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Differential miRNA Expression in the Hippocampus Following Aerobic Exercise: Implications for Adult Neurogenesis

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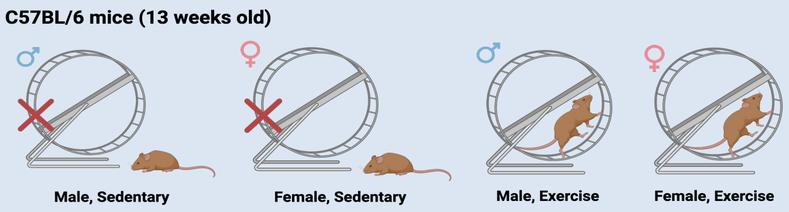
INTRODUCTION & AIM

- miRNAs are small, endogenous, noncoding RNAs that post-transcriptionally regulate gene expression.
- In the hippocampus, miRNAs impact processes in neurogenesis and cell proliferation.
- Physical exercise performed regularly is well known for preventing cardiovascular diseases, stroke, hypertension, and diabetes.. It also enhances bone, muscle, and mental health
- Aerobic exercise is correlated with greater hippocampal volumes→ increased cell proliferation and memory formation
- In an experimental mouse model, running activity increased adult neurogenesis, facilitating synaptic plasticity in the dentate gyrus of the hippocampus
- There is a group of people that are not capable of performing active exercise: The elderly, those with chronic injuries, Alzheimer's disease, Parkinson's disease, certain cancers, or stroke

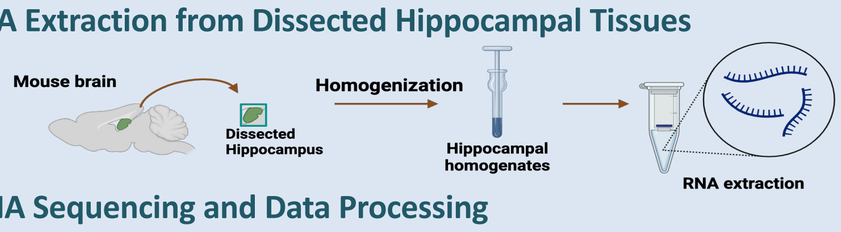
This study aimed to identify target miRNA candidates regulated by aerobic exercise that may contribute to enhanced hippocampal neurogenesis. The use of miRNAs as a therapeutic approach could provide better outcomes for those who cannot engage in active exercise.

METHODS

Animal Model: Voluntary Wheel Running for Two Weeks

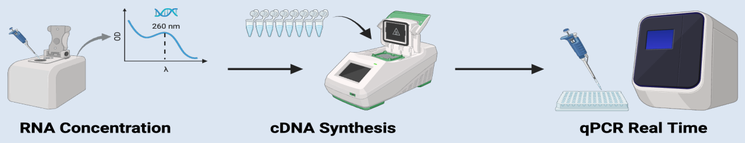


Total RNA Extraction from Dissected Hippocampal Tissues



Small RNA Sequencing and Data Processing

Confirmation of miRNA Expression: cDNA Synthesis and qPCR



RESULTS

Summary of differential analysis for 698 detectable miRNAs:

Table I. Two-way ANOVA Results

Table II. Tukey tests examining sex, condition, and interaction effects

Table I. 2-Way ANOVA Results

Variable name	ANOVA: Sex	ANOVA: Condition	ANOVA: Interaction:Sex:Condition
Lowest P value	9.26E-05	6.66E-06	3.26E-04
Count P<0.05	67	87	55
Count FDR<0.1	3	28	0

Table II. Tukey Results

Variable name	Tukey: Male vs Female at Exercise	Tukey: Male vs Female at Sedentary	Tukey: Exercise vs Sedentary at Female	Tukey: Exercise vs Sedentary at Male
Lowest P value	6.98E-04	1.49E-03	1.91E-06	3.10E-04
Count P<0.05	63	43	78	63
Count FDR<0.1	0	0	1	3

RESULTS & DISCUSSION

Table III. List of the Top 10 Most Differentially Expressed miRNAs

P < 0.01 or FDR < 0.05
P < 0.05 or FDR < 0.1

Mature miRNA Name	ANOVA P Value for Sex	ANOVA P Value for Condition	ANOVA P Value for Interaction:Sex:Condition	ANOVA FDR Value for Sex	ANOVA FDR Value for Condition	ANOVA FDR Value for Interaction:Sex:Condition	Tukey P Value for Male vs Female at Exercise	Tukey P Value for Male vs Female at Sedentary	Tukey P Value for Exercise vs Sedentary at Female	Tukey P Value for Exercise vs Sedentary at Male
mmu-miR-374b-5p	9.26E-05	2.20E-01	1.52E-02	3.33E-02	6.53E-01	4.85E-01	7.37E-04	9.46E-02	9.90E-03	3.91E-01
mmu-miR-191-5p	1.33E-04	3.63E-02	2.17E-03	3.33E-02	3.15E-01	2.85E-01	1.71E-01	1.49E-03	2.98E-01	5.62E-03
mmu-miR-381-3p	1.52E-04	4.97E-03	1.59E-01	3.33E-02	1.03E-01	7.42E-01	6.26E-03	7.56E-03	3.16E-01	1.99E-03
mmu-miR-488-5p	1.08E-03	6.59E-01	7.11E-01	1.65E-01	9.12E-01	9.03E-01	1.18E-02	3.21E-02	9.66E-01	4.80E-01
mmu-miR-671-3p	1.25E-03	9.89E-01	1.84E-02	1.65E-01	9.95E-01	4.85E-01	2.91E-01	4.23E-03	1.65E-01	3.72E-02
mmu-miR-488-3p	1.54E-03	7.90E-01	3.29E-01	1.69E-01	9.38E-01	8.07E-01	2.87E-03	1.22E-01	5.12E-01	4.75E-01
mmu-miR-484	1.88E-03	1.40E-02	9.52E-01	1.77E-01	1.77E-01	9.78E-01	1.53E-02	5.05E-02	9.38E-02	8.22E-02
mmu-miR-151-3p	2.25E-03	5.19E-01	1.80E-03	1.86E-01	8.26E-01	2.85E-01	9.20E-01	2.75E-03	1.02E-01	3.76E-03
mmu-miR-935	3.52E-03	6.71E-01	4.74E-01	2.58E-01	9.14E-01	8.12E-01	8.94E-03	5.67E-02	4.20E-01	8.43E-01
mmu-miR-138-1-3p	4.74E-03	5.48E-01	9.26E-01	3.03E-01	8.43E-01	9.75E-01	2.23E-02	7.76E-02	7.28E-01	6.26E-01

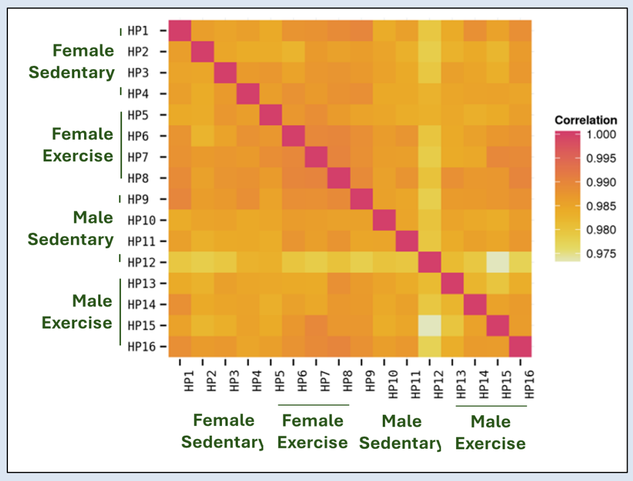


Figure 1. The sample correlation matrix calculated using log10-transformed RPM values from 698 perfect-matched and detectable mouse miRNAs.

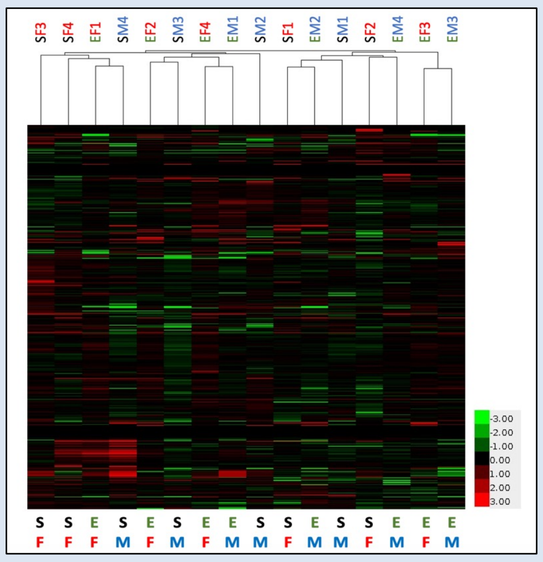


Figure 2. Clustering data of miRNA expression based on sex and exercise conditions.

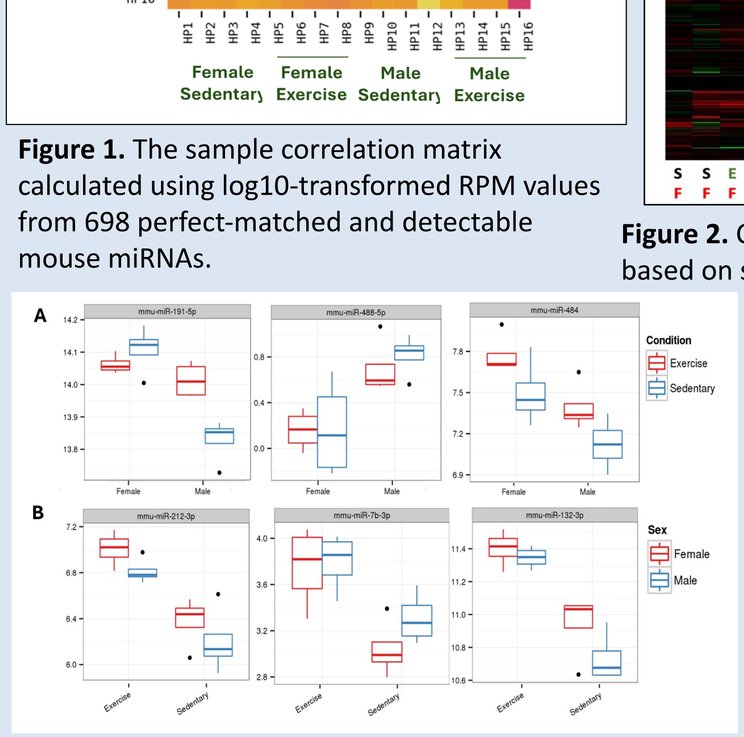


Figure 3. ANOVA P-Value for Source. The box plots show log2 RPKM data for three selected miRNAs with a low ANOVA P-Value for the *sex* condition (A) or the *exercise* condition (B)

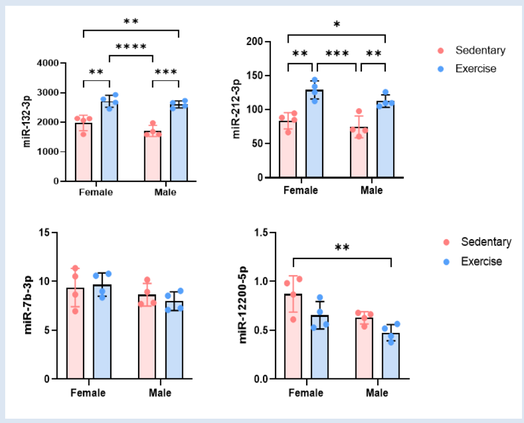


Figure 4. 2-way ANOVA analysis of miRNA expressions in female/male & sedentary/exercised mice; Exercise effect was observed in all 4 miRNAs; additional gender effect was observed in miR-12200-5p

CONCLUSION

Aerobic exercise was found to alter the expression of certain miRNAs in the hippocampus. miR-7b-3p, miR-212-3p, and miR-132-3p were significantly increased by exercise in both sexes, while miR-12200-5p was reduced. Some miRNAs also showed sex specific differences, indicating additional sex-dependent regulation. These findings highlight the potential role of miRNAs in exercise-induced neurogenesis and suggest their importance in overall brain health. It also contributes to a growing understanding of potential sex-specific differences in brain function.

FUNDING SOURCES

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