RNA interference pathways regulate genome integrity and early mouse development programs

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Résumé

Stem cells are central to emerging concepts in health, medicine and therapy. A basal network of gene regulation orchestrates the processes ensuring maintenance of cellular identity, pluripotency and genome integrity. Long interspersed elements 1 (L1) are non-long-terminal-repeat retrotransposons that dominate the mouse genomic landscape, and are expressed in germ cells, during early development and in mouse Embryonic Stem Cells (mESCs). In particular, L1 elements continue to affect our genome, and their movement can lead to sporadic cases of diseases. We recently established a role for RNA interference and other epigenetic pathways in the regulation of L1 transcription and mobilization in mESCs, in addition to their role in microRNA biogenesis. We further found that genetic ablation of Dicer or the sRNA effector proteins AGOs has complex and profound consequences on L1 transcription and mobilization in mESCs. Mutant mESCs for Dicer and Dgcr8 show profound defect in their differentiation capabilities. Based on these previous findings that RNAi act also as a guardian of genome integrity in mammals, we now started to access the role of LINE-1 elements on the maintenance of pluripotency of mouse ESCs and their differentiation. Using CRISPR/Cas9 engineering tools, we established independent mutant ESCs affecting L1 expression and investigated the impact on several biological processes: transcriptome, splicing events, cell cycle, metabolomics...The impact of LINE-1 elements regulation for stemness and differentiation defect phenotypes will be presented.

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