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Telomere and telomerase in stem cells: relevance in ageing and disease

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1. ABSTRACT

Telomeres, at the end of chromosomes provide genomic stability. During embryonic development, telomerase, a reverse transcriptase elongates the ends of the DNA. In somatic cells, the activity of telomerase decreases after birth leading to shortening of telomere with cell division, which thereby triggers senescence. In embryonic stem cells and germ cells, telomere length is maintained. In adults, the tissue specific stem cells have telomerase activity, but it is not enough to maintain the length of telomere. The stem cells also undergo the process of ageing but it is delayed as compared to the somatic cells. Studies on the genetic disorder, dyskeratosis congenital, caused by mutations in the human telomerase, reiterate the importance of telomere maintenance in human stem cells. This review covers the role of telomere and telomerase in stem cells and their relevance in disease and ageing.

2. INTRODUCTION

Telomeres are present at the ends of the chromosomes and protect DNA from terminal degradation and chromosomal fusion (1). In eukaryotes, telomeres are characterized by the presence of short guanine-rich repeats, which vary in length from 5 to 20 Kb depending on the age and the renewal potential of tissue or cell type in an individual (2). During replication, DNA polymerase fails to completely copy the end of chromosomes leading to loss of telomere repeats (3). This gradual shortening of the telomere is considered as one of the mechanisms underlying aging and critically short telomeres lead to senescence and loss of cell viability (2, 4, 5). The 3' end of the telomere is single-stranded, which folds back into D-loop (double-stranded DNA) forming a "T-loop" structure. The double-stranded region of telomere is bound by two sequence-specific DNA binding proteins, telomeric repeat

binding factor 1 (TRF1) and telomeric repeat binding factor 2 (TRF2) along with other telomeric DNA-binding complex of proteins known as Shelterin (6) (Figure 1). TRF2 has been shown to bind to ATM and interfere with the DNA damage response at the ends of the chromosome (7, 8). It has also been shown to interact with DNA damage signaling and repair factors, particularly MRE11 complex (5). Telomere length and capping is also controlled by the proteins known to be involved in DNA damage and response, both nonhomologous DNA endjoining (Ku and DNA-PKCs) and homologous recombination (RAD51d, RAD54, XRCC3) pathways (9-13).

Telomerase is a ribonucleoprotein complex consisting of a protein component with reverse transcriptase activity (TERT) and an RNA component which serves as template for telomere synthesis (TERC) (14-17). The RNA component of telomerase is characterized by the presence of a box H/ACA small nucleolar (sno RNA-like) RNA- like domain, which is bound by dyskerin protein, which binds to three other small proteins (NHP2, NOP10 and GAR1). Another domain CAB (Cajal body box) is bound by a protein TCAB1 (18, 19) which also interacts with dyskerin. TCAB1 is essential for telomerase localization to Cajal bodies. Absence of TCAB1 leads to telomere shortening with each cell division. In humans, mutations in the telomerase core component have been detected in patients suffering from aplastic anemia and dyskeratosis congenital (DKC). In human beings, telomerase is known to be expressed during early embryogenesis, before blastocyst implantation, and then gradually decrease in the differentiated tissues of the embryo. In adults, most of the somatic tissues except for highly proliferative tissues such as that of hematopoietic system, intestinal crypt cells and skin cells lack any detectable level of telomerase (20). In germ cells, telomerase activity is maintained at a similar level, throughout the life of an individual. Telomerase activity and telomere maintenance have been correlated with the unlimited potential of growth in cancer cells, embryonic stem cells and germ-line cells. The role of telomerase in aging and cancer has been studied extensively, but recently, the interest has shifted towards the understanding of role of stem cells in the progression of cancer and ageing (21).

3. TELOMERE AND TELOMERASE ACTIVITY IN HUMAN AND MOUSE STEM CELLS

Most of the adult tissues have a resident stem cell population. These cells were identified based on their ability to retain BrdU (Label-retaining technique) (22-24). In mice tissues, longer telomeres have been mapped to the stem cell compartment in hair, skin, small intestine, testis, cornea and brain (25). Telomere length, shortened in the stem cell compartment as well as the differentiated cells, concomitant with decreased telomerase activity and loss of stem cell function with age (25). Disruption of a component of telomerase (Terc) showed decreased efficiency in tissue renewal and life span of mice (26, 27). The deficiency of Terc in mice led to male and female infertility, heart failure, immunosenescence, and decreased regeneration of the digestive system, the skin, and the hematopoietic system (28-31). On the other hand, Tert transgenic mice showed longer telomeres in stem cells and differentiated cells. These mice showed a decrease in ageing associated inflammatory processes, and an increase in the median survival rate (32). It has also been shown that telomere length influences the ability of epidermal stem cells to regenerate tissues in mice (33). Deficiency of Shelterin components in mouse (Trf1, Trf2 and Tin2) are embryonically lethal and therefore it is not possible to study their affect on aging (34). On the other hand overexpression of Trf2 in skin led to short telomere and premature deterioration of skin and also UV induced skin cancer (35). Thus, the studies from mouse mutants of telomere binding proteins and telomerase complex show that the telomere length can be correlated to the renewal potential of the tissues, aging and cancer.

3.1. Hematopoietic Stem Cells (HSCs)

In adult hematopoietic and non-hematopoietic human stem cells, low level of telomerase activity has been detected (36). Although telomerase is present, it is not sufficient for maintaining the length of the telomere (Table 1). Hematopoiesis is one of the processes which occur throughout the lifetime of an individual and therefore serves as a good model to study the changes in stem cells during aging and disease progression. Hematopoietic stem cells (HSCs) give rise to progenitor cells, which then differentiate into multiple cell types which include granulocytes, monocytes, and mast cells of myeloid lineage, which is important for innate immune response and T and B lymphocytes of lymphoid lineage, which are responsible for adaptive immune response. Decline in both innate and adaptive immune response has been observed with aging (37), which could be correlated with the shortening of telomere, as observed in the peripheral blood T- and B-lymphocytes (38, 39). *In vivo*, comparative analysis of telomere length of leukocytes between donor and recipient after bone marrow (BM) transplantation showed that all the cell types from different lineages showed loss of telomere following extensive cell division (40-42).

HSCs purified from bone marrow have shorter telomeres when compared to HSCs from fetal liver (FL) or umbilical cord blood (UCB). The HSCs from younger individuals have longer telomeres than that of older individuals (43). Average telomere length of CD34 positive cells of UCB, BM and peripheral blood, was around 10.4 Kb, 7.6 Kb and 7.4 Kb, respectively (44, 45). The level of telomerase also varied between HSCs and their differentiated progeny (46-51) (Figure 2). Telomerase was expressed in the progenitor cells of both lymphoid and myeloid origin but downregulated in mature, resting cells (52). Unlike mature myeloid cells, which do not express telomerase after activation, in mature lymphocytes expression can be detected during development, differentiation and activation (53). Telomere shortening has been observed in T-cells with age *in vivo* and *in vitro (*54). In this regard, T-cells from Down's syndrome patients showed higher loss of telomere with age when compared to age matched controls (55). Loss of telomere in B-lymphocytes occurs with age (56) although the shortening

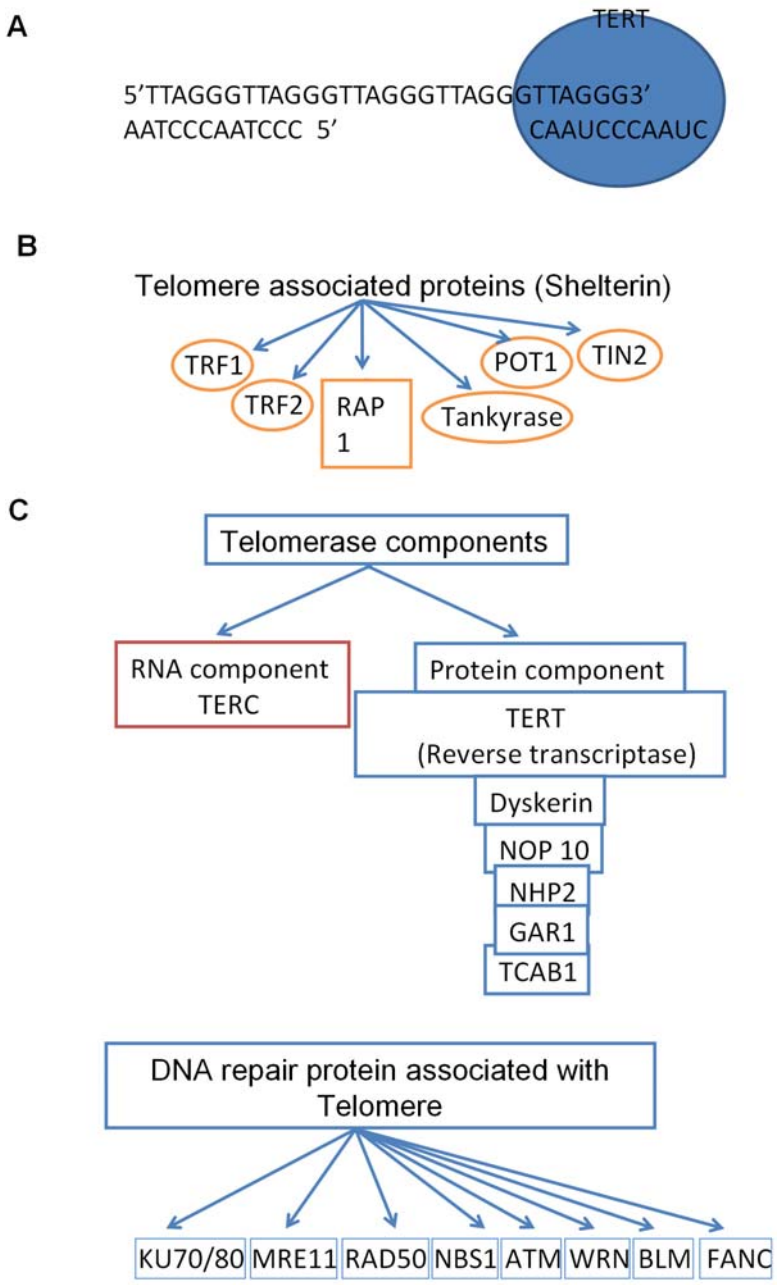

Figure 1. Human telomeric, telomerase and telomere repair components. A. Sequence of the telomeric DNA in human cells, which is normally composed of 4-12 kb of G-rich repeats (TTAGGG). Telomerase is a ribonucleoprotein complex consisting of a protein component with reverse transcriptase activity (TERT) and an RNA component which serves as template for telomere synthesis (TERC). B. The six subunit "shelterin" complex proteins TRF1, TRF2, tankyrase, TIN2, RAP1 and POT1 are all involved in interacting with the telomere . TRF1 and TRF2 with bind to duplex telomeric DNA. TIN2 interacts with both TRF1 and TRF2 but not with telomeric DNA. POT1 interacts specifically with single-stranded G-rich telomeric DNA. C. Telomerase is a reverse transcriptase which adds telomere repeats to end of the chromosomes. Telomerase is composed of RNA subunit, TERC and protein component, TERT. The RNA component is stabilized by additional protein factors. Dyskerin binds to 3′ end of TERC. Proteins NHP2, NOP10, GAR1 and TCAB1 interacts with Dyskerin and helps in maintenance of telomere. Other proteins, which are DNA damage response proteins such as KU70/80. MRE11, RAD50, NBS1, ATM, WRN, BLM, FANC, are important for telomere length regulation and telomere capping.

Table 1. Telomere and telomerase in human and mouse stem cells

Cell type	Growth	Telomerase	Telomere	Reference
Embryonic	Unlimited	High	Maintained	131
Hematopoietic	Limited	Absent/low	Shortened	132
Mesenchymal	Limited/unlimited	Absent/low upregulated by stimuli	Shortened/maintained	74, 133, 134
Skin	Limited	Low	Shortened	135, 136
Hair follicle	Limited	Low	Shortened	
Intestinal crypt	Limited	Low	Shortened	137
Neuronal	Limited	Low/absent	Shortened	138
Pancreatic	Limited	Absent	Shortened	139
Liver epithelial	Limited (durable)	Low	Maintained/shortened	140
Cancer stem cell	Unlimited	High	Maintained	141
Cardiac stem cell	Limited	Low/absent modulated by IGF-1	Shortened	47,48
Neural Stem cells	Limited	Low/Absent	Shortened	79-84
Primordial Germ Cells	Limited/Unlimited	High	Maintained	91-95
Muscle satellite stem cells	Limited	High	maintained	96-99

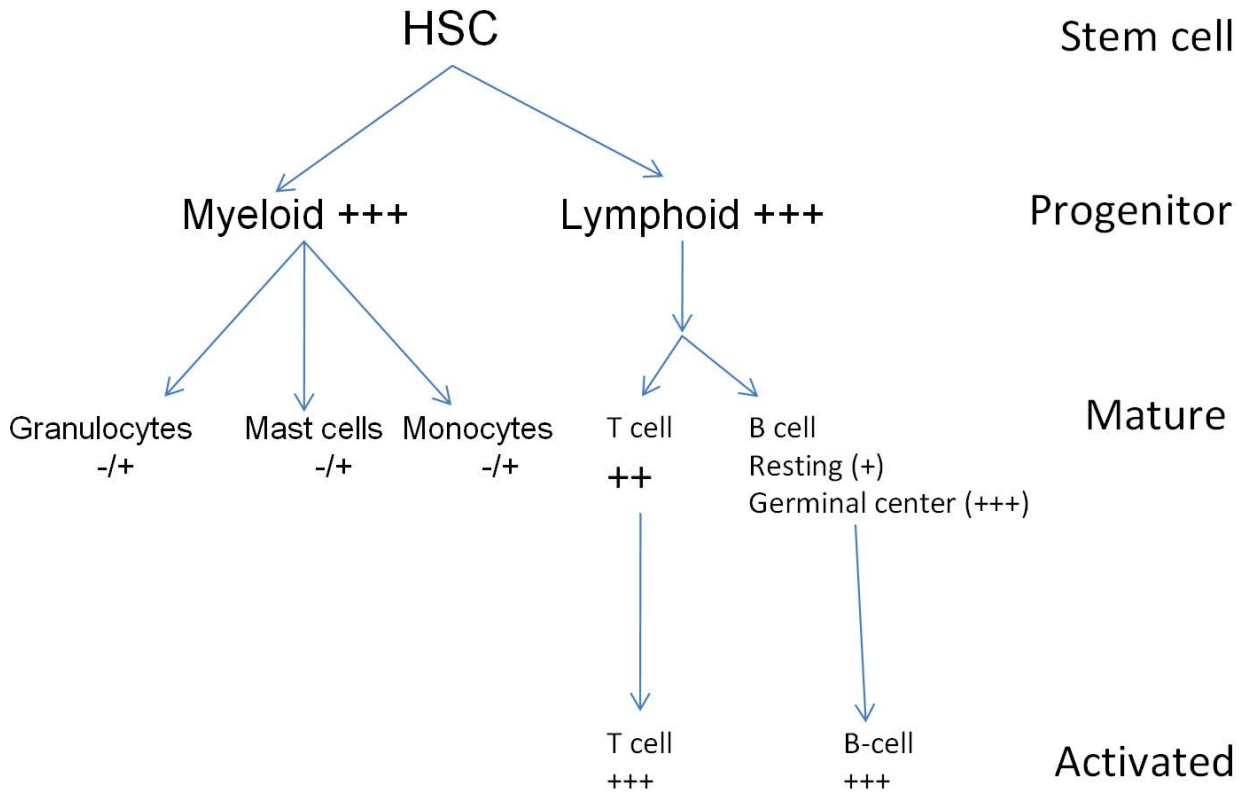

Figure 2. Telomerase expression in hematopoietic-derived cells. Telomerase expression is highly regulated during development of hematopoietic cells. Telomerase is expressed in progenitor lymphoid and myeloid cells but down-regulated in mature, resting lymphoid and myeloid cells. Mature myeloid-derived cells that do not express telomerase after activation whereas lymphocytes are capable of expressing telomerase after antigenic stimulation.

of telomere is slower than T-cells. Telomerase activation is observed after antigenic activation of B-cells (57).

Shortening of telomere length in blood cells has also been observed in many diseases (Table 2). Examples include hematologic neoplasias such as myelodysplastic syndrome (MDS) wherein telomeres were shortened (58). In the case of chronic myeloid leukemia (CML), a clonal myeloproliferative disorder characterized by the Philadelphia chromosome (Ph), studies showed changes in telomere length and telomerase activity between chronic phase (CP) and blast phase (BP) (59-61). A high level of telomerase activity was observed in patients with CML-BP, but not in patients with CP. In dyskeratosis congenita (DKC) (62), which is caused by mutation in the components of telomerase, bone marrow failure has been observed. In these cases, haematopoetic progenitors are reduced in number, both in bone marrow and peripheral blood. This could be because the cells reach a critically

short length of telomere, earlier than normal and thereby enter replicative senescence (63).

3.2. Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) can be derived from many sources like BM, Wharton's jelly and adipose tissues. These cells are selected on the basis of their plastic adherence property (64). MSCs can differentiate into mesodermal cell lineages, adipocytes, chondrocytes, osteocytes and endothelial cells as well as non–mesodermal lineage to neuronal like cells (65, 66). Human MSCs can grow until senescence at approximately 22 population doublings (67). The MSCs obtained from young (18-29) and old (68-81yrs) donors showed difference in their proliferative capacity as younger ones could undergo more population doubling than older ones and the senescent phenotype was seen in MSCs obtained from aged individuals earlier than young ones (68). The differentiation capacity also decreased with age (69, 70). The analysis of telomere length from early and late passages of MSCs did not show any major difference in the telomere length. These cells do not display detectable telomerase activity (71) (Table 1). Several growth factors (PDGF, TGF-b, FGF, EGF) enhance the mitogenic potential of human MSCs (hMSCs) (72, 73). In the presence of basic FGF (74), MSCs can undergo 100 PDs and the telomere length is maintained. Telomerase immortalized human MSCs cells grown for 189 PDs also showed stable telomere length pattern (67, 75) and enhanced differentiation potential (76). It is likely that there is an alternative to telomerase in MSCs which help in maintaining telomere length. Overexpression of telomerase in hMSCs led to better proliferation and differentiation capacity (76). In mice, MSCs express telomerase and they can be passaged for more than 100 PDs (77). In telomerase knockout mMSCs, the cells did not differentiate into adipocytes or chondrocytes even at earlier passages (78). It therefore seems that telomere length is the criteria in MSCs that determines retention of their proliferative and differentiation ability inspite of low levels of telomerase.

3.3. Neural Stem Cells

Most of the studies on neural stem cells have been done in mice. Stem cell based neurogenesis is restricted to two areas in the brain, the sub granular zone of the dentate gyrus and the sub ependymal zone (SEZ) of lateral ventricles (79) . The neural stem cells (NSCs) are reduced in Terc deficient mice and the absence of telomerase leads to reduction in neurogenesis (80). Telomerase expression in neural progenitors is downregulated during differentiation (81, 82). Overexpression of telomerase inhibits neuronal differentiation in neural cell lines (83). Telomere shortening occurs with age in NSCs of SEZ. Telomere shortening in adult NSCs has been shown to disrupt neuronal differentiation and neuritogenesis in mice (84). In human, neural progenitor cells from embryos (hNPCs) showed a very low level of telomerase and shortening of telomere length was observed with each passage (Table 1). These cells could undergo only 40-50 population doubling before they ceased to divide (85). Upon transplantation, hNPCs grown in culture were shown to grow and make axonal connections. These cells can differentiate into neurons and glia (86, 87). Shortening of the telomere and low levels of telomerase is seen with age in NSCs.

3.4. Cardiac Stem Cells

Cardiac stem cells (CSCs) reside in heart and are characterized by the presence of shorter telomeres and expression of $p16_{INK4a}$ (88). These cells, under the influence of CDK inhibitors do not undergo division and maintain CSC pool. The increase in myocyte death leads to a need for myocyte replacement. The c-kit positive $p16_{INK4a}$ - negative cells differentiate to myocyte leading to an overall decrease in CSC population (89). Insulin Growth Factor -1 in myocytes has been shown to bind to receptors on CSCs and modulate telomerase expression. CSCs have been shown to delay organ ageing and dysfunction of heart by differentiating to myocytes. Telomerase activity is markedly decreased in dividing cells leading to telomeric shortening and growth arrest. In heart, the presence of nuclear phospho-Akt prevents the onset of myopathy. Nuclear phospho-Akt can modulate the expression of telomerase by phosphorylating it, thereby increasing enzyme activity (89, 90). Increase in phospho-Akt was observed more in acute phase CSC concomitant with increase in telomerase activity and other telomere binding proteins. As compared to controls, CSCs with $p16_{INK4a}$ expression and shorter telomeres increased in number in acute followed by chronic phase. This decrease in the number of functional CSCs in the chronic phase would account for progression of the disease and terminal failure. This suggests that although resident stem cells are present and can revive the disease early on, lack of telomerase activity and short telomere would make CSCs also enter senescence.

3.5. Primordial Germ Cells

The male and female germ cell lineages are derived from specialized stem cells in the embryo called as primordial germ cells (PGCs). In both human and mice, telomerase activity is observed in oocytes (91, 92) (Table 1) and in testis (93, 94) but not in spermatozoa (92, 95). Normally telomere length is maintained in germ line. In absence of telomerase in successive generations, shortening of telomere and male sterility has been reported. In female both immature and mature oocytes express telomerase. The PGCs in male stop expressing telomerase as the cells enter a phase of growth arrest. Spermatogonial stem cells have been grown in culture and have been shown to differentiate into multiple lineages. This also suggests that telomerase activity in stem cells can be correlated to its renewal and differentiation potential.

3.6. Satellite Stem Cells

Satellite stem cells are quiescent mononucleated myogenic cells, located between the sarcolemma and basement membrane of terminally-differentiated muscle fibers. They are quiescent in adult muscle, but can proliferate in response to injury and regenerate muscle (96). The study in humans showed that the telomere length is not affected in satellite stem cells in young vs adult but there was a reduction in the number of satellite stem cells in adults which would correlate with low regenerative

capacity of muscle with aging (98). Mouse satellite stem cells have been shown to have high telomerase activity and it decreases upon differentiation (97). But under diseased condition where muscle undergoes degeneration and regeneration (DMD) resulting in loss of the muscle mass and extensive fibrosis, telomere shortening was 14 times greater in satellite stem cells than that observed in controls. Under these conditions satellite cells enter senescence much earlier than normal owing to the decrease in regenerative capacity (98, 99).

3.7. Cancer Stem Cells

The evidence of presence of cancer stem cells (CSCs) came from the studies of hematopoietic malignancies (100). Telomere shortening is the characteristic feature of cancer cells. This leads to chromosomal instability and malignant transformation. It is debatable whether CSCs have longer telomeres, which would be a requirement if CSCs have to replicate and divide. It is also not clear whether the CSCs have telomerase activity or not, owing to the difficulty in isolating CSCs from solid tumors. One of the recent studies showed that telomerase is downregulated in brain cancer stem cells and they have shorter telomere than other cancer cells (101). In contrast, breast cancer stem cells showed similar level of telomerase activity and telomere length as other tumour cells (102) which was shorter than the telomeres in the normal stem cells. This suggests that telomerase is present in CSCs, but gets activated in the later stages of cancer. One of the major therapeutics for cancer which has been gaining grounds, is the treatment using drugs which can block telomerase activity in the resident cancer stem cells (103).

4. EMBRYONIC STEM CELLS AND INDUCED PLURIPOTENT STEM CELLS

Embryonic stem cells (ESCs) are pluripotent cells capable of indefinite self renewal and differentiation into cells of all the lineages. ESCs have very high telomerase activity and hTERT expression (Table 1). The level of telomerase decreases as they undergo differentiation (104). TERT overexpressing ESCs showed increase in proliferation, self renewal and differentiation (104). Telomerase is reactivated during reprogramming of human fibroblasts to induced pluripotent stem cells (iPS) (105, 106). It was shown that telomere length is significantly increased in 3F and 4F iPS cells compared to parental differentiated cells, reaching intermediate levels to those of control ES cells in early passages but reaching telomere length comparable to control ES cells at later passages (107). Telomere heterochromatin was also remodeled in iPS cells, to a conformation similar to that of telomeric chromatin of ESCs. As in ES cells, iPS also showed a significant decrease in the density of histone heterochromatic markers (H3K9m3 and H4K30m3) at telomeric regions compared to differentiated mouse embryonic fibroblast (MEF) cells. The donor cells with short telomeres obtained from old animals showed telomere elongation and functional telomere capping during reprogramming into iPS cells, suggesting that telomere length and telomerase activity are important for cells to undergo indefinite self renewal.

5. TELOMERE, TELOMERASE DURING AGING AND DISEASE

With ageing most of the normal human tissues and organs (108) including peripheral blood cells, lymphocytes, kidney epithelium, hepatocytes, intestinal epithelial cells, lung epithelial cells, muscle show telomere shortening (Table 3). As mentioned above stem cells from each of these tissues also show telomere shortening or is maintained (see Table 1). Telomere shortening could be correlated to low telomerase levels in tissue resident stem cells with few exceptions such as primordial germ cells, and muscle satellite stem cells (Table 1) (109). As a result of telomere shortening in the stem cell compartment during aging, there is loss of stem cell function (110). Telomere shortening has been observed in many diseases (Table 2). Some of these are associated with mutations in the genes encoding for the telomere binding proteins (Figure 1) such as TRF2 and components of the enzyme telomerase (TERT, TERC and Dyskerin). Few of such diseases are also due to mutations in the DNA DSB repair proteins associated with telomere such as Mre11, Rad50, Nbs1 complex, ATM, BLM and WRN. Loss of function of telomerase components have been seen in DKC, which is discussed below. In patients with Aplastic Anemia, mutations in telomerase TERC and TERT genes have been observed, which is associated with telomere shortening and premature death (111, 112). Elevated telomerase levels are seen in most of the cancers discussed below. Telomere shortening has also been observed in patients with heart failure, coronary artery disease and others (Table 2). In this regards it has been observed that individuals with short telomeres had a 3.18-fold higher mortality rate from heart diseases, and 8.54-higer mortality rates from infectious diseases compared to those with relatively long telomeres. Some other studies have shown a relationship between telomere shortening and the evolution of cardiac disease (24, 25). Studies on various diseases put together (Table 3) indicate accelerated telomere shortening in disease compared to the normal individuals. Accelerated telomere shortening leads to loss of tissue regeneration (34). The studies on mice deficient in the telomerase components or overexpression as discussed above, have been the direct evidence linking aging with telomere shortening (5, 34).

6. TELOMERE AND STEM CELL DYSFUNCTION

Dyskeratosis congenital in humans is widely considered to be due to defects in telomerase or telomere maintenance (113). Patients with DKC show three distinctive features, nail dystrophy, oral leukoplakia and abnormal skin pigmentation. The other complications are bone marrow failure, pulmonary fibrosis and cancer (114, 115). Mutations in DKC1 and homozygous mutations in TERT have been shown to cause Hoyeraal-Hreidarsson syndrome (HH), which is characterized by bone marrow failure, severe growth retardation, immunodeficiency and cerebrellar hypoplasia (116, 117). Heterozygous TERT and TERC have been implicated in 5-10% of aplastic

Table 2. Human diseases and telomere shortening

Human disease	Telomere protein affected	Reference
Atherosclerosis	Not known	142, 143
Heart failure	TRF2	144
Liver cirrhosis	Not known	145
AIDS	Not known	146
Ulcerative colitis	Not known	147
Dyskeratosis congenital	TERC, TERT, Dyskerin	62, 148-150
Aplastic anemia	TERC, TERT	111, 112, 151-153
Idiophatic pulmonary Fibrosis	TERC,TERT	120, 154
Werner syndrome	WRN	155
Bloom syndrome	BLM	156
Fanconi anemia	*FANC* genes	5
Ataxia telangiectasia	ATM	106
Nijmegen breakage syndrome	Nbs1	5
Ataxia telangiectasia disorder	Mre11	5
MDS	TERC	157, 158
Cri du chat syndrome	TERT	159
Coronary artery disease	TERT	160
Hypertension and diabetes mellitus	Not known	161
Down syndrome (DS)	Not known	162
Duchenne muscular dystrophy	Not known	99
Crohn disease	Not known	163
Li Fraumeni Syndrome (LFS)	Not known	164
Alzheimer's disease (AD)	Not known	165, 166

Table 3. Ageing and telomere shortening in human organsO

Human organs	References
Kidney	167-171
Cardiovascular system	172, 173
Liver	145, 167, 168, 174-176
Colon	177, 178
Stomach	179
Esophagus	177
Spleen	168
Blood	43, 55, 180
Lung	170
Skin	170, 181
Skeletal muscle	170
Thyroid	182
Pancreas	183
Brain Cerebral cortex	168

anemia (AA) (118, 119) and pulmonary fibrosis (117, 120) leading to respiratory failure. The presence of shortened telomeres is suspected to be the cause of the abnormalities (121, 122). Mutations in DKC1, TERC, TERT, NOP10, NHP2 and TINF2 have been implicated in DKC. Mutation in DKC1 which codes for protein dyskerin causes X-linked form of the disease (123). During development, when the cells have to divide rapidly in the absence of telomerase, telomere would be shortened more than in healthy individuals. The bone marrow, gut and skin are the tissues where renewal and differentiation of stem cells are continuous processes, thus explaining the defect in stem cell leading to the disease symptom. Reduced telomerase and short telomeres might compromise the number as well as replicative potential of stem cells.

7. TELOMERE AND CANCER

Telomerase is upregulated in majority of human cancers (93, 124-126). The patients with DKC or mutations in telomerase gene develop leukemia (127). In DKC patients, the loss of stem cells by telomerase dysfunction could stimulate the growth of abnormal cells. A heritable hypomorphic mutation in the telomerase reverse transcriptase gene could predispose to acute myeloid leukaemia (AML) (128). The mutant telomerase showed a decrease in its enzymatic activity by 50%. The SNPs on the TERT locus could be correlated to the risk of developing lung cancer (129, 130). It seems that different mutations in TERT would lead to different levels of telomerase activity and also predispose to different kinds of cancers and disease symptoms.

8. CONCLUSION AND PERSPECTIVES

Studies from mouse indicate the presence of longer telomere in the stem cell compartment of the tissues, which also undergo telomere shortening with age. The mice mutants of the telomerase complex hTERT and hTERC, implied the importance of telomerase and telomere length in stem cells and their potency to differentiate. It has been shown that the differentiation potential for NSCs decline in telomerase deficient mice. Differentiation of cardiac stem cells to myocytes reduces with age. The human genetic disorder, dyskeratosis congenita is widely considered to be due to defects in telomerase or in telomere maintenance. Heterozygous TERT and TERC have been implicated in 5-10% of aplastic anemia (AA) and pulmonary fibrosis. The patients with DKC or mutations in telomerase gene develop leukemia. Mutations in TERT might lead to difference in

telomerase activity and also predispose to different kinds of cancers and disease symptoms. Studies on the length of telomere and telomerase activity from tissue resident stem cells show that they possess low telomerase activity which can be induced during the disease state and that is important for the self renewal of stem cells and their differentiation ability. With age telomere length shorten in the stem cells, which are accelerated in diseases leading to reduced function of stem cells. All these studies with regard to telomere length and telomerase suggest that stem cells from young individuals have better capacity to regenerate the tissue.

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