Predicted overlapping microRNA regulators of acetylcholine packaging and degradation in neuroinflammation-related disorders.

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Abstract:

MicroRNAs (miRNAs) can notably control many targets each and regulate entire cellular pathways, but whether miRNAs can regulate complete neurotransmission processes is largely unknown. Here, we report that miRNAs with complementary sequence motifs to the key genes involved in acetylcholine (ACh) synthesis and/or packaging show massive overlap with those regulating ACh degradation. To address this topic, we first searched for miRNAs that could target the 3'-untranslated regions of the choline acetyltransferase (ChAT) gene that controls ACh synthesis; the vesicular ACh transporter (VACht), encoded from an intron in the ChAT gene and the ACh hydrolyzing genes acetyl- and/or butyrylcholinesterase (AChE, BChE). Intriguingly, we found that many of the miRNAs targeting these genes are primate-specific, and that changes in their levels associate with inflammation, anxiety, brain damage, cardiac, neurodegenerative, or pain-related syndromes. To validate the in vivo relevance of this dual interaction, we selected the evolutionarily conserved miR-186, which targets both the stress-inducible soluble "readthrough" variant AChE-R and the major peripheral cholinesterase BChE. We exposed mice to predator scent stress and searched for potential associations between consequent changes in their miR-186, AChE-R, and BChE levels. Both intestinal miR-186 as well as BChE and AChE-R activities were conspicuously elevated 1 week post-exposure, highlighting the previously unknown involvement of miR-186 and BChE in psychological stress responses. Overlapping miRNA regulation emerges from our findings as a recently evolved surveillance mechanism over cholinergic neurotransmission in health and disease; and the corresponding miRNA details and disease relevance may serve as a useful resource for studying the molecular mechanisms underlying this surveillance.

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