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Review

Probing the structural basis of RecQ helicase function

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ABSTRACT

RecQ helicases are a ubiquitous family of DNA unwinding enzymes required to preserve genome integrity, thus preventing premature aging and cancer formation. The five human representatives of this family play non-redundant roles in the suppression of genome instability using a combination of enzymatic activities that specifically characterize each member of the family. These enzymes are in fact not only able to catalyze the transient opening of DNA duplexes, as any other conventional helicase, but can also promote annealing of complementary strands, branch migration of Holliday junctions and, in some cases, excision of ssDNA tails. Remarkably, the balance between these different activities seems to be regulated by protein oligomerization. This review illustrates the recent progress made in the definition of the structural determinants that control the different enzymatic activities of RecQ helicases and speculates on the possible mechanisms that RecQ proteins might use to promote their multiple functions.

Contents

1. Introduction

Approximately 1% of the open reading frames in the human genome encode for proteins that function as DNA or RNA helicases. These enzymes operate in all aspects of nucleic acid metabolism where the complementary strands of DNA:DNA, DNA:RNA, or RNA:RNA duplexes require to be opened. They can be divided into two classes on the basis of their translocation directionality that can be either 3′-5′ or 5′-3′. The reaction of translocation and transient separation of the complementary strands catalyzed by helicases is coupled to the binding and hydrolysis of nucleotide triphosphate (NTP) which provides the "fuel" for the helicase motor [1–3]. A detailed description of the different Superfamilies of helicases and their properties is outside the scope of this article, and we refer readers to recent reviews [3–5].

RecQ helicases are a sub-family of helicases that play an essential role in the maintenance of genome stability by acting at the interface between DNA replication, recombination and repair [6–9]. They derive their name from the prototypical member of the family discovered in *Escherichia coli* over 20 years ago [10]. Mutations in the genes encoding three of the five human RecQ homologs are linked to defined genetic disorders associated with genomic instability, cancer predisposition, and features of premature aging; namely, Bloom's

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Table 1
RecQ helicase members for which structural data are available to date. In parenthesis are indicated the amino acid residues in the respective domains that have been studied by X-ray crystallography or NMR.

RecQ helicase	RecQ domain structurally studied			References
E. coli RecQ		Helicase + RQC domain (1–516)	HRDC domain (524–609)	[42,65]
S. cerevisiae Sgs1			HRDC domain (1271–1351)	[68]
D. radiodurans DrRecQ			HRDC domain (751–824)	[66]
Human RECQ1		Helicase + RQC domain (63–592)		[43]
Human WRN	Exonuclease domain (1–333)	RQC domain (949–1092)	HRDC domain (1142–1242)	[53,54,67,73]

syndrome (*BLM*-defect), Werner's syndrome (*WRN*-defect), and Rothmund-Thomson, RAPADILINO and Baller-Gerold syndromes (all caused by *RECQ4*-defects) [11–15]. The different clinical features of these disorders support the notion that these human helicases have distinct functions in cells. No heritable cancer predisposition disorder has yet been associated to mutations in the remaining two human RecQ helicase genes, *RECQ1* and *RECQ5*. However, recent studies have linked a single nucleotide polymorphism present in the *RECQ1* gene to a reduced survival in pancreatic cancer patients [16].

Two important features distinguish RecQ helicases from the other helicases. First is their ability to unwind a variety of DNA structures in addition to standard B-form DNA duplexes. Biochemical studies have demonstrated that RecQ helicases unwind DNA with a 3′ to 5′ polarity and, although with some differences, are capable of unwinding a variety of DNA structures including forked duplexes, displacement loops (D-loops; an intermediate in homologous recombination reactions), triple helices, 3- or 4-way junctions, and G-quadruplex DNA [17–21]. Second is the capacity of RecQ helicases to catalyze multiple enzymatic activities in addition to DNA unwinding; they can promote branch migration of Holliday junctions for several kilobases [22,23], annealing of complementary single stranded DNA molecules [24–28], and, in some cases, nucleotide excision with a 3′ to 5′ polarity [29,30]. Consistent with their ability to unwind various DNA structures and promote multiple enzymatic activities, several cellular functions have been attributed to RecQ proteins, including roles in stabilization and repair of damaged DNA replication forks, telomere maintenance, homologous recombination, base excision repair, and DNA damage checkpoint signaling [6–8,31,32]. Moreover, recent studies pointed to important and distinct roles of the human RECQ4 and RECQ1 helicases in DNA replication initiation [33]. Thus, understanding how these enzymes function and regulate their various DNA processing activities is important to untangle the mechanisms that control the integrity of our genome, and prevent cancer and aging.

In this review, we provide an overview of the structural information available for the distinct domains responsible for the translocation, unwinding, strand annealing, branch migration, and exonuclease activities of RecQ helicases (Table 1 and Fig. 1). Interestingly, many of these activities seem to be regulated by protein oligomerization [34–37]. The function of the different assembly states of RecQ helicases is still the subject of debate. On the basis of the results obtained for some representatives of the family so far, it is tempting to speculate that RecQ helicases might share a common mechanism whereby smaller oligomers, are required for DNA unwinding, while higher-order oligomers are required for more specialized activities, such as Holliday junction branch migration/disruption and DNA strand annealing [37,38]. The current evidence that supports or contradicts this model is discussed. From a comparison of the RecQ helicase structures with the structures of other enzymes characterized by only one of the above mentioned activities, we speculate on the possible mechanisms by which RecQ helicases promote their multiple enzymatic activities.

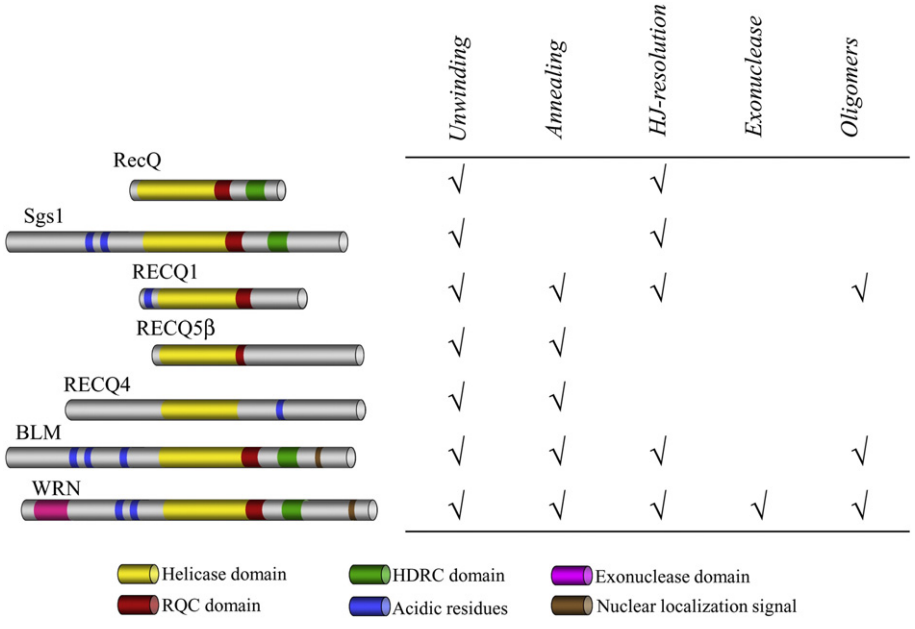

Fig. 1. The multiple enzymatic activities of RecQ helicases are regulated by their different domain organization and oligomeric states. (Left) Schematic representation of some of the best characterized members of the RecQ family color coded according to their structural domains: *E. coli* RecQ, *S. cerevisiae* Sgs1, and the five human RecQ helicases. Proteins are aligned according to the conserved helicase domain, which is shown in yellow. The conserved RQC and HRDC domains are shown in red and green, respectively. The exonuclease domain in the amino-terminal region of WRN is shown in pink. Regions containing patches of acidic residues are shown in blue. The nuclear localization signal sequences identified at the extreme carboxyl terminus of certain family members is shown as a brown bar. The remaining portions of each protein (gray) represent regions that are poorly conserved. The sizes of the individual domains are not to scale. At least three splice variants of the human RECQ5 protein are expressed, of which only the largest (β-isoform) is shown. (right) The different enzymatic activities reported for each helicase to date are indicated (unwinding, annealing, Holliday junctions (HJ) resolution, and exonuclease), along with their ability to form oligomers.