Dysregulation of mir-106a in Non-Cancer Diseases

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Contributor: Maryam Daneshpour , Ali Ghadimi-Daresajini

MicroRNAs (miRNAs) comprise a class of non-coding RNA with extensive regulatory functions within cells. MiR-106a is recognized for its super-regulatory roles in vital processes. MicroRNAs (miRNAs) are small, endogenous, non-coding RNAs that control gene expression at the translation and even transcription levels. miRNAs are critical regulators of biological processes, including cellular proliferation, differentiation, development, apoptosis, and modulation of the host response to viral infection.

miR-106a microRNA cancer Hepatitis B Myasthenia gravis Multiple sclerosis cardiac hypertrophy

1. Introduction

MicroRNAs (miRNAs) are small, endogenous, non-coding RNAs that control gene expression at the translation and even transcription levels. miRNAs are critical regulators of biological processes, including cellular proliferation, differentiation, development, apoptosis, and modulation of the host response to viral infection [1][2]. Moreover, extracellular miRNAs have been widely reported as potential biomarkers for different diseases and disorders while also serving as signaling molecules to mediate cell–cell communications [3][4].

The biogenesis process of these tiny biomolecules generally begins with RNA polymerase II/III activity and can be classified into canonical and noncanonical pathways. While the intron and exon parts of the genome are involved in processing intragenic miRNAs, intergenic miRNAs are believed to be transcribed independently of genes and regulated by their own promoters [5]. miRNAs may be transcribed in the form of long transcripts named clusters. If the clusters share similar seed regions, they are considered to be an miRNA family [4][5].

2. mir-106a: Dysregulation in Non-Cancer Diseases

2.1. Hepatitis B

The Hepatitis B virus (HBV) was one of the first viruses demonstrated to be associated with cancer [6]. Although HBV is well known today as the cause of acute and chronic hepatitis, cirrhosis, and hepatocellular carcinoma, it does not directly cause malignancy [7]. It is believed that HBV infection makes the immune system release complex

and abnormal responses that are the cause of liver destruction. Thus, exploring the mechanisms of the immune response in chronic hepatitis B (CHB) patients has been the focus of intense research [7][8].

Continuous release of cytokines by immune cells in response to virus infections frequently results in harmful impacts due to recruiting inflammatory cells, constraining virus replication and spread, and inducing adaptive immunity [9]. In the case of HBV infection, IL-8 is one of the main involved inflammatory cytokines that can stimulate immune responses via granulocytes, NK cells, and T-cell chemotaxis [10].

In a study by Hong et al., the qRT-PCR results suggested that the miR-106a level of peripheral blood mononuclear cells was decreased in CHB patients [11]. Using luciferase activity assays, the authors indicated that IL-8 levels were inversely correlated with miR-106a levels in CHB and they identified IL-8 as a target of miR-106a. Moreover, it was confirmed that IL-8 overexpression in CHB was attenuated by inducing miR-106a to reverse the damage. These results have represented miR-106a as an important player to be considered in the molecular research of CHB [11].

2.2. Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune disease that impacts the brain's white matter and spinal cord (central nervous system). The rate of MS is higher in women than in men, with a ratio of three to one [12][13]. There are four major types of MS, including primary progressive multiple sclerosis (PPMS), relapsing-remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS), and progressive relapsing multiple sclerosis (PRMS) [13].

With evidence regarding the involvement of miRNAs in modulating the immune response, inflammatory diseases, and autoimmunity [14][15][16], Rahimirad et al. performed a multi-stage experimental study to identify MS-associated miRNAs and their target genes. The qRT-PCR results indicated that miR-106a levels tended to decrease in the blood samples of MS patients. A gene target interaction network of hsa-miR-106a-5p was constructed using the miRTarBase file deposited in Cytoscape and 28 targets with strong support interactions were identified. RBL2, APP, CYP19A1, and BMP2 were upregulated during MS progression and reasonably reported as the potential targets of miR-106a. Hence, miR-106a may be therapeutically valuable in MS condition attenuation [13].

2.3. Myasthenia Gravis

Myasthenia gravis (MG) is an antibody-mediated and T cell-dependent autoimmune disease of the neuromuscular junction (NMJ), the pathogenesis of which is poorly understood. About 50%-85% of ocular myasthenia gravis (OMG) patients progress to generalized myasthenia gravis (GMG), and approximately 15%-20% of patients with MG will experience potentially fatal myasthenic crises due to respiratory muscle weakness [17]. In recent years, many studies have revealed that miRNAs are key regulators of MG pathogenesis [17][18].

In a study by Xu et al., the expression of plasma exosomal miRNAs in MG and their involvement in MG pathogenesis were investigated [19]. The authors used deep sequencing and qRT-PCR analyses to reveal that

exosomal miR-106a-5p was significantly downregulated in patients with OMG and GMG compared to healthy control subjects. They additionally indicated that levels of this miRNA were notably reduced in patients with GMG compared to OMG [19].

2.4. Cardiac Hypertrophy

It is now believed that cardiac hypertrophy is a pathological process, as it can lead to heart failure, arrhythmia, and even sudden death [20]. Cardiac hypertrophy is a condition associated with growth of cardiomyocyte size and the overexpression of many fetal genes, causing left ventricular (LV) wall thickness and diminished normal cardiac function [21].

The reports on miRNA involvement in the regulatory network of cardiovascular disease have shown the upregulation of miR-106a in cardiac hypertrophy, and mitofusin 2 (Mfn2) was identified as the potential target gene for this miRNA. Mfn2, a key member of the mitofusin protein family, is located in the outer membrane of mitochondria and acts to maintain this organelle's structure [22][23]. Mfn2 is known as a cell proliferation suppressor gene, probably by inhibiting the MAPK/ERK pathway. Recent studies indicate that Mfn2 deficiency is involved in cardiovascular disease [21][23][24].

Based on these facts, a study was conducted by Guan et al. to investigate the role of miR-106a in hypertrophic growth of the heart by targeting Mfn2 using a mouse model of cardiac hypertrophy and a cellular model of cardiomyocyte hypertrophy [21]. They showed that miR-106a overexpression was sufficient to induce hypertrophic growth via directly targeting Mfn2. It was confirmed that the knockdown of miR-106a could inhibit the damage while reversing the hypertrophic alterations. Thus, miR-106a may be a promising molecular target in treating pathological hypertrophy and other cardiac disorders [21][25].

References

1. Leitao, A.L.; Enguita, F.J. A Structural View of miRNA Biogenesis and Function. Non-Coding RNA 2022, 8, 10.
2. Pan, Y.J.; Zhuang, Y.; Zheng, J.N.; Pei, D.S. MiR-106a: Promising biomarker for cancer. Bioorganic Med. Chem. Lett. 2016, 26, 5373–5377.
3. Kennel, P.J.; Schulze, P.C. A Review on the Evolving Roles of MiRNA-Based Technologies in Diagnosing and Treating Heart Failure. Cells 2021, 10, 3191.
4. Sempere, L.F.; Azmi, A.S.; Moore, A. microRNA-based diagnostic and therapeutic applications in cancer medicine. Wiley Interdiscip. Rev. RNA 2021, 12, e1662.
5. O'Brien, J.; Hayder, H.; Zayed, Y.; Peng, C. Overview of MicroRNA Biogenesis, Mechanisms of Actions, and Circulation. Front. Endocrinol. 2018, 9, 402.

6. Lok, A.S.; McMahon, B.J. Chronic hepatitis B: Update 2009. Hepatology 2009, 50, 661–662.
7. Loureiro, D.; Tout, I.; Narguet, S.; Benazzouz, S.M.; Mansouri, A.; Asselah, T. miRNAs as Potential Biomarkers for Viral Hepatitis B and C. Viruses 2020, 12, 1440.
8. Morgan, M.; Keeffe, E.B. Diagnosis and treatment of chronic hepatitis B: 2009 update. Minerva Gastroenterol. Dietol. 2009, 55, 5–22.
9. Boltjes, A.; Groothuismink, Z.M.; van Oord, G.W.; Janssen, H.L.; Woltman, A.M.; Boonstra, A. Monocytes from chronic HBV patients react in vitro to HBsAg and TLR by producing cytokines irrespective of stage of disease. PLoS ONE 2014, 9, e97006.
10. Zhang, C.; Gao, Y.; Du, C.; Markowitz, G.J.; Fu, J.; Zhang, Z.; Liu, C.; Qin, W.; Wang, H.; Wang, F.; et al. Hepatitis B-Induced IL8 Promotes Hepatocellular Carcinoma Venous Metastasis and Intrahepatic Treg Accumulation. Cancer Res. 2021, 81, 2386–2398.
11. Hong, Z.; Hong, H.; Liu, J.; Zheng, X.; Huang, M.; Li, C.; Xia, J. miR-106a Is Downregulated in Peripheral Blood Mononuclear Cells of Chronic Hepatitis B and Associated with Enhanced Levels of Interleukin-8. Mediat. Inflamm. 2015, 2015, 629862.
12. Basak, J.; Majsterek, I. miRNA-Dependent CD4(+) T Cell Differentiation in the Pathogenesis of Multiple Sclerosis. Mult. Scler. Int. 2021, 2021, 8825588.
13. Rahimirad, S.; Navaderi, M.; Alaei, S.; Sanati, M.H. Identification of hsa-miR-106a-5p as an impact agent on promotion of multiple sclerosis using multi-step data analysis. Neurol. Sci. 2021, 42, 3791–3799.
14. Sanctuary, M.R.; Huang, R.H.; Jones, A.A.; Luck, M.E.; Aherne, C.M.; Jedlicka, P.; de Zoeten, E.F.; Collins, C.B. miR-106a deficiency attenuates inflammation in murine IBD models. Mucosal Immunol. 2019, 12, 200–211.
15. Zailaie, S.A.; Siddiqui, J.J.; Al Saadi, R.M.; Anbari, D.M.; Alomari, A.S.; Cupler, E.J. Serum Based miRNA as a Diagnostic Biomarker for Multiple Sclerosis: A Systematic Review and Meta-Analysis. Immunol. Investig. 2022, 51, 947–962.
16. Zhu, D.; Pan, C.; Li, L.; Bian, Z.; Lv, Z.; Shi, L.; Zhang, J.; Li, D.; Gu, H.; Zhang, C.Y.; et al. MicroRNA-17/20a/106a modulate macrophage inflammatory responses through targeting signal-regulatory protein alpha. J. Allergy Clin. Immunol. 2013, 132, 426–436 e8.
17. Bo, C.; Wang, J.; Zhang, H.; Cao, Y.; Lu, X.; Wang, T.; Wang, Y.; Li, S.; Kong, X.; Sun, X.; et al. Global pathway view analysis of microRNA clusters in myasthenia gravis. Mol. Med. Rep. 2019, 19, 2350–2360.
18. Saghazadeh, A.; Rezaei, N. MicroRNA expression profiles of peripheral blood and mononuclear cells in myasthenia gravis: A systematic review. Int. Immunopharmacol. 2022, 112, 109205.

19. Xu, H.; Bao, Z.; Liang, D.; Li, M.; Wei, M.; Ge, X.; Liu, J.; Li, J. Plasma exosomal miR-106a-5p expression in myasthenia gravis. Muscle Nerve 2020, 61, 401–407.
20. Holvoet, P. Non-Coding RNAs in Cardiomyopathy and Heart Failure. In Non-Coding RNAs at the Cross-Road of Cardiometabolic Diseases and Cancer; Springer International Publishing: Cham, Switzerland, 2021; pp. 119–147.
21. Guan, X.; Wang, L.; Liu, Z.; Guo, X.; Jiang, Y.; Lu, Y.; Peng, Y.; Liu, T.; Yang, B.; Shan, H.; et al. miR-106a promotes cardiac hypertrophy by targeting mitofusin 2. J. Mol. Cell. Cardiol. 2016, 99, 207–217.
22. Sun, D.; Li, C.; Liu, J.; Wang, Z.; Liu, Y.; Luo, C.; Chen, Y.; Wen, S. Expression Profile of microRNAs in Hypertrophic Cardiomyopathy and Effects of microRNA-20 in Inducing Cardiomyocyte Hypertrophy Through Regulating Gene MFN2. DNA Cell Biol. 2019, 38, 796–807.
23. Zhang, W.B.; Qi, Y.F.; Xiao, Z.X.; Chen, H.; Liu, S.H.; Li, Z.Z.; Zeng, Z.F.; Wu, H.F. CircHIPK3 Regulates Vascular Smooth Muscle Cell Calcification Via the miR-106a-5p/MFN2 Axis. J. Cardiovasc. Transl. Res. 2022, 15, 1315–1326.
24. Xin, Y.; Wu, W.; Qu, J.; Wang, X.; Lei, S.; Yuan, L.; Liu, X. Inhibition of Mitofusin-2 Promotes Cardiac Fibroblast Activation via the PERK/ATF4 Pathway and Reactive Oxygen Species. Oxidative Med. Cell Longev. 2019, 2019, 3649808.
25. Jung, J.H.; Ikeda, G.; Tada, Y.; von Bornstadt, D.; Santoso, M.R.; Wahlquist, C.; Rhee, S.; Jeon, Y.J.; Yu, A.C.; O'Brien, C.G.; et al. miR-106a-363 cluster in extracellular vesicles promotes endogenous myocardial repair via Notch3 pathway in ischemic heart injury. Basic. Res. Cardiol. 2021, 116, 19.