WERNER SYNDROME AS A MODEL OF AGING: THE ROLE OF WRN AT TELOMERES AND THE IMPACT OF TELOMERASE

Anna Esteve Garcia. Facultat de Biociències. Curs acadèmic 2013-2014. Universitat Autònoma de Barcelona (Catalunya, Espanya)

INTRODUCTION

Werner Syndrome (WS) is a rare genetic disorder that mimics the characteristics of normal human aging. Since aging is likely caused by numerous genetic and environmental factors acting simultaneously, it is very difficult to dissect the roles of individual genes in this process. In order to simplify such complexity, the goal of this review is focused on the relationship between three key components: aging, telomeres and the enzyme telomerase, taking Werner syndrome as a model of human aging.

WERNER SYNDROME AS A MODEL OF HUMAN AGING

Normal human aging

Progeroid aging syndromes

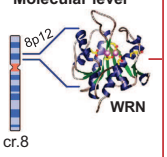
Bloom Syndrome
Cockayne Syndrome
Xeroderma Pigmentosum
Rothmund-Thomson Syndromes
Hutchinson-Guilford Progeria Syndrome

WERNER SYNDROME

Main features

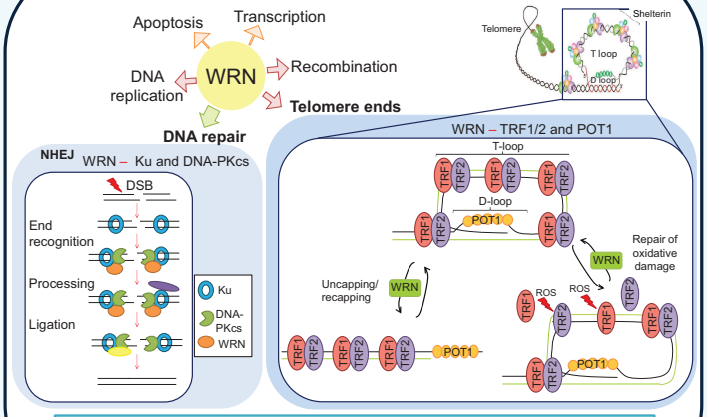
Bilateral cataracts
Greying hair and hair loss
Short stature
Scleroderma-like skin
Atherosclerosis
Ischemic heart disease
Osteoporosis
Type II diabetes mellitus
Hypogonadism
Cancer predisposition (sarcomas)

Molecular level



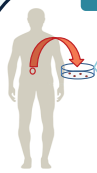
- Human RecQ helicase family
- Exonuclease and helicase activities
- Multiple functions

WRN INTERACTS WITH RESIDENT TELOMERIC PROTEINS



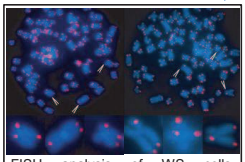
WRN participates in several important DNA metabolic pathways. These include DNA repair, replication, recombination and telomere maintenance. WRN plays a role at telomeres as it interactions with other resident telomeric proteins.

TELOMERE DYSFUNCTION CONTRIBUTES TO WS PATHOLOGY



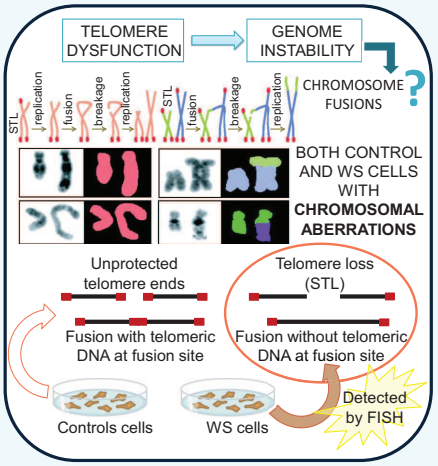
WS patient

Slow growth rates
Premature senescence
Genome instability
Telomere dysfunction

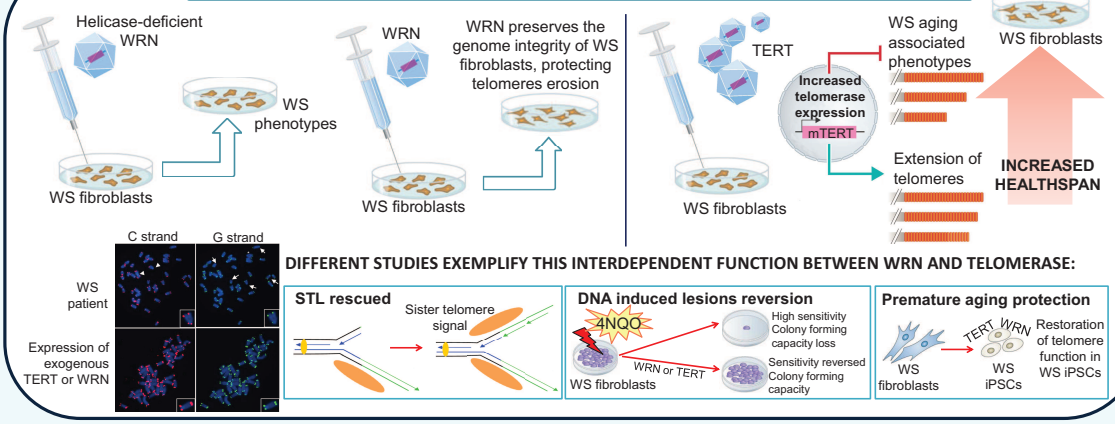


FISH analysis of WS cells. Telomeres were hybridized with a TRITC-$[TTAGGG]_4$ probe and are shown in the red channel. Arrows indicate missing telomeric staining from single sister chromatids.

Because of their G-rich nature, telomeres are fraught with potential obstacles to DNA replication that block replication forks. WRN is capable of unwinding such structures, preventing collapse in telomere forks. In its absence, telomeric signals are only detected at a single chromatid, phenotype termed sister telomere loss (STL).



BOTH WRN AND TELOMERASE RESCUE DEFICIENCIES IN WS FIBROBLASTS



DIFFERENT STUDIES EXEMPLIFY THIS INTERDEPENDENT FUNCTION BETWEEN WRN AND TELOMERASE:

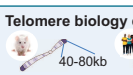
STL rescued

DNA induced lesions reversion

Premature aging protection

MOUSE MODEL OF WERNER SYNDROME

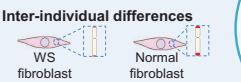
1. **Telomere biology differences**

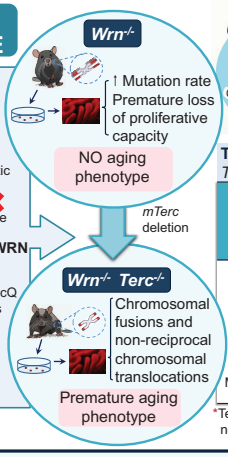


2. **Telomerase activity**

3. **Redundant function of murine WRN**

4. **Inter-individual differences**





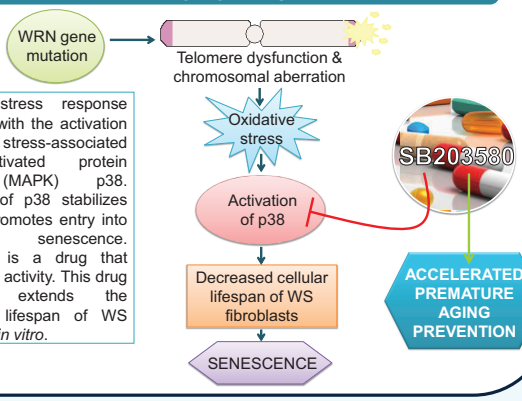
Both shortened telomeres and a lack of telomerase are required, at least in mice, for WS disease manifestation.

Table 1. Summary of phenotypes observed in the *Wrn*$^{+/+}$ *Terc*$^{-/-}$ and *Wrn*$^{-/-}$ *Terc*$^{-/-}$ mouse models

HUMAN WS	MOUSE MODELS		
	Wrn$^{-/-}$ *Terc*$^{-/-}$ Long telomeres	*Wrn*$^{+/+}$ *Terc*$^{-/-}$ Control*	*Wrn*$^{-/-}$ *Terc*$^{-/-}$ Short telomeres
Osteoporosis	No	No	++++
Cataracts	No	No	++++
Type II diabetes	No	No	++++
Skin defects	No	++	++++
Hypogonadism	No	++	++++
Atherosclerosis	No	No	No
Genome instability	No	+++	++++
Mesenchymal tumours	+	+	++++

*Telomerase null animals display a subset of aging phenotypes but do not display many of the symptoms associated with human aging.

DRUG INTERVENTION IN PREVENTING ACCELERATED AGING IN WS



Elevated stress response correlates with the activation of the stress-associated mitogen-activated protein kinase (MAPK) p38. Activation of p38 stabilizes p21 and promotes entry into cellular senescence. SB203580 is a drug that targets p38 activity. This drug treatment extends the replicative lifespan of WS fibroblasts *in vitro*.

CONCLUDING REMARKS

- WRN loss induces the wide range of premature aging phenotypes seen in Werner Syndrome.
- The key event, caused by WRN mutations, is the dysfunction of telomeres. Thus, the cascade started by telomere dysfunction explains the majority of the WS pathological phenotypes.
- Telomerase phenotypes recruitment as well as the WS mouse model generation reinforce this hypothesis.
- The SB203580 drug treatment may lead to novel therapies involving MAPK.

FUTURE APPROACHES