Telomere dynamics in adult hematological malignancies

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Telomeres are repetitive DNA sequences protecting physical ends of linear chromosomes against degradation and end-to-end chromosomal fusion. Telomeres shorten with each cell division, which regulates the cellular lifespan in somatic cells and limits their renewal capacity. Cancer cells are often able to overcome this physiological barrier and become immortal with unlimited replicative capacity. In this review, we present current knowledge on the role of telomeres in human aging with a focus on their behavior in hematological malignancies of adults. Associations of telomere length to age-related diseases and to the prevention of telomere shortening are also discussed.

Key words: telomere, telomerase, leukemia, lymphoma, hematooncology, aging

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Telomeres and their functions

Telomeres are complex repetitive DNA sequences binding multiple interacting proteins (Fig. 1), protecting the ends of linear chromosomes against end-to-end fusion and degradation. Human telomeres are composed of ~5–15 kb long hexameric 5'-TTAGGG-3' repeats^{1,2}. At the end of the chromosome, there is a 3'-overhang³, which coils up into a T-loop and creates shelterin complex with telomere-binding proteins⁴ (Fig. 1). Telomeric DNA is transcribed into a non-coding telomeric repeat-containing RNA (TERRA) (ref.⁵), which binds to the telomeric re-

gion creating DNA-RNA hybrids, and has a regulatory function⁶. When a cell divides, the semiconservative DNA replication complex goes through many obstacles when approaching the telomeric regions. The replication fork needs the assistance of DNA helicases to resolve DNA-RNA hybrids and T-loops^{5,7} and the support of stability by shelterin proteins to successfully proceed through the telomeric region. Later, nucleases end-process the terminal nucleotides to generate the 3'-overhang⁸. By this mechanism, the telomeres are shortened with each cell division. The telomeric region can be prolonged by an

Fig. 1. A chromosomal end with telomeric repeats forming shelterin complex with T-loop that binds telomeric repeat binding factors 1 and 2 (TRF1 and TRF2), TRF1-interacting nuclear protein 2 (TIN2), human repressor activator protein 1 (RAP1) and single-stranded D-loop on 3'-overhang binding protection of telomeres 1 (POT1) and tripeptidyl peptidase 1 (TPP1).

enzyme called telomerase, composed of the catalytic subunit TERT (telomerase reverse transcriptase) and RNA template telomerase RNA component (TERC) (ref.^{9,10}). Another mechanism of telomere prolongation is called alternative lengthening of telomeres (ALT) based on homologous recombination. ALT is active in a minority of human cancer types and this underlies resistance to therapy based on anti-telomerase drugs^{11,12}. It has been shown that TERRA levels are elevated in cells with active ALT (ref.¹³). Overall, telomere replication and prolongation include many complex processes and interactions; the detailed mechanism is not fully understood yet.

Telomere maintenance strategy is specific for each cell type. While telomeres of somatic cells shorten with each cell division, germ cells are capable of maintaining stable telomere length to sustain cell immortality¹⁴. In stem cells, telomerase activity is limited and during lifetime the proliferative capacity of these cells is exhausted, causing senescence and loss of ability to renew tissues^{15,16}. However, many cancer cells are able to overcome short telomeres and activate telomerase to ensure cell immortality, thus increasing the aggressiveness of a tumor⁹.

Telomeres influence the health of aging individuals

Overall healthy lifestyle, including balanced diet, physical activities, and avoiding smoking and stress exposure, has great potential to reduce the rate of excessive telomere shortening and thus to delay the onset of age-associated diseases and increase lifespan¹⁷. Most unhealthy lifestyle factors have been linked to increased cellular oxidative stress¹⁸⁻²¹. Due to the high guanine content and a lack of repair of single-stranded breaks, telomeric regions are susceptible to damage caused by oxidative stress²², therefore reducing oxidative stress in cells results in better telomere maintenance. In many epidemiologic studies, short telomeres were associated with age-related diseases including cardiovascular diseases, osteoporosis, cancer, and overall mortality, although, probably due to different methodology and cohort selection, these results are often contradictory (epidemiologic studies reviewed in detail in Sanders and Newman²³).

Telomere length in hematological malignancies of adults

Acute myeloid leukemia

Acute myeloid leukemia (AML) typically progresses rapidly with leukemic cells undergoing extensive cell division. Therefore, compared to age-matched healthy controls, short telomeres caused by gradual replicative erosion are frequently represented, with cytogenetically abnormal leukemic cells having shorter telomeres than leukemic cells with normal karyotype^{24,25}. In AML, approximately half of the patients do not carry cytogenetic lesions at the time of diagnosis^{26,27}; however, it was shown that 50% of patients with normal karyotype have sub-microscopic losses or duplications in terminal regions suggesting impaired telomere stability²⁸. AML cells with *FLT3* mutations have shorter telomeres than *FLT3* wild-type cells²⁴. Telomere length differs among AML cases divided based on the French-American-British (FAB)

classification system; with more differentiated cells the telomere length was shorter²⁴. AML0 and AML3 subtypes express lower amount of TERT than other AML FAB subtypes²⁵. Compared to less common adult acute lymphoblastic leukemia (ALL), AML patients have longer telomeres and lower expression of telomerase^{24,25}.

Chronic myeloid leukemia

Most patients with chronic myeloid leukemia (CML) have no distinctive early disease symptoms as the disease typically evolves slowly in the chronic phase but later on progresses rapidly in the accelerated and blast phases. CML arises from cells with translocation *t(9;22)(q34;q11)*, creating Philadelphia chromosome, and resulting in the *BCR-ABL1* fusion gene with a high tyrosine kinase activity. CML patients have highly variable but generally shorter telomeres and normal or slightly higher expression of telomerase, than age-matched controls^{29,30}. CML patients with shorter telomeres at the time of diagnosis represent a high-risk subgroup and enter the accelerated phase earlier³¹. Similarly, patients entering the blast phase within 2 years after diagnosis had significantly shorter telomeres³². Most of the studies focused on overall telomere length, while Samassekou et al. studied telomere length of individual chromosomes in CML patients and found that p-arms harbored longer telomeres and the q-arms shorter because of high shortening rate on q-arms³³. The telomere length on individual chromosomes differed greatly within the study; telomeres on 5p, 9p, 11p, 12p, 14p, 14q, 16p, 17p, 18p, 19p, 20p, Xp, and Xq were maintained or prolonged in most CML cases. Patients with a higher telomerase activity had a higher frequency of additional cytogenetic aberrations, in the blast phase the telomerase activity was increased compared to the chronic phase³⁰. These findings suggest a potential association between individual telomere length and chromosomal (in)stability in CML.

Myelodysplastic syndrome

Myelodysplastic syndrome (MDS) is a highly heterogeneous disease with many subtypes harboring various genetic mutations. MDS originates from an undifferentiated hematopoietic stem cell and causes ineffective hematopoiesis, predisposition to infections, and frequently progresses to AML (ref.³⁴). Risk factors for MDS include advanced age, previous exposure to chemotherapy, radiation, chemicals and some inherited genetic syndromes related to abnormalities in DNA repair. Compared to age-matched healthy controls, the MDS telomere length is shorter in peripheral blood leukocytes³⁵⁻³⁷ and even non-tumor buccal swabs³⁶. There is no significant difference in telomere length between distinct MDS subtypes; however, patients with isolated monosomy 7 have significantly longer telomeres³⁷. Shorter telomeres were detected in patients with professional exposure to paints and pesticides³⁶. Overall, telomere dysfunction could be caused by deregulated RNA splicing and associates with high-risk MDS phenotypes³⁸. Higher telomerase activity is associated with shorter survival in MDS patients³⁹.

Chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the Western world with very heterogeneous features and disease course. Similarly to other indolent lymphoproliferative malignancies, at the time of diagnosis, CLL has none or ambiguous symptoms and many patients are diagnosed randomly. Patients divide into two main prognostic groups based on the somatic hypermutation status of their rearranged immunoglobulin heavy chain variable gene region (IGHV): mutated IGHV is associated with better prognosis, while unmutated IGHV with worse prognosis^{40,41}.

Thoroughly studied in CLL, telomere length has been associated with markers of poor prognosis, such as unmutated IGHV, shorter time to first treatment, reduced overall survival, increased genomic complexity and mutated *ATM* and *TP53* (ref.^{42,48}).

Telomere length is considered to be stable in the disease course of most CLL cases⁴⁹, although our recent unpublished data suggest that due to clonal evolution, telomere length might vary under specific circumstances.

Telomerase activity in CLL has been shown to be significantly higher in IGHV-unmutated cells compared to IGHV-mutated cells^{42,50}. Despite this, the telomerase activity in CLL was similar to normal B lymphocytes and was not shown to associate with patients' prognosis⁴². In contrast, other studies show a significant association between telomerase activity and survival in CLL (ref.^{50,51}). Of note, IGHV-mutated CLL originates from cells activated in germinal center (GC) where telomeres in normal B cells are naturally prolonged by telomerase. In contrast, the IGHV-unmutated CLL cells originate likely at the pre-GC developmental stage where telomeres are naturally shorter⁵². Discrepancies in the activity of telomerase might be caused by the complexity of telomere maintenance and the role of shelterin and other proteins in this process. Mutations in *POT1*, an important member of the shelterin complex maintaining 3'-overhang stability, have been described in 3.5% of IGHV-mutated, and 9% of IGHV-unmutated cases⁵³. Expression levels of telomere maintenance proteins TRF1, RAP1, and POT1 were shown to be reduced and levels of TPP1 increased⁵⁴ in newly diagnosed CLL patients at an early stage; TPP1 and TIN2 were down-regulated⁵⁵. Expression of other proteins interacting with telomeres remains to be investigated further.

Non-Hodgkin lymphomas

Non-Hodgkin lymphomas (NHL) are the most common malignancies among adult hemato-oncological patients. They originate from B lymphocytes at various developmental stages, less frequently NHL can arise from T lymphocytes. In this review, we will focus on the most common types of NHL diagnosed in Europe.

Diffuse large B cell lymphoma

Diffuse large B cell lymphoma (DLBCL) is the most common NHL characterized by rapid cell division and fast growth of lymph nodes. Typically, treatment is immediately needed and induces various responses in different

disease subtypes. DLBCL cells originate from GC B cells. Two main subgroups are GC-like DLBCL with ongoing mutagenesis and better prognosis and activated B cell-like (ABC) DLBCL with poor prognosis⁵⁶. At molecular level, DLBCL harbors a large number of aberrations, often including del(1p), del(2p), and del(13q) in GC-like DLBCL and 3+, del(6q), del(9p), gain 18q, and gain 19q in ABC-DLBCL (ref.⁵⁷). Like CLL, telomere length of both DLBCL subgroups corresponds to cellular origin. Thus GC-like DLBCL originating from GC has longer telomeres than post-GC ABC-DLBCL (ref.⁵⁸). GC-like DLBCL and ABC-DLBCL have different overall survival; however, telomere length detected in the subgroups does not further separate patients according to overall survival⁵⁸.

Mantle cell lymphoma (MCL)

Mantle cell lymphoma (MCL) has intermediate cell growth and high clinical and genetic heterogeneity with typical recurrent genomic aberrations including t(11;14)(q13;q32) juxtaposing *CCND1* gene in a close proximity of IGH locus which leads to cyclin D1 overexpression. Gene mutations in *ATM*, *TP53*, *CCND1*, and *NOTCH1* are used as markers of prognosis^{59,61}. Genomic instability expressed by various genomic alterations in MCL suggests a possible role of telomere dysfunction. Telomere length in MCL is shorter than in normal B cells, DLBCL, and FL. Overall MCL cells have longer telomeres than IGHV-unmutated CLL cells but shorter than IGHV-mutated CLL cells⁵⁸. No significant association of telomere length with IGHV somatic hypermutation, *TP53* mutations, proliferation index, or overall survival was found^{58,62}.

Follicular lymphoma (FL)

Follicular lymphoma (FL) is an indolent lymphoma with slow cell growth, where the watch and wait approach is often employed. FL cells originate from GC, 90% of cases carry typical t(14;18)(q32;q21) juxtaposing *BCL2* gene in a close proximity of the IGH locus causing overexpression of anti-apoptotic proto-oncogene *BCL2* (ref.⁶³). Telomere length in FL is similar to DLBCL but longer than in MCL (ref.⁶⁴).

Overall, in NHLs, telomerase is naturally active following a cellular origin based on GC activation and is not overexpressed compared to normal reactive lymph node tissues; overexpression was detected only in Burkitt's lymphoma^{52,65}. In DLBCL, MCL, and FL, a constantly low level of telomerase activity was noted, although proliferation levels in these NHLs vary. In normal lymph nodes, DLBCL, MCL, and FL, the expression of TRF1, TRF2, and PIF1 was reported to differ only marginally⁶⁵. Since no other information about telomere maintenance strategy in NHLs has been found, this field appears relatively unexplored.

Hodgkin lymphoma

Hodgkin lymphoma (HL) is a malignancy featuring a low number of malignant cells in affected lymph nodes, consisting of multi-nucleated Reed-Sternberg cells and their precursors, mono-nucleated Hodgkin cells, derived

Table 1. Comparison of telomere length and telomerase activity and their association with disease prognosis in hemato-oncological malignancies.

Malignancy	Telomere length comparison	Telomere length associated with prognosis	Telomerase activity associated with prognosis	Ref.
AML	> ALL = CML; < MDS	yes	yes	25,81
CML	= AML; < MDS	yes	yes	81
MDS	> AML, CML	no	yes	81
CLL	= MCL; < DLBCL, FL	yes	contradictory	58
DLBCL	>CLL, MCL; = FL	no	no	58
MCL	= CLL; < DLBCL, FL	no	no	58
FL	>CLL, MCL; = DLBCL	no	no	58
HL	< healthy donors	yes	yes	67
MM	<MGUS	yes	yes	25

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; MCL, mantle cell lymphoma; MDS, myelodysplastic syndrome; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma.

from GC-B cells⁶⁶. Short telomeres were found in both malignant cells and non-tumor blood cells compared to healthy donors⁶⁷. Patients with refractory disease have shorter telomeres even before first treatment administration⁶⁸. Short telomeres in HL are associated with increased genomic instability⁶⁷. Telomerase is expressed in low levels in some cases but it is not detectable in other cases^{69,70}. In HL the telomeres can be prolonged by both telomerase and ALT as well. The occurrence of ALT is associated with disease progression and shorter overall survival in HL (ref.⁷¹).

Multiple myeloma

Multiple myeloma (MM) originates from antibodies-producing GC-experienced plasma cells. MM evolves from a mostly asymptomatic condition known as monoclonal gammopathy of undetermined significance (MGUS) (ref.⁷²) and in an advanced stage is typically characterized by severe bone pain caused by osteolytic skeletal lesions⁷³. MM is very heterogeneous at the molecular level with 40% of cases characterized by trisomies and with most of the remaining cases having a translocation involving IGH locus on chromosome 14q32 or deletion of 13q14 (ref.^{74,75}). The presence of aberrations influences prognosis and therapy response⁷⁶. Whole genome sequencing of MM samples revealed multiple mutations in genes belonging to the NF-κB pathway and genes involved in protein translation and histone methylation⁷⁷. Telomere length in MM is shorter than in MGUS and displays heterogeneity among patients⁷⁸. Shorter telomere length and higher telomerase activity correlate with poor prognostic features in MM (ref.^{78,79}). In particular, telomerase activity is a strong predictor of 1- and 2-year survival⁷⁹. It has been shown in *in vitro* experiments that telomerase inhibition could represent a promising treatment option in MM (ref.⁸⁰).

CONCLUSION

Telomeres are protective structures at the ends of linear chromosomes. They are naturally shortened within each cell division causing senescence after a large number of divisions; telomere maintenance is a complex process. Telomere length, expression of telomerase and activity of telomere-related proteins are more or less associated with various cancer types including hematological malignancies of adult age. The role of telomeres and their maintenance have been studied in individual hematological malignancies (Table 1) using various approaches. Unfortunately, the accuracy of the methods used is open to question. Repetitive telomeric regions are difficult to approach and it is challenging to collect reproducible results even with a single assay. Therefore, although the diagnostic use of telomere length could have validity in prognostication, it is currently not usually used, as other disease-specific markers are more accessible. In some malignancies, the results can be significantly influenced by the presence of non-tumor cells in an analyzed sample. Overall, it would be valuable to conduct a comparative study across hematological malignancies studying telomere length, telomerase activity, and telomere-associated proteins and genes, with the use of reproducible approaches, samples with high tumor cell content and a sufficient number of samples per each disease entity.

Search strategy and selection criteria

English-written original scientific articles and reviews from 1980 to 2018 were searched using PubMed and Google Scholar.

Key words for the search were as follows: "telomere length in leukemia", "telomere length in lymphoma", "telomere structure", "telomere replication", "telomere maintenance", "telomeres and epidemiology", "telomeres and oxidative stress", "telomere shortening prevention".

ABBREVIATIONS

ABC, activated B cell like; ABL1, ABL proto-oncogene 1 non-receptor tyrosine kinase; ALL, acute lymphoblastic leukemia; ALT, alternative lengthening of telomeres; AML, acute myeloid leukemia; ATM, ATM serine/threonine kinase; BCL2, BCL2 apoptosis regulator; BCR, breakpoint cluster region; CCND1, cyclin D1; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; DLBCL, diffuse large B cell lymphoma; DNA, deoxyribonucleic acid; FAB subtypes, French-American-British subtypes; FL, follicular lymphoma; FLT3, fms related tyrosine kinase 3; GC, germinal center; HL, Hodgkin lymphoma; IGH, immunoglobulin heavy locus; IGHV, immunoglobulin heavy chain variable region; MCL, mantle cell lymphoma; MDS, myelodysplastic syndrome; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NOTCH1, notch 1; PIF1, PIF1 5'-to-3' DNA helicase; POT1, protection of telomeres 1; RAP1, repressor activator protein 1; RNA, ribonucleic acid; TERC, telomerase RNA component; TERRA, telomeric repeat-containing RNA; TERT, telomerase reverse transcriptase; TIN2, TRF1-interacting nuclear protein 2; TP53, tumor protein p53; TPP1, tripeptidyl peptidase 1; TRF1, telomeric repeat binding factor 1; TRF2, telomeric repeat binding factor 2.

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