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Review

RecQ helicases and PARP1 team up in maintaining genome integrity

Sebastian Veith, Aswin Mangerich*

University of Konstanz, Molecular Toxicology Group, Department of Biology, D-78457 Konstanz, Germany

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ABSTRACT

Genome instability represents a primary hallmark of aging and cancer. RecQL helicases (*i.e.*, RECQL1, WRN, BLM, RECQL4, RECQL5) as well as poly(ADP-ribose) polymerases (PARPs, in particular PARP1) represent two central quality control systems to preserve genome integrity in mammalian cells. Consistently, both enzymatic families have been linked to mechanisms of aging and carcinogenesis in mice and humans. This is in accordance with clinical and epidemiological findings demonstrating that defects in three RecQL helicases, *i.e.*, WRN, BLM, RECQL4, are related to human progeroid and cancer predisposition syndromes, *i.e.*, Werner, Bloom, and Rothmund Thomson syndrome, respectively. Moreover, PARP1 hypomorphy is associated with a higher risk for certain types of cancer. On a molecular level, RecQL helicases and PARP1 are involved in the control of DNA repair, telomere maintenance, and replicative stress. Notably, over the last decade, it became apparent that all five RecQL helicases physically or functionally interact with PARP1 and/or its enzymatic product poly(ADP-ribose) (PAR). Furthermore, a profound body of evidence revealed that the cooperative function of RECQLs and PARP1 represents an important factor for maintaining genome integrity. In this review, we summarize the status quo of this molecular cooperation and discuss open questions that provide a basis for future studies to dissect the cooperative functions of RecQL helicases and PARP1 in aging and carcinogenesis.

Contents

Abbreviations: ARTD, ADP-ribosyltransferase diphtheria toxin-like; BER, base excision repair; BG, Baller-Gerold syndrome; BLM, Bloom syndrome protein; BRCT, BRCA1 C-terminus domain; BS, Bloom syndrome; CPT, camptothecin; dHJ, double Holliday junction; DSB, DNA double-strand break; HJ, Holliday junction; HR, homologous recombination; HRDC, helicase and RNase D-like C-terminal domain; KIX, interactor of kinase inducible domain; NER, nucleotide excision repair; NHEJ, non-homologous end-joining; NLS, nuclear localization signal; OB-fold, oligonucleotide/oligosaccharide-binding fold; PAR, poly(ADP-ribose); PARG, poly(ADP-ribose) glycohydrolase; PARP, poly(ADP-ribose) polymerase; PBM, PAR binding motif; PbR, PAR-binding regulatory motif; RQC, RecQ C-terminal domain; RTS, Rothmund-Thomson syndrome; SRI, set2 Rbp1 interacting; SSA, single-strand DNA annealing; SSB, DNA single-strand break; SUMO, small ubiquitin-related modifier; WRN, Werner syndrome protein; WS, Werner syndrome.

* Corresponding author. Tel.: +49 7531 884067; fax: +49 7531 884033.
E-mail address: aswin.mangerich@uni-konstanz.de (A. Mangerich).

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1. Introduction

Genome instability, telomere attrition, epigenetic alterations, and loss of proteostasis have been recently defined as four primary hallmarks of aging (Lopez-Otin et al., 2013). Among those, in particular, genome instability and telomere attrition are considered important causative factors of human aging, which is impressively underscored by the fact that all known human progeroid syndromes are a result of mutations in genes involved in DNA metabolism (reviewed in Vijg and Suh, 2013). To date, four categories of human segmental progeroid syndromes have been identified. Those are caused by hereditary defects in genes that are involved in nucleotide excision repair (*e.g.*, xeroderma pigmentosum and Cockayne syndrome), nuclear organization (*e.g.*, Hutchinson Gilford progeria), DNA damage signaling (*e.g.*, ataxia telangiectasia), and RecQL helicase function (see below) (reviewed in Ghosh and Zhou, 2014). To ensure integrity of the genome a multifaceted network of maintenance mechanisms has evolved relying on the concerted action of nucleases, ligases, topoisomerases, polymerases and helicases (reviewed in Ciccia and Elledge, 2010). This review addresses the intriguing connection between two major players in genome maintenance and mammalian aging biology: RecQL helicases and poly(ADP-ribose) polymerase 1 (PARP1).

2. RECQ helicases

Helicases, in general, are molecular motors that unwind double- or multi-stranded DNA or RNA structures in a 3′–5′ or a 5′–3′ directionality by using ATP as an energy source. They participate in many aspects of DNA metabolism, such as replication and transcription (reviewed in Brosh, 2013; Singleton et al., 2007). In particular, the members of the RecQ helicase family act as guardians of the genome to assure proper DNA metabolism in response to genotoxic stress, such as replicative, transcriptional, and telomeric stress. The family of RecQ helicases is highly conserved across species, with members identified in bacteria (*Escherichia coli*), fungi (*e.g.*, *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*), plants (*Arabidopsis thaliana*), and animals (*Caenorhabditis elegans*, *Drosophila melanogaster*, *Xenopus laevis*, *Mus musculus*) (Karow et al., 2000). In mammals five RecQ-like (RECQL) helicases exist, *i.e.*, RECQL1, WRN, BLM, RECQL4, RECQL5 (reviewed in Croteau et al., 2014) (Fig. 1). To date, monogenic diseases have been associated with defects in three out of five RecQL helicases. Thus, mutations in *WRN*, *BLM*, and *RECQL4*, cause Werner syndrome (WS), Bloom syndrome (BS), and Rothmund Thomson syndrome (RTS), respectively (reviewed in Hanada and Hickson, 2007). [*N.B.* Two additional diseases were linked to mutations in *RECQL4*, *i.e.*, RAPADILINO and Baller-Gerold syndrome (Croteau et al., 2014)]. All three diseases are characterized by growth and skin abnormalities, cancer predisposition, a reduced life expectancy, and signs of premature aging; however, they are clearly distinguishable in their precise clinical features. In particular, WS patients recapitulate many (but not all) aspects of normal human aging with life expectancies of ~50 years of age. WS patients develop normally until adolescence, thereafter evolving symptoms, such as cataracts, osteoporosis, atherosclerosis, hair graying, type II diabetes, and cancer predisposition (reviewed in Bernstein et al., 2010; Chu and Hickson, 2009; Hanada and Hickson, 2007). In contrast to *WRN*, *BLM*, *RECQL4*, so far no genetic diseases have been linked to *RECQL1* and *RECQL5* mutations, however, there is convincing evidence that all RecQL helicases work as tumor suppressive factors in mice and humans (reviewed in Brosh, 2013; Chu and Hickson, 2009). Evidently, clinical findings from RecQL helicase disorders raised considerable interest in the underlying biochemical and cellular mechanisms of how these enzymes are involved in normal human aging.

Specifically, RecQL helicases are involved in the replicative stress response, DNA repair, telomere maintenance, and transcription. Thus, many substrates of RecQL helicases resemble DNA repair intermediates and unusual DNA structures, such as 3′ overhangs, forked and bubbled structures, D-loops, Holliday junctions (HJ), four-way junctions, and G-quadruplex DNA (reviewed in Bernstein et al., 2010; Chu and Hickson, 2009; Croteau et al., 2014). In addition to their 3′–5′ helicase function, all five RecQL helicases exhibit ATP-independent single-strand DNA annealing (SSA) activities. ATP binding induces conformational changes in RECQL structures, switching their activity from SSA to DNA helicase activity (Sami and Sharma, 2013; Sharma et al., 2005). Structurally, RecQL helicases share three highly conserved domains: a core helicase domain, the RecQ C-terminal (RQC) domain, and the helicase and RNase D-like conserved (HRDC) domain, however RECQL1/4/5 lack the HRDC domain (Fig. 1). Furthermore, each helicase comprises specific domains that confer unique functional characteristics to each homolog, being responsible for subcellular localization, specific protein–protein interactions, oligomerization, or further enzymatic activities (reviewed in Croteau et al., 2014). For example, unlike all other RecQLs, WRN possesses an N-terminal exonuclease domain (Croteau et al., 2014). It is interesting to note that RecQL helicases themselves interact with each other, and redundant (RECQL5-BLM), synergistic (RECQL4-BLM, WRN-RECQL5, WRN-BLM), complimentary (RECQL5-WRN), as well as distinct functions have been described (reviewed in Croteau et al., 2014). For the proper function of RecQL helicases, it is important that their action is orchestrated in a spatio-temporal manner with other DNA metabolizing factors (Croteau et al., 2014). Furthermore, their action needs to be tightly controlled until it is needed, because uncontrolled unwinding of the DNA (or nuclease activity in case of WRN) can cause genome instability, leading to catastrophic consequences for cells (Singleton et al., 2007). Consistent with this view, a variety of stimulating and inhibiting binding partners as well as post-translational modifications (PTMs) regulate the activities of the individual RecQL helicases (reviewed in Bohm and Bernstein, 2014; Croteau et al., 2014). Besides phosphorylation, ubiquitination, and SUMOylation, poly(ADP-ribosyl)ation plays an important role in the regulation of RecQL helicases, as it will be discussed in this review. For a more detailed discourse on general RecQL biochemistry and biology the reader is referred to several excellent reviews on this topic (Bernstein et al., 2010; Bohr, 2008; Brosh, 2013; Chu and Hickson, 2009; Croteau et al., 2014; Mason and Cox, 2012).

3. Poly(ADP-ribose) polymerases and poly(ADP-ribosyl)ation

Poly(ADP-ribosyl)ation (PARylation) is an ubiquitous and reversible post-translational modification that takes place in the

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