TERT increased transcriptional activity and oncogenic _TERT_ promoter mutations in GIST.

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BACKGROUND: Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors, which are molecularly characterized by activating *KIT/PDGFRA* mutations that constitute important predictive biomarkers of imatinib response in these patients. Recently point mutations in the promoter of telomerase reverse transcriptase (*TERT*) gene, mainly at positions c.−124 and c.−146 bp, were described in several human cancers, representing a novel mechanism of telomerase activation in cancer. In GIST, there is few data on *TERT* promoter mutations. Herein, we searched for the presence and clinicopathological association of *TERT* promoter mutations in a series of 130 bona fide GISTs.
HYPOTHESIS: We investigated the functional importance of the *TERT* promoter mutations in terms of transcriptional activity in a GIST cell line. METHODS: Genomic DNA from 130 paraffin tumor tissues was extracted and the hotspot *TERT* promoter region was amplified by PCR followed by direct sequencing. In the GIST-T1 cell line, a reporter assay system with the relevant portion (c.−290 to c.− 47) of the mutant or wild-type *TERT* core promoter was cloned upstream of the firefly luciferase gene and evaluated its luciferase activity RESULTS: We found *TERT* promoter mutations in 3.8% (5/130) of GIST. No statistical correlation was found between *TERT* mutation and GIST clinical or molecular (*KIT/PDGFRA/BRAF*) features. Yet, *TERT* mutations appeared in tumors of slightly older patients, and no *TERT*-mutated cases were detected in benign/very low malignancy risk GIST. *In vitro*, we showed that in comparison to the wild-type *TERT* promoter, both mutations conferred increased transcriptional activity. In conclusion, in the present study we showed that *TERT* promoter mutations are present in a small fraction of GIST. The mutations identified (c.−124 and c.−146 bp) are associated with increase of the *TERT* transcriptional activity in GIST cell line. Further studies are needed to extend and validate these findings in order to determine its clinical and biological impact in GIST.