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A Reverse Transcriptase-dependent mechanism is active in embryo development and in tumorigenesis

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Long Interspersed Nuclear Elements (LINE-1) and endogenous retroviruses represent the most abundant families of retrotransposable elements in mammalian genomes. They encode a reverse transcriptase (RT) protein as part of the ORF2, which is required for their own mobilization as well as that of non-autonomous Alu/SINE retrotransposons. We have shown that LINE-1-derived ORF2p, encoding RT, is abundantly expressed and specifically localized in murine embryo early stages and in a variety of human cancers, while being virtually absent from normal somatic differentiated tissues. We also detected a progressive increase of LINE-1 and SINE copy numbers in murine preimplantation developmental stages and in tumor progression. Conversely, RT inhibition arrests early embryo development and inhibits cancer cell proliferation, promotes their differentiation and antagonizes tumor growth in animal models. In line with this, the nonnucleoside RT inhibitor efavirenz recently proved effective in phase II trials with prostate carcinoma metastatic patients. To get insight into the RT mechanism in diverse processes as early embyrogenesis and cell transformation, we have examined global expression profiles in native and RT inhibited cells. We find that: i) RT inhibition causes a global reprogramming of expression of coding genes, microRNAs (miRNAs) and genomic ultra-conserved regions (UCRs) (the latter two are enriched in Alu sequences, often organized as pairs of inverted repeats), ii) Alu- and LINE-1-containing RNA:DNA hybrid molecules are abundant in cancer but not in normal cells or in RT inhibitor-treated tumor cells. We therefore propose that the abundant RT in embryos and cancer cells reverse-transcribes RNA precursors, generating RNA:DNA hybrids that affect the overall production of various RNA classes, including regulatory miRNAs, with an ensuing impact on global gene expression. RT inhibition restores the 'normal' RNA expression profiles. Thus, LINE1-RT drives a novel regulatory mechanism, required in early embryogenesis, which, when erroneously reactivated in adult life, drives cell transformation and tumorigenesis.

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