Chapter 7

Telomeres and Cellular Senescence in Metabolic and Endocrine Diseases

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Abstract

A number of observations suggest a close connection between telomere length and mortality and age-related disease, suggesting that telomere length is a useful marker of individual biological aging and the shortening of telomere length is causally related with the pathogenesis in age-related diseases. To date, the significance of telomere length in metabolic and endocrine diseases has also been clarified. It has been reported that obesity, type 2 diabetes mellitus (T2DM), NAFLD, and hypertension were associated with shortened telomere length. In endocrine diseases, polycystic ovary syndrome (PCOS), Cushing's syndrome, and acromegaly were associated with shortened telomere length. In these conditions, an increased oxidative stress associated with the metabolic and hormonal abnormalities appears to play a pivotal role in the shortened telomere length. Recently, a large population-based study demonstrated that shortened telomeres at baseline were associated with an increased risk of metabolic diseases, suggesting that the shortened telomere itself plays a causal role for the onset or development of the metabolic diseases. In this chapter, the pathophysiological role of shortened telomere length in metabolic and endocrine diseases and the significance of cellular senescence are discussed.

Keywords: metabolic disease, endocrine disease, telomere, oxidative stress, cellular senescence

1. Introduction

Telomeres consist of repetitive DNA sequences, thousands of "TTAGGG" tandem repeats, which are located at the ends of linear chromosomes in most somatic cells [1]. Telomere ends form a cap-like structure to protect the ends of chromosomes from degeneration and fusion. However, telomeres shorten during each cell division, and when they reach a critically short

length, cell cycle arrest and cellular senescence occur in the cellular level. In the body, telomeres gradually shorten with aging [2]. A number of observations suggest a close connection between telomere length, generally assessed in leukocytes, and mortality or age-related disease, suggesting telomere length as a "mitotic clock," a marker for individual biological aging [3]. In this regard, to date, telomere length in various diseases has been investigated, including cancers, immune insufficiency, and cardiovascular disease. In addition, metabolic diseases, such as obesity and diabetes mellitus (DM), have shown a strong association with telomere shortening. Several endocrine disorders, such as polycystic ovary syndrome (PCOS), Cushing's syndrome, and acromegaly, are also reportedly associated with telomere shortening (**Figure 1**).

Furthermore, several recent studies have focused on the pathophysiological role of telomeres for metabolic or endocrine diseases. Telomere shortening is one of the important causes of cellular senescence, and recently, it has emerged that cellular senescence plays a pivotal role in the aging and pathogenesis of age-related disease [4]. Actually, several clinical studies have shown that shortened telomeres at baseline are associated with an increased risk for development of age-related diseases.

Here, we review the association and pathophysiological role of telomere length in metabolic and endocrine diseases. Furthermore, we discuss the mechanistic insight and significance of shortened telomeres and associated cellular senescence. Finally, we discuss a possible therapeutic approach for these diseases in the aspect of telomere shortening.

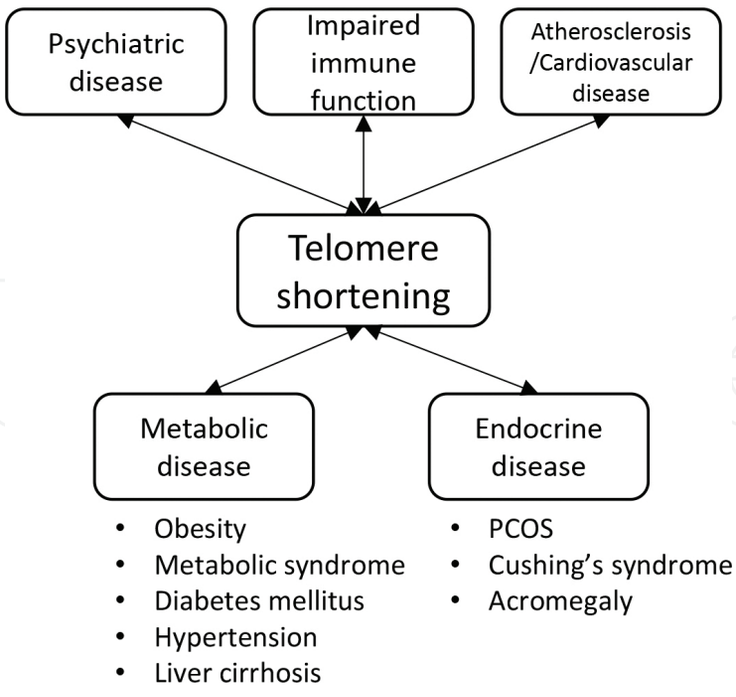

Figure 1. Telomere shortening and human diseases. Shortened telomere length is associated with various disorders, including psychiatric disease, impaired immune function, and atherosclerotic disease as well as metabolic and endocrine diseases.

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2. Telomeres and cellular senescence

2.1. Telomeres

Telomere is a dynamic complex at chromosome ends, which consists of repetitive DNA sequences [1,5]. In human cells, telomeres consist of thousands of "TTAGGG" tandem repeats. This base sequence is universal and consistent among most species. Human telomere complex consists of chromosomal-terminal tract of telomeric repeats bound by protective shelterin component proteins, with additional protective proteins. This complex, which binds specifically to telomeres, forms a cap-like structure and prevents end-to-end fusion or damage of the chromosome ends.

The general chromosomal DNA replication cannot completely copy the DNA sequence in the ends of the linear chromosomes, which is called "end replication problem." During the course of cell divisions, this leads to attrition of chromosome ends. Therefore, normal telomere maintenance requires the ribonucleoprotein enzyme named telomerase, which can add telomeric repeat sequences to the end of the chromosomes [6]. However, in most of the human somatic cells, the levels of telomerase are limited and telomeres shorten throughout the life span. Other genetic or environmental factors can also contribute to telomere shortening; defects of telomere maintenance system, DNA replication stress, increased oxidative stress, chemical damage, and inflammatory status are involved in telomere shortening [1].

2.2. Cellular senescence and senescence-associated secretary phenotype (SASP)

Cellular senescence refers to the irreversible growth arrest that occurs when cells experience potentially oncogenic insults [7]. Telomere shortening is one of the most important causes of cellular senescence. Telomere shortening causes DNA damage response (DDR), a signaling pathway, in which cell cycle progression is blocked through an increased production of p53 and cyclin-dependent kinase (Cdk) inhibitor p21 protein. DDR subsequently induces cellular senescence. Recently, accumulating evidences suggest that senescent cells are also important for age-related pathologies, including metabolic diseases such as obesity and DM [8,9]. Elimination of senescent cells can delay age-related dysfunctions in mouse model [10], indicating that a presence of senescent cells itself plays a causal role in the process of aging. Aging tissues, in which senescent cells are increased, show a low-level chronic inflammation, termed "sterile inflammation" [11]. Sterile inflammation is, at least in part, derived from senescent cells, which secrete proinflammatory cytokines, chemokines, and proteases, which is called "senescence-associated secretary phenotype (SASP)" [12]. Proteins that are associated with SASP, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, matrix metalloproteinases (MMPs), and monocyte chemoattractant protein (MCP)-1, increase in multiple tissues with chronological aging in conjunction with sterile inflammation [13]. These SASP-related cytokines, such as TNF-α and IL-6, are reportedly associated with insulin resistance and the development of DM [14,15]. Although whether the SASP actually causes age-related diseases including metabolic diseases *in vivo* is still unclear, at least, telomere shortening and subsequent cellular senescence have revealed a strong association with age-related diseases including metabolic diseases that are discussed in the following sections.

3. Telomeres in metabolic diseases

3.1. Obesity

Obesity is a leading preventable cause of death and growing health problem worldwide with increasing rate in both adults and children. A number of studies have reported the association of telomere length with obesity. Although the results were inconsistent and the relationship of telomere shortening and obesity is still inconclusive, several large population-based studies showed telomere shortening in obesity. In cross-sectional epidemiological studies, shortened telomeres were associated with body mass index (BMI), waist-to-hip ratio, visceral fat, and weight gain [3,16,17]. Consistently, calorie-restricted diets and subsequent weight loss were associated with the increased telomere length in obese men [18]. These results indicated the relationship between obesity and shortened telomeres. As an underlying mechanism of telomere shortening in obesity, leptin might be involved. Leptin plays an essential role in the regulation of body fat mass, and it has some proinflammatory properties with increasing oxidative stress [19]. Valdes et al. reported that age, smoking, and serum leptin concentration were independently associated with telomere length, but BMI did not, suggesting that leptin may directly contribute the telomere shortening.

3.2. Diabetes mellitus

The number of patients with type 2 DM has drastically been increasing worldwide in association with the changes in lifestyle and increased prevalence of obesity. DM is categorized into several clinical types: type 1 DM (T1DM), type 2 DM (T2DM), gestational DM, and others. In particular, T2DM accounts for the majority of DM patients and the pathophysiology of T2DM has an age-related aspect. DM increases the risk of cardiovascular and cerebrovascular events, and cognitive dysfunction, which are known as age-related diseases. Telomere length in patients with DM has been examined in many studies [20]. In 1998, Jeanclos et al. [21] showed that patients with insulin-dependent DM (IDDM) had shorter telomeres in peripheral leukocytes than non-DM individuals. Patients with T2DM also showed shortened telomeres [22,23]. Furthermore, it has been reported that telomere shortening rate increased with the duration of T2DM [24]. As an underlying mechanism of the telomere shortening in DM, increased production of reactive oxygen species (ROS) caused by hyperglycemia and hyperinsulinemia is supposed. Polyol pathway activation, protein kinase C pathway activation, and increased production of advanced glycation end products (AGEs) also play a pathological role in increased levels of oxidative stress [25]. In fact, Sampson et al. [23] showed an inverse correlation between the level of oxidative stress marker, 8-hydroxy-deoxyguanosine, and the telomere length. These results suggest that the increased oxidative stress in DM may accelerate the telomere shortening.

To date, several studies have focused on the relationship between telomere length and the mortality and progression of DM complications. In a prospective follow-up study, telomere length in T1DM was associated with all cause of mortality [26]. However, the association of telomere length with DM complication has been controversial. Several studies exhibited that DM patients with shorter telomeres has tended to show severer complications of DM [27,28].

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On the other hand, Astrup et al. [26] reported that telomere length did not differ between patients with and without nephropathy. Although further studies are needed, these results suggest that telomere length could be used as a surrogate marker for mortality and some of the morbidity in patients with DM.

3.3. Hypertension

Hypertension can develop with various genetic and environmental factors, which is considered to be an essential risk factor for cardiovascular or cerebrovascular diseases. However, most of the pathogenesis remains unclear. Recent evidence suggests that telomere length may be, at least in part, involved in the pathogenesis of hypertension [29]. Jeanclos et al. [30] reported the results of a twin study, in which 49 twin pairs were assessed their relation of blood pressure parameters with telomere length in leukocytes. They showed that telomere length were highly familial and negatively correlated with pulse pressure, implying that telomere shortening might be genetically regulated and associated with vascular aging. The Framingham Heart Study also demonstrated that hypertensive individuals exhibited shorter telomere length in leukocytes compared with normotensive individuals [31]. Furthermore, telomere shortening is associated with an increased atherosclerosis and cardiovascular risk [32–34]. These results suggest a close connection of telomeres and hypertension and its complications.

The underlying mechanism of telomere shortening in hypertension is still unclear. Mice lacking telomerase activity showed hypertension as a result of increased plasma endothelin-1 levels [35]. Telomerase activity was decreased in endothelial progenitor cells from both hypertensive rats and patients with essential hypertension [36]. These data suggest that endothelial cells play a key role in the association of telomere length and premature vascular aging.

3.4. Nonalcoholic fatty liver disease/nonalcoholic steatohepatitis

The role of telomeres in chronic liver diseases, such as viral hepatitis, nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH), and liver cirrhosis, has been investigated [37]. It is well known that in these conditions, fibrosis generally determines the severity and prognosis of the disease. Older age and duration of chronic liver disease are the major risk factors for fibrosis [38].

Kitada et al. [39] first reported that telomere shortening was accelerated in hepatocyte of chronic liver disease, including chronic viral hepatitis or liver cirrhosis. Aikata et al. [40] also confirmed that telomere length was significantly shorter in the liver with chronic viral hepatitis or cirrhosis. Telomere length was significantly shorter in cirrhotic liver induced by broad etiologies compared with noncirrhotic liver [41]. Furthermore, telomerase-deficient mice showed impaired hepatic regenerative potential and developed liver cirrhosis. The regenerative potential of organ depends on the amount of the cells with sufficient telomere length, which reserves the potential for cell proliferation. Telomere shortening restricts the replicative capacity of these cells. Interestingly, adenoviral telomerase gene delivery inhibited the progression of liver cirrhosis [42]. These data indicate that telomere shortening in hepatocytes

might impair the regenerative capacity in response to liver injury, which might result in liver fibrosis.

4. Telomeres in endocrine diseases

4.1. Polycystic ovary syndrome (PCOS)

To the best of our knowledge, the first endocrine disease, in which telomere length was investigated, was polycystic ovary syndrome (PCOS) [43]. PCOS is characterized by polycystic ovaries, irregular menstrual cycles, androgen excess, and insulin resistance [44]. PCOS is a complex and multigenetic disorder, in which single nucleotide polymorphisms (SNPs) in several genes have been found to be associated. Phenotypes of the disease vary according to the ethnic origin, race, genetic factors, and other environmental factors [45,46]. In addition, no single etiologic factor was able to fully account for the pathogenesis of this disorder. Interestingly, patients with PCOS exhibited a significantly shorter telomere length than the controls after adjusting for age [43]. In addition, significant negative correlation between telomere length and dehydroepiandrosterone sulfate (DHEA-S) was observed. There are several lines of evidences, which suggest that oxidative stress plays a role in the pathogenesis of PCOS [47, 48]. Telomere shortening can cause dysregulation of the insulin sensitivity, mitochondrial function, and Ca^{2+} metabolism [49,50], suggesting a causal role of shortened telomere length in the development of PCOS. Conversely, an elevated oxidative stress associated with the androgen excess, abdominal adiposity, insulin resistance, and obesity might play a role in telomere shortening.

4.2. Cushing's syndrome

Cushing's syndrome is characterized by excessive secretion of cortisol, which leads to increased mortality and severe morbidity, including cardiovascular risk, obesity, fatigability, osteopenia, and impaired quality of life [51]. These comorbidities are not completely reversible after the biochemical control [52]. Hyperstimulation of hypothalamus-pituitary-adrenal (HPA) axis and subsequent hypercortisolemia may also occur in several kinds of psychiatric disorders or life stressors [53]. Interestingly, these situations are reportedly associated with shortened telomeres, in which chronic stress and enhanced HPA axis are observed. For example, patients with depression exhibited shorter telomere length than healthy controls [54]. Telomere length of newborn baby was shorter in proportion to the stress levels experienced by the mother during her pregnancy [55]. The exposure to violence or neglect in childhood was associated with shorter telomere length either in children or retrospectively in adults [56]. *In vitro* analysis has revealed that high levels of glucocorticoid reduce a 50% of telomerase activity in lymphocytes [57]. In this aspect, to elucidate the reason why comorbidities of Cushing's syndrome are not completely recover after a biochemical control, Aulinas et al. [58] hypothesized that shortening of telomere might occur in Cushing's syndrome and evaluated the telomere length in patients with Cushing's syndrome. They evaluated 77 patients with Cushing's syndrome (59 pituitary adenoma, 17 adrenal adenoma, and 1 ectopic; 21 with active

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disease). Although mean telomere length in patients with Cushing's syndrome and age-, sex-, and smoking-matched controls were comparable, in the longitudinal evaluation, telomere length was shorter in active disease than controlled disease after adjustment for age. They also showed that dyslipidemic patients with Cushing's syndrome had shorter telomere length than non-dyslipidemic patients with Cushing's syndrome and total cholesterol and triglycerides negatively correlated with telomere length. In addition, inflammatory markers and serum levels of CRP and IL-6 were also negatively correlated with telomere length in patients with Cushing's syndrome [59]. These observations suggested that hypercortisolism might negatively regulate telomere maintenance through the production of inflammatory cytokines or lipids.

4.3. Acromegaly

Patients with acromegaly exhibit reduced life expectancy and increased comorbidities, such as DM, hypertension, cardiovascular and cerebrovascular diseases, and malignant diseases, which are also known as age-related diseases. Underlying mechanisms of these increased age-related diseases are mainly explained by over secretion of GH and IGF-I; however, precise mechanisms have not been fully elucidated. Therefore, we investigated the telomere length of peripheral leukocytes in patients with acromegaly [60]. Intriguingly, patients with acromegaly exhibited shorter telomere length compared with patients with nonfunctioning pituitary adenoma or healthy control subjects. In addition, telomere length in acromegaly was negatively correlated with the disease duration, suggesting that exposure to increased serum GH or IGF-I levels may reduce telomere length. *In vitro* analysis revealed that not GH but IGF-I increased the telomere shortening rate per one cell division in human skin fibroblasts. Furthermore, IGF-I–treated cells showed cellular senescence and increased expression of SASP-related cytokines (e.g., IL-6). It has been reported that the development of age-related diseases, such as DM and vascular diseases, is associated with cellular senescence and SASP [8]. Together with our data, it is suggested that cellular senescence induced by telomere shortening may be involved in the increased morbidity and mortality in acromegalic patients.

The underlying mechanisms of how excess IGF-I induces telomere shortening and subsequent cellular senescence remain unclarified. It has been reported that various factors, including ROS, defects in the telomere repair system, inflammatory reactions, and increased cellular turn over, cause telomere shortening [61]. Intriguingly, oxidative stress was enhanced both in GH-transgenic rats and patients with acromegaly [62]. In addition, it has been reported that IGF-I enhances ROS-p53 pathway and subsequent cellular senescence in cultured cells with a confluent status [63]. Bayram et al. [64] also reported that patients with acromegaly exhibited increased oxidative stress and DNA damage. Furthermore, the causal role of increased oxidative stress in telomere shortening has been reported. Human fibroblasts cultured under 40% oxygen, in which oxidative stress is increased, exhibited an accelerated rate of telomere shortening [33] and inhibition of the glutathione-dependent antioxidant system results in telomere shortening and senescence in human endothelial cells [65]. Taken together, although further investigations are needed, we speculate that the increased oxidative stress associated

with the increased serum levels of IGF-I may lead to the telomere shortening in patients with acromegaly.

5. Telomere shortening as a risk for onset of metabolic diseases

Telomere length is closely associated with morbidity and mortality [66,67]. Therefore, telomere length has been thought as a marker for individual cellular aging [68,69]. However, several recent studies have focused on the possibility of causal role of shortened telomeres as a risk for the development of several age-related diseases, including metabolic diseases [70–72].

5.1. Diabetes mellitus

Telomere length is already reduced in pre-diabetic stage; impaired glucose tolerance and this is recognized as a risk factor for the onset of T2DM [73]. To date, several prospective studies have focused on the telomere shortening as a risk factor for the onset of T2DM [74–76]. Although these results have been inconsistent, some studies showed positive results. You et al. [76] conducted a large-scale prospective study of healthy postmenopausal women with 6-year follow-up. However, there was no relationship between telomere shortening and the onset of DM. Recently, Zhao et al. [75] also reported the results of a large-scale cohort study of American Indians. Among 2328 participants who were free of DM at baseline, 292 subjects developed DM during an average 5.5 years of follow-up. Subjects in the lowest quartile of telomere length showed approximately twofold-increased risk of DM incidence compared with the highest quartile. Willeit et al. [74] also reported the similar results of prospective cohort study of healthy subjects. Over 15 years of follow-up, 44 of 606 participants developed DM. The adjusted hazard ratio for DM comparing the lowest and highest quartile of baseline telomere length was 2.0. These results may indicate that telomere shortening is not only a mere marker of biological aging but also plays a causal role in the development of DM.

5.2. Metabolic syndrome

As shown above, many studies have demonstrated that the components of metabolic syndrome individually exhibited a significant association with shortened telomeres [21,30,33]. Very recently, Revesz et al. [70] reported the result of a large population-based study with 6 years of follow-up, which included 2981 adult individuals (age: 18–65 years); the subject consists of 1701 persons with a diagnosis of depression and/or anxiety disorder, 907 persons with subthreshold depressive or anxiety symptoms, and 373 healthy controls. They assessed that whether shorter telomere length at baseline was associated with a worse metabolic profile. This study demonstrated that shorter telomere length at baseline was not only cross-sectionally associated with metabolic syndrome components (decreased HDL and increased waist circumference, triglycerides, and fasting glucose) but also associated with an increased risk of having an abnormal metabolic profile, which continues to be unfavorable even after a follow-up period of 6 years. Based on the results, they advocated that cellular aging assessed by telomere length might play a role in the metabolic alterations.

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5.3. Liver cirrhosis

Liver cirrhosis is the end-stage complication of chronic liver disease, which leads to impairment of liver function and increased risk of hepatocellular carcinoma. In particular, viral hepatitis, fatty liver disease, and alcohol consumption have been reportedly associated with an increased risk of cirrhosis, and the majority of the patients have these risks. However, even in the same condition, a part of the patients progress to cirrhosis, whereas others do not. The reason that determines the progression remains still unclear. Several SNPs have been reportedly associated with the development of cirrhosis. Interestingly, it has been recently reported that telomere shortening might be a risk factor for the liver cirrhosis [77]. In the liver tissue with chronic liver injury, because a high cellular turnover was required for the regeneration and repair process, telomere shortening was accelerated. Telomerase-deficient mice were prone to develop cirrhosis in response to chronic liver injury, and restoration of telomerase activity was able to improve fibrosis and liver function [42]. Furthermore, patients with telomere diseases, in which telomerase complex gene mutation was identified, such as dyskeratosis congenita showed a shortened telomeres and increased prevalence of liver disease including fibrosis and cirrhosis [61]. These data suggest that shortened telomeres are causally involved in the development of liver cirrhosis.

6. Telomere as therapeutic targets

The analysis of mouse genetic models demonstrated the causal role of shortened telomeres in aging. Mice deficient for *TERC* show accelerated telomere shortening, chromosome instability, premature aging phenotype, and premature death [78,79]. Another mouse model, *TERT*-deficient mice also showed a shorter telomere length and genome instability [80,81]. In contrast, mice with increased transgenic telomerase expression were able to maintain longer telomeres through their lifespan and showed decreased appearance of age-related disorders and increased longevity. These results indicate that the maintenance of telomere length, at least in mice, plays an essential role in the regulation of aging and longevity [82]. In this regard, to prevent the onset of age-related diseases, telomere and telomerase as a potential therapeutic target have been emerged [83].

6.1. Telomerase activator

Small molecule named TA-65 derived from an extract of a plant used in traditional Chinese medicine, *Astragalus membranaceus*, upregulates telomerase activity *in vivo* [84]. TA-65 has been shown a mild increase in telomere length in mice [85] and humans [84]. However, there was no increase in longevity in mice [85]. Recently, the result of a randomized control study conducted on 117 healthy subjects using TA-65 has been reported [86]. Low dose oral administration of TA-65 significantly increased telomere length over the 12-month period, whereas subjects in the placebo group significantly lost telomere length. The high dose administration of TA-65 showed a trend of improvement in telomere length; however, it did not reach statistical significance. Although it remains elusive that telomerase activator can increase life

span and delay the onset of age-related diseases, these findings suggest a possibility of telomere/telomerase as a therapeutic target for preventing aging.

6.2. Danazol

Androgen has been used to treat bone mallow failure and aplastic anemia with the anabolic effect on bone marrow [87], although precise mechanisms have not been fully understood. It has been reported that telomere diseases with mutations in genes responsible for telomere maintenance and repair lead to bone mallow failure [88]. Interestingly, considerable evidence suggests that androgen directly regulates telomerase activity [89]. Recently, it has been reported that the treatment with androgen leads to telomere elongation in a mouse model of telomerase dysfunction [90]. In addition, serum dihydrotestosterone and estradiol levels and aromatase gene polymorphisms were associated with telomere length [91]. Very recently, Townsley et al. reported that danazol, the synthetic sex hormone, which has androgen activity, was efficacious to elongate the telomere length in bone marrow cells [92]. Patients with mutations in the genes related to the telomere maintenance or repairment, such as *TERT*, *TERC*, and *DKC1*, were enrolled and orally administered danazol at a dose of 800 mg/day for a total of 24 months. Surprisingly, almost all the patients (11 of 12) had a substantial gain in telomere length at 24 months when compared with baseline. Hematologic responses were also observed in 10 of 12 patients at 24 months. As an underlying mechanism, *in vitro* study showed a direct effect of androgen on telomerase activity by upregulation of *TERT* expression [93]. Although whether androgen is also effective to subjects without gene mutations in telomere-related genes is still unclear, there is a possibility that pharmacological intervention for telomere elongation may be applicable for the treatment of age-related disease.

7. Conclusion

In summary, telomere length assessed in peripheral leukocytes is associated with various metabolic and endocrine diseases **Figure 2A**. In addition, recent studies suggest that shortened telomeres may have a causal role in the pathophysiology of age-related diseases, such as T2DM, metabolic syndrome, and cardiovascular disease **Figure 2B** [70,94]. However, it has not yet been elucidated that how shortened telomeres cause these age-related diseases. One possible explanation is SASP. Shortened telomeres activate DDR pathway, which results in apoptosis and/or cell cycle arrest, and cellular senescence. Recently, it has emerged that cellular senescence and the related SASP play important roles in the development of age-related diseases [8,9,95,96]. In conclusion, although there is a strong association between telomere shortening and metabolic and endocrine diseases, further studies are needed to understand the mechanisms underlying these associations. Also, it is suggested that interventions that restore telomere length may be a potential therapeutic target for age-related disease **Figure 2C**.

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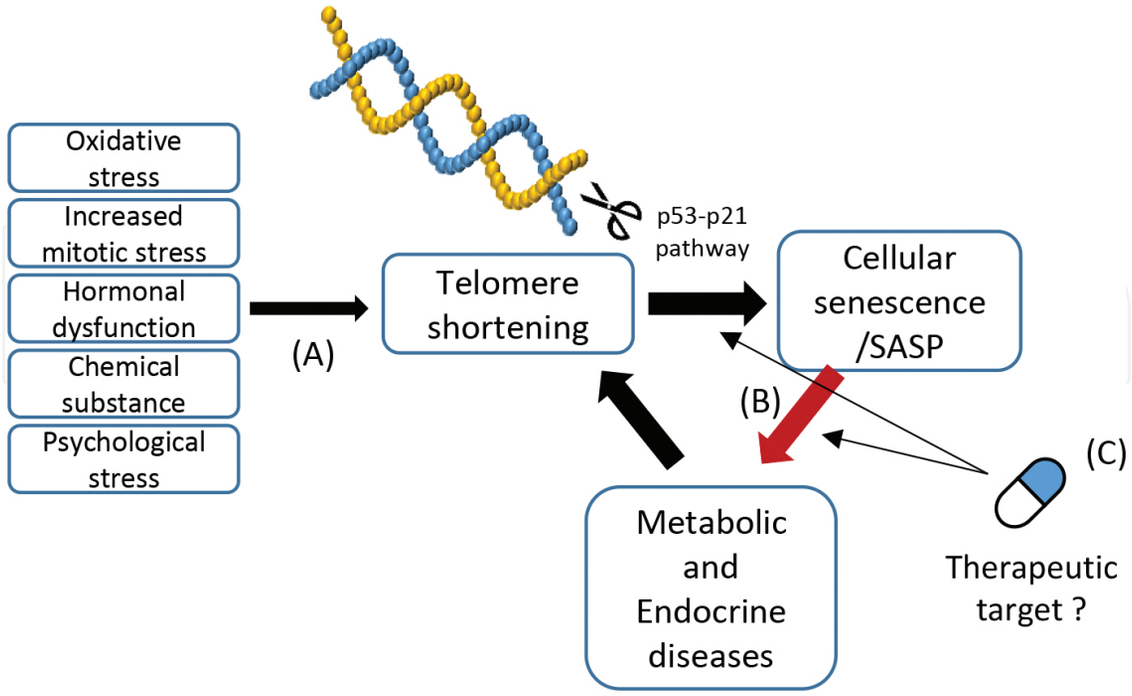

Figure 2. Schematic summary. A) Various factors such as oxidative stress, mitotic stress, and hormonal dysfunction can shorten telomere length. B) Shortened telomeres are not a mere marker for individual aging but a pathological contributor to the development of age-related disease, including metabolic and endocrine diseases. As the underlying mechanism, cellular senescence and/or SASP might be involved. C) These pathways might be potential therapeutic targets for prevention of these age-related disorders.

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