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Review

# Distinct roles of RECQ1 in the maintenance of genomic stability

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ABSTRACT

Five human RecQ helicases (WRN, BLM, RECQ4, RECQ5, RECQ1) exist in humans. Of these, three are genetically linked to diseases of premature aging and/or cancer. Neither RECQ1 nor RECQ5 has yet been implicated in a human disease. However, cellular studies and genetic analyses of model organisms indicate that RECQ1 (and RECQ5) play an important role in the maintenance of genomic stability. Biochemical studies of purified RECQ1 protein demonstrate that the enzyme catalyzes DNA unwinding and strand annealing, and these activities are likely to be important for its role in DNA repair. RECQ1 also physically and functionally interacts with proteins involved in genetic recombination. In this review, we will summarize our current knowledge of RECQ1 roles in cellular nucleic acid metabolism and propose avenues of investigation for future studies.

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## 1. Introduction

RECQL or RECQL1 (hereafter designated RECQ1) belongs to a class of DExH-containing DNA helicases that have been implicated in diseases of premature aging, cancer, and chromosomal instability (for review, see [1,2]). These include Werner syndrome, Bloom's syndrome, and Rothmund–Thomson syndrome that have mutations in the *WRN*, *BLM*, and *RECQ4* genes, respectively. Although the clinical importance of RECQ1 is yet to be fully appreciated, it is becoming increasingly apparent that RECQ1, the first of the human RecQ helicases to be discovered, has unique and important roles in cellular DNA metabolism. RECQ1 is the most abundant of the five human RecQ helicases, and RECQ1 depletion studies indicate its importance in human cells for chromosomal stability. Genetic studies of model organisms with mutations in genes encoding proteins with sequence homology to RECQ1 also demonstrate its importance in genome homeostasis. Advances in understanding the structural and biochemical properties of RECQ1 have led to further insights to its proposed molecular functions. These topics will be discussed to provide a conceptual basis for how RECQ1 might help cells to cope with DNA damage. We also suggest important avenues for RECQ1 research that may help in understanding one of the less characterized human RecQ helicases.

### 1.1. RECQ1-like helicases and their genetic functions in model organisms

Close inspection of the RECQ1 amino acid sequence reveals similarity in the helicase core domain to a number of RECQ1-like proteins from different species, as shown in Fig. 1A. In addition to the helicase core domain containing the seven conserved amino acid motifs, two additional regions can be found in a number of the RecQ helicases [3], including the RECQ1-like helicases. The RecQ C-terminal region (RQC) that has been implicated in protein interactions and DNA binding is present in all the RECQ1-like proteins shown. However, the Helicase and RNase D C-terminal Domain (HRDC), necessary for the function of BLM in Holliday Junction (HJ) dissolution and important for DNA structure binding [4], is absent in human and mouse RECQ1, but can be found in RECQ1-like helicases for certain species. The human *RECQ1* gene was identified by two groups [5,6] a decade after the discovery of the *E. coli RecQ* gene [7]. Phylogenetic analysis of the RECQ1-like helicases reveals that human RECQ1 is most closely related by sequence to mouse and chicken (Fig. 1B).

Cellular studies demonstrate that RECQ1 plays an important role in human and mouse for chromosomal stability and the DNA damage response ([8], and discussed below). The use of model genetic systems have enable researchers to study the functions of RECQ1-like helicases in whole organisms, and in some cases suggests diverse physiological roles. Because chicken B-lymphocyte DT40 cells are genetically easy to manipulate, they have been widely used to study DNA repair genes, including those encoding the RecQ helicases [9]. Although recq1 single knockout DT40 cells were not significantly different from the wild-type cells in cell growth, sensitivity to methyl methanesulfonate (MMS), or sister chromatid exchange (SCE) frequency, recq1 blm double knockout DT40 cells grew slower than blm single knockout cells due to an increased population of dead cells [10]. A higher incidence of SCE was observed in mitomycin C-treated recq1 blm mutant cells compared to blm cells [10], suggesting that recq1 can compensate for a blm deficiency. However, Otsuki et al. reported that disruption of the recq1 gene in a req5 blm mutant background did not affect UV or MMS survival, UV-induced SCE, or the frequency of damage-induced mitotic chiasma, leading the authors to conclude that RECQ1 might not function in DNA replication or repair in chicken cells [11].

In *Neurospora crassa*, two helicases (QDE3, RecQ-2) sharing sequence similarity to RECQ1 exist, and both are important for the DNA damage response [12,13]. Mutation in the gene encoding the RECQ1-like helicase QDE3, an RNA-dependent RNA polymerase (QDE1), or an Argonaute protein containing a PIWI domain (QDE2) result in a quelling defect in RNA silencing [14–16]. QDE3 alone is involved in a key step of activation and maintenance of RNA silencing [17]. Recently, a novel small RNA (qiRNA) was identified on the basis of its interaction with QDE2 [18]. The newly found qiRNA is 20–21 nucleotides long with a strong preference for uridine at the 5′ end, and mostly from the ribosomal DNA locus. It is likely that this qiRNA is the counterpart of mammalian piRNA (for review, see [19,20]), which was first observed in fruit fly to be associated with PIWI protein, QDE2 in *N. crassa*. Interestingly, the *qde3* mutation abolished qiRNA production, indicating that QDE3 is required for qiRNA biogenesis [18]. Consistent with the *Neurospora* genetic results, RECQ1 was found in a piRNA complex isolated from rat testis [21]. The piRNA protein complex contained ATPase and DNA helicase activities as well as RNA cleavage activity that would be predicted to be catalyzed respectively by RECQ1 and a conserved Argonaute protein responsible for RNA-guided cleavage of target RNAs.

Proteins sharing sequence similarity with RECQ1 have been identified in the plants *O. sativa* and *A. thaliani* (Fig. 1A). Expression of rice RecQ1 increased with exposure to various DNA damaging agents, suggesting that RecQ1 may be involved in DNA repair [22]. In addition to its role in the DNA damage response, rice RECQ1 is required for RNA silencing induced by particle bombardment for inverted-repeat DNA, which is likely formed by transposon elements [23]. It has been proposed that mammalian RecQ helicases might also have a function in gene silencing, but studies using mouse models for Wrn, Blm, and RecQ1 suggest that they are not essential for sequence-specific mRNA degradation in response to dsRNA [24]. It is possible that certain mammalian RecQ helicases are involved in the production of small RNA molecules. With novel small RNAs and gene silencing pathways being discovered, the importance of mammalian RECQ1-like helicases in defending genome integrity through gene silencing remains to be determined.

## 2. Prospective importance of RECQ1 in mammalian cells

Although a human disease has not yet been genetically liked to mutations in the *RECQ1* gene, cellular phenotypes associated with RECQ1 deficiency in mouse and human indicate that RECQ1 has a uniquely important role in genomic integrity. We will summarize what is known about the cellular importance of RECQ1, pointing out some hypotheses for the functions of RECQ1 that will be considered more extensively at the molecular level in the section entitled *Structural Features and Biochemical Functions of RECQ1*.

### 2.1. Chromosomal instability in RECQ1-deficient cells

Primary embryonic fibroblasts from *Recql*-null mice display aneuploidy, spontaneous chromosomal breakage, frequent translocation events, and elevated SCE [25]. In RECQ1-deficient human [26] and mouse [25] cells there is an increased load of DNA damage as exemplified by the accumulation of γH2AX foci, a marker of double strand breaks. Transient knockdown of RECQ1 in human cells resulted in significantly elevated spontaneous SCE [26]. It is plausible that a role of RECQ1 in homologous recombinational repair helps cells to cope with strand breaks that arise directly from DNA damage or are a consequence of broken replication forks at sites of replication blockage [8]. An alternative hypothesis is that RECQ1 helps cells to circumvent the consequences of DNA damage that may occur at replication forks. However, given the genetic evi-