Identification of mechanism of cancer-cell-specific reactivation of hTERT offers therapeutic opportunities for blocking telomerase specifically in human colorectal cancer

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Abstract

Transcriptional reactivation of hTERT is the limiting step in tumorigenesis. While mutations in hTERT promoter present in 19% of cancers are recognized as key drivers of hTERT reactivation, mechanisms by which wildtype hTERT (WT-hTERT) promoter is reactivated, in majority of human cancers, remain unknown. Using primary colorectal cancers (CRC) we identified Tert INTeracting region 2 (T-INT2), the critical chromatin region essential for reactivating WT-hTERT promoter in CRCs. Elevated β-catenin and JunD level in CRC facilitates chromatin interaction between hTERT promoter and T-INT2 that is necessary to turn on hTERTexpression. Pharmacological screens uncovered salinomycin, which inhibits JunD mediated hTERT-T-INT2 interaction that is required for the formation of a stable transcription complex on the hTERT promoter. Our results showed for the first time how known CRC alterations, such as APC, lead to WT-hTERT promoter reactivation during stepwise-tumorigenesis and provide a new perspective for developing cancer-specific drugs.

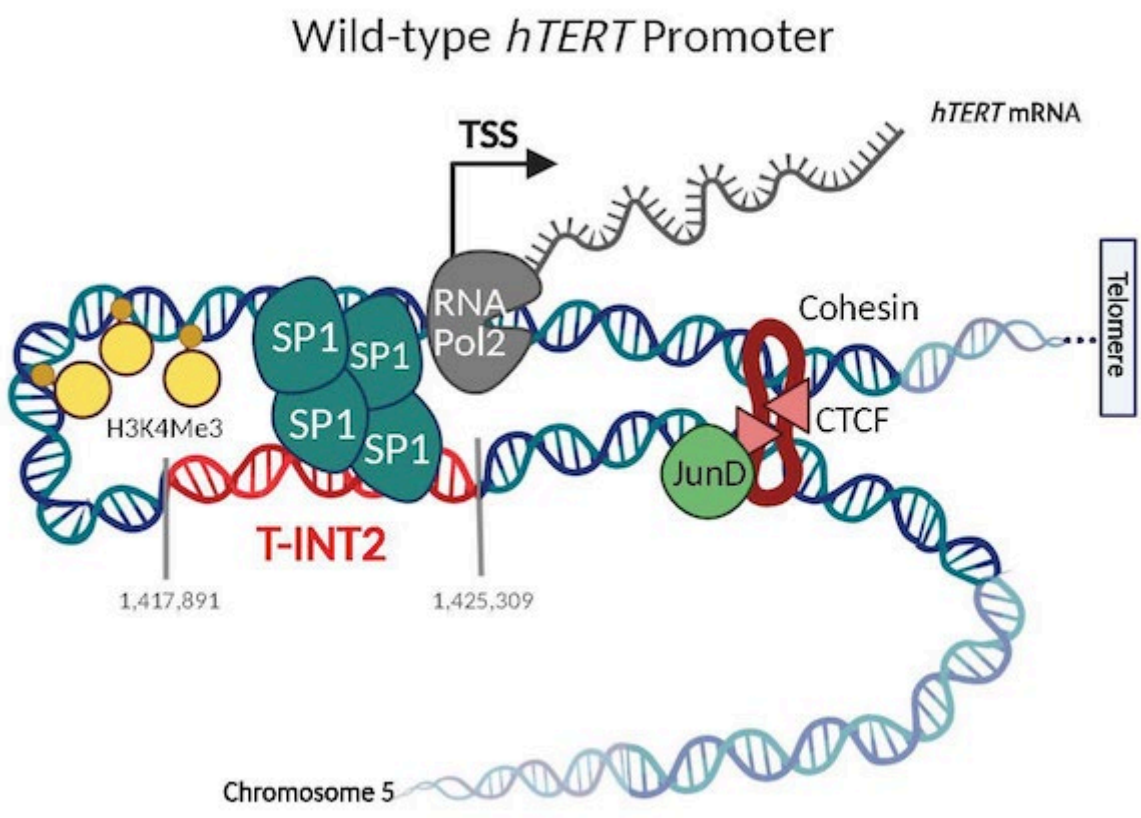

Figure legend: Reactivation of *hTERT*gene in cancer cells. Cancer-specific long-range chromatin interactions switch on wild-type *hTERT*promoter.