ONCOGENIC TERT PROMOTER MUTATIONS INCREASE THE TERT TRANSCRIPTIONAL ACTIVITY IN GASTROINTESTINAL STROMAL TUMORS (GIST).

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Introduction and Objectives: GISTs are the most common mesenchymal tumors molecularly characterized by activating KIT/PDGFRA mutations that constitute important predictive biomarkers of imatinib response. 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 GISTs, there is no 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. Furthermore, we investigated the functional importance of the TERT promoter mutations in terms of transcriptional activity in a GIST cell line. Materials and 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 and Conclusion: We found TERT promoter mutations in 3.8% (5/130) of GISTs. 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 GISTs. In vitro, we showed that in comparison to the wild-type TERT promoter, both mutations conferred increased transcriptional activity. In the present study we showed that TERT promoter mutations are present in a small fraction of GISTs. 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 GISTs.
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Key Words: gastrointestinal stromal tumors, telomerase reverse transcriptase, promoter mutations.