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Review

Human

Helicases involved in the repair of DNA inter-strand crosslinks

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Abstract

Introduction

Helicases are motor proteins that couple the energy derived from ATP hydrolysis to DNA strand separation. Eukaryotic genomes often encode hundreds of helicase genes because these enzymes are involved in multiple processes that maintain genome stability in the face of endogenous and exogenous sources of DNA damage. A particularly harmful type of DNA lesion is an inter-strand crosslink (ICL) because covalent linkage of both DNA strands blocks replication and transcription. This review focuses on the functions of Fanconi Anemia and RecQ family helicases, as well as other helicases, known to function in ICL repair.

Conclusion

Mutations in repair helicases can lead to pleiotropic clinical features, many of which are related to cancer. Examining even a single type of DNA lesion, such as an ICL, demonstrates the incredible molecular machinery cells must utilize to repair the damage.

Introduction

DNA inter-strand crosslinks (ICLs) are covalent linkages between both strands of the double helix and a physical block to both DNA replication and transcription[1]. Thus, if unrepaired, they are a considerable obstacle to the maintenance of genome stability and can ultimately result in cell death. Being such dangerous lesions, a vast network of coordinated and/or redundant repair pathways involving a variety of enzymatic functions exists to deal with ICLs, including nucleotide excision repair (NER), translesion synthesis, and homologous recombination (HR) (Figure 1)[2]. These processes are complex, due at least in part to the overlapping nature of the various pathways involved and the necessity for proteins with different biochemical functions.

DNA helicases are perhaps the most important enzyme family necessary for ICL repair[3]. They are traditionally thought to simply unwind duplex DNA to produce single strands as templates for polymerases in DNA replication, recombination, and repair. However, their known and suspected in vivo roles are less mundane, as helicases are often implicated in multiple facets of genomic integrity.

In humans, the Fanconi Anemia (FA) pathway is the canonical ICL repair pathway (Figure 1), and mutations in any of the 15 FANC genes lead to ICL sensitivity and compromised repair function[2]. The FA pathway proteins include two helicases (FANCJ and FANCM), both of which play an important role in ICL resolution. However, non-FA-related helicases are also required for ICL repair[4]. Together, both sets of helicases and their roles in ICL repair are the focus of this review (Figure 2).

Discussion

The authors have referenced some of their own studies in this review. The protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed.

FA Family Helicases

FANCM

FANCM, a DNA translocase with a putative N-terminal helicase domain, plays an important signalling role in the FA-associated ICL repair pathway (Figure 1 and Figure 2)[5]. It was previously thought that the FANCM-FAAP24 complex (FAAP24 is a FA-associated protein) recognizes and stabilizes stalled replication forks at ICLs (described in[6]).

In this model, the FANCM-FAAP24 complex coordinates the recruitment and subsequent phosphorylation of multiple FA core complex proteins via the ATR-CHK1 checkpoint kinase.

The activation of the FA core complex then leads to the monoubiquitylation-mediated conjugation of FANCD2 and FANCI; the ubiquitylated FANCD2-I complex plays an important role in initiating the ICL repair mechanisms. However, a recent study suggests that FANCM phosphorylation by ATR is required before the FA repair pathway can be initiated[7].

FANCM residue S1045 is a putative site for ATR-dependent phosphorylation, and a S1045A mutation results in failure to induce the appropriate FA pathway signalling. These data reveal that ATR may be required for ICL recognition and that there is a possible feedback mechanism that closely links FANCM and ATR.

The translocase activity of FANCM may also be used in bypassing ICLs[8]. This process requires the presence of additional FANCM binding partners MHF1/MHF2.

The ICL transversion ability of FANCM may support the role of FANCM in the signalling of ICLs, though the exact mechanism of this function is not yet known. However, it has been proposed that FANCM may help translocate the replisome to the other side of the ICL to allow for continued replication.

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Review

Although biochemical analysis of FANCM helicase activity has been difficult, the Saccharomyces cerevisiae homolog Mph1 has well defined helicase activity (see[9] and references therein), but the involvement of Mph1 in ICL repair is less direct. Disruptions of FANCM result in a sensitivity to ICL-inducing agents in humans, but mph1 cells are resistant to such treatments.

Double mutants that do not express Mph1 or Pso2, an exonuclease involved in ICL repair, are more sensitive to ICLs than pso2 cells, suggesting that Mph1 functions in an alternative ICL repair pathway instead of the main yeast repair pathway with Pso2. The double mutant sensitivity also suggests a redundant role for Mph1 in ICL repair.

FANCJ/CHLR1

FANCJ is a 5' to 3' superfamily II helicase containing an iron sulphur cluster domain[10]. In humans, FANCJ directly interacts with BRCA1 (Figure 2)[11], and mutations in both proteins are linked to a predisposition to early-onset breast cancer[10]. However, mutations in FANCJ are also linked to FA[10], and many of its known protein-protein interactions and functions occur independently of BRCA1[11]. When FANCJ helicase activity is disrupted through catalytic inactivation, cells display increased sensitivity to crosslinking agents such as mitomycin C (MMC), as well as an increase in DNA double-stranded break (DSB) formation[10].

These results suggest that the helicase activity of FANCJ is required for its role in ICL repair. Recruitment of FANCJ to ICLs is dependent on FA core complex member FANCA, but monoubiquitylation of FANCD2 is not dependent on FANCJ (Figure 2), demonstrating that FANCJ likely acts downstream of the FA core complex[12]. FANCJ also interacts with the RecQ family helicase BLM (discussed below)[12], the MRE11-RAD50-NBS1 HR repair complex, the mismatch repair complex MutLα[11], and the single-stranded DNA binding protein RPA[4].

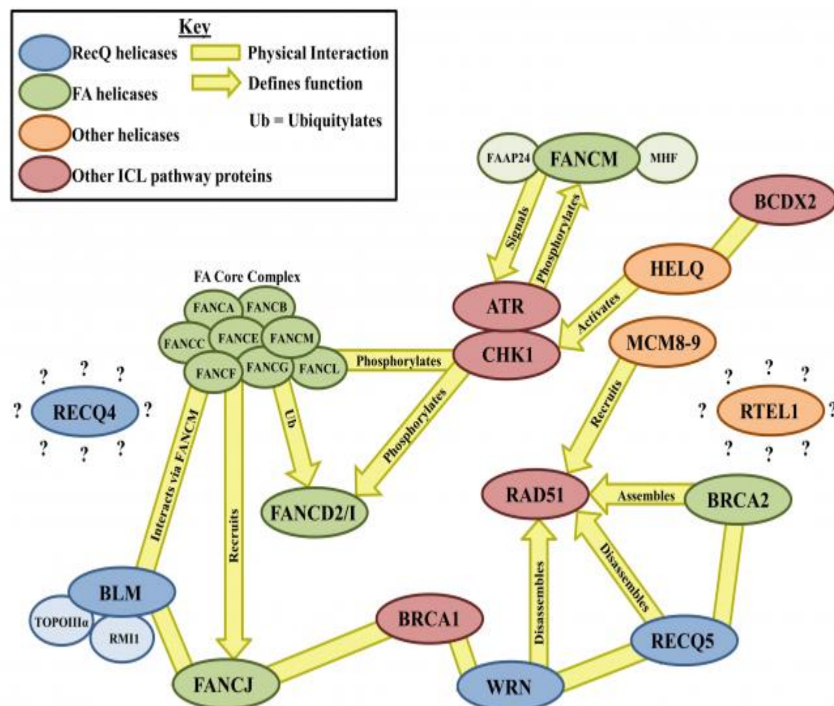

Figure 1: Model of ICL repair focusing on the main components and processes of the Fanconi Anemia pathway. Replication fork stalling at an ICL is recognized by FANCM. Phosphorylation of FANCM by ATR results in FANCM signaling the ATR-CHK1 checkpoint response to phosphorylate the FA Core Complex, FANCI, and FANCD2. The FA Core Complex then monoubiquitylates FANCI and FANCD2, which form a heterodimer that is recruited to the site of the ICL. This complex recruits nucleases to cut the DNA flanking the ICL, ultimately creating a DSB. Translesion synthesis (TLS) functions to repair the mono-adduct-containing DNA strand, and other downstream FA proteins aid in the repair of the DSB via HR. NER removes the remaining ICL adduct.

These interactions, combined with the ability of FANCJ to unwind G-quadruplex structures, simple duplex DNA substrates, and D-loop structures in HR, implicate FANCJ as a multifunctional player in the ICL response and DSB-induced HR repair[10]. Its role in HR is hypothesized to occur early, possibly in end resection, to aid in efficient HR[12].

Other FANCJ-related helicases involved in ICL repair include the FANCJ homolog in Caenorhabditis elegans, DOG-1 (deletions of guanine-rich DNA), as well as the human XPD and yeast RAD3 helicases, which share sequence homology with FANCJ and function as subunits of the TFIIH/DNA repair complex in NER[13]. Also related to FANCJ are the yeast Chl1 and human CHLR1 helicases[14].

Both Chl1 and CHLR1 interact with factors involved in sister chromatid cohesion (SCC)[15]. A CHLR1 mutation that disrupts its helicase activity is responsible for Warsaw Breakage Syndrome (WABS), a cohesinopathy-related disease with phenotypes similar to FA. Observations in WABS patient cells that are treated with MMC suggest that CHLR1 plays a role in ICL-induced DNA damage repair.

CHLR1-depleted cells display a significant reduction in the rate of replication recovery after exposure to the DNA crosslinker cisplatin, and show sensitivity to agents that cause DNA breaks during replication. Defects in DSB repair and sister chromatid exchange (SCE) are also observed in such cells. Thus, it has been concluded that CHLR1 has a role in DSB repair to assist with restart and progression of the replication fork. It is also hypothesized that CHLR1acts in HR to help establish SCC at the replication

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fork, possibly by enhancing lagging strand synthesis.

RecQ Family Helicases

BLM

Bloom's syndrome (BS) is caused by mutations in the RecQ family helicase BLM. The characteristic trait of BS is an elevated SCE rate[16], but BLM also has strong ties to the FA pathway in ICL repair[17]. Phenotypic similarities in BS and FA patients indicate a correlation between their respective diseases, and the bridge between the RecQ and FA families appears to be FANCM (Figure 2).

Co-immunoprecipitation of FANCM fragments identified two important binding sites: one for FANCF in the FA core complex, and one for TopoIIIα and RMI1 of the BLM-containing BRAFT complex. Furthermore, the disruption of FANCM association with either the FA or BRAFT complexes results in sensitivity to MMC and elevated SCE rates, but interactions between FANCM and BRAFT are not required for monoubiquitylation of FANCD2.

BLM also directly interacts with FANCJ in vivo, and deficiencies in FANCJ result in proteasome-mediated degradation of BLM, though the mechanism is not well understood[18]. Additionally, HeLa cells exposed to MMC demonstrate FANCJ and BLM co-localization. Furthermore, phosphorylation of BLM is an indicator of activation in response to DNA damage, and in the presence of DNA ICLs, the FA complex is required for phosphorylation of BLM. A role for BLM in ICL repair is also evolutionarily conserved as deletion of the yeast BLM homolog, Sgs1, results in sensitivity to MMC[19].

WRN

WRN is a RecQ helicase that also possesses exonuclease activity, both of which function in the 3'-5' direction[20]. Mutations in WRN lead to Werner syndrome (WS), which is characterized by a predisposition to cancer and premature aging. The genomic instability characteristic of WS may be linked to defects in ICL repair[21]. Indeed, the proliferation of HeLa cells that do not express FANCD2 decreases when they are exposed to both low levels of MMC and a recently discovered WRN inhibitor (NSC 617145). Therefore, WRN likely functions parallel to the FA pathway in ICL repair. Co-treatment with NSC 617145 and MMC in FANCD2-mutant cells leads to a significant increase in RAD51 foci relative to DMSO-treated control cells or cells with wildtype FANCD2. RAD51 filament formation at DSBs is critical in coordinating HR by promoting the recognition of the homologous duplex[22]. An increase in RAD51 foci formation (i.e., an indicator of failed HR intermediate resolution) in NSC 617145-treated cells suggests that WRN plays a role in the disassembly of RAD51 filaments (Figure 2).

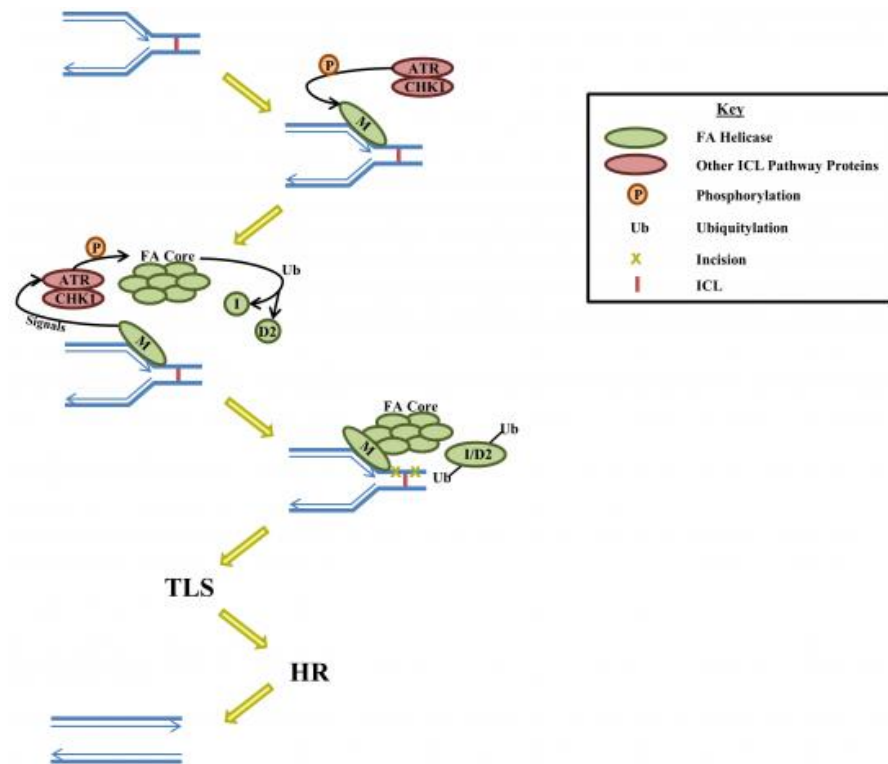

Figure 2: Outline of the interactions between the helicases and other proteins involved in ICL repair mentioned in this review. The network of proteins involved is vast, and thus, the figure is not intended to be comprehensive.

WRN function appears to be mediated through interactions with BRCA1 in the presence of DNA ICLs[23]. Interactions with BRCA1 stimulate both the exonuclease and helicase activities of WRN, but only the helicase activity is required for ICL repair induced by the crosslinker psoralen.

RECQ4

Mutations in the RECQ4 helicase are associated with Rothmund-Thomson syndrome (RTS), RAPADILINO, and Baller-Gerold syndrome, which share clinical characteristics such as a predisposition to cancers and premature aging[3]. RECQ4 is a 3'-5'-directed helicase that also functions as a DNA replication initiation factor.

The sensitivities of RTS patient cells to genotoxic agents show conflicting results, possibly owing to the variety of RECQ4 mutations found in these various cell lines. For example, the sensitivity of RTS fibroblasts to genotoxic agents, including those that induce DNA ICLs, was examined in two independent studies. Cells exposed to the crosslinkers MMC, 8-methoxypsoralen, and cisplatin

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Table 1: Human helicases and their homologs discussed in the text.

Human helicase	Homolog(s)	Role in inter-strand crosslink (ICL) repair	References
FANCM	Mph1 (*Saccharomyces cerevisiae*)	Translocase activity over ICL and Fanconi Anemia (FA) pathway signaling	5, 6, 7, 8, 9
FANCJ	Dog-1 (*Caenorhabditis. elegans*); XPD, RAD3 (*S. cerevisiae*)	Double Strand Break (DSB)-induced HR repair	4, 10, 11, 12
CHLR1	Chl1 (*S. cerevisiae*)	DSB-induced Homologous Recombination (HR) repair via Sister Chromatid Cohesion at Replication fork	14, 15
BLM	Sgs1 (*S. cerevisiae*)	Assists in ICL repair through interactions with FA proteins	16, 17, 18, 19
WRN	Not Discussed	Facilitates ICL repair in a FA independent manner, likely through RAD51 filament disassembly	20, 21, 23
RECQ4	Hrq1 (*S. cerevisiae*)	ICL repair in RECQ4 is not well understood, but Hrq1 is important for repair in yeast	3, 19, 24, 25
RECQ5	Not Discussed	Late ICL repair possibly regulating RAD51 filament disassembly	26, 29, 30
HELQ	Hel-308 (*C. elegans*)	Possible signaling role for DNA damage and ICL repair	31, 32, 33, 34
Mcm8-9 complex	Not Discussed	HR repair recruiting RAD51 to DSB sites	37, 38, 39
RTEL1	Not Discussed	Hypothesized role in HR repair	40, 41

displayed no sensitivity to ICLs in one report[24], while a similar study demonstrated moderate sensitivity to cisplatin[25]. The RECQ4 mutations in the five patients examined in Cabral et al.[24] were different than the six patients in Jin et al.[25], possibly accounting for differences in ICL sensitivity.

In addition, the ratio of crosslinks (i.e., intra- vs. inter-) varies between cisplatin and MMC. This also likely leads to confusion in the field as cisplatin is primarily an intra-strand crosslinker [26], and even MMC only produces ~80% ICLs [27]. Ultimately, the role of RECQ4 in ICL repair is unclear (Figure 2), though experiments involving Hrq1, a RECQ4 homolog in S. cerevisiae, suggest a role for RecQ4 family helicases in a non-FA ICL repair pathway[19]. Deletion of HRQ1 leads to sensitivity to ICL-inducing agents, but direct comparisons of RECQ4 to Hrq1 in vivo (e.g., can expression of RECQ4 in hrq1S. cerevisiae rescue ICL sensitivity?) have not yet been reported.

RECQ5

RECQ5 is another human RecQ helicase and a known tumour suppressor[28,29]. RECQ5 operates in vivo as an anti-recombinase to suppress SCE and has putative roles in DSB processing, DNA replication, and transcription[29]. A physical interaction with the WRN helicase supports the role of RECQ5 in replication and at DSBs (Figure 2)[30]. Although there is currently no known genetic disease associated with RECQ5 mutation, knocking out RECQ5 in DT40 chicken cells and Drosophila melanogaster results in sensitivity to cisplatin and MMC, implicating RECQ5 in ICL repair[29].

Indeed, the amount of chromosomal aberrations in RECQ5 KO cells is similar to that seen in cells deficient for proteins involved in the FA pathway. An ICL repair function for human RECQ5 was also observed with cisplatin-treated HeLa cells.

Experiments relating RECQ5 to the FA core component FANCC, RAD17 (which phosphorylates CHK1 for replication checkpoint activation), and BRCA2 (which is involved in RAD51 filament formation) indicate that RECQ5 functions in the same pathway as BRCA2 but different pathways than FANCC and RAD17 (Figure 2). This epistatic relationship between RECQ5 and BRCA2 suggests involvement of RECQ5 in ICL-induced HR repair.

FANCD2 monoubiquitylation, CHK1 phosphorylation, and RAD51 filament formation in RECQ5 KO cells also implies that RECQ5 does not act early in ICL repair. Subsequent experiments showing a delay in the disappearance of RAD51 foci in RECQ5 KO cells, as well as related functions to RAD54 (which functions after RAD51 filament formation), suggest that RECQ5 acts in a late step of ICL repair, possibly regulating filament disassembly.

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Review

Previous studies investigating the function of RECQ5 in HR support this involvement in the catalytic disassembly of RAD51 filaments[28].

Other Helicases

HELQ

HELQ (originally named HEL308) is a 3'-5' helicase that unwinds substrates resembling the nascent lagging strand at replication forks in vitro[31]. Furthermore, HELQ localizes to stalled replication forks in camptothecin-treated U2OS cells. These results, combined with the sensitivity of HELQ KO U2OS cells to MMC and cisplatin[32], implicate HELQ in ICL repair. Further, co-depleted FANCD2 and HELQ knockdown cells are more sensitive to MMC than either single knockdown.

Therefore, HELQ appears to function in a repair pathway that is not FA associated. The independence of HELQ from the FA pathway has also been demonstrated in mice[33] but not in C. elegans[34]. Rather, C. elegans HEL-308 is epistatic to FCD-2 (the FANCD2 homolog[35]). The role of the C. elegans HEL-308 in the FA pathway suggests that there could be overlap between the HELQ and the FA ICL repair pathways in humans[34]. HELQ involvement in ICL repair appears to be related to its interactions with RAD51 paralogs (specifically those that form the BCDX2 subcomplex, which functions upstream of RAD51 filament assembly on DSBs[36]; Figure 2), though the function of the RAD51 paralogs in ICL repair is not known[32]. HELQ does have a role in ATR-mediated phosphorylation of CHK1, which indicates that HELQ is important in signalling DNA damage.

Mcm8-9 complex

MCM8 and MCM9, members of the mini-chromosome maintenance (Mcm) family of proteins, are uniquely expressed in higher eukaryotes[37]. Current evidence shows that they function together as a dimeric complex[37] with helicase activity that operates independently of the Mcm2-7 hexameric replicative helicase[38]. The hypersensitivity of MCM8 and MCM9 KO cells to both cisplatin and MMC suggests a role for the Mcm8-9 complex in ICL repair[39]. Based on FANCD2 monoubiquitylation levels in MCM8 and MCM9 KO cells, as well as CHK1 phosphorylation after treatment with MMC, it has been suggested that the Mcm8-9 complex either works downstream of FANCD2 or independent of the FA pathway (Figure 2). A role for Mcm8-9 in ICL-induced HR has also been hypothesized.

In individual KO cells, HR efficiency is reduced, while depletion of both MCM8 and MCM9 results in nearly complete loss of HR activity[38]. Recruitment of RAD51 is regulated by Mcm8-9, while loading of Mcm8-9 to DSBs occurs independently of RAD51. This is supported by ~40% reduction of RAD51 binding to ICLs in cells depleted of MCM9. Therefore, the Mcm8-9 complex likely acts in HR upstream of RAD51 recruitment to bring RAD51 to DSB sites and cisplatin-induced lesions (Figure 2).

RTEL1

RTEL1 (Regulator of Telomere Length 1) is an essential helicase involved in telomere maintenance and DNA repair with important functions in DSB repair[40]. Experiments with C. elegans rtel-1/dog-1 mutants, human RTEL1/FANCJ KO cells[40], and mouse mRtel1 KO cells show sensitivity to MMC (Figure 2)[41]. A role for RTEL1 in ICL repair is supported by the co-localization of mRtel1 foci with mFancD2 in the presence of MMC.

Additionally, mRtel1-deficient embryonic stem cells display a significantly high frequency of spontaneous SCE compared to wildtype cells, which mimics defects in observed in BLM-mutant cells. However, the difference in SCE frequency between wildtype and mRtel1-deficient cells in the presence of MMC is not significant, though there is a possibility that MMC induces DNA damage to a maximum threshold frequency above which cells die. Subsequent experiments in the HR sub-pathway that mediates gene targeting show that SCE frequencies in mRtel1-deficient ESCs are significantly lower than wild type, supporting a role for RTEL1 in HR.

Conclusion

The helicases mentioned in this review comprise the known members of this enzyme family involved in ICL repair (Table 1). Defects in many of these helicases are linked to genetic diseases, some of which result in a predisposition to cancer. Because several cancer chemotherapeutics are ICL-inducing agents (e.g., MMC and cisplatin), studying their effects on cells deficient for these helicases is important to understanding their roles in patients with these diseases. The molecular mechanisms of the helicases involved in ICL repair are not well understood and were therefore not discussed in detail. This lack of definitive data regarding the functions of helicases in ICL repair is at least partly due to the conflicting reports of crosslinker sensitivity reported for the vast array of clinical alleles of certain helicases (e.g., RECQ4), which are not all directly comparable. Similarly, different drug treatments are used to induce ICLs in these reports, though most frequently involving cisplatin and MMC. Thus, future work revisiting the helicases described above and using reagents that exclusively produce ICLs is needed.

Abbreviations

Inter-strand crosslink, ICL; nucleotide excision repair, NER; homologous recombination, HR; Fanconi Anemia, FA; mitomycin C, MMC; double-stranded break, DSB; sister chromatid cohesion, SCC; Warsaw Breakage Syndrome, WABS; sister chromatid exchange, SCE; Bloom's syndrome, BS; Werner syndrome, WS; and Rothmund-Thomson syndrome, RTS.

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Review

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Review

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