Telomere maintenance as therapeutic target in embryonal tumours.

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Abstract
Embryonal tumours most commonly occur in the first few years of life and account for approximately 30% of childhood malignancies. Knowledge of these tumours' genetics has already impacted on their clinical management and further knowledge of their cellular immortalization will hopefully result in novel therapies. The ends of human chromosomes are capped and protected by telomeres; cellular replication, however, causes their loss. A critical length of telomere repeats is required to ensure proper telomere function and avoid the activation of DNA damage pathways that result in senescence and cell death. To proliferate beyond the senescence checkpoint, cells must restore their telomere length. Hence stabilization of telomere is an important step in cell immortalization and carcinogenesis. Telomere maintenance is evident in virtually all types of malignant cells, including embryonal tumours, where either a telomerase-dependent or alternative lengthening of telomeres (ALT) mechanism is employed in order to ensure their limitless replicative potential. For this reason effective strategies targeting telomere maintenance in cancer cells require a combination of telomerase and ALT inhibitors. In this review, we are giving an overview about telomere maintenance in childhood tumours and discussing its potential as a new therapeutic target.

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Different telomere maintenance mechanisms in alveolar and embryonal rhabdomyosarcoma.

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Abstract
The activation of a telomere maintenance mechanism (TMM) is crucial for the immortalization of tumor cells. Most human cancers apply telomerase-dependent TMM but some use a mechanism called alternative lengthening of telomeres (ALT). The latter was suggested to be mainly characterizing sarcomas with nonspecific complex karyotypes, whereas telomerase activation is typical of sarcomas generated by specific translocations. In this study, we investigated the TMM and its association with survival in rhabdomyosarcoma (RMS), which is characterized by two major subtypes: one that is harboring a specific translocation (alveolar) and one that has a nonspecific karyotype (embryonal). Telomerase activity (TA), using telomerase repeat amplification protocol (TRAP) assay, and telomere length (TRF), using Southern blotting, were analyzed in tumor samples from 31 patients (16 embryonal and 15 alveolar). Alveolar RMS tumors exhibited no ALT phenotype and the majority presented TA. Some embryonal tumors exhibited an ALT or "ALT-like" phenotype which lacked TA, whereas others expressed telomerase-dependent TMM, and neither TA nor ALT correlated with outcome. The average TRF length of the embryonal tumors was significantly higher than that of the alveolar tumors (10.8 vs. 7.2 kb, P = 0.003). Interestingly, some tumors of both subtypes presented no TMM. These observations suggest that alveolar RMS predominantly use telomerase-dependent TMM, whereas in embryonal tumors both telomerase and ALT may play a role. These findings have important implications for understanding the role of TMM in the development of RMS tumors, and for future designing adapted treatment strategies.

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Telomeres and telomerase in sarcomas.

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Abstract
Telomeres of human tumor cells have two types of telomere maintenance mechanisms by telomerase activation and alternative lengthening of telomeres (ALT). Although over 80% of all carcinomas rely on telomerase activity to maintain stable telomere length, many types of sarcoma elongate telomeres consistent with ALT in the absence of telomerase activity. Recently, the presence of telomerase activity and ALT in several sarcomas was examined extensively, and recent studies indicate a positive correlation between the telomere maintenance mechanism and tumor aggressiveness in several sarcoma types. We reviewed both the activation of telomere maintenance in a variety of common bone and soft tissue sarcoma subtypes, and the consequences of telomere maintenance mechanisms with respect to the clinical characteristics.

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