Peripheral Blood Leukocyte Expression of lncRNA MIAT and Its Diagnostic and Prognostic Value in Ischemic Stroke

Man Zhu, MM, Nandi Li, MM, Ping Luo, MM, Wei Jing, MM, Xue Wen, MM, Chunzi Liang, MD, and Jiancheng Tu, MD

Background: Ischemic stroke (IS) is an extremely heterogeneous disease with variable pathogenesis. Due to the lack of early diagnostic markers, the mortality rate of IS remains high. Cumulative evidence shows that long noncoding RNAs among noncoding RNAs play important roles in cardiovascular diseases. In the present study, we focused on the expression pattern of myocardial infarction–associated transcript (MIAT) and its clinical significance in IS. *Methods:* Blood samples were obtained from IS patients (n = 189) and healthy controls (n = 189). The National Institutes of Health Stroke Scale (NIHSS) was measured at the time of admission. Short-term functional outcome was measured by the modified Rankin Scale (mRS) at 3 months after admission. Multivariate analyses were performed using logistic regression models. The receiver operating characteristic (ROC) curve was used to evaluate the accuracy of MIAT in the diagnosis and prognosis of IS. *Results:* In IS patients, MIAT expression level was significantly upregulated and correlated with NIHSS scores (r = .421, $P < .001$), mRS (r = .339, $P < .001$), high-sensitivity C-reactive protein (r = .309, $P < .001$), and infarct volume (r = .318, $P < .001$). ROC curves indicated that MIAT could serve as a potential marker for discriminating IS patients from the controls with an area under the curve of .842 (95% confidence interval, .802-.881). The overall survival analysis showed that patients with higher MIAT expression had a relatively poor prognosis. Meanwhile, the multivariate analysis revealed that MIAT was an independent prognostic marker of functional outcome and death in patients with IS. *Conclusion:* Our data suggested that MIAT might be a potential diagnostic and prognostic indicator in IS. **Key Words:** Cerebral infarction—long noncoding RNA—MIAT—diagnosis—prognosis.
© 2017 National Stroke Association. Published by Elsevier Inc. All rights reserved.

Introduction

Stroke is the leading cause of death and long-term disability in developed countries.[1,2] According to the WHO report, stroke affects 15 million people worldwide, and about 5 million patients suffer from subsequent permanent disability.[3] Ischemic stroke (IS) is the most common form of stroke, accounting for approximately 87% of all cases.[4,5] Currently, the diagnosis of stroke mainly relies on clinical examination and imaging techniques, including computed tomography scans and magnetic resonance imaging (MRI). Although imaging-based techniques are relatively sensitive and specific, small infarcts are still difficult to detect within 6 hours from onset.[6,7] Moreover, these diagnostic modalities are costly and inconvenient,

From the Department of Clinical Laboratory & Center for Gene Diagnosis, Zhongnan Hospital of Wuhan University, Wuhan, China.
Received May 31, 2017; revision received August 29, 2017; accepted September 6, 2017.

Grant support: This study was supported by 2012 US-China Biomedical Cooperation Projection (81261120403) and the National Basic Research Program of China (2012CB720605).
Address correspondence to Jiancheng Tu, MD, Department of Clinical Laboratory & Center for Gene Diagnosis, Zhongnan Hospital of Wuhan University, No. 169 Donghu Road, Wuchang District, Wuhan 430071, China. E-mail: jianchengtu@whu.edu.cn.
1052-3057/$ - see front matter
© 2017 National Stroke Association. Published by Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.09.009

especially for patients from remote and poor areas. An early assessment that can estimate the severity and prognosis of IS is pivotal for optimized care and the allocation of health-care resources to improve the outcome.[8] Nowadays, advanced applications of various blood biomarkers of cardiovascular diseases have greatly improved diagnosis and treatment strategy on myocardial infarction (MI).[9-11] However, limited progress has been made with respect to the measurement of blood biomarkers for IS. Thus, developing a noninvasive high-sensitive blood biomarker for early screening and monitoring of brain ischemia patients is feasible and valuable.

Noncoding RNAs can be subdivided into small noncoding RNAs and long noncoding RNAs (lncRNAs) according to their transcript size. LncRNAs are nonprotein coding transcripts longer than 200 nucleotides. Previous studies suggested that lncRNAs might be involved in cardiovascular diseases.[12-14] For example, increased antisense noncoding RNA in the INK4 locus had long been investigated as a potential biomarker in the plaque and plasma of atherosclerosis patients.[15] Michalik et al[16] demonstrated that metastasis-associated lung adenocarcinoma transcript 1 expression was augmented by hypoxia in endothelial cells (ECs). H19 lncRNA is highly expressed in neointima after injuries and human atherosclerotic lesions but barely in normal arteries.[17,18] Wang et al[19] and Xu et al[20] found that 2 lncRNAs in foam cells, lncRNA-RP5-833A20.1 and lncRNA-DYNLRB2-2, could contribute to the regulation of foam cell cholesterol efflux and inflammation. Recently Mehta et al[21] reported that lncRNA FosDT could promote ischemic brain injury by interacting with REST-associated chromatin-modifying proteins, suggesting lncRNA can be therapeutically targeted to minimize poststroke brain damage. Moreover, Zhang et al[22] found that metastasis-associated lung adenocarcinoma transcript 1 could protect cerebral microvasculature and parenchyma from cerebral ischemic insults by inhibiting EC death and inflammation response. Unfortunately, the functional roles of lncRNAs in IS are still under debate.[23,24]

Myocardial infarction–associated transcript (MIAT) is an lncRNA predominantly expressed in heart and fetal brain tissue.[25] Increasing evidence has indicated the correlation between MIAT and cardiovascular diseases, including MI, microvascular dysfunction, diabetic retinopathy, and cardiac hypertrophy.[25-27] To our knowledge, proatherogenic stimuli such as inflammatory mediators, and reactive oxygen could initiate endothelial dysfunction and lead to the development of atherosclerotic arterial disease.[28] MIAT has been observed to participate in the pathogenesis of endothelial inflammation, and MIAT knockdown could partially reduce the upregulation of proinflammatory cytokines induced by diabetes mellitus. In 2015, Yan et al[27] found that overexpression of MIAT was associated with diabetic-induced retinal neovascularization, vascular leakage, and inflammation in vivo. Under a diabetic condition, lowering the expression of MIAT could improve visual functions and reduce the diabetes mellitus-induced proinflammatory protein expression, thereby alleviating retinal vessel impairment. Additionally, through a large-scale case-control association study utilizing gene-based genome-wide tag single nucleotide polymorphisms, Ishii et al[29] demonstrated that altered expression at 6 single nucleotide polymorphisms in the MIAT gene might confer genetic susceptibility to MI. Moreover, Vausort et al[26] indicated that expression levels of MIAT in peripheral blood leukocytes were regulated after MI, were correlated with markers of cardiac injury, were affected by cardiovascular risk factors, and were associated with prognosis. A more recent study by Qu et al[30] demonstrated that MIAT was a profibrotic factor that both controls cardiac fibrosis and regulates cardiac function in the setting of MI. IS is an extremely heterogeneous disease with a variable pathogenesis. The causative pathogenesis and physiological mechanisms for the formation of a thrombus differ across stroke subtypes. Up to now, only 1 study has evaluated the association between MIAT and neurovascular dysfunction, and demonstrated that MIAT was a critical regulator of vascular integrity and neuronal function.[31] Neurovascular dysfunction plays an important role in the pathogenesis of IS. However, the role of MIAT in IS is still unknown.

The aim of the present study was to investigate the lncRNA MIAT expression of the peripheral blood leukocytes in IS patients and to explore the correlation between MIAT expression and clinical characteristics. We had also evaluated the diagnostic and prognostic value of MIAT, providing an important basis for early diagnosis and prognosis in IS patients.

Materials and Methods

Experimental Subjects

We recruited 189 patients who were diagnosed with IS between July 2015 and April 2016 at Zhongnan Hospital of Wuhan University, Wuhan, China. Patients were included in this study if they experienced their first IS with symptom onset within 24 hours. IS was defined according to the World Health Organization criteria.[32] In addition, 189 controls were collected from the Physical Examination Center. The median age of controls was 69 (interquartile range [IQR], 64-76) years, and 32.8% were women. The exclusion criteria included acute or chronic renal dialysis, malignant tumors, autoimmune disease, acute or chronic infections, or inflammatory diseases.

Clinical Variables and Neuroimaging

Demographic and clinical information, including gender, age, weight, height, hypertension (systolic/diastolic blood pressure ≥ 140/90 mmHg or prior diagnosis of hypertension or on antihypertensive medication),

Download English Version:

https://daneshyari.com/en/article/8595593

Download Persian Version:

https://daneshyari.com/article/8595593

Daneshyari.com