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Significant Up-regulation of Mir-17 in an Alzheimer's Disease Mouse Model

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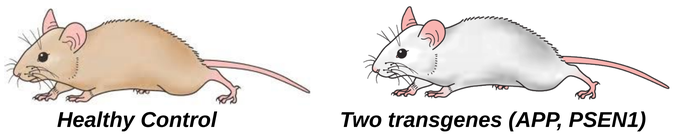
Gene Expression, AD, and Epigenetics

- AD development does not follow typical Mendelian inheritance patters.
- In fact, lines of evidence suggests that AD development is tied to epigenetic modifications.
- Previous work by our group has identified epigenetic changes in the AD brain.
- Several genes encoding micro RNA (miRNA) were identified to have epigenetic modifications, particularly changes to methylation status.

In Vivo AD Mouse Model



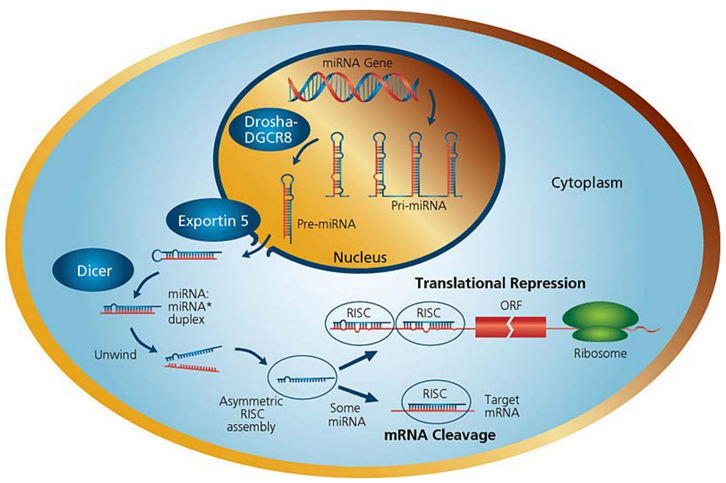
Healthy Control

Two transgenes (APP, PSEN1)

•APP and PSEN1 transgenic mice (Jackson Lab).
•Isolate RNA from mouse brain and blood samples (n=3).
•Determine the differential expression levels of miRNA.

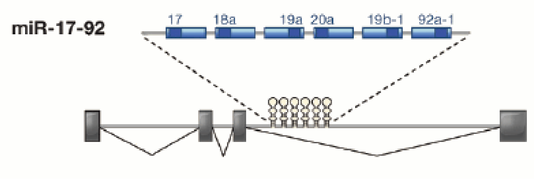
Micro RNA Overview

- miRNA are small (~22nt) non-coding RNA.
- These RNAs function as post-transcriptional regulators of various protein-coding genes.
- miRNAs are estimated to be responsible for regulating over 1/3 of the mammalian genome.
- Since their discovery in 1993, miRNA have been shown to be key regulatory elements in various fundamental biological processes, including apoptosis.



miR-17-92 Cluster

- miR-17-92 is a polycistronic miRNA cluster.
- This cluster is among the best-studied miRNA clusters and has gained an incredible amount of attention over the past 3 years.
- Dysregulation of this cluster has been shown to be involved in a variety of pathologies, including tumorigenesis and neurodegeneration.



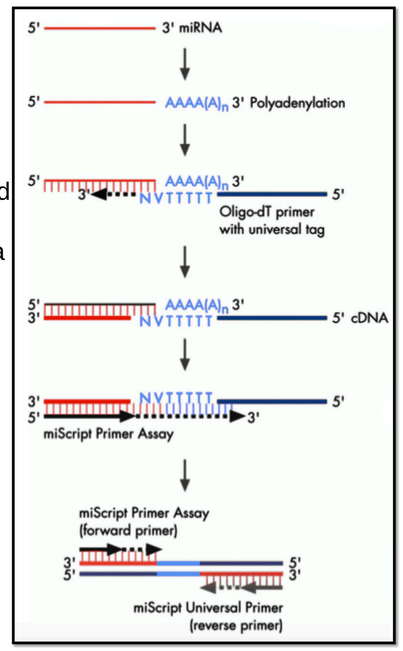
miRNA Expression Analysis

Total RNA isolated from the hippocampus of AD and control mice.

miRNA were polyadenylated and an miRNA-specific universal tag was added via 5' end of Oligo-dT primer.

miScript primer assay (Qiagen) was used to determine relative expression of miRNA.

Differential expression analyzed based on fold change.

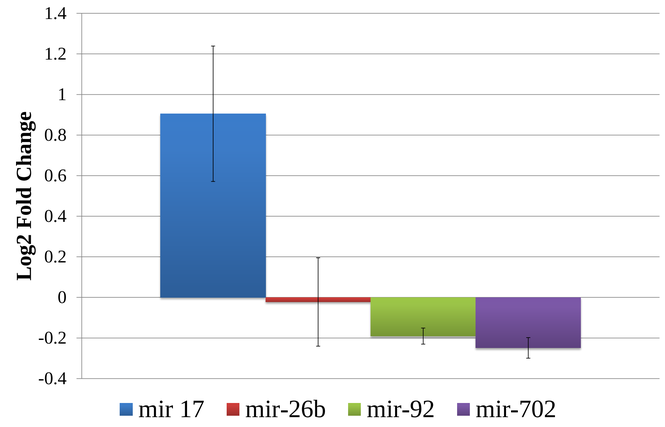


miRNA Investigation Criteria

- Previous research by our group revealed epigenetic modification of genes that code for miRNA, including some members of the miR-17-92 cluster.
- Investigation criteria of miRNA was based on those which exhibited epigenetic modifications.

Differential miRNA Expression

- Expression changes analyzed in mir-17, mir-26b, mir-92, and mir-702.
- GAPDH and Tubb3 were used to normalize expression data.
- Of those analyzed, miR-17 displayed consistent up-regulation in all AD mice when compared to controls.
- Results identify a novel association between miR-17 and AD.



Evaluation of miR-17 Targets

- miR-17 has been shown to target Beclin-1 directly, downregulating its expression in other tissues.
- Additionally, dysregulation of Beclin-1 has been shown to modulate amyloid beta accumulation in mice.
- This could indicate a possible epigenetic basis for amyloid beta deposits in the AD brain.

Looking Forward

- Identification of other dysregulated miRNA that also display epigenetic modifications.
- Future studies will investigate the validity of miR-17 targeting Beclin-1 in the hippocampus of mice and if its dysregulation results in amyloid beta accumulation in our model.
- miR-17: passenger or molecular driver of AD pathology?
- Potential for Anti-miR AD therapy.