

## ***Sperm transcriptional state associated with paternal transmission of stress phenotypes.***

Cunningham AM, Walker DM, Ramakrishnan A, Doyle MA, Bagot RC, Cates HM, Peña CJ, Issler O, Lardner C, Browne C, Russo SJ, Shen L, Nestler EJ. Sperm transcriptional state associated with paternal transmission of stress phenotypes. *J Neurosci*. 2021 Jun 7;41(29):6202–16. doi: 10.1523/JNEUROSCI.3192-20.2021. Epub ahead of print. PMID: 34099514; PMCID: PMC8287983.

### **Abstract**

Paternal stress can induce long-lasting changes in germ cells potentially propagating heritable changes across generations. To date, no studies have investigated differences in transmission patterns between stress-resilient and -susceptible mice. We tested the hypothesis that transcriptional alterations in sperm during chronic social defeat stress (CSDS) transmit increased susceptibility to stress phenotypes to the next generation. We demonstrate differences in offspring from stressed fathers that depend upon paternal category (resilient vs susceptible) and offspring sex. Importantly, artificial insemination reveals that sperm mediates some of the behavioral phenotypes seen in offspring. Using RNA-sequencing we report substantial and distinct changes in the transcriptomic profiles of sperm following CSDS in susceptible vs resilient fathers, with alterations in long noncoding RNAs (lncRNAs) predominating especially in susceptibility. Correlation analysis revealed that these alterations were accompanied by a loss of regulation of protein-coding genes by lncRNAs in sperm of susceptible males. We also identify several co-expression gene modules that are enriched in differentially expressed genes in sperm from either resilient or susceptible fathers. Taken together, these studies advance our understanding of intergenerational epigenetic transmission of behavioral experience.

My statement of significance is:

This paper provides evidence that stress-induced epigenetic modification of sperm can result in paternal transmission of a complex behavioral and neuroendocrine phenotype. In this study, stress susceptibility of male mice was transmitted to only to male offspring even when insemination was artificial but only when the father was chronically stressed. RNA analysis of sperm revealed a primary difference in sperm transcription of long non-coding RNA, providing a candidate molecular mechanism. This study is of interest because it identifies a novel mechanism for sex-specific, transgenerational transmission of a clinically relevant behavioral trait.