
Reprogramming somatic cells into iPS cells activates LINE-1 retroelement mobility.

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Public Summary:

Long interspersed element-1 (LINE-1 or L1) retrotransposons account for nearly 17% of human genomic DNA and represent a major evolutionary force that has reshaped the structure and function of the human genome. However, questions remain concerning both the frequency and the developmental timing of L1 retrotransposition in vivo and whether the mobility of these retroelements commonly results in insertional and post-insertional mechanisms of genomic injury. Cells exhibiting high rates of L1 retrotransposition might be especially at risk for such injury. We assessed L1 mRNA expression and L1 retrotransposition in two biologically relevant cell types, human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs), as well as in control parental human dermal fibroblasts (HDFs). Full-length L1 mRNA and the L1 open reading frame 1-encoded protein (ORF1p) were readily detected in hESCs and iPSCs, but not in HDFs. Sequencing analysis proved the expression of human-specific L1 element mRNAs in iPSCs. Bisulfite sequencing revealed that the increased L1 expression observed in iPSCs correlates with an overall decrease in CpG methylation in the L1 promoter region. Finally, retrotransposition of an engineered human L1 element was approximately 10-fold more efficient in iPSCs than in parental HDFs. These findings indicate that somatic cell reprogramming is associated with marked increases in L1 expression and perhaps increases in endogenous L1 retrotransposition, which could potentially impact the genomic integrity of the resultant iPSCs.

Scientific Abstract:

Long interspersed element-1 (LINE-1 or L1) retrotransposons account for nearly 17% of human genomic DNA and represent a major evolutionary force that has reshaped the structure and function of the human genome. However, questions remain concerning both the frequency and the developmental timing of L1 retrotransposition in vivo and whether the mobility of these retroelements commonly results in insertional and post-insertional mechanisms of genomic injury. Cells exhibiting high rates of L1 retrotransposition might be especially at risk for such injury. We assessed L1 mRNA expression and L1 retrotransposition in two biologically relevant cell types, human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs), as well as in control parental human dermal fibroblasts (HDFs). Full-length L1 mRNA and the L1 open reading frame 1-encoded protein (ORF1p) were readily detected in hESCs and iPSCs, but not in HDFs. Sequencing analysis proved the expression of human-specific L1 element mRNAs in iPSCs. Bisulfite sequencing revealed that the increased L1 expression observed in iPSCs correlates with an overall decrease in CpG methylation in the L1 promoter region. Finally, retrotransposition of an engineered human L1 element was approximately 10-fold more efficient in iPSCs than in parental HDFs. These findings indicate that somatic cell reprogramming is associated with marked increases in L1 expression and perhaps increases in endogenous L1 retrotransposition, which could potentially impact the genomic integrity of the resultant iPSCs.

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