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Review

Aging in Rothmund-Thomson syndrome and related RECQL4 genetic disorders

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ABSTRACT

Rothmund-Thomson Syndrome (RTS) is a rare autosomal recessive disease which manifests several clinical features of accelerated aging. These findings include atrophic skin and pigment changes, alopecia, osteopenia, cataracts, and an increased incidence of cancer for patients carrying RECQL4 germline mutations. Mutations in RECQL4 are responsible for the majority of cases of RTS. RECQL4 belongs to RECQ DNA helicase family which has been shown to participate in many aspects of DNA metabolism. In the past several years, accumulated evidence indicates that RECQL4 is important not only in cancer development but also in the aging process. In this review, based on recent research data, we summarize the common aging findings in RTS patients and propose possible mechanisms to explain the aging features in these patients.

Contents

1. Introduction

The detailed molecular mechanisms underlying the normal aging process continue to be an ongoing topic of active investigation. Aging increases the susceptibility to many diseases, such as cancer, cardiovascular disease, neurologic decline including Alzheimer's disease, and osteoporosis. Therefore, studying the aging process could potentially provide novel therapeutic avenues for age-related disorders. Over the past decades, research on premature aging disorders has provided many insightful mechanisms into this process. Germline mutations in RECQ DNA helicase genes cause several human disorders including Bloom's syndrome (BS) and Werner syndrome (WS) (Monnat, 2010), both of which display many aspects of accelerated aging (Brosh and Bohr, 2007), indicating that genome instability plays an important role in the aging process. Mutations in *RECQL4*, another member of the RECQ DNA helicase family, cause a rare autosomal recessive genetic disease Rothmund-Thomson Syndrome (RTS) (OMIM 268400) (Kitao et al., 1999), a disorder which also bears many aging phenotypes (Croteau et al., 2012b; Wang et al., 2001). *RECQL4* homozygous or compound heterozygous mutations have been identified in approximately two-thirds of RTS patients (designated Type 2 RTS). The

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gene(s) responsible for the other one-third of RTS patients (Type 1) remains unknown.

The clinical features of RTS are extremely heterogeneous. Patients can have many or just a few of the associated findings, and the severity can range from mild to severe. All patients have some form of the characteristic skin rash called poikiloderma, which consists of hyper- and hypo-pigmentation, atrophy, and telangiectases. Other features can include: sparse or even absent scalp hair, eyebrows, and eyelashes; symmetrical small stature; dental and nail abnormalities; skeletal defects including hypoplastic or aplastic bones, fusions, and osteopenia; and increased risk of cancer, particularly a form of bone cancer called osteosarcoma, as well as squamous cell and basal cell carcinomas of the skin (Wang et al., 2003; Wang et al., 2001).

In addition to RTS, *RECQL4* mutations are also associated with two other rare genetic conditions: RAPADILINO syndrome (OMIM 266280), and Baller-Gerold syndrome (BGS) (OMIM 218600) (Siitonen et al., 2003; Van Maldergem et al., 2006). The name RAPADILINO is an acronym for a series of clinical features seen in patients with this disorder: radial ray defects (RA), patellae hypoplasia/aplasia and cleft or high arched palate (PA), diarrhea in infancy and dislocated joints (DI), small stature (LI, little size), and long slender nose and normal intelligence (NO). Many of these features, except for lack of poikiloderma, are also seen in patients with RTS. RAPADILINO patients also have an increased risk of developing lymphoma and osteosarcoma (Siitonen et al., 2009). BGS is characterized primarily by radial ray defects and craniosynostosis, and lymphoma has been reported in a single BGS patient (Debeljak et al., 2009). Some BGS patients also exhibit poikioderma. There are many overlapping clinical findings between RTS, RAPADILINO, and BGS. In addition, a few patients of the three disorders share the same *RECQL4* genetic alteration. Therefore, these three conditions are now considered to be part of the *RECQL4* spectrum of disorders.

The function of RECQL4 has been implicated in DNA replication, homologous recombination, DNA damage repair, and maintenance of telomere and mitochondrial DNA integrity, all of which play an important role in the aging process. RECQL4 associated diseases have many aging related clinical findings that could be attributed to the role that RECQL4 plays in these various processes.

2. Aging phenotypes in RTS

RTS patients display several clinical features consistent with aging (Table 1). Many patients have sparse scalp hair or even alopecia, as well as thinning of the eyebrows and eyelashes (Wang et al., 2001). Their skin demonstrates areas of atrophy in conjunction with irregular pigmentation. Cataracts are also a prominent features of RTS. Some patients have bilateral juvenile cataracts usually before the age of 10 years (predominantly in Type 1 RTS patients), but others can develop later onset cataracts which are unilateral (mainly Type 2 RTS patients) (Wang et al., 2001). About a quarter of the patients have evidence of osteopenia by skeletal survey (Mehollin-Ray et al., 2008), and many of these patients report frequent fractures. Importantly, these patients harbor an increased risk of cancer. RTS patients have an increased risk of developing squamous and basal cell carcinomas (Larizza et al., 2010), which are typical forms of skin cancer seen in the elderly population. RTS patients with *RECQL4* mutations also have an extremely high risk of developing osteosarcoma, a primary malignant tumor of the bone (Lu et al., 2014b). While osteosarcoma is often considered a childhood cancer with a peak in the adolescent period, there is a second incidence peak in the older population (Mirabello et al., 2009). RTS patients treated with chemotherapy for osteosarcoma often experience increased toxicities, particularly to doxorubicin and methotrexate (Hicks et al., 2007), which could reflect RECQL4's function in repair of DNA damage induced by these cytotoxic agents.

Table 1
Clinical features of aging in RTS patients

	Clinical findings
Skin	Poikiloderma (atrophy and irregular pigmentation, telangiectases)
Skin Accessories	Sparse scalp hair, alopecia, sparse eye brows and lashes
Eye	Cataracts
Skeletal System	Osteoporosis, frequent fractures
Malignancy	Osteosarcoma, skin cancer (squamous and basal cell carcinomas)

3. Possible mechanisms of RECQL4 in aging

Given the function of RECQL4 in DNA replication, homologous recombination, DNA damage repair, and in the maintenance of telomere and mitochondrial DNA integrity, there are several potential ways that RECQL4 could contribute to the features of premature aging seen in RTS patients as well as the normal aging process.

3.1. Genome stability and DNA damage repair

One of the hallmarks of aging is elevated accumulation of genomic instability (Lopez-Otin et al., 2013). During the normal life span of cells, the genetic material is constantly exposed to endogenous and exogenous genotoxic agents. Endogenous DNA-damaging agents may arise from replicative errors, DNA hydrolyses, and normal cellular metabolism which generates reactive oxygen species (ROS), while exogenous genotoxic agents include solar ultraviolet (UV) radiation, ionizing radiation, and chemical agents. The genotoxic damage is continuously removed by DNA repair systems, including homologous recombination (HR) and non-homologous end-joining (NHEJ) for DNA double strand breaks (DSB), nucleotide excision repair (NER) for UV DNA damage, base excision repair (BER) for oxidative DNA damage, and DNA mismatch repair (MMR) for single base mismatches and small nucleotide insertions and deletions. Therefore, it is not surprising that patients carrying mutations in genes important for DNA repair may not only have increased risk of developing cancers, but also exhibit many aspects of premature aging disorders, e.g., Werner, Bloom, and Fanconi anemia (FA) disorders (see other related reviews in this issue).

RECQL4 has been shown to participate in multiple DNA repair pathways, including HR, NHEJ, NER, and BER. For example, RECQL4 was shown to co-localize and co-immunoprecipitate with RAD51 (Petkovic et al., 2005), a key component of the HR pathway of DSB repair. Interestingly, Shamanna et al. demonstrated that RECQL4 co-immunoprecipitates with Ku70/Ku80 heterodimer, a component of the NHEJ pathway, and that depletion of RECQL4 in human cells causes decreased NHEJ activity (Shamanna et al., 2014). In addition, as Fan and Luo have shown, RECQL4 may function in NER by interacting with a major NER factor xeroderma pigmentosum group A (XPA), and this interaction was intensified in human cells treated with UV irradiation (Fan and Luo, 2008). The role of RECQL4 in BER was also investigated by various groups who showed that RECQL4 could directly participate in BER pathways (Schurman et al., 2009; Werner et al., 2006; Woo et al., 2006).

In addition to defective DNA repair systems, mutations in *RECQL4* can also cause replication stress which leads to genomic instability (Burrell et al., 2013; Flach et al., 2014; Zeman and Cimprich, 2014). During the past decade, researchers have begun to reveal the detailed function of RECQL4 in DNA replication, especially in the process of replication initiation. RECQL4 amino-terminus contains a domain of ~200 amino acid sequences which share homology with the yeast replication initiation protein Sld2 in

S. cerevisiae and DRC1 in *S. pombe* (Chu and Hickson, 2009; Matsuno et al., 2006; Sangrithi et al., 2005). This N-terminal domain has been demonstrated to be essential for DNA replication and cell viability (Abe et al., 2011; Ichikawa et al., 2002; Matsuno et al., 2006; Sangrithi et al., 2005). In addition, RECQL4 has been shown to interact biochemically with pre-replication complex minichromosome maintenance complex (MCM) (Im et al., 2009; Im et al., 2015; Kliszczak et al., 2015; Xu et al., 2009), which controls replication licensing. The frequency of DNA replication initiation was reduced in human cells depleted of *RECQL4* (Thangavel et al., 2010), as well as in cells expressing human *RECQL4* mutants that abolish the binding of MCM10 (Kliszczak et al., 2015). Therefore, *RECQL4* mutations could cause under-replication of DNA by affecting RECQL4 protein stability (Jensen et al., 2012), splicing of pre-messenger RNA (Colombo et al., 2014; Wang et al., 2002), or the interaction with other replication factors (Im et al., 2009; Im et al., 2015; Kliszczak et al., 2015; Xu et al., 2009), resulting in replication stress. Although depletion of *RECQL4* in unstressed cells had no significant effect on replication fork progression (Thangavel et al., 2010), the detailed effects of *RECQL4* mutations, especially missense mutations, on replication elongation require further investigation.

Recently, replication stress has been associated with chromosomal abnormalities and aging (Burhans and Weinberger, 2007; Burrell et al., 2013; Flach et al., 2014; Lamm et al., 2016). Interestingly, RTS patient cells have been reported to display some chromosomal abnormalities, such as trisomy 8 and/or 7 (Der Kaloustian et al., 1990; Lindor et al., 1996; Miozzo et al., 1998; Orstavik et al., 1994; Wang et al., 2001; Ying et al., 1990). In addition, primary cells from *Recql4* mutant mice displayed premature centromere separation and aneuploidy (Mann et al., 2005). Therefore, *RECQL4* mutations could cause DNA replication stress which then leads to genome instability and premature aging phenotypes.

3.2. Cellular senescence

Aged tissues exhibit elevated cellular senescence (Wang et al., 2009) which is thought to be one of the characteristics of aging (Lopez-Otin et al., 2013). Some reports have shown that *RECQL4* mutant cells and tissues also have increased cellular senescence. In three primary dermal fibroblasts cell lines isolated from RTS patients carrying *RECQL4* mutations, Davis et al. detected increased activation of p38 MAP kinase signaling, indicating elevated stress-induced premature senescence (Davis et al., 2013). Although they were shown to have mild reduction of replicative life span compared to M1 senescent normal control fibroblasts, the RTS cells exhibited increased protein levels of p53, $p21^{WAF1}$, and $p16^{INK4a}$ (Davis et al., 2013), all of which are closely associated with cellular senescence (Kuilman et al., 2010). Using more pure genetic approaches, Lu et al. showed that knock-down of *RECQL4* in human primary dermal fibroblasts caused not only increased senescence-associated β-galactosidase (SA-β-gal) activity, but also elevated expression of senescent markers $p16^{INK4a}$ or/and $p21^{WAF1}$ (Lu et al., 2014a). Both the N-terminus and the helicase domain of RECQL4 were required to rescue the increased senescence in these cells depleted of RECQL4. In addition, elevated SA-β-gal activity and DNA damage were also detected in the mouse tail fibroblasts and hair follicles, as well as bone marrow cells from a *Recql4* mouse model which targets the helicase domain (Lu et al., 2014a). Compared to a global knockout mouse model targeting exons 5–8 in the N-terminal region of the putative helicase domain of Recql4 which showed early embryonic lethality (Ichikawa et al., 2002), conditional knockout mice lacking this region of *Recql4* specifically in the mouse osteochondral progenitor cells displayed increased DNA damage and elevated p53 activation and $p21^{WAF1}$ in the cartilage tissues (Lu et al., 2015). Primary mouse chondrocytes from these mice exhibited strongly increased SA-β-gal activity. These data suggest that the severity of the senescence phenotype could be variable depending on the location of *RECQL4* mutations and/or the expression levels of mutant RECQL4 protein.

In contrast, depletion of *Recql4* in Kusa4b10 cells, a mouse primary osteoblastic cell line, had no effect on cellular SA-β-gal activity, and these cells displayed severe proliferation defects and morphology changes (Ng et al., 2015), indicating that RECQL4 could function differently in preventing senescence in different cell types. It appears that the senescence phenotypes were more obvious in tissues that require continuous proliferation and differentiation, such as skin and growth plates. The cause of the increased senescence could be due to the increased DNA damage in cells lacking RECQL4, as p53 activation and DNA damage response were also detected. However, other mechanisms, for example, stress-induced senescence, could also contribute to the increased senescence in *RECQL4* mutant cells and tissues.

It is worth noting that in contrast to previous data, some *in vivo* evidence in mice showed that moderately increased senescence actually increased life span (Matheu et al., 2009; Matheu et al., 2007). This opposite finding could be explained by the fact that the physiological function of senescence is to prevent damaged cells from expanding. The key appears to be the extent and degree of senescence activity in cells and tissues. The life span of RTS patients with *RECQL4* mutations in the absence of cancer has not been well studied. Correlating life span with the degree of senescence in patients will provide important information to assess the role of senescence in aging in RTS patients.

3.3. Mitochondrial function

Mitochondrial dysfunction has been strongly associated with the aging process (Bratic and Larsson, 2013). Recently, several groups have discovered that, in addition to its known nuclear and cytoplasmic localization, RECQL4 is also localized to the mitochondria (Chi et al., 2012; Croteau et al., 2012a; De et al., 2012; Gupta et al., 2014; Wang et al., 2014). Importantly, they also revealed the molecular functions of mitochondrial RECQL4. Depletion of RECQL4 in human cells caused increased mtDNA damage and reduced mitochondrial reserve capacity (Croteau et al., 2012a). RECQL4 deficient cells also exhibited decreased mtDNA copy number and reduced mtDNA replication (Chi et al., 2012; De et al., 2012). Gupta et al. demonstrated that RECQL4 could strengthen the proofreading and polymerization functions of the subunit A of mitochondrial DNA polymerase-γ (PolγA) (Gupta et al., 2014), which is essential for the maintenance of mtDNA integrity. In addition, Wang et al. showed that RECQL4 directly interacted with mitochondrial helicase PEO1 (also known as Twinkle), and that such interaction was enhanced in cells carrying a *RECQL4* mutation frequently found in RAPADILINO patients (Wang et al., 2014). This mutation causes an internal deletion of 44 residues just before the helicase domain of RECQL4. They found this mutation abolished the interaction between mutant RECQL4 and p32 in the mitochondria, resulting in increased interaction between RECQL4 and PEO1 and elevated mtDNA copy number (Wang et al., 2014).

It appears that complete loss of RECQL4 may lead to reduced mtDNA replication and increased mtDNA damage by affecting mitochondrial DNA polymerase-γ activity (Chi et al., 2012; De et al., 2012; Gupta et al., 2014), while RECQL4 mutations may cause increased mtDNA copy number by enhancing RECQL4 mitochondrial localization (Wang et al., 2014). Both mechanisms could be deleterious to normal cells as shown by abnormal mitochondrial functions (Chi et al., 2012; Croteau et al., 2012a; Kumari et al., 2016; Wang et al., 2014) which could contribute to aging and tumorigenesis. In addition, the expansion of mtDNA mutations by mutant RECQL4 could also lead to accelerated aging (Payne et al., 2011).

3.4. Telomere maintenance

Telomeres, the complexes that are composed of repetitive DNA sequences and proteins (shelterin complex), are localized at the ends of chromosomes protecting genomic DNA (Blackburn et al., 2015). Telomere attrition is one of the major contributors to the aging process (Lopez-Otin et al., 2013). Germline mutations in multiple genes critical to telomere maintenance result in dyskeratosis congenita (Mason and Bessler, 2011; Mitchell et al., 1999), a human disorder characterized by several clinical features which overlap with the RECQL4 disorders, including skin pigmentation defects, nail dysplasia, osteoporosis, and increased cancer susceptibility (Alter et al., 2009). RECQL4 has been shown to participate in the maintenance of telomeres (Ferrarelli et al., 2013; Ghosh et al., 2012). Ghosh et al. demonstrated that RECQL4 was localized to the telomeres and that RECQL4 co-immunoprecipitated with shelterin protein TRF2 (Ghosh et al., 2012). Both RTS patient cells and human cells depleted of RECQL4 displayed elevated fragile telomeres (Ghosh et al., 2012). In addition, RECQL4 was found to be able to unwind the telomeric D-loops and oxidatively damaged D-loops, indicating a role for RECQL4 in telomere maintenance (Ferrarelli et al., 2013; Ghosh et al., 2012). Given the overlap in clinical symptoms of aging between patients with RTS and dyskeratosis congenita, further study of the telomere defects in RTS patients is warranted.

4. Comparison with other RECQ disorders

Patients with *RECQL4* diseases share several clinical features with other RECQ disorders BS and WS. For example, skin abnormalities and increased cancer susceptibility are very common in all these syndromes. RTS and BS patients have short stature, while WS patients are smaller than average. Both RTS and WS patients have cataracts, and osteoporosis. Compared to BS and WS patients, RTS patients have no apparent increased risk of diabetes mellitus or cardiovascular disease. In addition, *RECQL4* patients are predisposed to osteosarcoma, lymphoma, and squamous cell and basal cell carcinomas of the skin, while BS patients are susceptible to all cancer types in the general population, and WS patients have a high risk of developing rare mesenchymal sarcomas. While WS is considered a prototypical segmental progeroid syndrome exhibiting early-onset age-related diseases, RTS and BS display clinical features that can be seen in the aged population, but they may not represent true accelerated aging disorders. For a detailed comparison of clinical features between the three disorders, please refer to the companion manuscript in this review series by de Renty and Ellis on Bloom's Syndrome.

The five RECQ helicases, RECQL1, BLM, WRN, RECQL4, and RECQL5, are essential for maintaining genomic stability (Chu and Hickson, 2009; Croteau et al., 2014). All five RECQL helicases have been reported to participate in DNA replication either under unperturbed or stressed condition, and to play a role in DNA damage repair, including base excision repair, and DNA double strand break repair (Croteau et al., 2014). In addition, three disease causing RECQ helicases, BLM, WRN, and RECQL4, also participate in telomere maintenance (Croteau et al., 2014). However, RECQL4 has several unique cellular functions. For example, RECQL4 has an important role in DNA replication initiation in unperturbed cells (Abe et al., 2011; Matsuno et al., 2006; Sangrithi et al., 2005; Thangavel et al., 2010). In addition, RECQL4 is currently the only RECQ helicase that is reported to be localized to the mitochondria and to maintain mtDNA integrity (Chi et al., 2012; Croteau et al., 2012a; De et al., 2012; Gupta et al., 2014; Wang et al., 2014). Further investigation is required to understand the detailed molecular functions of RECQL4 in order to better understand its role in the aging process and in tumorigenesis.

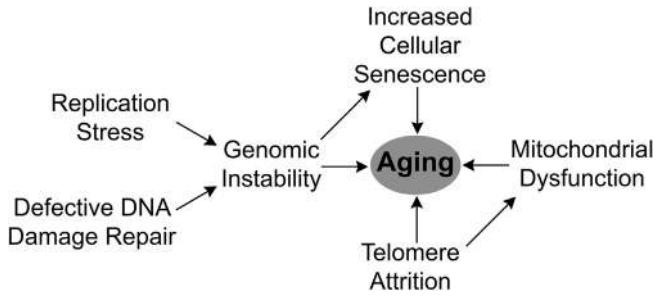

Fig. 1. Possible mechanisms for mutant RECQL4's effects on aging. Mutations in the *RECQL4* gene could result in increased genomic instability caused by replication stress and/or defective DNA damage repair, increased cellular senescence, mitochondrial dysfunction, or telomere attrition, leading to aging phenotypes. Genomic instability may induce cellular senescence, and telomere attrition could affect mitochondrial function.

5. Conclusions

RTS patients have several clinical features of aging which may be attributed to the function of the disease causing gene *RECQL4* in DNA replication, DNA damage repair, senescence, and maintenance of mtDNA and telomeres (Fig. 1). These functions of RECQL4 might be inter-connected to cause the various aging phenotypes. For example, increased DNA damage in *RECQL4* mutant cells could cause elevated senescence, and telomere malfunction could lead to mitochondrial abnormalities (Sahin et al., 2011). In addition to the possible mechanisms described above, stem cell exhaustion may also account for the aging findings in RTS patients (Lopez-Otin et al., 2013). Mutations in *RECQL4* could lead to exhaustion of tissue/organ stem cells as demonstrated by the critical role of RECQL4 in hematopoiesis (Smeets et al., 2014). It is interesting to note that some type I RTS patients who lack *RECQL4* mutations (Wang et al., 2003) also demonstrate some of the aging phenotypes, e.g., juvenile cataracts and squamous cell carcinoma, as well as chromosomal instability (Wang et al., 2001), indicating these patients might have mutations in other genes that are also important for aging. Studying the genetic alterations in these patients might also reveal potential new pathways important for preventing aging related diseases.

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