

TELOMEROPATHIES – RARE DISEASE SYNDROMES

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ABSTRACT

Telomeres are located at the end of the chromosomes. They protect chromosomes from fusion and degradation. Every cell division causes a shortening of the telomeres. A special enzymatic complex called telomerase is responsible for maintaining telomere length in intensively dividing cells, such as epithelial cells and bone marrow cells. The enzymatic complex includes the TERT subunit, which has reverse transcriptase activity, and the TERC subunit, which acts as a template. Other important components of telomerase are the proteins that are responsible for structural stability. Telomerase remains active only in the dividing cells of the body. The rate of telomere shortening depends on many factors including age, sex, and comorbidities. Faster shortening of telomeres is caused by gene defects, which have an impact on telomerase action. Collectively, these are called telomeropathies. Common causes of telomeropathies are mutations in the TERT and TERC telomerase genes. Types of telomeropathies include dyskeratosis congenita, idiopathic pulmonary fibrosis, and aplastic anaemia, among others. Clinical manifestations and prognoses depend on the type and quantity of mutated genes. Diagnosis of telomeropathies is often problematic because they present with the same symptoms as other diseases. So far, no effective therapeutic methods have been developed for telomeropathies. A therapeutic method for patients with bone marrow failure may be the transplantation of hematopoietic stem cells. For patients with idiopathic pulmonary fibrosis, treatments include immunosuppressive therapy, lung transplantation, or palliative care. In the future, gene therapy may be an effective treatment strategy for telomeropathies. Lifestyle changes may also have a positive impact on the person. Physical activity combined with a healthy diet rich in antioxidants and unsaturated fatty acids can decrease the oxidative stress levels in cells and lead to a slower shortening of the telomeres.

KEYWORDS: telomeres, telomerase, telomeropathies

BACKGROUND

Telomeres, which are located on the ends of chromosomes, are composed of multiple six-nucleotide sequences (5'-TTAGGG-3') (fig. 1). They play an important role in determining the biological age of a cell because they are shortened with each division. Achievement of the telomeres' critical length signals the cell to begin the process of apoptosis (programmed death). The average length of human telomeres is 10–20 kbp (kilobase pairs). The dynamic of telomere shortening is differential and depends on sex, lifestyle, coexisting diseases, and exposure to harmful factors [1]. Depending on the rate of telomere shortening, the biological age of the cells may differ from the recorded age of the human. The increased rate of telomere shortening is accompanied by some illnesses including atherosclerosis, esophageal and breast cancer, and obesity [2–4]. This is why telomere length has become a biomarker for the risk of developing some diseases, including lifestyle diseases.

TELOMERASE

Several disease syndromes associated with the faster shortening of telomeres have been defined. They are referred to as telomeropathies [5]. The main causes of telomeropathies are defects of the genes involved in maintaining telomere length. In the dividing cells of the body, such as progenitor cells, stem cells, or activated leukocytes, telomeres are elongated due to telomerase activity. In other cells, telomerase activity remains low and decreases with age. Telomerase consists of the RNA strand, which is a template for the telomere repeat sequence (TERT), and a protein with reverse transcriptase activity (TERC). The telomerase complex also includes the dimer of the dyskerin complex (including the dyskerin, NOP10, NHP2, and GAR1 proteins) (fig. 2). Telomeres' DNA is protected by the shelterin protein complex, which is responsible for the stability of the genome. It consists of the following proteins: TRF1, TRF2, TIN2, POT1, RAP1, and TPP1.

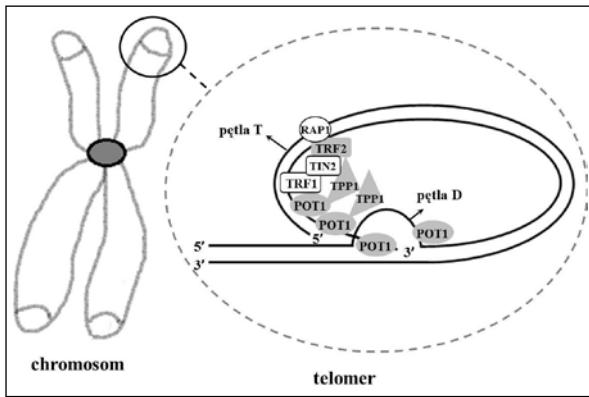


Figure 1. Diagram of telomere structure

Mutations within the genes encoding the telomerase subunits and proteins of the shelterin complex are the cause of telomeropathies (tab. 1) [6].

TELOMEROPATHIES

Dyskeratosis congenita (DC) is a rare disease that is detected at a frequency of less than 1 case per 1 million per year. The first symptoms of DC can be observed in childhood. These symptoms include skin hyperpigmentation, nail dystrophy, and leukoplakia (white keratosis), most commonly in the oral cavity. Dyskeratosis congenita may be diagnosed following the observed occurrence of a total of three symptoms. The average age at which all three symptoms are present is 8. DC is caused by hereditary autosomal mutations of the TERC, TERT, TIN2, and DKC1 genes, which are located at chromosome X [7–10]. In addition to the typical aforementioned symptoms, people with dyskeratosis also tend to have a number of other disorders including haematological, respiratory, or neuropsychiatric disorders. Thus, dyskeratosis congenita is now treated as a multi-organ disease [9]. Neuropsychiatric disorders affect 55% of children and 75% of adults with DC. These include anxiety, psychotic disorders, attention deficit disorders, and learning problems [11]. In addition, kin problems affect the vast majority of DC patients and include nail atrophy and hyperhidrosis of hands and feet. Some patients also suffer from symptoms of mucosal disorders like narrowing of the esophagus, tear ducts, or urethra. About 5% of people with DC have abnormalities in the structure of the skeletal system and osteoporosis [12]. In addition,

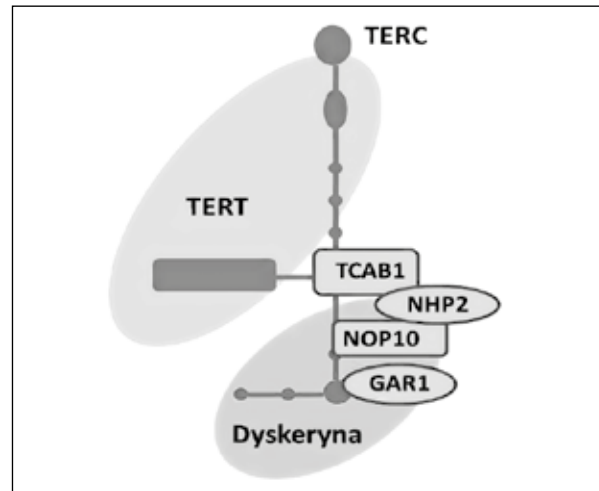


Figure 2. Telomerase complex structure

people with dyskeratosis congenita have an increased risk of squamous cell carcinoma and leukemia [13].

Hoyeraal-Hreidarsson syndrome (HHS) is one manifestation of DC that is characterized by extremely severe symptoms. Clinical symptoms of HHS can be observed during gestation and infancy. These include delayed intra-uterine development, microcephaly, and hypoplasia of the cerebellum. In addition to the typical symptoms of DC, the majority of patients with HHS also have immunodeficiency, lymphopenia, and nervous system disorders (including demyelinating disorders and convulsive tendencies). Digestive system disorders such as abnormalities in esophageal constriction and enteropathies can also be symptoms of HHS [14,15]. HHS patients have extremely short leukocyte telomeres (with telomere lengths below 1 centile for a given age) due to mutations in the genes responsible for maintaining telomere length: TERT, DKC1 (dyskerin gene), TIN2 [16,17]. Another manifestation of dyskeratosis congenita is the Revesz syndrome (RS). RS was named and characterized for the first time in 1992 by Revesz and coworkers who were diagnosing a one-and-a-half-year-old child with the following symptoms: bilateral exudative retinopathy and bone marrow failure [18]. Clinical symptoms of this disease syndrome also include intrauterine growth retardation, intracranial calcification, developmental delay, and nail dystrophy. The molecular cause of RS is associated with a mutation in the TIN2 gene, coding for the TIN2 protein, which is part of the shelterin complex [19].

Table 1. Gene mutations that cause telomeropathies

Gene	Gene function	Disease
TERC	Encodes a protein with reverse transcriptase activity	DC, aplastic anaemia, IPF
TERT	Encodes RNA that is a template for amplifying the telomere sequence	DC, aplastic anaemia, IPF, HHS
DKC1	Encodes the dyskerin, a protein responsible for the stability of the RNA molecule	DC, aplastic anaemia, IPF, HHS
TIN2	Codes the shelterin protein, regulates telomerase access to telomeres	DC, HHS, RS
RTEL1	Encodes a protein with helicase activity and plays an important role in maintaining genome stability	DC, HHS
CTC1	Encodes a protein that is a component of the CST complex	Coats plus syndrome
NOP10	Encodes a protein that is a component of the dyskerin complex	DC, aplastic anaemia, IPF
NHP2	Encodes a protein that is a component of the dyskerin complex	DC, aplastic anaemia, IPF

Coats plus syndrome, also known as cerebral microangiopathy with calcifications and cysts, is another telomeropathy. Clinical symptoms include bilateral exudative retinopathy, retinal telangiectasia (presence of enlarged small blood vessels), intracranial calcification, and anomalies in bone formation. In addition, some patients have thin hair and anaemia [20]. The cause of Coats plus syndrome is a mutation in the CTC1 gene responsible for telomere extension [21].

Aplastic anaemia is one of the clinical symptoms of telomeropathy in adults. It occurs with a frequency of 1–2 cases per million inhabitants per year in Europe and North America [22]. In some patients, significantly shortened telomeres [23] are observed as a result of mutations in the TERT and TERC genes. Aplastic anaemia usually is accompanied by other symptoms like mild cytopenia, leukaemia, pulmonary fibrosis, and squamous cell carcinoma.

Idiopathic pulmonary fibrosis (IPF), also called interstitial pneumonitis, is a serious disorder with a poor prognosis. It occurs with a frequency of 5–32 cases per 100,000 people, depending on the region [24]. The average survival period is 2–3 years from the diagnosis. Lung inflammation is often accompanied by bronchial inflammation and emphysema. Autosomal dominant TERT and TERC gene mutations are identified in familial pulmonary fibrosis (FPF) which affects 20% of cases. These mutations are detected in 15–20% of patients without the familial burden of dyskeratosis congenita and 1–3% of sporadic cases of the disease occurrence. In addition to the aforementioned mutations, some patients also have mutations of genes such as DKC1, TIN2, RTEL1, and PARN [17].

DISCUSSION

Due to the genetic causes of telomeropathies, as well as their diverse pathways of progression, therapeutic strategies are limited. In patients with bone marrow failure, the only therapeutic method is the transplantation

of hematopoietic stem cells. For patients with idiopathic pulmonary fibrosis, treatment includes immunosuppressive therapy, lung transplantation, or palliative care [25]. Gene therapy seems to be a promising future treatment for patients with telomeropathies. Studies conducted by Bär et al. [26] on the aplastic anaemia mouse model showed that gene therapy can effectively induce telomerase expression in bone marrow cells and result in telomere extension and increased survival time.

Regular physical activity reduces the level of oxidative stress and, as a result, prevents telomere shortening [27]. On the other hand, smoking accelerates the shortening of telomeres [28], as does obesity [29,30]. Long-term alcohol abuse in people over 65 also results in shortened telomeres [31]. Changes in lifestyle and eating habits – may reverse the unfavorable trend of telomere shortening. This is indicated by the results of studies with people who have switched to the Mediterranean diet [32,33]. In turn, weight loss in obese patients who underwent bariatric surgery resulted in telomere elongation within 10 years of surgery [34].

CONCLUSIONS

Disorders related to telomere length, called telomeropathies, constitute a group of multi-organ diseases with various clinical symptoms but a common genetic etiology. Defects in telomere protection systems lead to their excessive shortening, which in turn result in faster ageing and cell death. This is extremely important for intensely dividing cells like bone marrow, lymphocytes, and epithelial cells. Heterogeneity of symptoms often causes problems in the diagnostic process. Some of the symptoms associated with telomeropathies are accompanied by other diseases. Telomere length measurement can be useful in determining the direction of further diagnostics. In turn, identification of a patient's gene mutations may provide information on possible therapeutic strategies and the future prognosis for the patient.

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