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Stem cell aging in adult progeria

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Abstract

Aging is considered an irreversible biological process and also a major risk factor for a spectrum of geriatric diseases. Advanced age-related decline in physiological functions, such as neurodegeneration, development of cardiovascular disease, endocrine and metabolic dysfunction, and neoplastic transformation, has become the focus in aging research. Natural aging is not regarded as a programmed process. However, accelerated aging due to inherited genetic defects in patients of progeria is programmed and resembles many aspects of natural aging. Among several premature aging syndromes, Werner syndrome (WS) and Hutchinson–Gilford progeria syndrome (HGPS) are two broadly investigated diseases. In this review, we discuss how stem cell aging in WS helps us understand the biology of aging. We also discuss briefly how the altered epigenetic landscape in aged cells can be reversed to a "juvenile" state. Lastly, we explore the potential application of the latest genomic editing technique for stem cell-based therapy and regenerative medicine in the context of aging.

Keywords: Werner syndrome, Stem cells, Aging, WRN

Werner syndrome: clinical features, genetics, and pathogenesis

Werner syndrome (WS) was first described by Otto Werner in 1904. Patients of WS are characterized by premature aging which are clinically apparent during 20–30 years old. WS patients show abnormal physical development such as a bird-like face, short stature, and slender limbs. They also display a high-pitched voice, remarkable loss and graying of hair, and scleroderma-like skin changes. Other common clinical presentations include bilateral cataracts, type 2 diabetes mellitus, hypogonadism (with reduced fertility), skin ulcers, premature arteriosclerosis, osteoporosis, and cancer predisposition [1, 2]. Ninety percent of WS is linked to mutations on *WRN*, a member of the *RecQ* family responsible for stable genome maintenance. Owing to autosomal recessive inheritance, biallelic mutation on *WRN* is pathogenic. The frequency of WS is estimated to be 1 in 20,000–40,000 in Japanese population and slightly lower in the world [3, 4].

The pathogenesis of WS due to loss of the WRN protein has been well elucidated by the biochemical nature of the WRN helicase. As a multifunctional nuclear protein, WRN is an ATP-dependent 3′–>5′ helicase and exonuclease. It unwinds secondary DNA structure such as tetraplex DNA and Holliday junction and resolves stalled replication fork during DNA replication. More importantly, WRN participates in multiple DNA repair pathways such as base excision repair, non-homologous end joining, and homologous recombination [5]. In addition to DNA replication and DNA repair, WRN is also involved in telomere maintenance. Telomere replication and protection are pivotal for maintaining genome integrity and stability and also serve as an aging marker. Accelerated aging due to loss of WRN function is well explained by its biochemical functions in relation to DNA replication, repair, recombination, and telomere maintenance [6]. From a developmental point of view, progressive cell loss due to apoptosis, cell cycle arrest, or senescence in actively dividing cells may be a consequence of WRN loss. Since WS is an adult onset disease, genetic instability accumulates with age. The manifestation of premature aging phenotypes becomes apparent when accumulated DNA damages are not properly repaired and WRN-deficient cells fail to maintain their genomic integrity [7]. WS cells thus, while being diagnosed and biopsied, display a variegated translocation

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mosaicism in skin fibroblasts and shorter telomere length [8]. WS fibroblasts also display premature senescence and accelerated telomere loss. From the view of pathogenesis, accumulation of deleterious DNA mutations and persistence of genomic instability eventually attain a pathogenic threshold to be reflected in different phenotypes - premature aging in many of the mesenchymal cell types and acquisition of neoplasm [9].

Stem cell aging in connection with segmental progeria in Werner syndrome

Progeroid syndromes such as WS and Hutchinson–Gilford progeria syndrome (HGPS) show phenotypes of accelerated aging resembling normal aging, such as the development of bilateral cataract, aging skin, graying and loss of hair, cardiovascular disease, and osteoporosis [1]. However, they are segmental in nature, meaning that only a specific category of tissues is predominantly affected. For WS, age-related dementia and cognitive impairment are rarely reported, leading to the hypothesis that progeroid syndromes are not seemingly an accelerated mode of aging. Nevertheless, how de novo mutation in, for instance, *WRN*, leads to segmental aging remains to be answered. A number of models of aging have been described to explain the aging mechanisms in stem cells as well as in model animals. These models are based on the molecular pathways known to regulate longevity, reactive oxygen species (ROS) production, mitochondrial function, telomere protection, cell cycle control and senescence, protein homeostasis, and systemic inflammation [10]. In WS, specific pathways are amplified and connected to the aging program leading to accelerated but lineage-specific aging. Our discussions below focus on the telomere function and epigenetic regulation in connection with stem cell aging in progeroid syndromes.

Telomere dysfunction as a hallmark of premature aging in WS cells

The hypothesis of telomere erosion as a chronological aging marker has been well documented by many investigations linking the telomere lengths to the biological age. A population in advanced age has a shorter average telomere length than younger groups, although variations exist within each age group [11]. In telomerase-null mice, shorter telomeres are found after several generations of interbreeding. Degenerated phenotypes are observed in late-generation, telomerase-null mice. However, reconstitution of telomerase can rescue these phenotypes, suggesting the telomere length as a pathological factor for aging [12]. Telomere is not only a biological clock counting the number of cell divisions but also a protective structure for ensuring genomic integrity and stability. Specifically, the telomere is highly organized and orchestrated by telomere-binding proteins called shelterin [13]. Loss of telomeric DNA or failure of telomere protection elicits telomere dysfunction, which subsequently induces cell cycle arrest, apoptosis, or senescence [14]. Telomere dysfunction-induced cell cycle arrest in stem cells serves as a protective mechanism to prevent propagation of genetically unstable daughter cells from passing on [15]. In many adult stem cells such as mesenchymal stem cells (MSC) and muscle stem cells, telomerase activity is restricted, indicating a finite number of divisions allowed. The adult stem cell pool is kept at a balanced quiescent and proliferative state in response to signals of differentiation or regeneration. The stem cell pool is believed to exhaust with age, thus giving less regenerative potential [16]. In laboratory mice, the longest telomeres are found in stem cell compartments requiring active proliferation such as hair follicle and small intestine stem cells [16].

How the WRN-deficient progeroid stem cells become depleted remains a challenging question to answer, mainly because adult stem cells from WS are difficult to acquire. A comparison of the in vivo telomere length from a cohort of WS patients with normal individuals demonstrates accelerated telomere attrition in muscles and skins [17]. Depletion of WRN protein in normal fibroblasts also shows a similar result, leading to the hypothesis that telomere dysfunction due to WRN deficiency is the primary cause for WS pathophysiology [18]. The mouse model for WS with *Wrn* deletion, however, is not sufficient to recapitulate the classical features of WS in human [19]. Such species-specific difference can be ascribed to the fact that laboratory mice possess a longer telomere reserve than human. In support of this notion, *Wrn* knockout mice in the background of critically short telomeres (G4-G6 $Terc^{-/-}Wrn^{-/-}$), but not in mice with normal telomeres ($Terc^{+/-}Wrn^{-/-}$), display aging phenotypes reminiscent of human WS [20]. However, WRN may not be an essential factor for telomere replication because telomerase-immortalized WS cells can extend the telomere length without inducing telomere dysfunction and senescence [21].

The role of WRN in telomere maintenance

The WRN protein plays a diverse role in protecting genome stability through interacting with different proteins in several pathways (refer to review by Bohr et al.) [5].

The current view suggests that WRN interacts with shelterin proteins to resolve G-quadruplex and Holliday junction structures in addition to aiding repair of DNA breaks during DNA synthesis [6, 7, 22]. G-quadruplex structures are common when DNA polymerase is synthesizing the G-rich, single-stranded D-loop found at telomeres. Consistent with this notion, WRN-depleted cells show defective synthesis at the lagging strand of sister telomeres perhaps due to the failure to resolve