Adipose-derived miR-133a-3p and its Role in Mechanical Sensitivity in Chronic Primary Pain Conditions

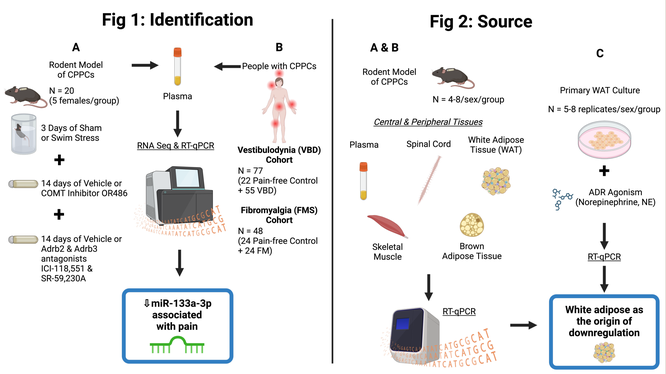
Nathaniel P. Hernandez[1,2], Jiegen Chen[1], Xin Zhang[1], Yaomin Wang[1], Xianglong Gao[1], Brittney P. Ciszek[1], Matt Kanke[3], Mohamad Karaky[4], Marguerita E. Klein[1], Praveen Sethupathy[3], Luda Diatchenko[4], and Andrea G. Nackley[1,2]

[1]Department of Anesthesiology, Duke University [2]Department of Pharmacology & Cancer Biology, Duke University [3]Department of Biomedical Science, Cornell University [3]Department of Anesthesia, McGill University

INTRODUCTION

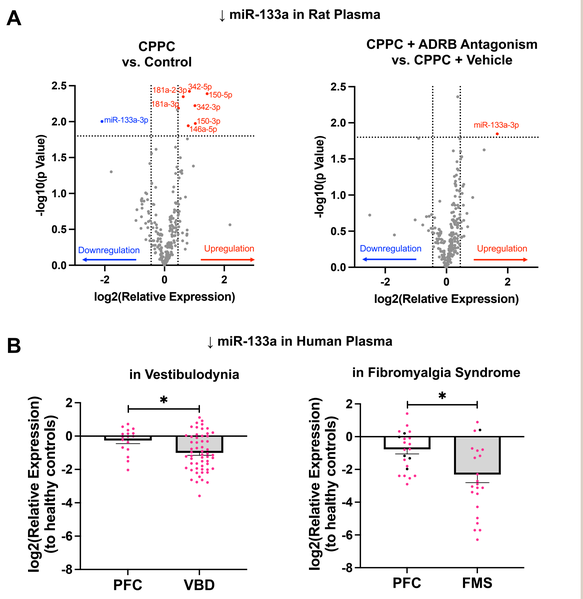
- **Chronic Primary Pain Conditions (CPPCs)** such as vestibulodynia (VBD) and fibromyalgia syndrome (FMS) affect ~1 in 3 individuals, predominately females
  - ~2 in 3 individuals w/ CPPCs have a loss-of-function mutation in catechol-o-methyltransferase (COMT) enzyme that metabolizes catecholamines
  - Catecholamine activation of beta-adrenergic receptor 3 (ADRB3) in adipose directly contributes to CPPC etiology
- **microRNAs (miRNAs):** small non-coding RNAs that regulate mRNA transcription and are thought to play a role in CPPC mechanisms
  - Predicted to regulate MAPK pathway in nervous tissue (e.g., MAP3K3, a kinase upstream of ERK), which plays a role in CPPC etiology
  - Can be secreted by distinct cell types and transported in plasma to distant target sites via exosomes or lipoproteins

METHODS

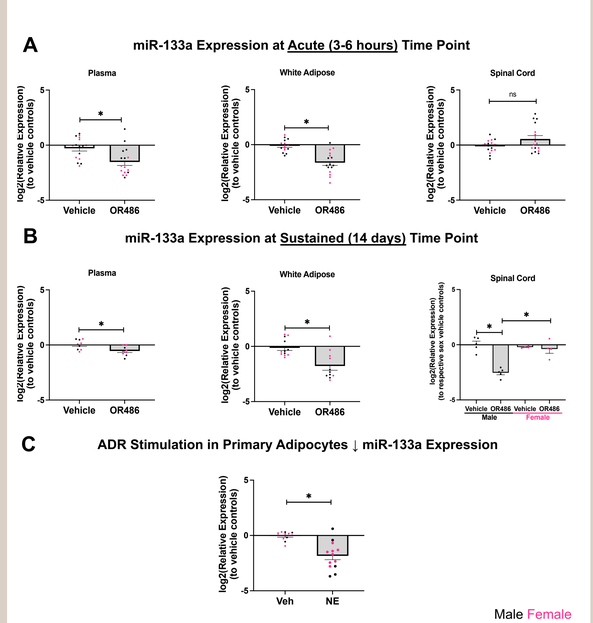


RESULTS

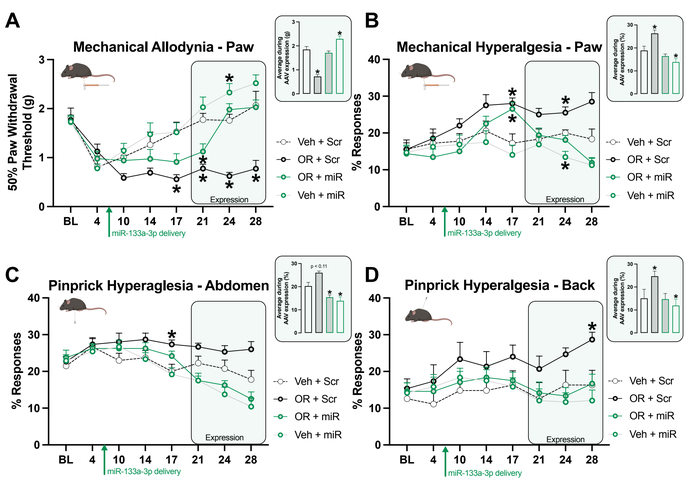
ADRB-dependent Downregulation of miR-133a is a Signature of Chronic Primary Pain



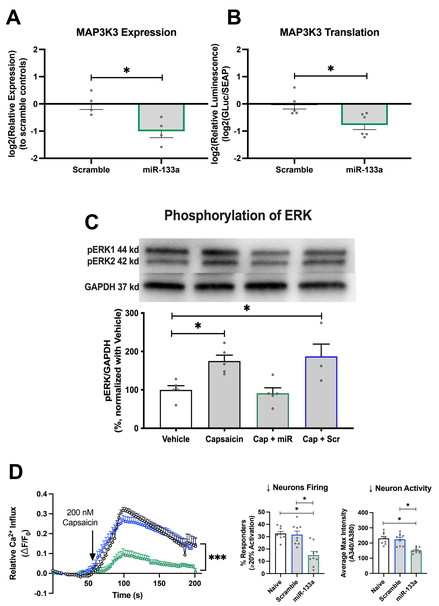
miR-133a Downregulation Likely Originates in White Adipose Tissue



Adipose-specific Overexpression of miR-133a Reverses Multi-site Mechanical Sensitivity

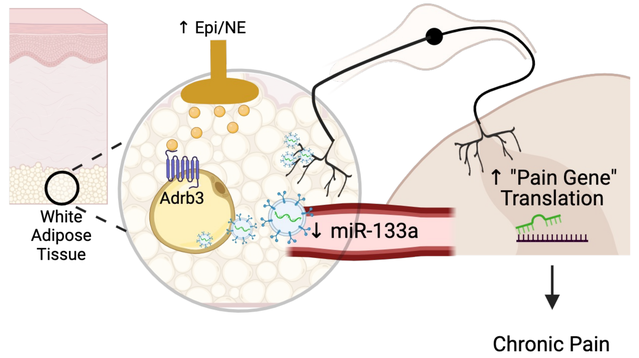


miR-133a Quiets Sensory Neurons Through Inhibition of MAPK Pathway



CONCLUSIONS

- ↓ miR-133a-3p is a purported biomarker for CPPCs
  - Decreases during adrenergic receptor activation
  - Synthesized in white adipose
- ↑ miR-133a-3p promotes analgesia
  - Silences sensory neurons
    - Inhibits translation of genes related to pain signaling



FUTURE DIRECTIONS

- Determine adipose-neuron crosstalk via exosomes
- Investigate cell type of origin through ISH-IHC
- Characterize regulated network of mRNA targets

ACKNOWLEDGEMENTS

Funding

NINDS R01 NS109541 to AN
NIDCR R56 DE025298 to AN
NIGMS T32 GM133352 to NH
NINDS F31 NS130861 to NH

Follow our Twitter/X @Nackley_Lab

Duke Anesthesiology
Duke University School of Medicine

Department of Pharmacology & Cancer Biology
Duke University School of Medicine

CTPM
Center for Translational Pain Medicine
Overcoming Pain Together