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Review

Homologous recombination and maintenance of genome integrity: Cancer and aging through the prism of human RecQ helicases

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ABSTRACT

Homologous recombination (HR) is a genetic mechanism in somatic cells that repairs DNA double-strand breaks and restores productive DNA synthesis following disruption of replication forks. Although HR is indispensable for maintaining genome integrity, it must be tightly regulated to avoid harmful outcomes. HR-associated genomic instabilities arise in three human genetic disorders, Bloom syndrome (BS), Werner syndrome (WS), and Rothmund–Thomson syndrome (RTS), which are caused by defects in three individual proteins of the RecQ family of helicases, BLM, WRN, and RECQL4, respectively. Cells derived from persons with these syndromes display varying types of genomic instability as evidenced by the presence of different kinds of chromosomal abnormalities and different sensitivities to DNA damaging agents. Persons with these syndromes exhibit a variety of developmental defects and are predisposed to a wide range of cancers. WS and RTS are further characterized by premature aging. Recent research has shown many connections between all three proteins and the regulation of excess HR. Here, we illustrate the elaborate networks of BLM, WRN, and RECQL4 in regulating HR, and the potential mechanistic linkages to cancer and aging.

1. Maintenance of genome integrity

Genome integrity is the capacity of the cell to avoid mutations. Tantamount to genome integrity is the accurate replication and faithful transmission of the genetic information. Tightly associated with the DNA replication and chromosome segregation mechanisms are biochemical pathways that contend with DNA damage. Because cells are continuously exposed to DNA damage, generated by either the products of normal cellular metabolism or the environment, cells have evolved biochemical pathways that respond to specific DNA lesions that are encountered (Friedberg et al., 2004). Cells coordinate proficient DNA repair with a highly regulated DNA damage-signaling network that controls the progression of cells through the cell-cycle, referred to as checkpoints (Hartwell, 1992).

Error-free repair of DNA damage preserves the genome and allows continued normal function. If DNA damage is too extensive, the cell may commit to apoptosis. Alternatively, the cell may repair the damage but introduce one or more errors, thereby surviving with acquired mutations that potentially compromise normal cellular functions. Mutations in proteins that are themselves important in the repair of DNA damage and cell-cycle checkpoints are especially insidious for the cell. Mutations in DNA repair and checkpoint functions increase the rate at which mutations accumulate in a cell, a condition referred to as genomic instability (Loeb, 2001). Genomic instability is a common condition of cancer cells (Lengauer et al., 1998). An increased rate of mutation increases the probability that cancer-causing mutations will occur, and failure to engage checkpoints allows cells to proliferate in the presence of DNA damage. Genomic instability is also the unifying characteristic of a group of hereditary disorders that contain germline mutations in the DNA repair or the checkpoint genes (Table 1). In these syndromes, mutations accumulate at higher rates than normal given the same level of exposure to the relevant mutagen. Although genetic defects in each repair or checkpoint pathway are associated with clinically distinct entities, as a group they are characterized by developmental abnormalities, cancer predisposition, and accelerated aging.

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Table 1
Genetically determined genomic instability disorders in humans[a]

Disorder	Gene mutated	DNA repair pathway	Cancer risk[b]
Autosomal recessive disorders			
Ataxia telangiectasia	*ATM*	Double-strand break signaling	+
Seckle syndrome	*ATR*	UV and replication damage signaling	?
AT-like disorder	*MRE11*	Double-strand break repair	–
Nijmegen breakage syndrome	*NBS1*	Double-strand break repair	+
Bloom syndrome	*BLM*	Regulation of recombination	+
Werner syndrome	*WRN*	Telomere maintenance[c]	+
Rothmund–Thomson syndrome	*RECQL4*	Double-strand break repair?	+
Fanconi anemia	*FANCA, -B, -C, -D1, -D2, -E, -F, -G, -I, -J, -L, -M, -N*	Homologous recombination and interstrand crosslink repair	+
Xeroderma pigmentosa	*XPA, -B, -C, -D, -E, -F, -G*	Nucleotide excision repair (NER)	+
XPF-ERCC1 progeroid syndrome	*XPF*	NER[d]	?
Xeroderma pigmentosum variant	*XPV*	Trans-lesion synthesis	+
Cockayne's syndrome	*CSA, -B, XPB, -D, -G*	Transcription coupled-NER	–
Trichothiodystrophy	*XPB, -D, TTDA, -B*	Transcription coupled-NER	–
Ligase I deficiency	*LIG1*	DNA replication	?
Radiation-sensitive severe combined immunodeficiency	*LIG4, Artemis, XLF*	Non-homologous end joining	+/?
Spinocerebellar ataxia with neuropathy	*TDP1*	Single-strand break repair	–
Ataxia oculomotor apraxia	*APTX*	Single-strand break repair	–
Autosomal dominant disorders			
Lynch syndrome	*MLH1, MHS2, -6*	Mismatch repair	+
Hereditary breast cancer	*BRCA1, -2*	Homologous recombination repair	+
Li-Fraumeni syndrome	*TP53*	DNA-damage signaling	+

[a] Information in table is from (Niedernhofer et al., 2006; Prigent et al., 1994; Rass et al., 2007; Taniguchi and D'Andrea, 2006; van Brabant et al., 2000a).
[b] A plus (+) indicates that cancer susceptibility is present, a minus (–) indicates it is absent, and a question mark (?) indicates that the presence of cancer susceptibility is undetermined.
[c] WRN protein has also been implicated in homologous recombination and base excision repair (see text for details).
[d] XPF-ERCC1 (XFE) progeroid syndrome is associated in humans with a single identified mutation in the *XPF* gene (Niedernhofer et al., 2006). The XPF and ERCC1 complex has been implicated in interstrand crosslink DNA repair, which may be defective in this syndrome.

2. Homologous recombination repair

A double-strand break (DSB) is the most toxic form of DNA damage that a proliferating cell can sustain. In the absence of DSB repair, the broken ends are inherently unstable because they are unprotected and therefore subject to nucleolytic degradation, resulting in deletion of genes both proximal and distal to the break. If a break occurs on one of the two sister chromatids, the resulting acentric fragment can be lost or attached to a non-homologous chromosome, leading potentially to segmental trisomy. If a break involves both sister chromatids, the ends distal to the break can join together; the ends proximal to the break can join together also. These rejoining events form an acentric fragment and a dicentric chromosome, respectively. The dicentric chromosome can form an anaphase bridge in metaphase; the stretched DNA is susceptible to breakage, which after DNA replication can again fuse with its sister, leading to additional bridge-breakage-fusion cycles (McClintock, 1951).

Exposure of cells to gamma irradiation generates high levels of reactive oxygen species (ROS), which in turn generates large numbers of strand breaks (both single and double) through oxidation and cleavage of the sugar-phosphate backbone. Endogenous DSBs, however, are relatively rare in most cells. A major source of DSBs originates from the process of DNA replication (Haber, 1999). During S phase, the DNA is unraveled and exposed, and the replication complex may clash with DNA lesions or proteins that have engaged the DNA. For example, if the replicative polymerase encounters a single-strand break or gap that was introduced during repair of DNA damage, then the replication fork will collapse and devolve to an intact duplex and a single DSB (Fig. 1A). The replication fork must be re-established by a process that involves homologous recombination (HR) (Kuzminov, 1999; Michel et al., 2007).

With a replication-associated DSB, only a single broken end is available (Cox, 2001). The broken end is first processed by a 5′ to 3′ exonuclease to expose a single-stranded DNA (ssDNA) tail with a 3′ end. The free ssDNA tail is rapidly complexed with ssDNA binding protein (referred to as SSB in bacteria and RPA in eukaryotes). Mediator proteins, such as RAD52 and the RAD55/57 complex, actively substitute recombinase (RecA protein in bacteria and RAD51 in eukaryotes) for ssDNA binding protein, and the recombinase-ssDNA nucleoprotein filament invades the intact duplex to produce a displacement loop (D-loop). The invading 3′ end creates a primer for DNA synthesis, which restarts the replication fork. Recombinase can also catalyze an expansion of the D-loop to generate a four-stranded recombination intermediate referred to as a Holliday junction, which can migrate away from the replication fork. A prevailing view is that the Holliday junction is resolved by cutting and rejoining, and half of the cutting/rejoining events lead to a crossover that produces a sister-chromatid exchange (SCE) (Wilson and Thompson, 2007).

Another potential source of SCEs is generated by base-damage encountered by the replicative polymerase during S phase. When DNA polymerase is stalled at base damage, DNA replication can restart downstream of the stalled fork, producing a daughter-strand gap (Fig. 1B). Hypothetically, recombinase is loaded onto the ssDNA gap by mediators, and the recombinase-ssDNA filament invades the intact DNA duplex. The available 3′ end can anneal with the displaced DNA strand of the D-loop, which primes DNA synthesis across the gap. By ligation with the 5′ end on the other side of the gap, a double Holliday junction can form (Agarwal et al., 2006; Cahill et al., 2006). The double Holliday junction can be resolved with or without SCE formation, depending on the molecular mechanism used for resolution (Fig. 1B depicts a case in which SCE did not occur). The result of this HR process is lesion bypass not DNA repair, which can be achieved at a later time.

If the ssDNA in the daughter-strand gap is nicked, a DSB with two ends would result (Fig. 1C). As in the replication restart pathway, the broken ends must be processed to expose ssDNA tails. Mediators displace SSB protein and load recombinase onto one of the tails.