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.

Telomeres are specialized structures containing unique (TTAGGG)n repeats at the ends of chromosomes which are thought to be important for the stabilization of chromosomes (1, 2). Lagging strand DNA synthesis at the very end of chromosomes cannot be completed. This phenomenon is the so-called ‘end-replication problem’ and this situation results in the progressive shortening of telomeric repeats with each cell division (3). Telomerase contains an RNA-dependent DNA polymerase, which compensates for the end-replication problem, and is expressed in germline cells but not in most somatic cells (4).

Telomere studies in many human carcinomas have been extensively reported for diagnostic and prognostic utility (5-9). Telomere maintenance is regarded as an important mechanism in evading senescence by tumor cells, and in most carcinoma cases is achieved by reactivating or up-regulating telomerase activity. In addition, in many types of carcinoma cell, there is a considerable shortening of telomeres despite telomerase expression (5-7). However, several types of sarcoma have been reported to have alternative lengthening of telomeres (ALT) without telomerase activity, indicating the existence of nontelomerase-based ALT mechanisms for telomere maintenance (10, 11). Cells with ALT usually exhibit a remarkable elongated and heterogeneous telomere length, and many types of sarcoma have been reported to have ALT in the absence of telomerase activation (10, 12).

Perrem et al. suggested that the co-existence of ALT and telomerase activity is unlikely (13). However, several reports have shown evidence of the presence of both ALT and telomerase activity (12, 14-16). In contrast, some sarcoma populations showed no evidence of either telomerase or ALT mechanisms, although these findings contradict the fundamental theory that telomere maintenance mechanisms are necessary for tumorigenesis (17, 18).

Human telomerase reverse transcriptase (hTERT) is the catalytic telomerase subunit and the close relationship between hTERT mRNA expression and telomerase activity suggests that quantification of mRNA expression of hTERT could be used as an alternative to the measurement of telomerase activity in carcinomas (19-21). In contrast, hTERT expression was heterogeneous in sarcoma and was not associated with telomerase activity.

The telomere maintenance mechanism has recently been reported as a prognostic factor for patients with sarcomas (12, 14, 16, 22-28), and ALT positivity correlated with worse survival of patients with several types of sarcomas. Therefore, studies of the telomere maintenance mechanisms may lead to novel therapeutic strategies to fight sarcomas.

Prevalence of Telomere Factors in Sarcomas

In previous reports of osteosarcoma, over 40% of osteosarcoma samples expressed telomerase activity (15, 24,
26, 29), suggesting that telomerase activation may be prevalent. However, one report revealed that only 32% of samples were hTERT positive (14). The frequency of ALT in osteosarcoma ranged from 11 to 66% among previous reports (14, 15, 29).

In reports of Ewing’s sarcoma, the frequency of telomerase activity expression ranged from 12 to 84% (24-26, 29, 30). Ulaner et al. reported that no ALT was observed in Ewing’s sarcoma samples (25).

The frequency of telomerase expression in previous reports of chondrosarcoma ranged from 0 to 43% (24, 26, 31). To the best of our knowledge, the proportion of ALT in chondrosarcoma has not been reported.

The rate of telomerase expression in malignant fibrous histiocytoma (MFH) samples ranged from 22 to 80% (22-24, 26, 28). Matsuo et al. reported that hTERT expression was demonstrated in approximately 90% of MFH samples, and 30% of tumor samples had evidence of engagement of the ALT mechanisms of telomere length maintenance (32).

In liposarcoma samples, the rate of telomerase expression ranged from 18 to 64% (17, 24, 28, 33), and the frequency of ALT ranged from 20 to 33% (12, 16-18, 33). Although the frequency of telomere factors varies greatly among different sarcoma subtypes and different reports, this may reflect the homogeneous characteristics of sarcomas. In almost all of the previous reports, one sample has been evaluated from each tumor type. Yan et al. demonstrated that telomerase activity and hTERT mRNA expression were heterogeneous according to the area of the sarcoma sampled (22). This finding also may indicate the prevalence of these factors reveals different results among previous reports.

Telomere Maintenance and Patient Prognosis in Sarcoma

Several papers have indicated that high telomerase activity is associated with poor survival of osteosarcoma patients (14, 24, 26, 29). In contrast, one paper has reported controversial data with no correlation between telomerase activity and prognosis (25). The ALT phenotype was also reported to be a poor prognostic factor in osteosarcoma patients (25), although one controversial report maintained that ALT was not clearly associated with a poor prognosis (12).

In terms of prognosis of Ewing’s sarcoma patients, Ohali et al. indicated a significant correlation between prognosis and high telomerase activity in blood samples, but not in tumor samples (30). In contrast, Sotillo-Pineiro et al. indicated that the presence of telomerase activity in tumor samples was associated with survival (29).

To the best of our knowledge, only one report has demonstrated an explicit correlation between telomere factors and prognosis in MFH patients. Matsuo et al. reported that being ALT positive was the only independent prognostic factor for death in MFH patients. Telomerase activity did not affect the prognosis in ALT-positive MFH patients. High telomerase expression was associated with a poor prognosis in ALT-negative patients (32).

Telomerase activity was shown to be related to a poor prognosis in liposarcoma patients (33). Costa et al. revealed that the presence of a telomere maintenance mechanism (ALT or telomerase activity) affected patient prognosis (18).

Telomerase Therapeutics for Sarcoma

There are several potential concerns that are raised about telomerase being a very attractive cancer target. The continuous growth of advanced malignancies in carcinomas almost universally correlates with the reactivation of telomerase. In addition, most carcinomas not only express telomerase but also have very short telomeres, whereas telomerase activity is undetectable in most normal somatic cells except embryonic cells and adult male germline cells (34, 35). Differences in telomerase expression and telomere length between normal and tumor tissues suggest that targeting telomerase would be relatively safe. In contrast to normal cells, tumor cells generally have a short telomere length so that telomerase inhibition shorten telomeres sufficiently for the cells to become senescence. Clinical phase I/II trials are ongoing with a telomerase inhibitor, GRN163L (36), and the primary results indicate safety with good tolerance (37). Telomerase inhibitors as novel anticancer drugs are expected to have a significant effect on patient survival.

Sarcoma cells have a relatively low telomerase expression compared to carcinoma cells and several types of sarcoma have ALT and exhibit a remarkable elongated telomere length, indicating telomerase inhibitor may not be effective theoretically. However, Jackson et al. reported that a telomerase inhibitor induced an anti-adhesive effect against ALT cell lines such as SUSM-1 and VA 13, suggestive of an unknown mechanism of telomerase inhibitor in ALT cell lines (38). In general, previous reports indicated a positive correlation between telomere maintenance mechanisms and prognosis in sarcoma patients, therefore, in the near future, a better understanding of the roles and regulation of telomere maintenance mechanisms should lead to novel therapeutic strategies to improve treatment of sarcoma patients using telomerase and telomere- targeting therapy.

References


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