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REVIEW

The BLM dissolvasome in DNA replication and repair

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Abstract RecQ DNA helicases are critical for proper maintenance of genomic stability, and mutations in multiple human RecQ genes are linked with genetic disorders characterized by a predisposition to cancer. RecQ proteins are conserved from prokaryotes to humans and in all cases form higher-order complexes with other proteins to efficiently execute their cellular functions. The focus of this review is a conserved complex that is formed between RecQ helicases and type-I topoisomerases. In humans, this complex is referred to as the BLM dissolvasome or BTR complex, and is comprised of the RecQ helicase BLM, topoisomerase IIIα, and the RMI proteins. The BLM dissolvasome functions to resolve linked DNA intermediates without exchange of genetic material, which is critical in somatic cells. We will review the history of this complex and highlight its roles in DNA replication, recombination, and repair. Additionally, we will review recently established interactions between BLM dissolvasome and a second set of genome maintenance factors (the Fanconi anemia proteins) that appear to allow coordinated genome maintenance efforts between the two systems.

Keywords RecQ helicase · Topoisomerase · Bloom syndrome · Fanconi anemia · DNA repair · Genomic stability

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Introduction

Genomic instability is a shared phenotype in multiple hereditary diseases where DNA repair or replication-dependent checkpoint genes are mutated. In these disorders, malfunctions in the normal genome maintenance pathways of cells increase the chance that disease-causing changes will occur that allow for uncontrolled cell proliferation [1–3]. Through the study of one such rare genetic disease, Bloom syndrome (BS), much has been learned about how cells ensure genomic fidelity. The gene mutated in BS encodes a RecQ family DNA helicase, BLM, and the pronounced genomic instability of BS cells reflects the protein's multiple roles in DNA replication, recombination, and repair [2, 4, 5]. In coordination with a large number of protein partners, BLM aids in cellular responses to replication stress and DNA damage. In this review, we focus on the discovery of a key BLM-containing complex referred to as the "BLM dissolvasome" or "BTR complex" [6] that includes topoisomerase IIIα (Topo IIIα) and the RMI proteins, and on recent advances in understanding its functions. The coordinated action of the BLM helicase and Topo IIIα in this complex is critical for untangling intertwined DNA structures that can arise during DNA replication or repair. Recent insights into interactions between the BLM dissolvasome and FANCM will also be reviewed to provide an overview of the importance of coordinating the functions of these proteins in cells, particularly for the prevention of crossover formation in mitotic cells.

Bloom syndrome

Bloom syndrome is a rare autosomal recessive genetic disorder that was first described in 1954 by dermatologist David Bloom [7]. BS manifestations include proportional

dwarfism, sun sensitivity, increased susceptibility to infections and diabetes, and a predisposition to a broad array of cancers. Cancer is a frequent cause of death in BS patients, with the first diagnosis often occurring early in life (mean age is in the mid-20s) [4, 8, 9]. Cells derived from BS patients display a remarkable increase in chromosomal damage as evidenced by DNA rearrangements, gaps, and breaks [8, 10]. The major distinguishing genomic instability feature of somatic BS cells, which is used in diagnosis, is a tenfold elevated frequency of sister-chromatid exchanges (SCEs) [4, 8, 11]. One proposed mechanism that would lead to formation of these crossovers is the asymmetric resolution of Holliday junction (HJ) intermediates formed during homologous recombination (HR) reactions. The abnormal genomic instability behavior of BS cells provided an early clue that the gene mutated in the syndrome (*BLM*) encoded a protein that had important roles in suppressing chromosomal crossovers and maintaining genomic stability [11].

BLM is a member of the RecQ family of DNA helicases

In the mid-1990s, the *BLM* gene was mapped to chromosome 15 and positional cloning techniques identified its gene product (BLM) as a member of the RecQ family of DNA helicases [12, 13]. Many of the mutations in *BLM* that give rise to BS are frameshift or nonsense mutations that lead to premature translation termination of BLM, resulting in a truncated protein. Since the nuclear localization signal (NLS) of BLM is encoded in its C-terminus, these truncation products are expected to fail to reach the nucleus (see the Bloom Syndrome Registry, http://med.cornell.edu/bsr/genetics/ and [14]) (Fig. 1a). In addition, there are 13 known BS-causing missense mutations, 7 in the helicase domain and 6 in the "RecQ C-terminal" (RQC) domain [13–17]. Through biochemical and structural studies, these mutations have been shown to confer loss of catalytic activity or are expected to hinder protein folding or stability [17–20].

The discovery of the *BLM* gene helped to explain the molecular basis for BS, since the RecQ helicase in *Escherichia coli* was already known to play a role in bacterial genomic integrity [21]. At the time that BLM was discovered, ATP-dependent DNA helicase activity had been demonstrated for *E. coli* RecQ and roles for the protein in the RecF recombination pathway had been established [22]. This background knowledge proved valuable for quickly ascertaining the functions of BLM and other eukaryotic RecQ DNA helicases. Bacteria and yeast typically code for a single RecQ protein, whereas humans have five: RecQ1, BLM, WRN, RecQ4, and RecQ5 (Fig. 1). In addition to BS, two other recessive genetic diseases are caused by mutations in the *WRN* and *RecQ4* genes [Werner's syndrome (WS) [23] and Rothmund–Thomson syndrome (RTS) [24], respectively]. Two more diseases, RAPADILINO syndrome and Baller–Gerold syndrome, both share some clinical characteristics with RTS and have also been linked to a subset of mutations of *RECQ4* [25, 26]. As with BS, WS and RTS are characterized by increased genomic instability and cancer predisposition, although the breadth of cancers observed in WS and RTS is narrower than that of BS, and the characteristic increase in SCEs of BS cells is not seen in cell lines derived from WS and RTS patients.

As is the case for all RecQ family members, BLM is a superfamily 2 (SF2) helicase that uses the energy derived from ATP hydrolysis to unwind DNA [13, 27]. In addition to a conserved helicase domain that provides the motor function for DNA unwinding, BLM and most other identified RecQs also contain RQC and the "helicase and RNaseD C-terminal" (HRDC) domains [28] (Fig. 1a). The RQC domain is comprised of a Zn^{2+}-binding scaffold and a winged-helix (WH) subdomain, and in some cases this domain has been shown to be important for structure-specific binding of RecQ proteins to replication fork, HJ, or G-quartet DNA structures [20, 29–33]. The HRDC domain is an independent globular domain that can confer further substrate specificity to RecQ helicases and can potentially enhance DNA unwinding processivity [34–37]. Interestingly, although nonsense and frame-shift insertion/deletion mutations that cause BS span the entire coding-region of the *BLM* gene, missense mutations are restricted to the helicase and RQC domains, indicating that DNA binding and unwinding functions are critical for BLM cellular functions [14]. In addition to these conserved domains, many eukaryotic RecQ helicases contain additional N- and C-terminal elements that encode for additional enzymatic functions (e.g., the exonuclease domain of WRN; Fig. 1a), provide binding sites for heterologous proteins, receive post-translational modifications, and/or facilitate proper subcellular localization [5, 27].

Biochemical properties of BLM

The BLM helicase is a 1,417-residue ATP-dependent 3′–5′ DNA helicase [4, 38]. The 3′–5′ directionality indicates that the preferred substrate for BLM unwinding contains a 3′ single-stranded (ss) extension to which the helicase is thought to bind and translocate along; this directionality is conserved among RecQ helicase family members. Although BLM is capable of unwinding simple double-stranded (ds) DNA substrates, it preferentially acts on more elaborate DNA structures such as G-quartet, D-loop, and HJ DNAs [32, 39–43]. When combined with the high level of chromosomal abnormalities observed in BS cell lines and the known roles for the prototypical RecQ in *E. coli*, these preferences suggested early on that the BLM helicase could

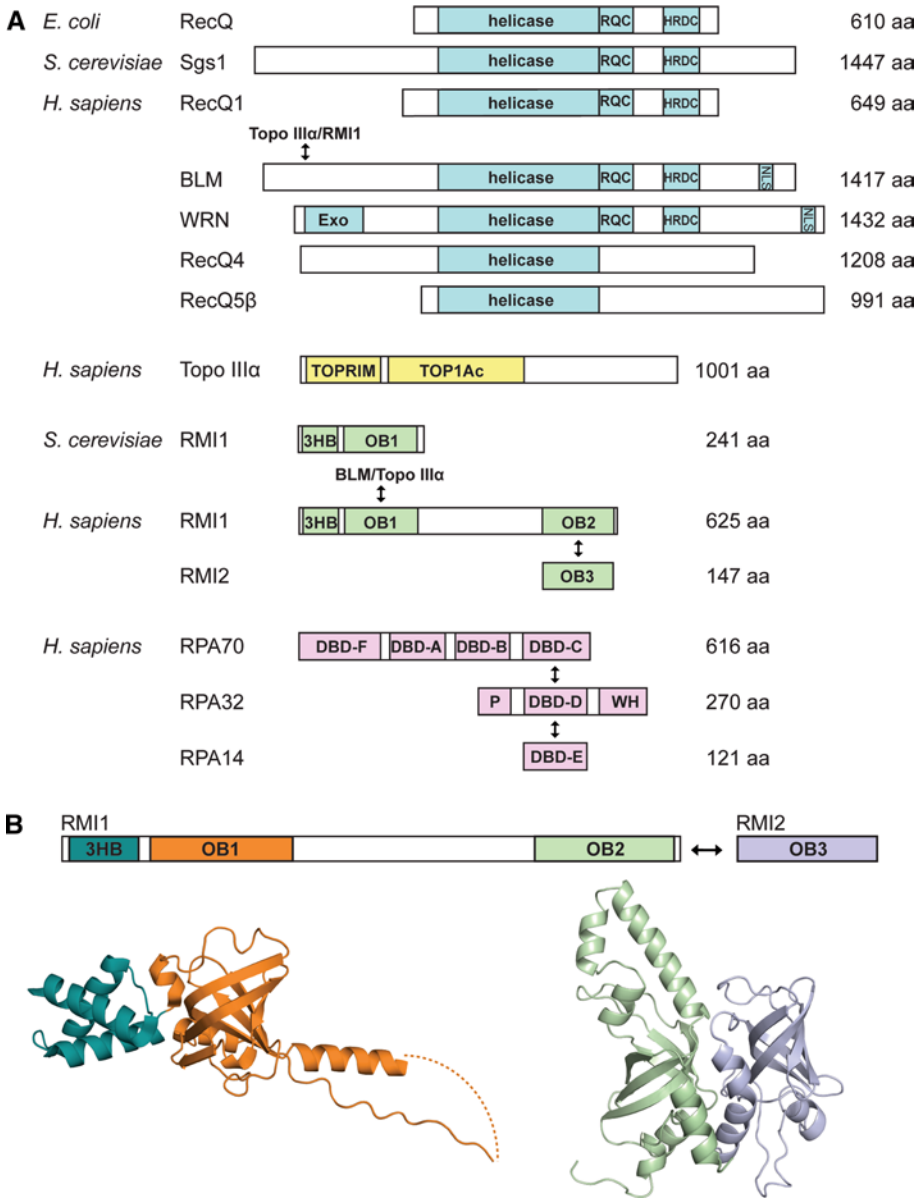

Fig. 1 Properties of the RecQ helicases and related proteins. **a** Domain architectures of RecQs, Topo IIIα, RMI1, RMI2, and RPA. Known interactions are depicted with *arrows*. RPA is shown because it shares sequence and structural similarities with the RMI subcomplex: RMI1 OB1 resembles RPA 70 DBD-F, RMI1 OB2 resembles RPA70 DBD-C, and RMI2 OB3 resembles RPA32 DBD-D. *RQC* RecQ-conserved, *HRDC* helicase and RNaseD C-terminal, *NLS* nuclear localization signal, *Exo* exonuclease, *TOPRIM* topoisomerase-primase, *TOP1Ac* topoisomerase IA conserved, *3HB* three helix bundle (also DUF1767), *OB* OB-fold, *DBD* DNA binding domain (also OB-folds), *P* phosphorylated region, *WH* winged helix, *aa* amino acids. **b** Structures of RMI1 and RMI2. The structures are indicated by the *colors* in the domains above. On the *left* is a *ribbon diagram* of the crystal structure of the N-terminus of RMI1 (residues 2–204, excluding residues 109–119, and this region is connected with a *dashed line*) [120]. On the *right* is a *ribbon diagram* of the crystal structure RMI1 OB2 (residues 475–625), and RMI2 (residues 17–147) [120, 121]. The diagrams were rendered using PyMol [220]

have an important role in resolving unusual DNA structures that can arise in cells through processes such as HR.

BLM has been shown to form a large number of functionally important homooligomeric and heterooligomeric complexes. Full-length BLM can form homohexameric structures in vitro, and an isolated domain comprised of the N-terminal 431 residues of BLM can self-associate, suggesting that this region aids in BLM oligomerization [44, 45]. More recent results have suggested that BLM oligomers can dissociate into monomers upon ATP hydrolysis, and the helicase may function as a monomer during DNA unwinding [46]. However, this does not rule out the possibility that higher-order oligomers are required to bind and/or unwind more complex DNA structures such as G-quartet and HJ DNA. Interestingly, the N-terminal region of another human RecQ, RecQ1, is required for both oligomerization and HJ unwinding [42]. Furthermore, RecQ1 has been shown to form higher-order oligomers upon binding DNA, but these dissociate to monomers or dimers upon ATP-binding, suggesting that RecQ1 may unwind DNA as monomers or lower-order oligomers [47]. The N-terminal exonuclease domain of WRN also appears to be responsible for hexamer formation, and this isolated exonuclease domain acts catalytically as a hexamer [48] (Fig. 1a). Oligomerization of full-length WRN is stimulated by DNA binding in a similar manner to RecQ1 [49, 50]. For BLM, constructs lacking the N-terminal oligomerization domain are able to unwind HJ DNA, and instead it appears that the HRDC domain is critical for HJ unwinding [37, 52] (Fig. 1a). More research will be required in order to elucidate the roles of oligomerization

for the BLM helicase for DNA binding and unwinding in vivo.

By itself, BLM is a poorly processive helicase and is only able to unwind duplexes of less than ~100 bp [53]. However, the addition of the eukaryotic single-stranded DNA-binding protein [replication protein A (RPA)] strongly stimulates BLM DNA unwinding of longer duplexes, whereas the *E. coli* single-stranded DNA-binding protein (SSB) fails to stimulate BLM unwinding [53]. Since BLM also interacts with RPA, it is thought that BLM/RPA complex formation is important for increasing the processivity of BLM DNA unwinding [53]. BLM has also been shown to possess ssDNA annealing activity; however, RPA inhibits this activity. Since RPA or other DNA-binding proteins are bound to exposed ssDNA, the cellular relevance of this activity is unclear [54]. Similar interactions and/or stimulation by SSBs have been observed in several other RecQ family members including *E. coli* RecQ/SSB, *Saccharomyces cerevisiae* Sgs1/RPA, human and *Caenorhabditis elegans* WRN/RPA, human RecQ1/RPA, and human RecQ5/RPA [51, 55–71]. In addition to its interactions with RPA, numerous studies have shown that BLM can interact with a large number of protein partners that have roles in DNA replication, recombination, and repair, including topoisomerase 3α (Topo IIIα), RMI1, Topo IIα, PICH, RAD51, EXO1, DNA2, FANCJ, RIF1, ATM, ATR, FEN1, DNA polymerase δ, MLH1, p53, WRN, and TRF2 [72–92]. The focus of this review is the complex formed by BLM, Topo IIIα, RMI1, and RMI2, and therefore many of these other important interactions will not be discussed further (see reviews[4, 5]).

RecQ complex formation with Topo III

Physical and functional interactions with topoisomerases have been found to be critical for the genome maintenance activities of many RecQ proteins. Topoisomerases function to relieve the torsional stress that arises from DNA supercoiling by transiently breaking the DNA backbone in either one (type-I) or both (type-II) strands and then passing intact DNA through the opening before resealing the break [93]. Although RecQ proteins have been found to associate with both type-I and type-II topoisomerases, the partner that we focus on in this review is Topo III, a type-I topoisomerase. Linkages between RecQ proteins and Topo IIIs have been apparent since the discovery of the *S. cerevisiae* RecQ protein (Sgs1) as a suppressor of the slow-growth phenotype of cells lacking Topo III [94]. The N-terminus of Sgs1 interacts with Topo III, and this interaction appears to be the sole function of the first 100 amino acids of Sgs1 [94–97]. The discovery of this interaction in yeast prompted investigations in other organisms; for example, *E. coli* RecQ was shown to functionally interact with Topo III as well to stimulate DNA catenation/decatenation and the resolution of converging DNA replication forks [98–100]. In humans, the N-terminus of BLM is responsible for interaction with Topo IIIα and both proteins localize to promyelocytic leukemia protein (PML) nuclear bodies [72, 101, 102]. Furthermore, a study examining the effects of deleting the Topo IIIα-interaction domain from BLM (residues 1–133) revealed an arrangement in which interaction with BLM recruits Topo IIIα to PML bodies and showed that this interaction is important in suppressing SCEs [102]. BLM appears to recruit Topo IIIα to DNA and to stimulate its decatenase activity [102–104]. These functional RecQ/Topo III interactions appear to be conserved from bacteria to humans, and, in all cases, the RecQ helicase stimulates the enzymatic activity of the topoisomerase [94, 98, 103, 104].

Although the cellular importance of RecQ/Topo III interactions had been established by the late 1990s, the precise substrates on which the BLM/Topo IIIα complex operated (especially with respect to the elevated SCEs observed in BS cells) remained unresolved for some time. An important breakthrough on this question was made by the Hickson group when they considered the types of substrate that might require both BLM and Topo IIIα [105]. Since there are no torsional constraints in simple HJ substrate that would mimic DNA in vivo, they sought out a constrained HJ-based substrate—a double Holliday junction (dHJ). It was discovered that BLM and Topo IIIα worked together to resolve this substrate in a way that prevented exchange of flanking DNA, a process termed "dissolution" [105] (Fig. 2a). This discovery also provided a satisfying explanation for the

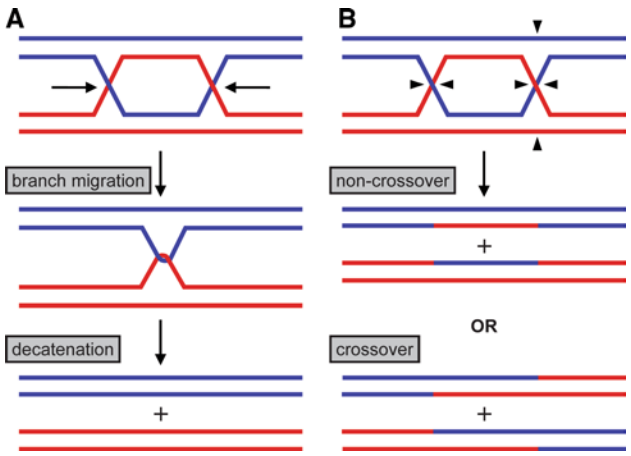

Fig. 2 Pathways for the resolution of dHJ structures. **a** Proposed pathway for dHJ dissolution. In this pathway, BLM migrates the two HJs towards each other, then Topo IIIα decatenates the structure in the second step, producing exclusively non-crossover products. **b** Pathway for HJ resolvases. In this pathway, each HJ is cleaved by an HJ resolvase and an equal mixture of non-crossover and crossover products result, depending on if the HJs are cleaved symmetrically or asymmetrically, as depicted by the *arrows*

high levels of SCEs in BS cells. dHJ structures can arise in HR-dependent double-strand break (DSB) repair [106], and can be acted upon by either the BLM/Topo IIIα dissolution pathway or by HJ resolvases, which cleave symmetrically or asymmetrically to form a mixture of crossover and non-crossover products [107, 108] (Fig. 2b). In BLM-deficient BS cells, resolvase-mediated cellular processes would be the dominant pathways for dealing with dHJ structures, which would lead to the exchange of large pieces of homologous chromosomes. In the process of dissolution, BLM is proposed to catalyze branch migration to merge the two HJs into a hemicatenated structure upon which Topo IIIα acts to create exclusively non-crossover products [6] (Fig. 2a). This exclusivity is thought to be important to avoid a "loss of heterozygosity" (LOH) that can occur when the chromatids are separated into daughter cells, which might be tied to the increased cancer predisposition seen in BS patients [109, 110]. While this mechanism provides an explanation for the increase in SCEs observed in BS cells, BLM and the BLM dissolvasome have multiple roles in cells beyond dHJ dissolution, and their roles in other pathways also prevent crossover formation (see "BLM and the BLM dissolvasome in DSB repair").

BLM interactions with RMI1 and RMI2

Although the BLM/Topo IIIα connection provided an important link for understanding the origins of SCEs in BS cell lines, two additional proteins were subsequently found to be important for stabilizing the complex in HeLa cell nuclear extracts—RMI1 and RMI2 (RMI stands for RecQ-mediated genome instability) (Fig. 1). Together, the BLM/Topo IIIα/RMI1/RMI2 complex is referred to as the "BLM dissolvasome" or "BTR complex."

RMI1 was identified as a 625-residue protein that co-purified at near-stoichiometric levels with human BLM and Topo IIIα [73] (Fig. 1). The N-terminus of RMI1 directly interacts with BLM and Topo IIIα and stimulates dHJ dissolution greater than tenfold in vitro [111–113]. This is accomplished by stimulation of Topo IIIα, since a variant of RMI1, K166A, which is able to bind BLM but not Topo IIIα, cannot stimulate dHJ dissolution [104, 113]. RMI1 contains N- and C-terminal oligonucleotide/oligosaccharide binding (OB) domains, which led to speculation that it may bind DNA and stimulate Topo IIIα through recruitment effects [73, 114] (Fig. 1). However, RMI1 has only very weak DNA binding affinity in its C-terminal OB domain, which is dispensable for dHJ stimulation in vitro [73, 111, 113, 115]. Instead, RMI1 appears to be important to the stability of the BLM/Topo IIIα/RMI1 complex, since depletion of RMI1 significantly increases SCE levels and affects cellular protein levels of Topo IIIα and, to a lesser extent, BLM [73]. Since RMI1 is able to stimulate Topo IIIα activity in vitro, it might also stabilize a conformation of Topo IIIα with increased catalytic activity [111, 112]. In *S. cerevisiae*, a homolog of the human RMI1 (Rmi1) was identified as a smaller, 241-residue protein that appears to be most similar to the N-terminus of human RMI1 in that it forms a complex with Sgs1 and Topo III and stimulates Topo III activity [116–118].

RMI2 was subsequently discovered as a binding partner to RMI1 in human cells, and the two together comprise the RMI subcomplex. RMI2 is a 147-residue protein comprised entirely of an OB fold that interacts with the C-terminal OB fold of RMI1 [115, 119] (Fig. 1). The RMI subcomplex is formed through interactions between these OB folds in a manner similar to that of RPA70/RPA32; however, the RMI subcomplex lacks the ability to bind DNA and there is no conservation with the DNA-binding residues found in the RPA complex [115, 120, 121] (Fig. 1). In HeLa cells, depletion of either RMI1 or RMI2 by siRNA significantly reduces the protein levels of the other, indicating their interdependence [115, 119]. Furthermore, their knockdown leads to a strong decrease in Topo IIIα protein levels and a more modest decrease in BLM protein levels [115, 119]. Therefore, it appears that RMI1, RMI2, and Topo IIIα are more highly interdependent in vivo (perhaps forming a stable complex), whereas BLM may be a dissociable component. In addition, studies in hyper-recombinant chicken DT40 cells reveal that knockdown of RMI2 leads to an increase in SCE levels, and when both BLM and RMI2 are knocked down the levels are the same as BLM alone, indicating that RMI2 works with BLM to prevent crossovers [73, 115] (Table 1). Mutations that destabilize the RMI1/RMI2 interface also lead to increased levels of SCEs [121]. In response to DNA damaging agents and replication inhibitors, RMI1 and RMI2 both co-localize with BLM to nuclear foci associated with DNA damage [115]. Additionally, when either RMI1 or RMI2 is depleted, BLM localizes to significantly fewer nuclear foci [73, 115]. These studies confirm the importance of the RMI subcomplex and highlight the central importance of the BLM dissolvasome in DNA repair.

BLM and the BLM dissolvasome in DSB repair

Numerous studies have identified both pro- and anti-recombinogenic activities for BLM in DSB repair, even though the high levels of crossovers that form in its absence suggest a primarily anti-recombinogenic role. In fact, BLM may shuttle DSB repair intermediates towards a "pro-recombination" pathway in order to ensure they are resolved via dissolution, and therefore without crossover [9]. Evidence supports roles for BLM in multiple steps in HR-dependent DSB repair, including 5′ end resection, RAD51 filament

Table 1 A summary of studies examining cellular SCE

Protein disrupted or mutated	WT SCE	Mean SCE	Fold increase	Cell line	Significance
BLM [11]	6.9	89.0	12.9	BS patient cells	Initial SCE report in BS cells
Topo IIIα [221]	–	–	–	Mouse embryonic	Embryonic lethal
Topo IIIα [222]	–	–	–	DT40	Knockout is lethal
BLM [223]	2.1	26.4	12.6	DT40	
RAD54 [223]	2.1	1.7	0.8	DT40	RAD54 is a DSB repair protein
BLM/RAD54 [223]	2.1	8.2	3.9	DT40	Many SCEs come from DSB repair
BLM [73]	~0.2[a]	~0.5[a]	2–3	HeLa siRNA[b]	
RMI1 [73]	~0.2[a]	~0.5[a]	2-3	HeLa siRNA[b]	BLM and RMI1: same pathway
BLM [115]	2.1	19.0	9.0	DT40	
RMI2 [115]	2.1	11.4/9.5	5.4/4.5	DT40	Two different experiments
BLM/RMI2 [115]	2.1	18.1	8.6	DT40	BLM and RMI2: same pathway
RMI2 Lys121Ala [115]	2.1	8.2	3.9	DT40	Disrupts RMI/FANCM interface
RMI2 [121]	1.85	11.3	6.1	DT40	
RMI2 Lys121Ala [121]	1.85	10.2	5.5	DT40	Disrupts RMI/FANCM interface
RMI2 Lys121Glu [121]	1.85	10.9	5.9	DT40	Also weakens RMI1/RMI2 (in Co-IPs)
RMI2 Asp141Lys [121]	1.85	15.3	8.3	DT40	Disrupts RMI1/RMI2 interface
RMI2 Lys121Glu/ Asp141Lys [121]	1.85	11.6	6.3	DT40	Disrupts both interfaces
FANCC [173]	1.4	5.1	3.6	DT40	
FANCC [175]	1.8	4.1	2.3	DT40	
FANCJ [175]	1.8	5.2	2.9	DT40	
FANCM [172]	1.8	9.0	5.0	DT40	SCEs higher than other FA disruptions
FANCC [172]	1.8	6.0	3.3	DT40	
FANCM/FANCC [172]	1.8	14.9	8.3	DT40	SCEs are additive: two pathways
FANCM D203A [172]	1.8	8.9	4.9	DT40	FANCM catalytic activity required
BLM [172]	1.8	14.0	7.8	DT40	
BLM/FANCM D203A [172]	1.8	15.2	8.4	DT40	BLM and FANCM: same pathway
FANCJ [79]	0.31	0.59	1.9	EUFA30-F[c]	Also no SCE increase in FA-C cells
FANCJ [79]	0.21	0.36	1.7	PSNF5[c]/FANCJ siRNA	
BLM [79]	0.21	1.38	6.6	PSNG13[c]	"WT" data is from above PSNF5 cells
BLM/FANCJ [79]	0.21	1.21	5.8	PSNG13[c]/FANCJ siRNA	BLM and FANCJ: same pathway
FANCM [156]	~6[a]	~12.5[a]	2-3	293 siRNA[b] with MMC	
FANCM FF >AA [156]	~6[a]	~12.5[a]	2-3	293 siRNA[b] with MMC	Disrupts RMI/FANCM interface [183]
FANCM [183]	2.0	17.7	8.9	DT40	
FANCM F1232A [183]	2.0	14.2	7.1	DT40	Disrupts RMI/FANCM interface [183]
RIF1 [80]	1.7	1.7	1.0	DT40	Not involved in SCE suppression

[a] Mean SCE was not reported, inferred from data

[b] Experiments using siRNA are known to not completely mimic the SCE levels observed in BS patients

[c] *EUFA30-F* FA-J fibroblasts, *PSNF5* $BLM^{+/+}$, *PSNG13* $BLM^{-/-}$

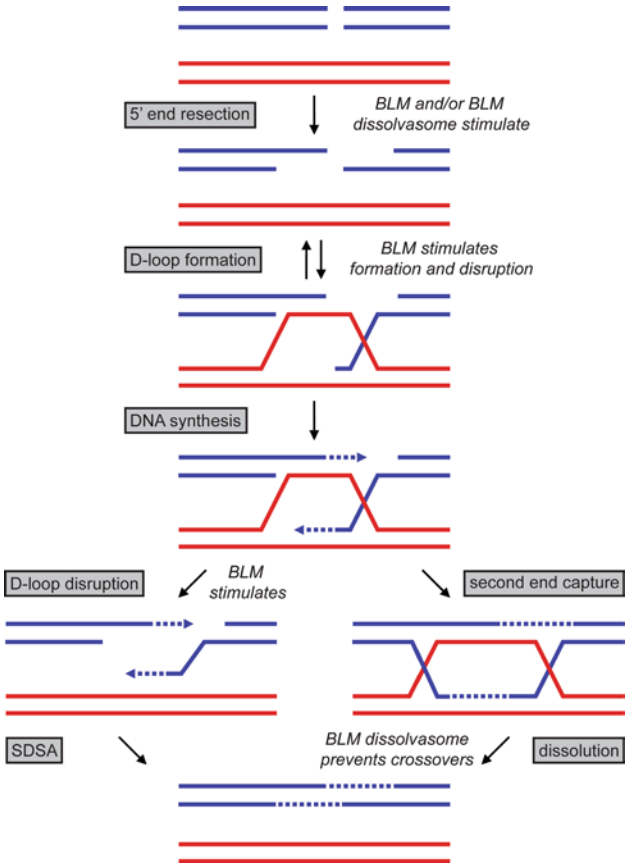

Fig. 3 Roles for the BLM dissolvasome in HR-dependent DSB repair. Shown here is the pathway for DSB repair, showing the different steps where BLM and/or the BLM dissolvasome may act or stimulate. The pathways shown here are resolved to non-crossover products, either via synthesis-dependent strand annealing (SDSA) (*left*) or dHJ dissolution (*right*); however, the dHJ substrate may also be resolved via HJ resolvases as shown in Fig. 2. New DNA synthesis is depicted with a *dashed line*

and D-loop formation, and, as described earlier, in resolving dHJ structures (Fig. 3). These roles are reviewed in the remainder of this section.

Multiple laboratories have shown that BLM is able to stimulate nuclease activity in 5′ end resection [9, 77, 78, 122] (Fig. 3). In humans, two pathways for end resection have been discovered, one involving the nuclease DNA2 and one involving exonuclease 1 (EXO1), and in both these pathways BLM physically interacts with and stimulates the nuclease [77, 78]. While both RecQ1 and WRN are able to simulate other EXO1 catalytic activities, only BLM has been shown to specifically stimulate the end resection activity of EXO1 and DNA2 in vitro [77, 78, 123, 124]. In *Xenopus laevis* cell-free extracts, WRN was shown to function with DNA2 in end resection, but more research is required to determine whether this represents a conserved role for WRN [125]. The most extensive studies have been performed in the yeast system, where Sgs1 has been shown to stimulate Dna2 [126, 127]. This is relevant in vivo, since, when *exo1* and *sgs1* are simultaneously deleted in yeast (thus disrupting both pathways for end resection), cells become sensitive to a wide range of DNA-damaging agents [122]. By monitoring end resection in cells, it was further shown that Sgs1, Topo IIIα, and Rmi1 are all involved in the same resection pathway [127]. In addition, the Sgs1/Dna2 pathway has been reconstituted in vitro, and end resection was stimulated by the addition of Rmi1/Topo IIIα [128, 129]. In this context, Rmi1/Topo IIIα are together able to stimulate the helicase activity of Sgs1 and are thought to aid Sgs1 DNA binding; however, this stimulation does not appear to require the catalytic activity of Topo IIIα [128, 129]. Further research will be required to determine the importance of this stimulation in vivo and whether similar biochemical attributes are conserved in humans. Nonetheless, the role of BLM in 5′ end resection is pro-recombinogenic since it aids in initiation of HR. This activity may serve to shuttle DSBs away from non-homologous end joining (NHEJ) pathways, which are more error prone and have been observed at higher levels in BS cells [130]. NHEJ is active during the entire cell cycle; however, it cannot be initiated from the free 3′ ssDNA end that results from end resection, and in this way BLM's role in end resection may be one of the factors that helps determine DSB repair pathway choice [131]. Since BLM is cell cycle regulated, this would help ensure that the HR-dependent DSB repair is the primary pathway when an available sister chromatid exists to act as a template [132–134]. Moreover, cells in S- and G2-phase appear to predominantly use HR to repair DSBs, and to complete this repair via dissolution to prevent exchange of genetic material [9].

In the second step of HR, the RAD51 recombinase forms a helical filament on the free 3′ DNA end. A homology search for the DNA in the RAD51/ssDNA complex produces a D-loop structure as a result of invasion of the ssDNA into a homologous sister chromatid or chromosome [135] (Fig. 3). In this step, BLM interacts with RAD51 and is able to migrate and unwind D-loops, which disrupts nascent pairing in the first steps of HR [43, 136, 137]. However, this activity appears to depend on the status of RAD51: BLM stimulates strand exchange of active ATP-bound RAD51 filaments, but dismantles inactive ADP-bound filaments [137–139]. This may indicate that BLM surveys nascent D-loops to assure they are appropriate for HR. This activity could be related to a function of the prototypical *E. coli* RecQ in preventing illegitimate recombination between homologous but non-identical DNA sequences [140]. Finally, some of the dismantled filaments may be repaired via single-strand annealing (SSA), which relies on flanking DNA repeat sequences commonly found in mammalian DNA [135].

Following D-loop formation and DNA synthesis, BLM has additional anti-recombinogenic rolls. First, in

synthesis-dependent strand annealing (SDSA), the resulting D-loop product is dismantled and the broken chromosome is then able to re-anneal for repair in a non-crossover fashion (Fig. 3). BLM may play a role in unwinding this D-loop [43, 136, 137]. Second, in the HR-dependent pathway, the D-loop remains intact and second end capture recruits the second strand to form a dHJ substrate (Fig. 3). This intermediate is the proposed substrate for dissolution via the BLM dissolvasome, as described above [6, 105] (Fig. 2a). However, the dHJ substrate could also be resolved through cleavage by HJ resolvases, which leads to an equal distribution of non-crossover and crossover products (Fig. 2b). Overall, it appears that BLM and potentially the entire BLM dissolvasome have multiple roles in HR, and while these roles may be categorized as pro- and anti-recombinogenic, it is likely that BLM activity is focused on ensuring HR fidelity and the prevention of crossovers.

The role of the BLM dissolvasome in replication restart

Early observations with BS cell lines revealed a replication deficiency and hinted that BLM might help repair stalled or damaged replication forks. Cells from BS patients are slower to progress through S-phase and accumulate abnormal replication intermediates [141–143]. Additionally, BLM levels are regulated in a cell cycle-dependent manner, accumulating in S-phase and persisting through G2/M before diminishing in G1 [132–134]. Cells from BS patients are hypersensitive to replication stalling with hydroxyurea (HU), and BLM localizes to these stalled forks [82, 144].

Multiple studies point to pivotal roles for BLM in the repair of stalled DNA replication forks [145, 146]. DNA replication processes can stall due to blockage of the replication fork by encounters with physical barriers, such as proteins that are tightly bound to the DNA template or impassable damage to the template. For example, replication through a nick in parental DNA creates a DSB when the replicative helicase proceeds through the nicked region. In these instances, the BLM-dependent DSB repair pathways described above would be triggered to drive replication restart (for review, see [147]). In addition, because BLM is a helicase that specifically acts upon DNA substrates that resemble replication and recombination substrates, a separate possible role for BLM is to produce DNA structures that are competent for replication restart. For example, a lesion on the leading strand that prevents progression of the replication fork could lead to replication fork regression and HJ formation (creating an intermediate referred to as a "chicken foot" structure), whose formation could be driven by BLM branch migration [148–150]. This structure can promote lesion bypass by supplying an intact template for the nascent leading strand (template switching) [145]. Following lesion bypass, BLM may also act to reverse the regressed fork via branch migration so that replication can proceed past the lesion, or, instead, replication may restart through an HR-mediated process that would proceed through a dHJ structure that the BLM dissolvasome could act on [149].

More recently, single-molecule DNA fiber and molecular combing techniques have allowed detailed interrogation of the roles of BLM in mammalian DNA replication [151]. These studies have shown that BLM is required for efficient recovery of replication forks blocked by aphidicolin or HU [152], and that BS cells exhibit reduced fork velocity and more incidences of fork pausing [153]. Moreover, the BLM dissolvasome has been implicated in fork progression, as a recent study has shown that depletion of RMI1 leads to a reduction in replication fork rate and a failure to recover from replication fork arrest [154]. Interestingly, these defects in replication fork rate can be suppressed when BLM is also depleted, which indicates that RMI1 and potentially the rest of the BLM dissolvasome act downstream of BLM [154]. Finally, the protein RIF1 has been shown to interact with the BLM dissolvasome to promote replication fork restart; however, RIF1 does not play a role in SCE suppression [80] (Table 1). RIF1 can bind directly to replication fork and HJ DNA and it may coordinate fork regression with BLM [80]. Therefore, the BLM dissolvasome may have roles in replication restart that are not related to its function in suppressing SCEs. In summary, a growing body of literature supports roles for the BLM dissolvasome at replication forks to help maintain integrity through DSB repair and efficient replication restart.

Link with Fanconi anemia protein FANCM

The discovery that the BLM dissolvasome was linked to proteins involved in the autosomal recessive disease Fanconi anemia (FA) made an important connection in genome maintenance that further solidified the importance of the BLM dissolvasome in DNA replication restart [155, 156]. As is the case for BS cells, FA cell lines have significantly heightened levels of chromosomal instability, although they are exemplified by radial chromosomes and a hypersensitivity to agents that induce DNA interstrand crosslinks (ICLs). Mutations in at least 15 genes [FANCA, B, C, D1 (BRCA2), D2, E, F, G, I, J, L, M, N, O, and P] give rise to this highly heterogeneous disease, which includes symptoms of developmental abnormalities, progressive bone marrow failure, and a high occurrence of cancer [157–160]. Prior to the discovery that key proteins in FA and BS directly interacted with one another, roles for the FA proteins in repair of DNA damage at ICL sites that have caused replication fork failure were known [161]. In this response, a core complex of eight FA proteins (FANCA, B, C, E, F, G, L, and M)

recognizes the DNA damage and catalyzes monoubiquitination of the FANCD2/FANCI heterodimer. Ubiquitinated FANCD2/FANCI in turn recruits downstream FA proteins such as FANCJ to facilitate removal of the ICL, which is followed by translesion synthesis, nucleotide excision repair, and HR to fully repair the DNA [160–162]. Further details on the FA pathway can be found in a recent review by Kim and D'Andrea [160].

The initial finding that linked the BLM dissolvasome to FA was identification of an ICL-induced super-complex called BRAFT (BLM, RPA, FA, and Topo IIIα) that included components of both the BLM dissolvasome and FA proteins [155, 163]. A subsequent study revealed that BLM and FA proteins co-localized in response to treatment with DNA crosslinkers or replication arrest and could be co-immunoprecipitated [164]. Of the FA proteins, FANCM is the most conserved, with orthologs in archaebacteria (Hef) and yeast (MPH1 in *S. cerevisiae*, and Fml1 in *Schizosaccharomyces pombe*) [165–168]. FANCM is a large, 2,048-residue subunit of the FA core complex that contains an N-terminal DEAH-box helicase domain and a degenerate C-terminal ERCC4-like endonuclease domain linked together by a highly dynamic linker element that has only short regions of conserved sequence [156, 165]. FANCM is thought to act as a sensor to detect blocked replication forks in coordination with partner proteins FAAP24 and MHF [169–171] (Fig. 4a). This complex is then thought to recruit other FA proteins in order to repair the DNA damage, and, subsequently, FANCM may act catalytically to remodel the replication fork in order for replication to proceed [158, 169, 170]. FANCM-deficient cells are also characterized by a large increase in SCEs, which has also been described for other FA proteins such as FANCC and FANCJ, though to a lesser degree than that observed with FANCM-depleted cells [172–175] (Table 1). This striking phenotypic parallel between FANCM- and BLM-deficient cells foreshadowed an interaction between FANCM and the BLM dissolvasome.

FANCM appears to have additional roles beyond recruitment of the FA core complex to ICL-damaged DNA [172, 176, 177]. FANCM might also aid in general coordination of replication restart, and only initiate the FA pathway under specific circumstances such as ICLs. While FANCM has not demonstrated helicase activity, as a translocase FANCM can act on DNA substrates that mimic replication forks and HJs, and has been implicated in replication fork remodeling [165, 176, 178, 179]. Molecular combing experiments have shown that the translocase activity of FANCM is important for the restart of stalled replication forks [180, 181]. Moreover, these stalled replication forks have been shown to be prone to collapse, which generates DSBs that are subsequently repaired through HR [182]. At these sites, the coordinated activity of the BLM dissolvasome and FANCM may be most evident.

A direct interaction between a conserved 34-residue motif in the middle of FANCM (called MM2, for FANCM Motif 2) and the C-terminal OB-fold of RMI1 was first demonstrated in 2009 [156] (Fig. 4). A recent crystal structure of a proteolytically stable RMI1/RMI2 fragment bound to the MM2 peptide has revealed that the full interface is comprised of both the C-terminal OB-fold of RMI1 and

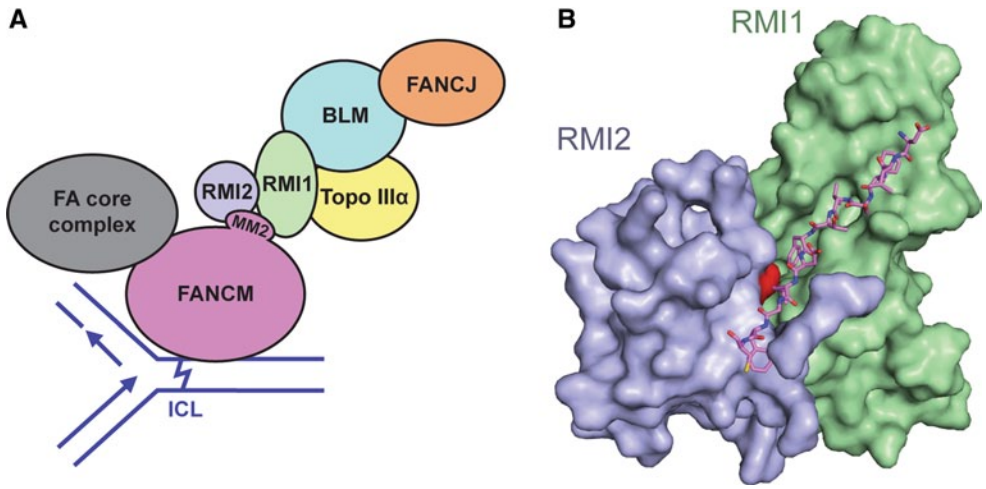

Fig. 4 BLM dissolvasome and FA protein interactions described in this review. **a** A potential model for the protein interactions between the BLM dissolvasome, FANCM, and FANCJ. FANCM is shown at a site of DNA damage, depicted as an ICL, that may be encountered during replication and impede fork progression. In this model, FANCM then recruits the BLM dissolvasome through the MM2 interaction with the RMI subcomplex. FANCM is also part of the FA core complex and can localize the rest of the core complex to an ICL. FANCJ may also be recruited to sites of DNA damage via its interaction with BLM. **b** The overall structure of the RMI core complex with bound MM2 peptide from FANCM. MM2 residues 1,226–1,237 are shown in *purple*, and RMI2 Lys121 is highlighted in *red* [183]

the full-length RMI2 protein [183] (Fig. 4b). In this complex, the side chains of conserved hydrophobic residues from FANCM MM2 dock into hydrophobic pockets on the RMI1/RMI2 surface, forming a stable tripartite complex [183]. A FANCM mutation in two of the docking residues from MM2 (FANCM FF >AA) leads to an increase in SCEs upon treatment with mitomycin C (MMC), which induces ICLs [156] (Table 1). Moreover, mutation of a key residue on the RMI surface (Lys121 of RMI2) leads to an increase of SCEs in chicken DT40 cells that is similar to levels seen when FANCM or members of the BLM dissolvasome are depleted [73, 115, 121, 169, 172, 183] (Table 1; Fig. 4b). These data indicate that coordination between FANCM and the BLM dissolvasome is critical in preventing crossover formation. Beyond their roles in SCE suppression, the BLM dissolvasome, FANCM, and FANCJ (see below) all appear to be important in replication fork progression, remodeling, and integrity. Further research will be required to delineate their specific roles and interdependence.

BLM/FANCJ interaction

In addition to the RMI/FANCM interaction, interactions between other FA- and BS-associated proteins have been reported. Notably, a functional and physical interaction has been described between BLM and FANCJ, a helicase that acts downstream of the FA core complex [79] (Fig. 4a). As with BS- and FANCM-deficient cells, SCEs are elevated in FANCJ-deficient cells (although only ~two- to threefold for FANCJ; see Table 1), and this elevation is synergistic with BLM [79, 175]. FANCJ is an ATP-dependent SF2 helicase that acts in the 5′–3′ direction and is also sensitive to replication stress, and therefore it may cooperate with BLM replication restart [79, 184] (for recent discussion on this interaction, see [185]). In addition, both BLM and FANCJ are able to unwind G-quartet DNA, and both may be important in replication to remove these secondary structure elements from DNA so that replication can proceed [39, 186, 187]. A recent study in DT40 cells implied a genetic interaction between FANCJ, BLM, and WRN that may allow coordination of replication through G-quartet DNA [188].

BLM and FA proteins both act at the replication-dependent checkpoint

In parallel with their activities in replication fork stability and restart, roles for BLM and multiple FA proteins have been established in the replication-dependent or S-phase cell cycle checkpoint. This checkpoint triggers cell cycle arrest when replicative processes are blocked due to DNA damage, which leads to the activation of ataxia-telangiectasia mutated (ATM) and ATM and Rad3-related (ATR) kinases [189]. ATM and ATR activation initiates a signaling cascade that stalls the cell cycle, providing the time needed to recover from replicative stress. While the two pathways are interdependent, ATR generally signals replication-dependent damage through checkpoint kinase 1 (CHK1), whereas ATM signals in response to DSBs via checkpoint kinase 2 (CHK2) [190, 191].

Within this checkpoint mechanism, BLM, FANCD2, and FANCI are targets of both the ATR/CHK1 and the ATM/CHK2 pathways within the pathway, whereas FANCA and FANCE appear to be acted upon preferentially by the ATR/CHK1 pathway [81, 82, 192–199]. BLM is phosphorylated at T99 and T122, and BS cells expressing an unphosphorylatable BLM variant are unable to recover following treatment with HU, and instead enter an extended arrest at the G2/M checkpoint [81, 82]. Furthermore, this recovery is dependent on the helicase activity of BLM [152]. Taken together, these data indicate a critical role for BLM at the replication-dependent checkpoint, and suggestthat, after replication has stalled, BLM is phosphorylated, which signals its localization to replication forks in order to aid in faithful restart. BLM may act without the rest of the BLM dissolvasome in this role, as phosphorylation on T99 by ATM or ATR causes BLM to dissociate from Topo IIIα, and presumably also from the RMI subcomplex [192].

FANCM and its binding partner FAAP24 have been implicated as upstream effectors in activation of the ATR pathway, which is independent from the rest of the FA core complex [179–181]. However, a more recent study has suggested that FANCM and FAAP24 have some independent functions, and that FAAP24 alone is responsible for checkpoint activation [200]. In a similar fashion, FANCJ appears to play a role in ATR activation [201]. These insights have led to a model in which FANCM/FAAP24 (or FAAP24 alone) and FANCJ act as sensors of replication stress in cells to initiate activation of ATR/CHK1 and the replication-dependent checkpoint. The activation of this checkpoint then leads to phosphorylation of other FA proteins and BLM to aid in DNA repair and replication restart [158, 181]. Further research will be required to tease apart the roles of each at different stages and how they vary depending on the type of genetic insult.

The BLM dissolvasome and FA proteins are both found associated with ultra-fine anaphase bridges

DNA staining of sister chromatids as they separate during mitosis has revealed the presence of anaphase DNA bridge structures that link the two chromatids. More recently, a subclass of anaphase bridges, termed “ultra-fine anaphase bridges” (UFBs), have been discovered [202–204]. These

UFBs are more thread-like and cannot be visualized with conventional DNA dyes; instead, they are localized with immuno-staining of proteins found on the UFBs. Several proteins, including members of the BLM dissolvasome and the PLK1-interacting checkpoint helicase (PICH), are localized to UFBs, and BLM may be specifically recruited by its interaction with PICH [75, 202, 203]. Localization of Topo IIIα and RMI1 to UFBs is dependent on BLM, and therefore it appears that BLM recruits the rest of the BLM dissolvasome to UFBs [203]. The majority of UFBs arise at centromeres, where it has been proposed that the BLM dissolvasome and PICH might cooperate to facilitate the association of Topo IIα, a type-II topoisomerase, to drive centromere disjunction [75, 203, 205–207]. To further support this hypothesis, BLM and Topo IIα have been shown to interact both in vitro and in vivo [74, 208]. The majority of these bridges appear to resolve as mitosis progresses without the formation of DSB intermediates, and may be normal structures that assist in centromeric cohesion [204].

A less common class of UFBs that are exclusively found at common fragile sites on chromosomes are proposed to result from incomplete DNA replication that is induced by replication stalling agents [209, 210]. Normally, under replication stress, additional replication initiation events will occur so that the DNA can be fully duplicated, but recent studies indicate that, at fragile sites, there is a lack of these extra initiation events, and so mitosis may begin before these regions have completed replication, resulting in a UFB [211, 212]. Apart from their spatial differences, the other distinguishing feature of this class of UFBs is the localization of FA proteins FANCD2 and FANCI at their termini, which is consistent with their presence being related to replication stress [209, 210]. FANCD2/I are proposed to be recruited to sites of incomplete replication in the late S- and G2-phases, which then become sites of UFBs that are coated by BLM and PICH in mitosis. FANCM has also been localized to UFBs in a BLM-dependent manner, though FANCM is observed on UFBs later in mitosis after BLM has already dissociated from UFBs [213]. It has therefore been hypothesized that the BLM dissolvasome can recruit FANCM to UFBs in a hand-off mechanism; however, another possibility is that BLM alters the structure of the DNA in the bridge to make it accessible for FANCM later in mitosis [204, 213].

Most of these FA-dependent bridges disappear as mitosis progresses, although some persist, and presumably the cell divides before replication is completed at these sites [209, 210]. One hypothesized fate of UFBs is to resolve before replication is complete and form symmetrical DNA lesions in daughter cells that are marked as sites of DNA damage with 53BP1 [214]. These sites become sequestered and protected by 53BP1 nuclear bodies until they can be repaired properly in the next S-phase [204, 214, 215]. Alternatively, a more detrimental result of unresolved UFBs is chromosomal breakage, which leads to the formation of micronuclei. These products are observed at higher frequency when BLM or FA proteins are depleted in cells [10, 203, 209, 210, 213].

Concluding remarks

From the initial studies of the relatively simple *E. coli* RecQ protein to the more complex BLM dissolvasome and its many interactions, it has become clear that RecQ proteins and protein complexes have evolved central roles in maintaining genomic stability in all organisms. In all cases, these proteins do not act alone, but instead function as components in direct and indirect networks that integrate diverse enzymatic activities and cellular regulatory systems. In this review, we have focused on BLM and its interactions with Topo IIIα, RMI1, and RMI2, which comprise the BLM dissolvasome in humans. Overall, BLM appears to coordinate its functions with these and other proteins in order to maintain genetic stability in somatic cells. These functions include roles in replication restart, HR-dependent DSB repair, the replication-dependent checkpoint, and at UFBs. In many of these pathways, a role for BLM has only recently been described, and future studies will be required to understand the precise role for BLM and/or other human RecQ helicases in vivo.

We have also explored the role of the interaction between the BLM dissolvasome and FA proteins, specifically FANCM and FANCJ. It appears that BLM and FA proteins work together in many pathways, and we have described one potential model for the localization of these proteins at ICLs (Fig. 4a). The BLM dissolvasome and FA proteins coordinate their roles in dHJ dissolution, both respond to stalled replication forks, are involved in the replication-dependent checkpoint, and are found at UFBs. Another interesting collaboration may also exist in DSB repair, as FA proteins have been speculated to be involved in repair pathway choice, especially if the damage is an ICL. Studies in *C. elegans*, chicken DT40, and mammalian cells have provided evidence that the FA pathway helps to suppress NHEJ and promote repair via HR [216, 217]. A recent study showing that DNA2 and FANCD2 can be copurified provides further evidence that the FA pathway is involved in end resection [218]. However, the network of direct protein–protein interactions required to support this function remains to be defined.

With the stark effects of mutations in three of the five human RecQ genes, the central nature for RecQ proteins is well appreciated. Future research will continue to define the biochemical and cellular roles for RecQ proteins, leading to a better understanding of the molecular basis by which these

critical enzymes function and the cellular consequences that result from their dysfunction. These studies may also pave the way for the development of new chemotherapeutics and allow for better treatment of patients with BS and FA. As an example, one recent study identified a small molecule that competitively inhibits BLM and induces an increase in SCEs [219]. This compound will be useful to more specifically target BLM inactivation in further studies and as a potential chemotherapeutic. Other compounds may similarly be discovered that inhibit specific proteins or interactions and could be used to sensitize cancer cells to DNA-damaging agents in cancer treatment.

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