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MicroRNA Trimming in the Nervous System

Introduction
MicroRNAs are small, single-stranded RNAs about 22 nucleotides long which are involved in post-transcriptional regulation of mRNAs. MicroRNAs base-pair with regions on the 3’ UTR of target mRNAs which show partial complementarity to microRNA sequence and downregulate them by translational repression or mRNA cleavage. To effect their biological functions, microRNAs require loading into the RNA-induced silencing complex by the Argonaute protein, the catalytic subunit of RISC. There are four proteins in the Argonaute protein family: Ago1, Ago2, Ago3 and Ago4. Ago2 mediates mRNA cleavage upon perfect sequence complementarity between mRNA and microRNA, whereas Ago1, 3 and 4 cause translational repression.

MicroRNA-124 is a microRNA which regulates neuronal differentiation and is expressed in immature and terminally-differentiated neurons. It occurs as a population of 20-25 nucleotide-long microRNAs in the mouse brain. Upon maturation of the nervous system, the miR-124 population slowly changes from 22-mer as the most abundant form to 21-mer as the most abundant form, a process called microRNA trimming.

Objectives
We aim to investigate if the different Argonaute proteins affect the trimming of miR-124.

Research Methods
1. Characterization of Argonaute protein levels in both the developing and mature nervous system via western blot of the four Argonaute proteins.
2. Coimmunoprecipitation of miR-124 with Ago1, 2, 3 and 4 and a comparison of the microRNA populations associated with each Argonaute protein via a northern blot.

Results
Expression of both Ago1 and Ago2 proteins decrease upon nervous system maturation, but the expression of Ago1 decreases more drastically compared to Ago2.

Overexpression of Argonaute proteins in HEK293T cells.

MicroRNAs seem to be trimmed in hAgo2 to a greater extent compared to in Ago1, 3 and 4.

Conclusions
The nervous system expresses mostly Ago1 and Ago2, with more Ago2 than Ago1. The ratio of Ago2 to Ago1 increases as the nervous system matures.

Trimming occurs more effectively for miR-124 loaded in Ago2.

The change in the ratio of Argonaute protein may explain the change from 22-mer species to 21-mer species during nervous system maturation.