**Mechanisms of telomerase reverse transcriptase reactivation in cancer**

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**Background:** Telomerase activity and telomere elongation are crucial for the limitless proliferation of cancer cells. Telomerase reverse transcriptase (TERT) gene is permanently activated in neoplastic cells via multiple mechanisms, including chromosomal rearrangements, amplification of TERT gene, generation of TERT structural variants, telomere position effect and activating mutations in the TERT promoter [1]. Mutations in TERT promoter have been recognized as early markers of tumour development and as major indicators of poor outcome in several cancer types. In addition, telomerase might represent a promising therapeutic target for cancer treatment [2].

**Aims:** This review aims to summarize recent findings on the role of telomerase and TERT promoter mutations in cancer development, their importance as early diagnostic and/or prognostic biomarkers and use of telomerase inhibitors for cancer treatment.

**Topics overviewed:** Main focus will be on the a) the pathogenesis of cancer types with a high prevalence of TERT promoter mutations, including HPV-related cancers [3]; b) Analysis of how specific transcription factors interact with and activate the mutant TERT promoter, influencing cancer progression; c) Insights into how TERT promoter mutations are acquired over the time and across different tissue environments, contributing to cancer heterogeneity [4, 5]; d) Exploration of potential therapeutic strategies targeting TERT promoter mutations and their pathways to improve cancer treatment.

**Conclusions:** The crucial role of telomerase activity and telomere maintenance in cell transformation and development of cancers has known since many years. Knowing the temporal occurrence of genetic and epigenetic changes in TERT locus during cancer growth is very important for the development of diagnostic and prognostic markers in diverse tumour types. Therapeutic strategies specifically directed to TERT promoter mutations will likely have an important clinical impact in. many types of human cancers

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