

LINE1-mediated retro-transposition in human pluripotent stem cells

Consequences for genomic stability and gene expression of hES and hiPS cells and its derivatives

Research project summary

The use of pluripotent stem cells derived from the inner cell mass of developing blastocysts (human embryonic stem cells, hESCs) or generated by reprogramming of fibroblasts (human induced pluripotent stem cells, hiPSCs) holds great therapeutic promise for regenerative medicine. However, a vital unanswered question is whether these cells or their derivatives are truly safe for administration. Specifically, it is unclear whether the integrity of the genome of pluripotent stem cells is maintained during their generation, expansion and differentiation. The appearance of genetic mutations during their expansion or differentiation could undermine stem cell therapies. Such mutations could be induced by human non-LTR retrotransposons (LINE1 or L1, Alu, SVA) which represent the currently mobilized group of human endogenous retroelements. This concern is emphasized by a recent report demonstrating that four defined hESC lines express endogenous L1 elements and support L1 retrotransposition in vitro. Which suggests that L1 retrotransposition might occur during early embryonic stages. Some retrotransposition events resulted in the concomitant deletion of genomic DNA at the target site. Also, an endogenous L1 retrotransposition event was identified in the CHM gene of a patient with choroideremia, an X-linked progressive eye disease, and found that the insertion occurred very early during the embryonic development of the patient's mother. These findings suggest that L1 retrotransposition events can occur during early stages of human development (e.g. at the blastocyst stage) and question the safety of the application of human pluripotent stem cells for regenerative medicine. Therefore, we set out to evaluate the risk of genetic destabilization inflicted on the genome of pluripotent stem cells by L1-mediated retrotransposition activity.