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Review

Telomere ResQue and preservation—Roles for the Werner syndrome protein and other RecQ helicases

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Abstract

Werner syndrome is an autosomal recessive disorder resulting from loss of function of the RecQ helicase, WRN protein. WS patients prematurely develop numerous clinical symptoms and diseases associated with aging early in life and are predisposed to cancer. WRN protein and many other RecQ helicases in general, seem to function during DNA replication in the processing of stalled replication forks. Genetic, cellular and biochemical evidence support roles for WRN in proper replication and repair of telomeric DNA, and indicate that telomere dysfunction contributes to the WS disease pathology.
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1. Werner syndrome and RecQ helicases

Progeroid syndromes are inherited disorders in which patients exhibit symptoms and diseases that resemble premature aging. Most are classified as segmental progerias since the patients do not exhibit the early onset of all features observed in normal aging (Kudlow et al., 2007). Among the human segmental progerias, Werner syndrome is the best well characterized with regard to telomere biology. Recent years have seen major advances in defining the precise telomere defects in WS, and how deficiencies in telomere function may contribute to the disease pathology. WS patients prematurely develop numerous clinical symptoms and diseases associated with aging in the second and third decades of life. These include hair graying, skin alterations and wrinkling, cataracts, osteoporosis, atherosclerosis, type II diabetes mellitus, and cancer (reviewed in Martin, 2005; Kudlow et al., 2007). Death occurs primarily as a result of atherosclerotic cardiovascular disease or cancer at a median of 54, previously reported to be 47 (Huang et al., 2006). The degree to which the disease pathology in WS represents accelerated mechanisms of normal aging is not known, and is difficult to determine partly due to the extreme heterogeneity that exists in the normal aging population. However, cDNA microarray analysis reveals strikingly similar patterns of gene expression changes in cells from older donors and young WS donors, compared to normal young donors (Kyng et al., 2003). As is typical of disorders with defects in DNA repair, WS is also characterized by genomic instability and a predisposition to cancer. However, WS patients are particularly predisposed to cancers of mesenchymal origin (Goto et al., 1996). Reasons for this bias are unknown, but may be related to a predisposition for utilizing telomerase-independent pathways for telomere elongation in sarcomas, compared to epithelial tumors (Bryan et al., 1997), that is increased in the absence of WRN (Laud et al., 2005) (see section on Homologous Recombination).

WS is an autosomal recessive disorder resulting from loss of function of the DNA repair protein WRN (Yu et al., 1996). All mutations in the *WRN* gene identified to date give rise to an unstable protein or truncated versions that fail to localize to the nucleus, since the nuclear localization signal resides in the C-terminus (von Kobbe and Bohr, 2002). WRN is a member of the highly conserved family of RecQ DNA helicases. *E. coli* and budding yeast each contain a single family member, whereas humans contain five and mutations in three give rise to genomic instability disorders. Blooms syndrome (BS) and Rothmund–Thomson syndrome (RTS) are caused by mutations in BLM and RecQL4, respectively (Hickson, 2003). Although these

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disorders are clinically distinct from WS, they are also marked by a predisposition to cancer and show some features of premature aging. RTS patients are primarily predisposed to osteosarcomas, whereas as BS is remarkable in that patients are predisposed to most types of cancer and are diagnosed with cancer at a mean age of 24 (Hickson, 2003). In general, RecQ helicases function primarily during DNA replication to prevent replication fork demise and to restore stalled or broken replication forks (for review see Wu and Hickson, 2006). Consistent with this, WRN protein is implicated in several pathways for replication fork repair, as well as other repair pathways including base excision repair and DNA double strand break (DSB) repair which have been reviewed elsewhere (Kudlow et al., 2007; Cheng et al., 2007). This review will focus primarily on WRN's role in telomere preservation, and will include relevant evidence for BLM function at telomeres as well.

2. Telomere dysfunction contributes to Werner syndrome pathology

Increasing genetic and cellular evidence in recent years support of a role for dysfunctional telomeres in the disease pathology and genomic instability observed in WS. Telomere maintenance is required to sustain cellular proliferative capacity. Most human somatic cells lack sufficient telomerase to maintain telomere length, and telomeres shorten with age (Harley et al., 1990). In the absence of telomerase, telomeres progressively shorten with each cell division, and eventually become dysfunctional, leading to genomic instability, irreversible growth arrest (replicative senescence) or apoptosis in cultured cells (reviewed in Blasco, 2005). The primary role of telomeres is to protect the ends of linear chromosomes and prevent them from being recognized as DNA double strand breaks (DSB) by the cellular DNA damage response machinery. They achieve this task by forming a protective cap that consists of telomeric DNA and a six member core of proteins termed the shelterin or telosome complex (de Lange, 2005). WRN and BLM proteins interact physically and/or functionally with at least three critical members of this protein core; namely TRF2 and TRF1 which bind duplex telomeric DNA, and POT1 which binds single stranded TTAGGG repeats (Opresko et al., 2002; Stavropoulos et al., 2002; Machwe et al., 2004; Lillard-Wetherell et al., 2004). Human telomeres contain 2–10 kb of TTAGGG tandem repeats and end in a 3′ single strand G-rich tail that serves as the substrate for telomerase (de Lange, 2005). The telomeric proteins remodel the telomere end into a structure that sequesters the 3′ tail. Electron microscopy and biochemical studies support a model whereby telomeric proteins modulate t-loop formation (lasso structure) in which the 3′ tail invades the telomeric duplex and forms a recombination-like D-loop (Griffith et al., 1999) (Fig. 1B). Loss of telomere structure and function induces a DNA damage response that involves several proteins that normally respond to and process DSBs (de Lange, 2005). There is also evidence that telomeres are transiently recognized as DNA damage during DNA replication, and that processing by repair enzymes is required to restore proper structure and function (Verdun and Karlseder, 2007). WRN has been implicated in a telomere-based DNA damage response that is induced by mimics of the telomeric ssDNA tails (Eller et al., 2006). However, WRN's precise role in responding to alterations in telomere structure and function remains to be determined. Telomere dysfunction can also induce genomic instability due to inappropriate processing by DNA repair enzymes, which leads to telomere loss or chromosome end to end fusions (de Lange, 2005). Therefore, the regulation of DNA repair enzymes at telomeric ends is critical for the maintenance of telomere integrity and function.

2.1. Evidence from model organisms

The study of WRN roles and consequences of WRN mutations in model organisms is challenging due to a lack of identified true WRN orthologs that contain all the mammalian protein domains. WRN is unique among most known RecQ helicases in that the protein also contains a 3′ to 5′ exonuclease domain, in addition to the 3′ to 5′ helicase activity (Fig. 1A). Currently, the only other known RecQ helicase with a 3′ to 5′ exonuclease domain on the same polypeptide is the *Xenopus laevis* FFA-1, which functions in the formation of replication foci (Chen et al., 2001). Furthermore, knockout of the WRN gene in mouse does not yield an obvious phenotype (Lombard et al., 2000). It has since been revealed that the reason for the lack of phenotype is related to differences in telomere biology between humans and laboratory mice. Common laboratory mouse strains normally have longer telomeres than humans, 40–80 kb, and murine somatic cells exhibit detectable telomerase activity while human somatic cells do not (Chang, 2005). When the *Wrn* gene is knocked out in telomerase null mice, and the mice are bred until the telomeres become shortened, the later generation mice exhibit nearly the full spectrum of WS symptoms. These include the early onset of osteoporosis and skeletal fractures, cataract formation, type II diabetes and increased incidence of mesenchymal cancers such as sarcomas (Du et al., 2004; Chang et al., 2004). Importantly, the pathologies listed above are not observed in the early generation $mTerc^{-/-}Wrn^{-/-}$ mice with long telomeres, in control mice that are singly null for telomerase, or late generation $mTerc^{-/-}Wrn^{-/-}$ littermates that maintained long telomeres (Chang et al., 2004). These studies indicate that shortened telomeres are required for WS disease manifestation in mice, rather than the lack of telomerase *per se*. The late generation double knock out mice also exhibit increased genomic instability as marked by elevated chromosomal fusions and nonreciprocal translocations (Du et al., 2004; Chang et al., 2004). Du et al. found that *Wrn* and *Blm* mutations introduced in a telomerase null background each accelerates the onset of phenotypes normally observed in very late generation telomerase null mice (Du et al., 2004). Triple *Wrn*, *Blm*, and *Terc* mutants exhibit more severe pathologies consistent with a synergistic, rather than additive effect, which includes increased telomere loss and chromosomal end fusions (Du et al., 2004). Thus, BLM and WRN may partially compensate

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