Review

Werner Syndrome: Symptoms, Hallmarks of Aging, Molecular Mechanisms and Therapeutic Pathway Inhibitors

Syndrome de Werner : symptômes, marques du vieillissement, mécanismes moléculaires et inhibiteurs des voies thérapeutiques

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Abstract | Résumé

Werner Syndrome (WS) is a rare autosomal recessive progeroid disorder characterized by accelerated aging and the premature onset of age-related conditions, such as stunted growth, cataracts, cardiovascular disease, malignancies, sarcopenia, osteoporosis, and diabetes. Clinical disease manifestations typically begin in adolescence to early adulthood, and result in a reduced lifespan compared to healthy individuals. WS arises from loss-of-function mutations in the WRN gene, which encodes a RecQ family helicase that has implications in DNA repair, replication, and telomere maintenance. Deficiency in functional RecQ helicase activity results in dysfunction that links WS to the hallmarks of aging, including genomic instability, telomere attrition, and premature cellular senescence. To date, there is no cure for WS, with current therapies primarily focusing on disease management through inhibition of important proteins in aging- and stress-related signaling pathways, namely mTOR and p38 MAPK. These emerging approaches have shown promising results in cellular models, but have yet to be tested in human clinical studies. This review therefore examines WS as a potential model for understanding the mechanisms of aging, and the implications of existing findings for informing new therapeutic strategies.

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Le syndrome de Werner (SW) est une maladie progéroïde autosomique récessive rare, caractérisée par un vieillissement accéléré et par l'apparition précoce de problèmes normalement associés à l'âge, comme un retard de croissance, des cataractes, des maladies cardiovasculaires, des cancers, la sarcopénie, l'ostéoporose et le diabète. Les manifestations cliniques commencent généralement entre l'adolescence et le début de l'âge adulte, puis entraînent une espérance de vie plus courte que chez les personnes en bonne santé. Le SW est causé par des mutations avec perte de fonction dans le gène WRN, qui code une hélicase de la famille RecQ impliquée dans la réparation de l'ADN, la réplication de l'ADN et le maintien des télomères. Lorsque l'activité fonctionnelle de cette hélicase RecQ est déficiente, plusieurs dysfonctionnements apparaissent et relient le SW aux grandes marques du vieillissement, notamment l'instabilité génomique, le raccourcissement des télomères et la sénescence cellulaire prématurée. À ce jour, il n'existe aucun traitement curatif pour le SW. Les thérapies actuelles visent surtout la prise en charge de la maladie, entre autres par l'inhibition de protéines importantes dans les voies de signalisation liées au vieillissement et au stress, comme mTOR et p38 MAPK. Ces approches émergentes ont donné des résultats prometteurs dans des modèles cellulaires, mais elles n'ont pas encore été testées dans des études cliniques chez l'humain. Cette revue examine donc le SW comme modèle potentiel pour mieux comprendre les mécanismes du vieillissement, ainsi que les implications des résultats actuels pour orienter de nouvelles stratégies thérapeutiques.

Keywords: Werner syndrome, WRN helicase, genomic instability, telomere attrition, cellular senescence, hallmarks of aging, mTOR signaling, p38 MAPK.

Introduction

Aging is accompanied by the gradual accumulation of DNA damage and genomic instability, which has emerged as a hallmark of the aging process (1). Failure of genomic maintenance systems can accelerate damage accumulation, contributing to age-related pathologies such as cancer (1). The importance of maintaining genome integrity in aging is underscored by rare hereditary disorders in which mutations in DNA repair pathways lead to premature aging syndromes (1). In these conditions, an excess of unrepaired DNA damage manifests as early-onset degenerative changes, directly linking genomic instability to accelerated aging. Premature aging (progeroid) syndromes serve as powerful biological models for studying aging mechanisms. These rare diseases recapitulate many features of normal aging and provide natural opportunities to probe how specific molecular defects drive aging phenotypes.

Among the DNA instability-driven progeroid disorders, Werner syndrome (WS) is a quintessential example. WS is a rare autosomal recessive disorder caused by loss-of-function (LOF) mutations in the WRN gene, first identified in 1996, which encodes a 1,432

amino acid RecQ-family DNA helicase (2). WS prevalence is estimated to be 1:1,000,000–1:10,000,000, with high prevalence in certain populations, such as Japan, due to founder effects that increase the frequency of disease-causing variants within a population (3). WRN is the only human gene whose LOF mutations give rise to WS, and loss of WRN function leads to genomic instability and a characteristic premature-aging phenotype (4). Affected individuals typically develop normally until adolescence, then begin to show early signs of aging such as loss and greying of hair, skin atrophy, and bilateral cataracts, followed by the onset of age-related diseases in early adulthood (5).

Despite its rarity, WS remains highly relevant to aging research because it directly links loss of genome maintenance to accelerated tissue decline. Recent studies have renewed interest in WS by highlighting both its mechanistic importance and its therapeutic potential. These findings not only provide a foundation for potential interventions in WS, but also offer broader insights into targeting aging-related pathways.

Discussion

Characteristics of the Disease

Age of onset and disease progression

WS is an autosomal recessive progeroid disorder with onset in adolescence or early adulthood. Typical development usually occurs until puberty, then WS patients fail to undergo the pubertal growth spurt, resulting in short stature as the first indicator of disease (5). Characteristic aging-like features begin to appear in their twenties, and by their thirties, most WS patients display greying and loss of hair, as well as an aged facial appearance with thin, atrophic skin (6). Bilateral cataracts also develop in most cases, often requiring surgery by their late twenties and into their early thirties (7). As the disease progresses through the third and fourth decades of life, patients start to accumulate multiple age-related pathologies including diabetes mellitus, osteoporosis, atherosclerosis, myocardial infarctions, and malignant tumours (6,7). As a result of this accelerated multi-system deterioration, WS patients display markedly shorter lifespans, with the median age at death of approximately 54 years (7).

Clinical features

WS patients display a broad spectrum of clinical features affecting dermatologic, endocrine, musculoskeletal, and metabolic systems. Patients develop scleroderma-like skin changes with tight, thin skin and a loss of subcutaneous fat, giving an aged and pinched facial appearance. Skin pigment changes and skin ulcers are also common, with approximately 40% of patients displaying skin ulcers in the distal one-third of the lower legs (8). These persistent ulcers are often linked to extensive calcification of soft-tissues and can lead to serious complications such as infections, with approximately 15% of WS patients eventually requiring a foot or lower leg amputation (6). In terms of musculoskeletal features, disproportionately short stature and premature osteoporosis are also observed in WS patients (7). Patients tend to have slender extremities with decreased muscle mass as a result of sarcopenia or can exhibit truncal obesity due to visceral fat accumulation (9). Mobility can be impaired due to joint contractures and tendon/soft-tissue calcifications.

Endocrine and metabolic features are also hallmarks of WS. Type 2 diabetes mellitus and dyslipidemia occur in a majority of patients by their thirties (6). In one study cohort, over 60% of participating WS patients had impaired glucose tolerance or diabetes along with hypertriglyceridemia (6). This diabetic tendency occurs despite a relatively low body mass index (BMI), due to severe insulin resistance and altered fat distribution as a result of the relative loss of peripheral subcutaneous fat. Hypogonadism is also observed in WS patients. These individuals experience gonadal atrophy and infertility, leading to premature menopause in women and testicular failure in men (5). Thyroid function is also impaired, with patients at risk of developing thyroid neoplasms (10). Other systemic features can include a high-pitched hoarse voice, cataracts, senile dementia, and brain atrophy; although not of Alzheimer's type (5).

Common complications and causes of mortality: Due to the accelerated nature of aging in WS, patients are predisposed to many complications that typically occur much later in normal aging. Cancer and cardiovascular disease are the most common causes of mortality in WS patients (10). Overall cancer risk is dramatically increased, but unlike ordinary age-related cancer, WS shows a distinct tumour spectrum. Uncommon tumour types are predominant, specifically those of mesenchymal or endocrine origins. Soft-tissue sarcomas, osteosarcomas, melanomas, and thyroid carcinomas account for about 57% of all reported WS cancers, compared to roughly 2% of cancers in an age-matched general population study conducted by Goto et al. (11). Meningiomas, leukemias, and bone malignancies are also overrepresented in WS (10). Since multiple primary tumours can occur in the same patient, this high incidence plays a role in significantly reducing the lifespan of WS patients. Tumour predisposition in WS patients can primarily be attributed to genome instability and telomere dysfunction, which together promote the accumulation of oncogenic mutations and chromosomal aberrations that drive malignant transformation. In addition to cancer, atherosclerotic cardiovascular disease is another primary fatal complication (10). Due to the aggressive and premature damage caused to artery walls, WS patients are at a significantly higher risk of myocardial infarction and death (10). Together, cancer and cardiovascular disease account for the majority of mortality cases in WS patients, leading to the relatively low median life expectancy (7). Less common causes of mortality include stroke, infection complications, and organ failure secondary to diabetes. Overall, the multisystem involvement in WS leads to an elevated mortality risk well before the seventh decade of life, in stark contrast to the normal aging population.

Molecular mechanism of Werner Syndrome

WRN deficiency in WS

The gene linked to the onset of WS is known as WRN, which encodes a 1432 amino acid protein product (2). The disease phenotype is caused by loss-of-function mutations in the WRN gene that are most commonly associated with small indels, premature stop codons or splice-site mutations, leading to truncated transcripts that are undetectable in patient-derived cells independent of mutation type (7,12). The resulting null alleles, which do not produce functional WRN proteins or have measurable enzymatic activity, are the direct cause of WS.

Helicase and exonuclease activity in WRN

At the molecular level, the WRN gene belongs to the RecQ family of helicases (13). Biochemical characterization confirmed that its unwinding activity occurs in the 3' → 5' direction and requires the presence of ATP. In a study by Moser et al (12), no WRN protein or immune-precipitable helicase activity was detected in patient cell lines, while WRN heterozygous cells showed reduced amounts of WRN protein and helicase activity (12). This suggests that WRN deficiency could directly impact DNA unwinding, impairing replication fork progression and stability. Consequently, stalled replication forks are more susceptible to collapsing, leading to increased DNA damage and genomic instability, which contributes to the onset of WS (14). Intrinsic 3' → 5' exonuclease activity was also found in the N-terminal region of WRN (15). Its activity is physically and functionally separate from the helicase domain of WRN. This domain preferentially catalyzes degradation of specific DNA secondary structures, such as bubbles, loops or stem-loops (16). Its exonuclease activity is further stimulated during non-homologous end joining (NHEJ), where WRN physically interacts with factors such as Ku70/80, DNA-PKcs and DNA ligase IV/XRCC4 to process DNA ends during repair (17). Loss of functional WRN protein extends the amount of time that cells need to complete the cell cycle, establishing the necessity of WRN for effective fork restart following DNA damage and replication arrest (18). WS patient and WRN-knockout cells also exhibited elevated levels of DNA breaks, suggesting genomic instability and/or impairment of DNA repair systems (19). The helicase and exonuclease functions of the WRN protein contribute to its functions during this DNA repair process, as well as during replication and recombination, however, how their combined dysfunction contributes to the disease phenotype of WS remains unclear (20).

Significance of WRN in telomere maintenance: The WRN protein also facilitates maintenance of telomeres, which contributes to the normal progression of aging. WRN's helicase activity is stimulated through its interaction with TRF2, a critical telomere maintenance protein that stabilizes T- and D-loop secondary structures in telomeres (21). In cooperation with Bloom syndrome helicase (BLM) and replication protein A (RPA) (21), WRN plays a role in unwinding this telomeric DNA such that it can be efficiently replicated (22). Telomeres replicated by lagging-strand synthesis were found to be affected by loss of WRN helicase activity, exhibiting loss of telomeres from individual sister chromatids. The shortening of telomeres can contribute to cellular senescence and trigger apoptosis by activating DNA damage responses, leading to tissue dysfunction (23). Loss of these sequences therefore directly contributes to the premature aging phenotype of WS, suggesting the importance of the WRN helicase activity.

Hallmarks of aging

The clinical and molecular features of WS align with several recognized hallmarks of aging, reinforcing the value of WS as a translational model for studying mechanisms that may also contribute to normal physiological aging. Central to WS pathology is genomic instability, one of the key hallmarks of aging. The WRN gene encodes a RecQ helicase involved in DNA repair and replication. Loss-of-function (LOF) mutations in WRN lead to DNA replication stress and accumulation of DNA damage. WS cells exhibit a mutator phenotype supported by increased chromosomal aberrations and large DNA deletions (10). WS also highlights the hallmark of telomere attrition. Studies have shown that telomere dysfunction is a major driver of premature aging in WS, with WRN-deficient fibroblasts displaying defective telomere lagging-strand synthesis, resulting in telomere shortening and instability (10). Since telomere attrition synergizes with WRN loss to induce premature aging, the consequence of this is an early onset of cellular senescence in proliferative tissues. WS patient cells have a reduced replicative lifespan and express senescence markers (e.g. DEC1 and p16) at a younger age than typical aging (10). This combination of accumulated DNA damage, telomere dysfunction, and cellular senescence likely drives many WS clinical features, mirroring the processes of normal aging but at an accelerated scale. In terms of other hallmarks, WS patients' metabolic disorders reflect deregulated nutrient sensing. Mitochondrial dysfunction has also been postulated, although the studies show no significant changes in mtDNA mutations from control groups (10). WS demonstrates how disruption of key aging mechanisms can generate an aging-like phenotype. Studies of WS have therefore provided important insight into human aging, supporting the idea that the hallmarks of aging play a causal role in disease development.

Pathway-based inhibitory therapeutic approaches

Therapeutic challenges

To date, there is no cure for WS, and effective treatment remains elusive. Despite extensive research, the mechanisms and genetic programs underlying human aging, including those disrupted in WS, remain unclear (24). As explored, WRN deficiency affects multiple cellular pathways across many tissues, making it challenging to design therapies that can safely and effectively correct the defect throughout the body. In addition, the genomic instability characteristic of WS cells raises concerns regarding the long-term safety and durability of gene-editing approaches, thus studies investigating genetic correction strategies in WS are relatively scarce, with most studies being limited to cellular models and pathway-based interventions (25). However, recent biochemical studies have shown that the WS protein functions in

several DNA metabolic pathways, highlighting the complexity of its role in cellular processes (24). As a result, current clinical management of WS centers on treating disease manifestations, preventing secondary complications, and screening for acquired diseases common to WS. Specifically, novel pathway-specific therapies have been proposed, most of which involve the inhibition of aging and stress-related pathway proteins.

mTOR Inhibitors

One notable therapy is the inhibition of mechanistic Target of Rapamycin (mTOR) (26). The mTOR signaling pathway is critical to aging and senescence as it contributes to the formation of protein aggregates, oxidative damage, and defective mitochondria and vacuoles, which are all hallmark features of cellular aging. Importantly, when it is inhibited in eukaryotic model organisms, prolonged lifespan is observed, reinforcing its role as a driver of aging (26).

Moreover, the mTOR signaling pathway has been directly linked to the cellular pathology of WS, particularly when the mechanistic Target of Rapamycin Complex 1 (mTORC1) complex is hyperactivated. In a study by Talaei et al. (27), WS-phenotype fibroblasts derived from WS patients showed increased phosphorylation of mTOR at Ser448, which reflects activation of mTORC1, and subsequently the cascade that leads to the phosphorylation of the downstream effector ribosomal protein kinase S6. These results were determined through Western blot analysis of enhanced expression of phosphorylated mTOR and S6 proteins in WS fibroblasts relative to normal fibroblasts, demonstrating elevated mTORC1 signaling in WS. This increased mTORC1 signaling was accompanied by the observation of typical hallmarks of aging in WS fibroblasts including excessive intracellular protein aggregation, elevated oxidative damage, and abnormal cellular morphology.

Talaei et al (27) treated these WS fibroblasts with hydrogen sulfide (H_2S) in the form of sodium hydrosulfide (NaHS), and compared results to WS fibroblasts treated with rapamycin, a known pharmaceutical inhibitor of mTORC1. Following treatment, mTOR pathway activity was assessed by Western blot analysis measuring levels of phosphorylated mTOR at Ser2448 and protein S6. In both NaHS and rapamycin-treated WS fibroblasts, it was observed that there were reduced levels of phosphorylated mTOR and S6, indicating lower mTORC1 signaling. In addition to this reduced marker expression, they observed the restoration of WS fibroblasts towards a more normal morphology as compared to the abnormal morphology accompanied by untreated WS fibroblasts (27).

p38 MAPK Inhibitors

Another emerging therapy is the inhibition of the p38 mitogen-activated protein kinase (p38 MAPK) pathway. In WS fibroblasts, senescence is accelerated and cells have a reduced cellular replicative life span (28-30), and therefore act similarly to fibroblasts of elderly individuals. It has been observed that WS is not only indicative of accelerated aging, but is also stress-associated, through the observation of slow growth rates, an extended cell cycle, and a normal aged morphology (31-34). The morphology of young WS cells has also been compared to fibroblasts subjected to premature senescence from oncogenic ras or arsenic, (35) both of which activate the p38 MAPK pathway through map kinase kinase 6 (MKK6) (35, 36). This leads to stabilization and upregulation of the kinase inhibitor p21, resulting in cell-cycle arrest. This is hypothesized to play a role in the premature senescence observed in WS (36-38).

In examining if the p38 MAPK pathway contributes to the cellular WS phenotype, Davis et al. (36) observed markers of stress-related senescence in patient-derived WS fibroblasts, including increased expression of phosphorylated p38 that is correlated with enhanced activation of p38 MAPK, as well as consequent enhanced expression of p21. The authors also treated WS fibroblasts with SB20358, a cytokine-suppressive, anti-inflammatory that inhibits p38 activity. Following treatment, they observed a reduction of p38 and p21 activity, and a reversion of the WS phenotype cell morphology back to the morphology of young normal fibroblasts, which was not observed in young normal cells. These results suggested that p38-mediated growth arrest is likely a contributing factor to premature aging in WS cells (39).

Implications of exploring WS therapeutics for aging research

The therapeutic potential of mTOR and p38 MAPK inhibitors can be applied beyond WS itself and have broader implications for aging research. Since these pathways are involved in processes such as cellular senescence and stress responses, the improvements seen in WS cells suggest that some aging-related changes may be slowed or modified through targeted therapies. Because WS displays many features of normal aging over a shorter period of time, it can also serve as a useful model for studying potential anti-aging treatments. As a result, research on pathway inhibitors in WS may help guide the future development of therapies for age-related diseases in the general population. However, although mTOR and p38 MAPK inhibitors have shown promising results in WS cellular models, they have not been tested in human clinical studies (25). The aforementioned findings should thus be applied to the progression of WS therapeutics with caution, as they are limited to fibroblast models and may not accurately predict therapeutic success in humans.

Conclusion

Werner Syndrome is a disease characterized by accelerated aging in humans, stemming from mutations in the WRN gene that produce null alleles. The resulting WRN deficiency negates its helicase and exonuclease activities, which impact the efficacy of DNA replication, repair, recombination and telomere maintenance in WS patients, though the impact of the combined loss of these functions remains relatively unexplored. Although no preventative cures currently exist, pathway inhibitors, such as mTOR and p38 MAPK inhibitors, have demonstrated effective reduction in senescence within experimental cellular systems. Therapies for Werner Syndrome directly targeting telomeric dysfunction and

compensatory models for loss of WRN function remain largely unexplored in humans, highlighting crucial gaps that require further investigation.

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