An indirect Regulation of LINE-1 elements by miRNAs in mouse embryonic stem cells

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Abstract

Mechanisms regulating LINE-1 transposition include DNA methylation in somatic cells and Piwi-interacting RNA (piRNA) pathway in the germline. During the blastocyst stage of mouse embryonic development however, both these pathways are inactivated leading to a critical window necessitating alternate means of L1 regulation. We previously observed an increase in L1 transcript and protein levels in mouse embryonic stem cells (mESCs) deprived of microRNAs (miRNAs). Curiously, the fold change in L1 expression levels in the miRNA KO mESCs did not translate into a similar increase in transposition rates, suggestive of an extra layer of regulation in keeping these mobile elements in check. Analysis of AGO2 CLIP-seq data from mESCs did not reveal a direct interaction between miRNAs and L1 mRNA, suggesting an indirect regulation of L1 expression by one or several miRNA target genes. Integrative analysis of transcriptomic and proteomic data from several miRNA mutant mESCs reported a consistent upregulation of the RNA helicase MOV10, a known regulator of L1 mRNA stability in cancer. We were able to demonstrate that Mov10 is directly regulated by miRNAs. Moreover, upon miRNAs depletion MOV10 is relocalized in the cytoplasm of mESCs, were it interacts with L1 RNA and protein to create L1-RNP condensates. Interestingly, unlike in cancer cells, these L1-RNP condensates do not appear to be stress granules (SGs), P-bodies or autophagosomes. In addition, while accumulation of L1 RNP and MOV10 in condensates is not a consequence of L1 mRNA upregulation, over-expressing MOV10 by transient transfection along with L1 mRNA upregulation leads to *de novo* condensate formation. On the other hand, siRNA mediated knockdown of MOV10 in *Dicer*_KO cells causes dissolution of L1-RNP condensate formation. We are currently investigating the molecular composition of these condensates and their role in regulating retrotransposition.

Keywords: LINE, 1, RNA interference, mouse embryonic stem cells, microRNAs

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