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How MicroRNAs Are Involved in Splitting the Mind

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This article provides an introduction to the role of microRNAs in the nervous system and outlines their potential involvement in the pathophysiology of schizophrenia, which is hypothesized to arise owing to a combination of environmental factors and genetic predisposition.

How MicroRNAs Enter the Spotlight

Related article

Genome-wide association studies have identified common genetic variants shared among patients with schizophrenia.[1] In these studies, most of the significantly associated single-nucleotide polymorphisms were found in noncoding DNA regions, where they could alter transcription factor binding sites, activity of gene promoters, or influence transcript splicing. Interestingly, several single-nucleotide polymorphisms were in close approximation to the gene loci of microRNAs, suggesting that these variants could influence microRNA expression levels. While such alterations may be subtle and not necessarily directly pathogenic, it is known that microRNAs also respond to environmental factors such as prenatal stress.[2] Such factors trigger changes in DNA methylation or histone modifications and alter access of transcription factors to the DNA, leading to varying levels of transcribed microRNAs. Thus, if the endogenous microRNA levels are already altered owing to even minor sequence variations in the microRNA gene locus, this could result in an atypical response to environmental stimuli, resulting in disease-associated changes at the molecular and cellular levels.

What Are MicroRNAs?

MicroRNAs exist in several hundred varieties and are highly conserved across species. Like messenger RNA (mRNA), microRNAs are transcribed from the genomic DNA, spliced, and polyadenylated. They are then subjected to a specific microRNA-processing cascade involving the Drosha and Dicer enzymes, with the end result being the mature 22 nucleotide long noncoding microRNA (**Figure**). This microRNA contains a seed region of 6 to 8 base pairs that is complementary to the 3'UTR of distinct target mRNAs. The microRNA binds in a Watson-Crick base pairing with the target mRNA and either represses mRNA translation, promotes mRNA degradation, or simply sequesters the mRNA in *stress* granules. Importantly, 1 microRNA can have several hundred downstream mRNA targets and, in this way, can manipulate multiple molecular pathways simultaneously. Because of this multifunctionality, microRNAs have been called *fine tuners* of cellular pathways.[3]

MicroRNAs Play a Multiplex Role in Cellular Mechanisms

MicroRNA-137 (*miR-137*) is the first prominent candidate microRNA gene in the schizophrenia field. Following its identification in multiple schizophrenia genome-wide association studies, intensive research has been performed to reveal the functional effects of alterations in miR-137 levels (Figure). We showed that miR-137 affects the levels of several target genes that encode presynaptic proteins involved in vesicle trafficking and neurotransmitter release.[4] Combined with the previously described roles for miR-137 in neuronal differentiation during development and adult neurogenesis[5] and AMPA receptor subunit (GluA1) trafficking at the dendrite,[6] these findings strongly support the hypothesis that schizophrenia is a disorder of the synapse. In addition, other miR-137 target genes are involved in the immune response, gene transcription, and epigenetic regulation such as histone and DNA methylation.[5,7] Interestingly, epigenetic mechanisms have long been implicated in both psychiatric disease and cognitive dysfunction and their involvement in schizophrenia continues to be supported by new evidence.[8]

In an article in this issue of *JAMA Psychiatry*, Hauberg and colleagues[9] took advantage of the previously published genome-wide association studies and analyzed whether schizophrenia risk genes are more likely to be regulated by microRNAs. They showed that next to *miR-137*, 2 additional microRNAs are associated with schizophrenia (*miR-9-5p* and *miR-485-5p*). MiR-9-5p is particularly interesting because it modulates the expression of dopamine D2 receptor and fragile X mental syndrome–related protein 1 gene. Even more striking is that miR-9 also affects *CoRest/Rest* and *FoxG1*,[10] which are interaction partners from Lsd1 and Jarid1b, respectively, that are modulated by miR-137 (Figure).

Open Questions Regarding MicroRNAs and Their Impact in Schizophrenia

MicroRNAs are novel promising candidate risk factors in the field of schizophrenia research. Their multiplex roles may be one facet underlying the complex phenotypes observed in psychiatric disorders. However, to define microRNAs as a new target for research into psychiatric therapy would be premature. We first have to understand more about microRNA dynamics. For example, the spatial-temporal dynamics of microRNAs within the cell are complex; microRNAs can act locally and interfere with spatially restricted processes such as protein translation at the dendrite. It is necessary to know where a particular microRNA functions within the cellular compartments. MicroRNAs can also be expressed at distinct developmental points. Moreover, we have to answer the question of how many target genes does a microRNA have and whether all genes targeted have the same affinity. The brain consists of billions of neurons. Will the microRNA have the same effects in an excitatory pyramidal cell in the prefrontal cortex as in an excitatory dentate granule cell in the hippocampus, both of which are implicated in schizophrenia? How can environmental factors alter microRNA levels, and is there a critical window of development during which dysregulation of microRNAs most affect the brain? What is a healthy level for each microRNA? For example, while increased miR-137 expression is associated with presynaptic dysfunction, abnormally low levels of miR-137 have been observed in Alzheimer disease.

Figure. Schematic Overview of MicroRNA (MiRNA) Generation in the Neuron and Their Consequences
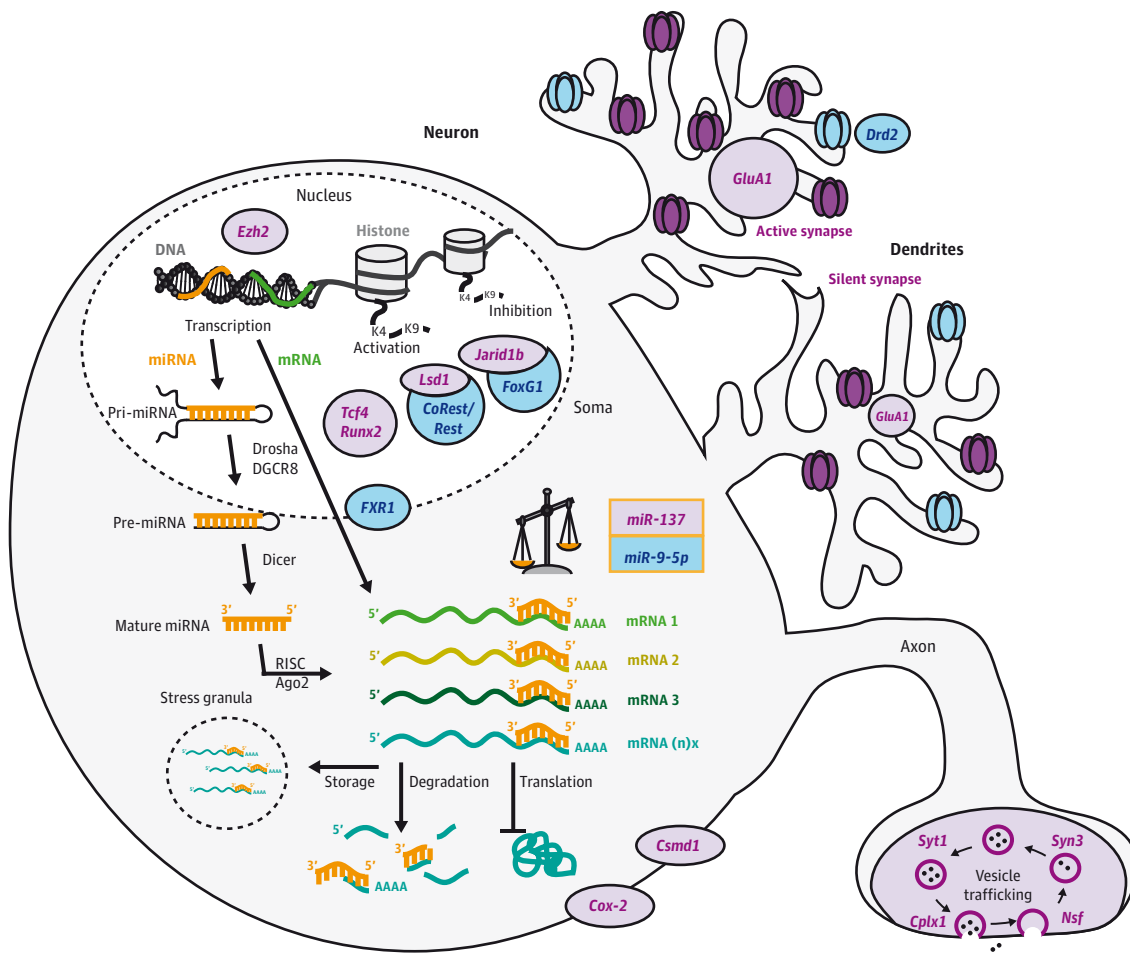
MicroRNA (orange) are transcribed from the DNA and processed into different precursor products via the enzymes Drosha and Dicer. The mature miRNAs interact with their target messenger RNAs (mRNAs; green), causing either degradation of the mRNA, inhibition of mRNA translation to a functional protein, or storing the mRNA. The gene names in purple outline a small number of confirmed target genes for the schizophrenia-associated miRNA-137 and their effect at the presynaptic site (*Cplx1*, *Nsf*, *Syn3*, and *Syt1*), the postsynaptic site (*GluA1*), in the immune response (*Csmd1* and *Cox-2*), and in epigenetic regulation (*Exh2*, *Jarid1b*, *Lsd1*, *Tcf4*, and *Runx2*). The gene names in blue are confirmed miRNA-9-5p target genes.

Conclusions

Despite all these questions, we are just beginning to reveal the effect of microRNAs in disease conditions. MicroRNAs, at the same time simple and complex, are providing a great example of how genetic predisposition, combined with environmental factors, may trigger disease phenotypes.

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