MicroRNAs dysregulation in MS patients

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Abstract

MicroRNAs (miRNAs) are small non-coding RNAs with 18-23 nucleotides that are included in posttranslational regulation of gene expression, cell proliferation, and cell metabolism processes.

KeyWords: MicroRNAs; metabolism; MS patients.

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Introduction:

Several studies have found different profiles of miRNAs expression isolated from the wholeblood, serum and lymphocytes of MS patients indicating that dysregulation of miRNA system components may have a role in the pathogenesis of MS. **(Bartel et al., 2004), (Jafari et al., 2014).**

MicroRNAs have a confirmed significant role in regulation of biological processes associated with the pathogenesis of various autoimmune and neurodegenerative disorders, including MS. **(Ferrante & Conti, 2017), (Dolati et al., 2017)**

MiRNAs are markedly stable structures that are resistant to endogenous RNase activity, easy to obtain, and highly sensitive to the related biological processes as they have selective expression level patterns, which are found to be characteristic to the specific disease. **(Ajit, 2012)**

Therefore, circulating miRNAs are considered as a potential promising diagnostic and prognostic biomarkers and widely studied in various human disorders, including neurodegenerativediseases and other neurological pathologies.**(Sheinerman et al., 2013)**

The formation of miRNA passes through serial steps, gene-encoding miRNA is transcribed by RNA polymerase II, leading to the production of a long primary transcript, termed primary miRNA (pri-miRNA). The pri-miRNA is cleaved in the nucleus by a microprocessor complex of the RNase III endonuclease Drosha with DiGeorge syndrome critical region 8 (DCGR8) protein into pre-miRNA. then, pre-miRNA is carried to the cell cytoplasm by exportin-5, where it is cleaved again by the RNase III endonuclease Dicer to produce an RNA duplex. **(Catalanotto et al., 2016)**

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At the end, the mature miRNA is transferred to Argonaute family proteins (Ago) in the RNA-induced silencing complex (RISC) core. **(Sheu-gruttadauria & Macrae, 2017)**

The duplex is formed of two strands, one strand (-3p) is typically degraded by Ago. The other strand (-5p) is loaded into RISC, however, in some miRNAs, both strands (-5p and -3p) may be loaded into RISC at similar frequencies. **(Desvignes et al., 2015)**

Actually, RISC loading may strongly help the involvement of one strand (-5p) with a small proportion of the -3p strand loaded into RISC for most of all miRNA families. **(Desvignes et al., 2015)**

Single-stranded miRNA, together with the RISC, produces the complementary sequences of the target messenger RNA (mRNA) in the 30 UTR (untranslated region) which is known as miRNA response element (MREs). The hybridization of the complementary sequences results in specific posttranscriptionalgene silencing—RNA interference (RNAi). **(Catalanotto et al., 2016)**

The effects of RNAi depend on the degree of the complementarity of miRNA with the

target mRNA. Perfect complementarity results in destabilization and degradation of the mRNA transcript. Whereas, partial or week complementarity (this is more common) leads to translational repression. **(Denzler et al., 2016)**

Through this way, miRNAs modify more than 60% of all mammalian mRNAs, and therefore regulation of cell development, differentiation, proliferation, metabolism, and apoptosis.**(Catalanotto et al., 2016)**

profiling of miRNA expression can be done using various methods, such as miRNA microarray platforms, quantitative real-time polymerase chain reaction (qRTPCR), digital PCR (dPCR), in situ hybridization, and next generation sequencing (NGS).

Recently, the NGS technique is the most frequently used as it profiles both known and unknown miRNAs unlike both qRT-PCR and microarrays, however, this method is still challenging due to its high cost, time consumption, and professional bioinformatics support for data analysis. Microarrays need a higher concentration of miRNAs and have lower specificity than qRT-PCR. whereas, sensitive and specific qRT-PCR remains the standard technique to measure miRNA expression with less time consumption but its quantification of samples with low concentrations of nucleic acids is challenging with this method unlike dPCR technology that enables absolute quantification through partitioning the reaction. **(Wang et al., 2019)**

Circulating miRNAs are present in different biological fluids, such as saliva, blood, plasma, serum, and CSF, can be released or produced in these fluids through different events, including (1) passive leakage from damaged cells after chronic inflammation, apoptosis, or necrosis.

(2) active secretion with the help of cell-derived microparticles, exosomes and apoptotic bodies. (3) active transport with protein such as Ago2.**(Redis et al., 2012)**

There are 1917 precursors and 2654 mature miRNAs in human that control the expression of hundreds of different genes. **(Kozomara & Griffiths-Jones, 2014)**

The human miRNA-associated disease database (HMDD) (www.cuilab.cn/hmdd; updated at 21 September 2021) produces rich resource for scientists to enable screening of the growing number of miRNA profiles for various diseases.

MiRNAs as Potential Biomarkers in MS

According to HMDD v3.2 updated list which is available online: https://www.cuilab.cn/hmdd, There are currently 148 different miRNAs associated with MS pathogenesis and are candidate for the research as a disease biomarker.

miRNAs are essential modulators of inflammatory responses and this encouraged researchers to focus on systematic profiling of miRNAs in different cells and biological fluids to understand their role in regulating the inflammatory process. **(Nejad et al., 2018)**

In addition, miRNAs modify the transcripts for proteins involved in remyelination, neurogenesis, and gliogenesis. **(Janowska et al., 2019)**

Dysregulated miRNAs in MS are either up- or downregulated in MS patients compared to healthy controls (HCs) and variably expressed in different disease phenotypes including RRMS and SPMS **(Vistbakka et al., 2017)**

In addition, certain microRNAs are found to correlate with EDSS score, disease duration, remission time and frequency of relapses. **(Gandhi et al., 2013)**

miRNAs that have been found to be upregulated in MS patients, in a minimum of four independent

studies, include: miR-142-3p, miR-145, miR-155, miR-146a/b, miR-22, miR223/-3p, miR-584 and miR-326. **(Piket et al., 2019)**

Several studies are needed to determine the pathogenic causative relation with these microRNAs.

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