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Review

Human RECQ helicases: Roles in DNA metabolism, mutagenesis and cancer biology

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ABSTRACT

Helicases use the energy of ATP hydrolysis to separate double-stranded nucleic acids to facilitate essential processes such as replication, recombination, transcription and repair. This article focuses on the human RECQ helicase gene and protein family. Loss of function of three different members has been shown to cause Bloom syndrome (BS), Werner syndrome (WS) and Rothmund–Thomson syndrome (RTS). This article outlines clinical and cellular features of these cancer predisposition syndromes, and discusses their pathogenesis in light of our understanding of RECQ helicase biochemical activities and *in vivo* functions. I also discuss the emerging role for RECQ helicases as predictors of disease risk and the response to therapy.

1. Prologue

Homer's *Odyssey* is a beguiling work, a bookend—literally—to Western literature together with the *Illiad*. The *Odyssey* is a literal and metaphorical travelogue, the forced decadal wanderings of Odysseus following the end of the Trojan war. Voyaging, wandering and sailing are recurrent themes in the *Odyssey*, and have served ever since as powerful metaphors for life's journey and all attempts to explore and to wrest meaning from the unknown. The muse in the following story is Nature; our goal is not Ithaca, home and rest, but an understanding of what experiments of Nature have revealed about our nature, the pathogenesis of disease and our fate.

2. Introduction

Helicase proteins are enzymes that use the energy of ATP hydrolysis to unwind double-stranded nucleic acids. DNA or RNA duplexes, together with DNA:RNA hybrid molecules all serve as physiologic substrates for these enzymes. Helicases can also perform a wider range of actions on nucleic acid or nucleoprotein templates to facilitate their metabolism. For example, helicases can act as DNA or RNA translocases, and as modulators of the structure and function of nucleoprotein filaments and complexes such as those involved in homologous recombination or replication fork restart [1,2]. The ubiquity of helicases reflects their important roles in virtually all aspects of nucleic acid metabolism.

This article focuses on the five members of the human RECQ helicase family, and their roles in DNA metabolism, human disease pathogenesis and the response to therapy. Mutations that lead to loss of function of three different human RECQ helicases cause different heritable cancer susceptibility syndromes. The observation that both Werner syndrome (WS) and Bloom syndrome (BS), two of the human RECQ helicase deficiency syndromes discussed below, were chromosomal instability and cancer predisposition syndromes provided early support for the idea that a mutator phenotype might provide particularly fertile soil for the emergence of cancer. We discuss and further elaborate on this idea below, and discuss how heritable or acquired loss of function of human *RECQ* helicase genes might promote genetic instability and cancer while, paradoxically, providing new opportunities to improve cancer therapy.

This review necessarily summarizes a large body of work from many different investigators. I have tried throughout to refer interested readers to recent reviews that cover some of the topics discussed here as well as other important areas that are not be discussed here. These reviews also provide fuller referencing of the primary literature on key points that could not be fully discussed and referenced here due to lack of space.

2.1. The RECQ helicase deficiency syndromes

The RECQ helicase deficiency syndromes were originally recognized and described on the basis of clinical findings and inheritance patterns. Bloom syndrome (BS), Werner syndrome (WS) and

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Rothmund–Thomson syndrome (RTS) are rare (≤1/50,000 live births), autosomal recessive Mendelian diseases that share an elevated risk of cancer together with additional, more variable features that include genetic instability and disease-specific developmental or acquired features. The clinical features of each syndrome are summarized below.

2.1.1. Bloom syndrome (BS)

Bloom syndrome (BS) was first identified in 1954 by David Bloom, who described three patients with congenital short stature and skin changes reminiscent of systemic lupus erythematosus [3,4]. Consistent features include marked intrauterine and post-natal growth retardation; congenital short stature; and a characteristic 'butterfly' rash across the bridge of the nose and cheeks that may extend to include the dorsum of the hands and forearms. This rash typically develops with sun exposure in the first years of life, then may become chronic with skin hyper- or hypopigmentation. Deficient cellular and humoral immunity is common, and may explain the elevated risk of otitis media and pneumonia. There is also an elevated risk of diabetes mellitus. BS patients have reduced fertility: males are typically infertile, whereas females are hypofertile but may give birth to normal offspring [5].

The most troubling aspect of BS is a high risk of cancer: BS patients are predisposed to a remarkably broad range of cancers, in contrast to almost all other genetically inherited cancer predispositions. There is an elevated risk of developing common adult epithelial tumors such as colon, breast and lung cancer; leukemias and lymphomas; sarcomas; and rare pediatric tumors such as Wilms' tumors [6]. Cancer is the most common cause of death in BS patients.

2.1.2. Werner syndrome (WS)

Werner syndrome (WS) alone among the human RECQ helicase deficiency syndromes has features strongly suggestive of premature aging. The key clinical findings, first reported by Otto Werner in 1904, include short stature; early graying and loss of hair; bilateral cataracts; and scleroderma-like skin changes [7–10]. The earliest and most consistent change observed is graying and loss of hair. This typically begins in the second decade of life with the scalp and eyebrows, and is progressive. Cataracts in WS are often bilateral; appear beginning in the second or third decade of life; and differ from the common 'senile' cataracts by involving the lens posterior cortex and subcapsular regions as opposed to lens nucleus. Vision is otherwise normal, and can often be restored by cataract removal. The short stature of WS patients results from a failure to undergo an adolescent or pubertal growth spurt. There is no suggestion that this acquired growth deficit is caused by an underlying endocrinopathy or other disease state. Subcutaneous connective tissue atrophy and dermal fibrosis together give skin a 'tight, white and shiny' or contracted appearance that over time contributes to a progressive sharpening of facial features, foot and ankle deformation with ulceration, and soft tissue calcification. WS patients are at increased risk to develop premature atherosclerosis, myocardial infarction and stroke; osteoporosis; and diabetes mellitus. The CNS is typically spared, and WS patients are not at elevated risk of Alzheimer or other types of dementia apart from those associated with vascular disease. Fertility is reduced in males and females [7–9,11].

Unlike BS, WS confers an elevated risk of only selected types of cancer [12–14]. The most frequently observed neoplasms in WS patients are soft tissue sarcomas, follicular thyroid carcinoma, meningioma, acral lentiginous malignant melanoma, malignant or pre-neoplastic hematologic disease (chiefly leukemias) and osteosarcoma. This spectrum is broader than the misleading characterization of the cancer predisposition in WS being limited to sarcomas or soft-tissue tumors. Cancer and premature cardiovascular disease are the leading causes of death in WS patients [15].

2.1.3. Rothmund–Thomson syndrome

Rothmund–Thomson syndrome (RTS) was first described by Rothmund in 1868 as a familial occurrence of unusual skin changes together with bilateral juvenile cataracts [16]. Subsequent cases were reported by Thomson in 1936, and in 1957 Taylor suggested that these reports were of patients with the same disease [16–18]. The characteristic skin changes of RTS typically appear within the first 3–6 months of life as a sun-sensitive rash with redness, swelling and blistering on the face. This rash spreads over the buttocks and extremities, while sparing the chest, back and abdomen. These skin lesions over time become variably pigmented with telangiectasias and areas of focal atrophy. Additional features include sparse or absent hair, eyelashes and eyebrows; congenital short stature in conjunction with frequent bone and tooth abnormalities; cataracts; and an elevated risk of cancer, most notably osteosarcoma [19].

The short stature of RTS patients is reminiscent, though not as severe, as that observed in BS: affected individuals are born small but proportionately developed and typically remain in the lower percentiles for height and weight throughout life. Bone and tooth abnormalities include dysplastic, malformed or absent bones, often involving the hand or thumbs; delayed bone formation or bone density loss; and malformed, missing or extra teeth. The cataracts originally noted by Rothmund have been found in only a minority of contemporary RTS patients [19,20]. Immunologic function appears to be intact, and fertility may be reduced although RTS females have given birth to normal offspring. Life expectancy in the absence of cancer appears to be normal [20].

Two additional, heritable human diseases have been associated with RTS, RAPADILINO syndrome and Baller–Gerold syndrome (BGS). RAPADILINO syndrome patients have joint dislocations and patellar hypoplasia or aplasia, but lack the characteristic poikiloderma seen in RTS patients. BGS patients have craniosynostosis with radial aplasia in addition to skin changes reminiscent of RTS [21,22]. Molecular analyses of clinically ascertained RTS patients have also identified RTS phenocopies, individuals whose clinical findings resemble RTS, though who lack *RECQL4* mutations (see below; [20,23]). The recurrent themes of genetic heterogeneity, phenocopies, variable clinical expression of mutations in the same gene and 'missing' diseases are all discussed below: collectively these themes emphasize important work to be done to correlate clinical, pathologic and molecular findings in these diseases.

2.2. RECQ genes, deleterious mutations and SNP variants

Cloning of the genes causally linked to BS, WS and RTS immediately identified all three as members of a human *RECQ* helicase gene family [24]. *BLM* was cloned in 1995 by making clever use of the mitotic recombination phenotype of BS cells [25], and led to naming of the family after the helicase domain shared with the *E. coli* RecQ protein. Positional cloning of the *WRN* gene followed in 1996, guided by prior linkage analyses [26], and confirmed earlier speculation that the gene responsible for WS might be a helicase [27]. The cloning of *RECQL4* and *RECQL5* were based on sequence homology [28,29]. The remaining family member, *RECQL*, was identified independently by two groups in 1994 as encoding a potent ATPase and helicase activity in human cell extracts [30,31]. *RECQL* and *RECQL5* have not been linked to either heritable or acquired human disease states, although there is abundant evidence from biochemical, cellular and mouse modeling analyses that loss of function would likely lead to disease [32–34]. The five human RECQ helicase genes, their chromosomal locations, predicted protein products,