergo morphological changes, proliferation, chemotaxis, and produce numerous chemokines and cytokines involved in brain immunomodulatory and inflammatory responses [2-4]. It can occur immediately in response to any kind of brain disturbance and is considered as a common early feature of many brain diseases [5].

MicroRNAs (miRNAs) are small noncoding RNAs
that control multiple developmental processes at the post-transcriptional level. A lot of evidences suggest that miRNAs dysregulations are responsible for many types of human disease, including pediatric central nervous system (CNS), cardiovascular and chronic disorders [6-8]. Recently, Ponomarev et al reviewed the role of miRNAs in microglia differentiation, activation, and polarization in normal and diseased CNS [9]. Furthermore, research of Zhang et al found that miR-21 ectopic expression partially protect the neurons form cell death caused by activated microglia in response to hypoxia, suggesting a novel potential therapeutic target for brain hypoxic diseases associated with microglial activation [10]. It was found that miR-424 over-expression decreased ischemic brain injury through suppressing microglia activation, suggesting a novel miRNA-based intervention strategy for stroke [11].

MiRNAs plays important roles in the extent and timing of the innate immune response pro-inflammatory phase [12]. Recent researches showed that inflammation-related miRNAs, including miRs (146a, 21, 181a, 221, and 222), have a close relationship with multiple CNS diseases, including mesial temporal lobe epilepsy (MTLE) [13-15], and ischemic injuries [16, 17]. Seventy percent of experimentally-detected miRNAs are found in mammalian brain tissues [18]; among these, at least seven brain-enriched miRNAs including miRs (124, 134, 9, 132, and 138) have been described. And they have been found to play a role in CNS development and multiple brain diseases [14, 19, 20].

Hypoxia is a major pathogenic factor in disturbing brain functions in seizure disorders, hypoxic-ischemic encephalopathy (HIE), and other ischemic brain diseases. It could result in proliferation and activation of microglia, and induce specific changes in miRNA expression [21].

In our recent study entitled “Changes in Microglial Inflammation-related and Brain-enriched MiRNAs Expression in Response to In vitro Oxygen-Glucose Deprivation” [22] we used primary rat microglia cells OGD activated model and detected the expressions of the above 10 inflammation-related and brain-enriched miRNAs at different activated conditions.

We found that the viability of the microglia was time-dependent after OGD pretreatment. The expression of miR-146a in response to different durations of OGD was significantly up-regulated. In accordance with recent report that miR-146a was found to negatively regulate the astrocyte-mediated inflammatory response [23]. And miRs (21, 181a, 221 and 222) have similar expression increase in OGD microglia after 10 minutes, which correspond to the maximal reactivity of the microglia in response to OGD, indicating a potential link between their over-expression and microglia activation. At the same time, we found that the expressions of miRs (124, 132, 134, and 9) were significantly up-regulated at 5 minutes of OGD before the maximal reactivity of microglia. This may reflect that they have a critical role in stopping the activation of microglia. In the research of human cancers, miR-138 was well correlated to an increase in telomerase activity [24], and was also obviously up-regulated in microglia after 10 minutes of OGD. This indicates that it may have some relationship with microglia’s protective role in CNS tumors. These findings are an important step in understanding how inflammation-related and brain-enriched miRNAs may influence microglias’ activation, which plays a very important role in the pathogenesis of multiple brain diseases.

Our research group is vigorously working to understand the mechanisms of many CNS diseases including meningitis [25-27], intractable epilepsy [13, 15, 28] and ischemic injuries [22]. Recent studies have shown that brain inflammation is an important factor contributing to almost all CNS diseases and activation of microglia is considered to be neuroinflammation hallmark. But the exact mechanism of microglia implication in neuroprotection and neurodegeneration is still not very clear. MiRNAs are a new class of endogenous, non-protein-coding, small RNAs. Their expressions are altered in multiple CNS injuries, suggesting an important role in the cellular response to stress. It is largely accepted that miRNAs play an important role in hypoxic stress cellular response [23, 29]. Researches about inflammation-related and brain-enriched miRNAs help us open another avenue to understand the brain diseases. Our research detected the effect of different OGD time to microglial viability in primary cultured cells by immunofluorescence, MTT assay and PI (propidium iodide) staining methods. And qPCR (real-time PCR) were performed to detect the dynamic changes in expressions of inflammation-related miRs (146a, 21, 181a, 221, and 222) and brain-enriched miRs (124, 134, 9, 132, and 138) in resting microglia and after challenge with OGD. These miRNAs may play a role in activation of the microglia and related neuroinflammation modulation. This is a better foundation to study the modulation mechanism of microglia activation on gene level. However, neuroinflammation is a complex process that involves astrocytes, macrophages and neurons. Further work is required to understand the function of these miRNAs so that we can provide novel targets for cell-specific therapeutic interventions in brain ischemic injuries.

To date, our group has demonstrated the differential expressions of inflammation-related and brain-enriched miRNAs in activated glia [22, 30] and MTLE rat model...
Next we have planned to modulate the expressions of some miRNAs in rat MTLE and meningitis models to discuss its potential as a therapeutic target for CNS diseases. We look forward to reporting our health outcome results in the near future.

Conflicting interests

The authors have declared that no competing interests exist.

Acknowledgements

Funding for this research was provided by the National Natural Science Foundation of China (nos. 30872790, 30901631, 81171226, 81100846, 81373414) and the Scientific and Technological Department of Hunan Province (2011FJ3163).

References

2. Streit WJ. Microglia as neuroprotective, immunocompetent cells of the CNS. GLIA 2002; 40:133-139.
10. Zhang L, Dong LY, Li YJ, Hong Z, Wei WS. miR-21 represses FasL in microglia and protects against microglia-mediated neuronal cell death following hypoxia/ischemia. GLIA 2012; 60:1888-1895.
