University of Massachusetts Medical School
UMASS

GRADUATE SCHOOL OF BIOMEDICAL SCIENCES

INTERDISCIPLINARY GRADUATE PROGRAM

Ph.D. THESIS DEFENSE

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LRB 8th Floor Conference Room

Mechanistic Basis for Control of Early Embryonic Development by a 5' tRNA Fragment

Ancestral environmental conditions can instruct offspring development, although the mechanism(s) underlying such transgenerational epigenetic inheritance is unclear. In murine models focused on paternal dietary effects, we and others have identified tRNA fragments (tRFs) in mature sperm as potential carriers of epigenetic information. In our search for molecular targets of specific tRFs, we observed that altering the level of 5'-tRF Glycine-GCC (tRF-GG) in mouse embryonic stem cells (mESCs) and preimplantation embryos modulates the expression of the endogenous retrovirus MERV-L and genes regulated by MERV-L. Intriguingly, transient derepression of MERV-L is associated with totipotency of two-cell stage embryos and a subset of two-cell-like mESCs.

Here, I reveal the mechanistic basis for tRF-GG regulation of MERV-L. I show that tRF-GG supports the production of numerous small nuclear RNAs associated with the Cajal body, in mouse and human embryonic stem cells. In particular, tRF-GG modulates the levels of U7 snRNA to ensure an adequate supply of histone proteins. This in turn safeguards heterochromatin-mediated transcriptional repression of MERV-L elements. Importantly, tRF-GG effects on histone mRNA levels, activity of a histone 3'UTR reporter, and expression of MERV-L associated transcripts can all be suppressed by appropriate manipulation of U7 RNA levels. I also show that hnRNPF and H bind directly to tRF-GG, and display a stark overlap of *in vivo* functions with tRF-GG. Together, this data uncovers a conserved mechanism for a 5' tRNA fragment in the fine-tuning of a regulatory cascade to modulate global chromatin organization during pre-implantation development.

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