Telomeres are protective structures present at the ends of chromosomes. These are highly conserved from primitive organisms to humans. These inevitably shorten with every cell cycle. Their attrition has been hypothesized to be fundamental to normal senescence of cell, tissues and organisms. Molecular mechanisms have evolved to maintain their length and protective functions. Schematic representation of telomere structure is shown in Figure 1.

To counter telomere shortening, highly proliferative cells such as haematopoietic stem cells express the enzyme telomerase. Telomerase is a reverse transcriptase enzyme. It uses a specific RNA molecule called “Telomerase RNA Component” (TERC) as the template to elongate the 3’ end of telomeres. The term “Telomerase complex” is used for a combination of TERT (the reverse transcriptase enzyme), TERC (the RNA component) and the ribonucleoprotein dyskerin which is important for the RNA component folding and stability. Shelterin is a collection of DNA-binding proteins that cover and protect telomeres. Mature cells, usually do not express telomerase and hence cannot elongate their telomeres.

Structure and function of the telomerase complex is shown in Figure 2.

Recently, inherited mutations in genes that function to repair telomeres have been discovered. These result in clinical disorders affecting diverse tissues, including haematopoiesis and leading to organ failure. Prototype of such telomere diseases include Dyskeratosis Congenital (DC) a type of congenital aplastic anaemia, idiopathic pulmonary fibrosis and liver cirrhosis. These disorders also have increased susceptibility to malignant diseases.1

Telomere erosion is abnormally rapid in patients with mutations in telomerase genes. With aging, telomeres become shorter. Environmental factors also modulate the rate of telomere shortening. Psychological stress and cigarette smoking induce accelerated telomere attrition.2 This also happens after haematopoietic stem cell transplantation. All of these conditions are associated with higher rates of malignant diseases.1

Adequate telomere length maintenance is pivotal for haemopoiesis. Excessive telomere loss permeates marrow failure, malignancy and fibrotic diseases. Short telomeres inhibit cell proliferation and

Fig. 1 : Schematic representation of telomere structure (with permission from de Lange T. Shelterin et al. Genes Dev 2005;19:2100-2110)
Identification of families with marrow failure, severe liver disease or pulmonary fibrosis has dramatically changed history-taking for the identification of telomerase mutations in patients with aplastic anemia.

Around the turn of century, shortening of telomeres was described in approximately one third of patients with acquired aplastic anemia (AAA). Those with the shortest telomeres have longest disease duration and are most likely to develop malignant clonal complications. It has been shown that such patients have poor response to immuno-suppression, a standard modality of treating AAA. In a large series of patients undergoing immunosuppressive therapy (n = 183), patients with shorter telomeres had the highest possibility of relapse, poorest overall survival and increased risk of evolving to myelodysplasia with monosomy 7 and even acute myeloid leukaemia. Interestingly, some of these respond, at least transiently, to androgen therapy which activates telomerase activity by its aromatization into estrogens. In fact, the most effective and permanent treatment for such patients will be stem cell transplantation. Thus, telomere length becomes critical in therapeutic decision making for treating AAA.

Telomere shortening was already known in congenital aplastic anaemias especially

premature, hereditary bone marrow failure syndromes such as dyskeratosis congenita (DC). Mutations in the TERC gene have been identified in DC. Such mutations, however, are infrequent in AAA. Hence, workers have looked for mutations in genes corresponding to other components of the telomerase ribonucleoprotein complex which could result in marrow failure. These have included TERT, DKC1, NHP2 and NOP10. In a large study of 200 patients with aplastic anemia,
Fig. 3: Mutations in telomerase complex genes and human disease. Mutations in green were described in patients with acquired aplastic anemia; mutations in red were described in patients with dyskeratosis congenita; mutations in black were described in patients with pulmonary fibrosis; and polymorphisms are represented in blue. Mutations found in more than one disease type are double-colored (with permission from Calado RT et al. Blood 2008;111:4446-4455).

Fig. 4: Proposed model for the role of dysfunctional and short telomeres in the pathogenesis of human disease (with permission from Calado RT et al. Blood 2008;111:4446-4455).

5 novel non-synonymous heterozygous mutations in TERT were identified in 5 patients. These were associated with very short telomeres and reduced telomerase activity. TERT and TERC mutations, therefore, may be viewed as genetic risk factors for human haematopoietic failure. Defects in the maintenance of telomere length result in a reduced haematopoietic stem cell compartment that may be specially vulnerable to environmental insults. Figure 3 depicts mutations in telomerase complex genes and their relationship with human diseases while figure 4 shows the proposed model for the role of dysfunctional and short telomeres in the pathogenesis of human diseases.

In this issue of JAPI, Mehta S et al\(^8\) have published their observations (a pilot study) regarding mutations in TERT in Indian patients of aplastic anaemia. Although the number of patients are small to draw a definite conclusion, none of their patients with TERT mutations had a response to immunosuppressive therapy.

References


