MicroRNA therapeutics in neurological disease.

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Abstract:

Developing microRNA therapeutics for neurological diseases is both a promising opportunity and an extremely challenging topic for several reasons. The promise stems from the very small size of microRNAs, which makes them amenable for manipulation via short synthetic oligonucleotides or engineered viruses. Also, the fact that each microRNA may regulate numerous target transcripts of the same pathway predicts that such manipulations may affect an entire pathway rather than a single gene and gives reason to hope that low dose therapeutic targeting of the top microRNA in such a hierarchic pyramid would suffice to induce a focused change in the entire pyramid. However, these same features, which make microRNAs such promising targets for therapeutic manipulations also present great challenges. Thus the plethora of functional targets for each microRNA in specific cell types is yet far from being elucidated, which implies that the targets to be affected may not be those planned to be manipulated (a risk of 'off-target' effects). Also, the hierarchic order of microRNA regulation is yet unknown, which predicts a risk of complex, multi-leveled consequences following the manipulation of a single microRNA; and the delivery of oligonucleotide therapeutics into the brain is a challenge due to the blood-brain barrier. In this chapter, we briefly outline the current state of knowledge regarding microRNA regulation in different neuropathologies and sketch the emerging principles for the development of microRNA therapeutics for these diseases. We address issues such as modes of delivery and consideration of the inherited and acquired variability between individuals in the susceptibility to such treatments. We further refer in a somewhat more in-depth manner to the issue of manipulating microRNA functioning in the parasympathetic system and the pathway of cholinergic signaling. Beyond the brain and within it, cholinergic signaling controls inflammatory reactions, and microRNA changes would likely affect this function as well. Furthermore, microRNA regulation of cholinergic signaling involves the elements of complexity and hierarchy noted above, and is relevant to numerous neuropathologies and neurodegenerative syndromes. Research and translational efforts that lead to the development of microRNA therapeutics merit thorough discussion.

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