Cell Research (2008) 18:99-113.

www.nature.com/cr

REVIEW

Homologous recombination in DNA repair and DNA damage tolerance

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Homologous recombination (HR) comprises a series of interrelated pathways that function in the repair of DNA double-stranded breaks (DSBs) and interstrand crosslinks (ICLs). In addition, recombination provides critical support for DNA replication in the recovery of stalled or broken replication forks, contributing to tolerance of DNA damage. A central core of proteins, most critically the RecA homolog Rad51, catalyzes the key reactions that typify HR: homology search and DNA strand invasion. The diverse functions of recombination are reflected in the need for context-specific factors that perform supplemental functions in conjunction with the core proteins. The inability to properly repair complex DNA damage and resolve DNA replication stress leads to genomic instability and contributes to cancer etiology. Mutations in the *BRCA2* recombination gene cause predisposition to breast and ovarian cancer as well as Fanconi anemia, a cancer predisposition syndrome characterized by a defect in the repair of DNA interstrand crosslinks. The cellular functions of recombination are also germane to DNA-based treatment modalities of cancer, which target replicating cells by the direct or indirect induction of DNA lesions that are substrates for recombination pathways. This review focuses on mechanistic aspects of HR relating to DSB and ICL repair as well as replication fork support.

***Keywords*:** DNA repair, double-strand breaks, genome stability, homologous recombination, interstrand crosslinks, stalled replication forks

Cell Research (2008) **18**:99-113. doi: 10.1038/cr.2008.1; published online 1 January 2008

Introduction

DNA damage is a fact of life as a consequence of endogenous sources and processes as well as exogenous sources [1]. Homologous recombination (HR) is a DNA metabolic process found in all forms of life that provides high-fidelity, template-dependent repair or tolerance of complex DNA damages including DNA gaps, DNA double-stranded breaks (DSBs), and DNA interstrand crosslinks (ICLs). In addition to its role in preserving the genome, HR plays a prominent role in faithfully duplicating the genome by providing critical support for DNA replication and telomere maintenance. The competition between the HR and non-homologous end-joining (NHEJ) pathways in the repair of DSBs is specifically addressed in the chapter by Shrivastav *et al.* (in this issue). HR competes in DNA damage tolerance with translesion synthesis (TLS) pathways, and TLS polymerases are discussed in dedicated chapters by Gan *et al.* and Andersen *et al.* (in this issue). In ICL repair, HR is envisioned to collaborate with nucleotide excision repair (NER), and NER is the topic of the chapter by Shuck *et al.* (in this issue).

Many aspects of HR have been reviewed previously, and the reader is referred to these outstanding contributions [2-9]. This review focuses on the mechanism of HR during DSB (Figure 1) and ICL repair (Figure 3), as well as in the recovery of stalled and broken replication forks (Figure 2), based on studies with proteins from the budding yeast *Saccharomyces cerevisiae* and humans (Table 1). The significance of the role of HR in maintaining genome stability and tumor suppression is highlighted by the tumor suppressor protein BRCA2 [6, 10, 11]. BRCA2 establishes a role of HR in cancer suppression, and also provides the nexus between HR and Fanconi anemia (FA), a classical DNA repair cancer predisposition syndrome that defines a molecular pathway with a function in ICL repair [12, 13].

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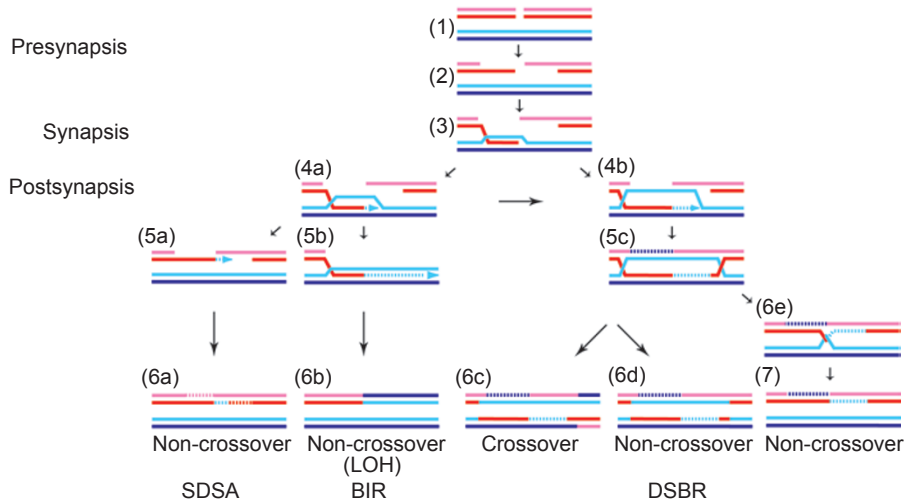

Figure 1 Pathways of recombination in DSB repair. Homologous recombination can be conceptually divided into three stages: presynapsis, synapsis, and postsynapsis. During presynapsis, DSB ends are recognized and processed to a 3′-OH ending single-stranded tail (steps 1-2). In synapsis, DNA strand invasion by the Rad51-ssDNA filament generates a D-loop (step 3). At least three different pathways are proposed after the D-loop intermediate. In synthesis-dependent strand annealing (SDSA, steps 4a - 5a - 6a), the invading strand is disengaged after DNA synthesis and annealed with the second end, leading to localized conversion without crossover. This process may involve multiple rounds of invasion, synthesis, and disengagement. In break-induced replication (BIR, steps 4a - 5b - 6b), the D-loop is assembled into a full replication fork, copying the entire distal part of the chromosome to result in loss-of heterozygosity (LOH). In double-strand break repair (DSBR, steps 4b - 5c - 6c-e - 7), both ends of the DSB are engaged, either by independent strand invasion or by second end capture, leading to double Holliday junction formation. The junction can be processed by either a resolvase into non-crossover or crossover products (steps 6c and d) or dissolved by a mechanism involving BLM-mediated branch migration and TOPOIIIα-catalyzed dissolution of a hemicatenane (step 6e), leading exclusively to non-crossover products (step 7).

Homologous recombination: the core mechanism of Rad51 filament formation and DNA strand invasion

The central reaction of HR is homology search and DNA strand invasion by the Rad51-ssDNA presynaptic filament, positioning the invading 3′-end on a template duplex DNA to initiate repair synthesis (Figure 1). In the nuclear environment ssDNA is initially bound by the eukaryotic ssDNA-binding protein RPA, which displays higher affinity and specificity for ssDNA than Rad51 [5, 14]. Hence *in vivo*, Rad51 must assemble to form the presynaptic filament on RPA-coated ssDNA. What are the proteins and mechanisms required for targeting Rad51 to ssDNA and allow filament formation on RPA-coated ssDNA? How is assembly of the presynaptic filament controlled, and what triggers disassembly after DNA strand invasion? Key to the answers to these questions are the biochemical properties of the DNA binding and ATPase activities of the Rad51 protein. Also of importance are cofactors that promote assembly or stabilization of the Rad51 ssDNA-filament as well as the disassembly of the Rad51-DNA complexes (Table 1).

Rad51 is the eukaryotic RecA homolog that catalyzes homology search and DNA strand exchange [15]. Similar to RecA, Rad51 binds cooperatively to ssDNA in a ternary complex with ATP at a stoichiometry of 1 protomer per 3-4 nucleotides, forming a right-handed filament with a helical pitch of 130 Å [16, 17]. Despite the overall similarity between RecA and Rad51, important differences exist [18]. Unlike RecA, which shows a kinetic delay in binding dsDNA relative to ssDNA, Rad51 exhibits only little preference of binding to ssDNA over dsDNA [18, 19]. Moreover, Rad51 protein exhibits an approximately 100-fold lower ATPase activity than RecA on ssDNA or dsDNA [15, 18]. How is Rad51 targeted to form filaments on ssDNA? What are the consequences of its reduced ATPase activity? The functions of Rad51 cofactors are important to rationalize these differences to RecA.

RPA is the heterotrimeric ssDNA-binding protein in eukaryotes and is involved in all DNA metabolic processes involving ssDNA [14]. The function of RPA in HR is complex. *In vitro*, RPA inhibits nucleation of the Rad51 filament on ssDNA, but stimulates recombination by eliminating secondary structure in ssDNA and by binding to the displaced strand of the D-loop [20, 21]. The inhibitory effect of RPA on Rad51 filament formation is overcome

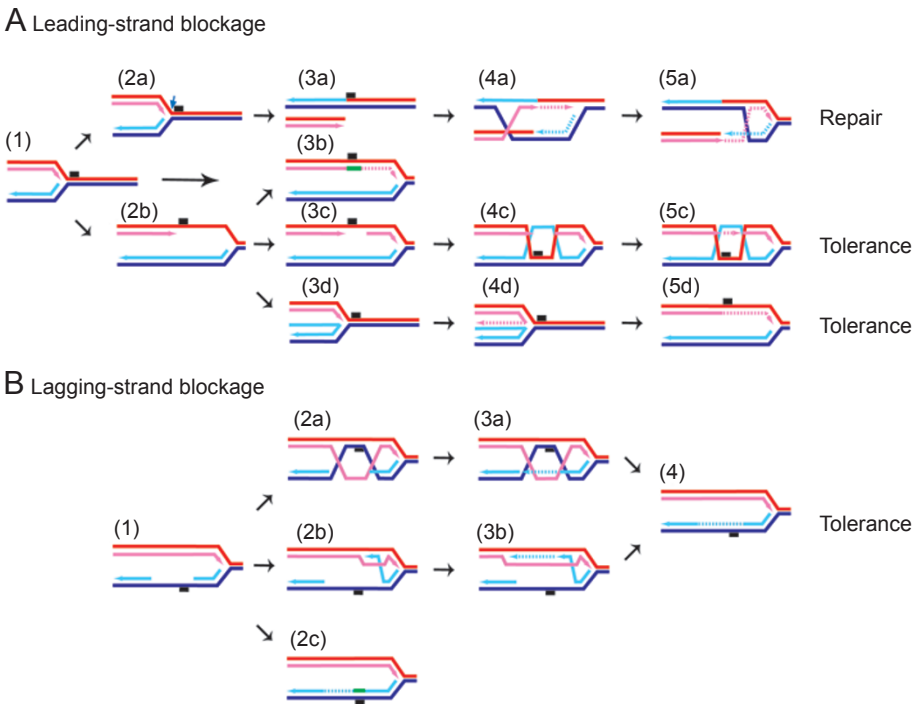

Figure 2 Pathways of homologous recombination at stalled/broken replication forks. **(A)** Possible pathways resolving leading-strand blockage. Stalled replication forks (step 1) can be cleaved by an endonuclease to generate a one-sided DSB. One-sided DSB repair by recombination (steps 2a - 3a - 4a - 5a) proceeds in analogy to BIR (**Figure 1**) involving DNA strand invasion and re-establishment of a functional fork. A single Holliday junction is created in the process. The initial blocking lesion must be either repaired or bypassed by TLS polymerases. TLS can also lead to direct bypass of the original blocking lesion (step 3b, green line). Uncoupling of lagging-strand synthesis (step 2b) can lead to direct lesion bypass by TLS (step 3b) or downstream re-initiation of leading strand synthesis, resulting in a leading strand gap, which can be repaired by recombination (steps 3c - 4c - 5c). The different strand invasion pathways are not detailed here, but are shown below for lagging strand gaps (see b; steps 2a - 3a - 4 and 2b - 3b - 4). The lesion may be repaired later or is tolerated. Alternatively, the fork could regress into a Holliday junction (also called a chicken foot), where the nascent lagging strand serves as a template for the leading strand (steps 3d - 4d). Reversal of the chicken foot enables fork progression, and the blocking lesion may be repaired later or is tolerated (step 5d). **(B)** Possible pathways resolving lagging strand blockage. Downstream re-initiation of lagging-strand synthesis after blockage leaves a gap on the lagging strand (step 1), which can be repaired by recombination (steps 2a - 3a/b - 4). Initiation from the uninterrupted strand of the gap (step 2a) leads to formation of a paranemic joint that involves partial Holliday junctions and possible double Holliday junctions. Initiation by the 3′ end strand of the interrupted strand generates a D-loop (2b - 3b). The blockage can also be directly bypassed by TLS (step 2c; green line).

by Rad51 cofactors, collectively called mediator proteins, because they mediate nucleoprotein filament formation on RPA-coated ssDNA [22]. *In vivo*, mediators are required to form Rad51 filaments, a process that is monitored by the appearance of cytologically observable Rad51 foci or by chromatin immunoprecipitation. Using these biochemical, molecular and cytological criteria, the Rad55-Rad57 complex and Rad52 have been identified as the key mediators of Rad51 filament formation in budding yeast [23-25].

Rad55 and Rad57 are two Rad51 paralogs in *S. cerevisiae* that form a heterodimer with mediator activity, as they enable Rad51-mediated *in vitro* recombination in the presence of RPA-coated ssDNA [26]. There are five human Rad51 paralogs (Rad51B, Rad51C, Rad51D, Xrcc2, Xrcc3; see Table 1), but the overall low sequence conservation makes it difficult to assign which of the human Rad51 paralogs correspond to Rad55-Rad57 [5, 27]. Rad51C associates with Xrcc3 and is also found in a complex with Rad51B, Rad51D, and Xrcc2 [28, 29]. A stable subcomplex of Rad51B-Rad51C was also shown to exhibit mediator function, allowing hRad51-mediated DNA exchange with hRPA-coated ssDNA *in vitro* [30]. The mechanism(s) by which the Rad51 paralogs function as mediators are unknown, but all are required *in vivo* for Rad51 filament formation. Genetic analysis suggests that the Rad51C-Rad51B-Rad51D-Xrcc2 and Xrcc3-Rad51C complexes have non-overlapping functions [31].

Rad52 forms a multimeric ring structure that binds

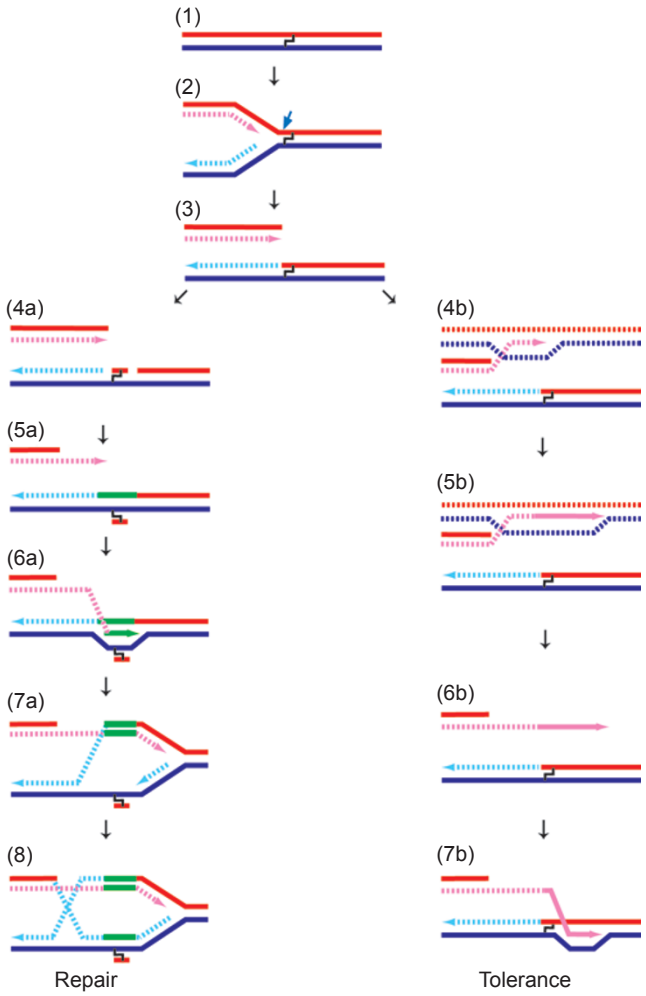

Figure 3 Homologous recombination and repair of DNA interstrand crosslinks. Possible pathways to resolve replication forks stalled at interstrand crosslinks. The stalled replication fork is recognized and cleaved by a specific endonuclease (hMus81-Eme1 [144]) in the leading-strand template to generate a one-sided DSB (steps 1-3). Introduction of a second incision on the other side of the ICL (step 4a) allows the lesion to flip out and to be bypassed by TLS (green line). The DSB is processed to form a 3′-OH ending single-stranded tail (step 5a) and to initiate DNA strand invasion (step 6a). The replication fork is restored (steps 7a) and the lesion is bypassed by TLS (green line). The lesion is eventually repaired, either after HR as drawn in step 8 or before (e.g. at step 5a). The DSB can also initiate DNA strand invasion using the homolog as a template (step 4b). DNA is synthesized across the lesion region (step 5b), disengaged (step 6b) and reinvasion of the sister chromatid behind the lesion site can lead to restoration of the replication fork and tolerance of the lesion (7b; the step from D-loop to recovered fork are not drawn and equivalent to Figure 2A, steps 3a-4a-5a). The hypothetical steps for ICL repair by nucleotide excision repair are not drawn here. For additional schemes for ICL repair/tolerance at stalled replication forks or in non-replicating DNA see refs. [138, 139, 145].

preferentially to ssDNA on the outside of the ring through an N-terminal DNA binding domain [32, 33]. Yeast Rad52 interacts with Rad51 as well as with RPA [34, 35], accelerates displacement of RPA from ssDNA by Rad51 [36], and allows efficient Rad51-mediated recombination involving RPA-coated ssDNA [37-39]. This mediator function of Rad52 does not account for the extreme HR defect of Rad52-deficient cells in yeast. This is because Rad52 also exhibits the unique ability to anneal homologous ssDNA coated by RPA [40]. Such an activity is thought to be critical in second-end capture [41], SDSA (synthesis-dependent strand annealing) and SSA (single-strand annealing) (see below). Unlike the yeast mutant, mouse *rad52* mutants display an exceedingly mild recombination defect and no ionizing radiation (IR) sensitivity [42]. The reasons for this are not understood, but genetic experiments in chicken DT40 cells suggest a partially overlapping function between Xrcc3 and Rad52 [43]. It is not known which mammalian proteins have taken over functions exerted by the yeast Rad52 protein, but one candidate is BRCA2, which is not found in budding yeast.

The tumor suppressor BRCA2 is of special interest among the mediator proteins. Heterozygous mutations in *BRCA2* predispose to breast, ovarian as well as other tumor types. Moreover, bi-allelic loss of *BRCA2* function causes FA (see below) [6, 10-12]. BRCA2 is required for IR-induced Rad51 focus formation *in vivo* [44]. Experiments with the full-length *Ustilago maydis* homolog, BRH2, and fragments of the human protein demonstrated that BRCA2 targets Rad51 filament formation to the ssDNA-dsDNA junction on RPA-coated ssDNA [45-47]. The mechanism is likely to be complex, considering the size of BRCA2 (3 418 amino acids), the multitude of Rad51-binding sites (8 BRC repeats and a C-terminal site), and the importance of its interaction partners (see below). The structure of the BRC4 repeat revealed a molecular mimicry of the Rad51 subunit-subunit interface, suggesting that BRCA2, through its BRC motif, might serve as a nucleation point of the Rad51 filament [48]. The C-terminal Rad51-binding site preferentially binds to the filament form of Rad51 [49, 50]. These results suggest that BRCA2 employs two mechanisms to favor Rad51 filament formation, nucleation and filament stabilization. The binding of the C-terminal site to Rad51 is negatively regulated by CDK phosphorylation on S3291, suggesting that BRCA2 function in HR is regulated throughout the cell cycle [51]. Besides its critical interaction with hRad51, BRCA2 was also found to physically interact with a number of other proteins [6, 10-12]. While the mechanistic function of these BRCA2-interacting proteins remains to be determined, genetic experiments have shown that depletion of DSS1 [52, 53], PALB2 [54] (FANCN, see below), and BCCIP [55] affects

Table 1 Homologous recombination proteins in *S. cerevisiae* and humans

	S. cerevisiae	Human
DSB processing	Mre11-Rad50-Xrs2 (MRX)	Mre11-Rad50-Nbs1 (MRN)
	Exo1	hExo1
	Sae2	?[1]
Anti-recombination	Sgs1	RecQL, RecQ4, RecQ5, BLM, WRN
	Srs2	hFbh1?[2]
Homologous pairing &	Rad51	hRad51
DNA strand exchange	RPA	hRPA
	Rad55-Rad57	Xrcc3-Rad51C?
	Shu1-Psy3-Shu2-Csm2	Xrcc2-Rad51D-Sws1
		Rad51B[3]
	Rad52	hRad52
	—[4]	BRCA2
	Rad54, Rdh54/Tid1	hRad54, hRad54B[5]
DNA heteroduplex extension	Rad54, Rdh54/Tid1	hRad54, hRad54B[5]
	Sgs1	RecQL, RecQ4, RecQ5, BLM, WRN
Junction resolution/dissolution	?[6]	Resolvase A
	Sgs1-TopIII-Rmi1	BLM-TopIIIa-BLAP75
	Mus81-Mms4	hMus81-Eme1

[1]No homolog has been identified yet in mammals.
[2]Based on phenotypes of the fission yeast *Schizosaccharomyces pombe fbh1* gene, it has been suggested that Fbh1 could function similarly to Srs2 as an anti-recombinase [159].
[3]At present, there is no obvious Rad51B homolog in budding yeast, although it should be noted that the homology between the Rad51 paralogs is quite low, so that assignment of homologs may be somewhat uncertain.
[4]No BRCA2 homolog has been identified in *S. cerevisiae*, although the smut fungus *Ustilago maydis* has a sequence and functional homolog, BRH2 (see ref. [45]).
[5]hRad54 is evidently a homolog of *S. cerevisiae* Rad54. It remains unsettled whether hRad54B is a homolog of Rdh54/Tid1 [60].
[6]No activity equivalent to Resolvase A has been identified in *S. cerevisiae*, and the identity (gene/protein) of the Resolvase A activity is unknown.

HR. BRCA2 appears to be a regulatory integration point of the HR pathway.

Rad54 is a core factor of HR in budding yeast, and cells deficient for this protein reveal DNA damage sensitivities that are identical to those of a *rad51* mutant [4, 56, 57]. In mice, Rad51 is essential, whereas Rad54-deficient cells or mice are viable [58, 59]. It is unclear whether this reflects functional differences between the yeast and vertebrate Rad51 proteins (discussion in ref. [3]), undiscovered redundancies with the vertebrate Rad54 protein [60], or other reasons. Rad54 is a bidirectional motor protein that translocates at ~300 bp/s on dsDNA powered by the hydrolysis of ATP [61]. Rad54 associates with and stabilizes the Rad51 presynaptic filament [62, 63], which targets Rad54 to the pairing site [64, 65]. Rad54 stimulates DNA strand invasion by Rad51 *in vitro* by a mechanism that is poorly understood but requires its ATPase activity [56, 57, 66]. Rad54 also functions after synapsis. The protein dissociates Rad51 from the heteroduplex DNA, effectively acting as a turnover factor that allows access of DNA polymerases to the invading 3′ end [67, 68]. The similarity to Snf2-like chromatin remodeling factors and the ability to slide nucleosomes suggest that Rad54 might also be involved in chromatin remodeling during HR [69-71]. In addition, it was shown that the Rad54 motor can migrate branched DNA structures, including Holliday junctions [72, 73]. *In vivo* Rad54 is not required for Rad51 focus formation, but Rad51 foci display an extended half-life in Rad54-deficient cells, suggesting that Rad54 exerts critical functions after Rad51 filament assembly [60, 74, 75]. The biochemical analysis of Rad54 has revealed an astounding versatility, but its exact *in vivo* function(s) remains to be determined

(reviews in refs. [56, 57]).

The core reaction of homology search and DNA strand invasion is central to all HR reactions. However, the different functional contexts of HR in DSB repair, replication fork support and ICL repair necessitate context-specific factors in the processing of the lesion, assembly of the Rad51 filament or in the processing of the primary DNA strand invasion intermediate, the D-loop. These factors and their functions will be discussed in the following sections within their specific functional contexts.

Homologous recombination and repair of DSBs

DSBs can be frank (two-sided) and one-sided; both are a major threat to genomic stability. Failure to repair DSBs or their misrepair can result in chromosome loss, chromosomal rearrangements, apoptosis, or carcinogenesis [76]. Endogenous sources or processes including mechanical stress (e.g. 'breakage-fusion-bridge cycles' [77]), transposition [78], immunoglobulin diversification [79], and meiosis [2] involve the accidental or programmed generation of two-sided DSBs. One-sided DSBs are primarily related to DNA replication and will be discussed in the next section. Of particular interest is the induction of DSBs by exogenous sources in the context of cancer therapy. IR exhibits potent anti-tumor activity. Random energy deposition by IR leads to a wide array of DNA damages, including DSBs, single-strand breaks, and a host of different base damages (e.g. thymine glycol) [80]. Among these, DSBs are the most genotoxic and are induced by clustered ionization from a single track of radiation leading to closely spaced single-stranded breaks at a single multiply damaged site [80]. IR-induced ssDNA breaks and base damages may interfere with DNA replication, potentially leading to one-sided DSBs (see below). IR-induced DSBs often contain modified bases at their 3′- and 5′-ends. Such ends with non-standard chemistry necessitate processing steps that are not needed when DSBs are introduced by nucleases in experimental model systems [4]. Intermediary metabolic products of *Streptomycetes*, including bleomycin, neocarcinostatin, and related compounds, have been effectively used in anti-tumor therapy [81]. They directly induce DSBs by attacking specific carbons in deoxyribose, leaving non-standard end-groups. A third class of DNA-based anti-tumor therapeutics is represented by topoisomerase inhibitors [82]. Topoisomerases are enzymes that open and close strands of DNA: type I topoisomerases open/close one strand, whereas type II topoisomerases open/close both strands at a time [83]. Both types involve a covalent DNA-protein bond in their catalytic cycle. This transition state can be stabilized by topoisomerase inhibitors leading to DSBs for type II inhibitors (e.g. etoposides) or single-stranded breaks for type I inhibitors (e.g. camptothecin) [82], which may become one-sided DSBs by replication run-off (Figure 2A; see ref. 84 for an alternative model). These damages pose a particular challenge for end-processing, as the topoisomerases are covalently attached to the 5′- ends (bacterial type I, bacterial and eukaryotic type II) or 3′-ends (eukaryotic type I) of the broken DNA. The existence of a specific enzyme, TDP1 (tyrosyl-DNA-phosphodiesterase), that cleaves the phosphodiester bond linking the active site tyrosine of eukaryotic type I topoisomerases to DNA shows that these complexes occur in normal cellular growth [85, 86]. In sum, the exact chemical nature of the DSB depends on the mechanism of its induction and will have an impact on its requirements for repair.

Several pathways compete for the repair of DSBs: HR, NHEJ, and SSA (see chapter by Shrivastav *et al.* in this issue and refs. [4, 87]). HR comprises a series of related sub-pathways that use DNA strand invasion and template-directed DNA repair synthesis, culminating in high-fidelity repair (Figure 1). Besides the classical DSBR (double-strand break repair) route [88], genetic and molecular studies have proposed two further variations of the HR theme in the SDSA [89] and BIR [90, 91] (break-induced replication) sub-pathways. Here, we will discuss the mechanisms and proteins that are specifically required in DSB repair mediated by HR in addition to the core proteins described above.

All sub-pathways of HR share the same initial steps in processing the DSB to a 3′ overhanging tail, to which the assembly of the Rad51 filament is directed. This phase of HR is termed pre-synapsis (Figure 1). Nucleolytic processing of the DSBs involving non-standard chemistry, e.g. DSBs induced by IR, appears to specifically require the Mre11-Rad50-Xrs2 (MRX) complex (Table 1). Defects in this complex lead to significant IR sensitivity, but the repair of a 'clean' DSB induced by the HO-endonuclease proceeds with no or little reduction in viability, involving only a minimal delay in repair kinetics [9, 92, 93]. The 5′-3′ exonuclease *Exo*1 [94] and the product of the *SAE2* gene [95] are also involved in 5′-end resection, probably acting in concert with the MRX complex.

The homology search and DNA strand invasion are collectively called synapsis and catalyzed by the core proteins discussed in the previous section. These generate the D-loop intermediate, where the 3′-end of the invading strand primes DNA synthesis off the template duplex DNA (Figure 1). The DSBR branch proceeds by engaging the second end of the DSB, by either second end capture through DNA annealing or a second invasion event. Annealing of the second end is catalyzed by the Rad52 protein, which exerts a unique function of being able to anneal complementary ssDNA bound to RPA [40, 41]. The resultant

double Holliday junction (dHJ) is a substrate either for dissolution into non-crossover products by BLM-TOPOIIIα or for resolution by a structure-specific endonuclease into crossover/non-crossover products (Figure 1, right). An endonuclease activity that exerts similar specificity for Holliday junctions as the bacterial RuvC protein has been identified in mammalian cell extracts [96]. The Resolvase A activity cleaves Holliday junctions into crossover and non-crossover products, but the identity of this activity has not yet been determined. Alternative processing of dHJs is afforded by the combined action of the BLM DNA helicase with the type I topoisomerase TOPOIIIα and their cofactor BLAP75/Rmi1 [97-99]. In a process termed dissolution, BLM migrates the two junctions towards each other [98], and TOPOIIIα removes the hemi-catenanes that topologically link the two duplexes. Importantly, this mechanism leads to an obligatory non-crossover outcome, providing a satisfying explanation for the increase in sister chromatid exchange in cells derived from Bloom's syndrome patients who are deficient for the BLM helicase. The corresponding budding yeast complex, Sgs1-Top3-Rmi1, has yet to be analyzed biochemically using dHJ substrates. Surprisingly, crossover suppression by Sgs1 does not require its helicase activity during DSB repair [100], suggesting that Sgs1 may utilize other mechanisms than dHJ dissolution for crossover suppression, a notion that was also developed from analysis of crossover suppression by Sgs1 during meiotic recombination in *S. cerevisiae* [101].

In SDSA, the D-loop is dissolved after some DNA synthesis and the disengaged invading strand reanneals with the second end of the DSB, always forming non-crossover products (Figure 1, left). Reannealing to the second DSB end is believed to proceed similarly to second-end capture in DSBR, involving the yeast Rad52 protein (see above). It has been speculated that the BRCA2 protein may have a similar function [102]. Dissolution of D-loops almost certainly requires a motor protein, and genetic experiments in yeast have implicated the Srs2 helicase [103]. However, biochemical experiments using purified Srs2 protein failed to detect dissolution of Rad51-mediated D-loops [104], suggesting that a cofactor might be missing or that other proteins catalyze this step. Genetic experiments in *Drosophila* implicated the BLM helicase in D-loop dissolution [105], and biochemical data support this possibility, as purified BLM helicase specifically dissociates D-loops [106]. The aspect of crossover avoidance is one of the key features of SDSA that made this model attractive for DSB repair in somatic cells. Recombination in somatic cells is rarely associated with crossovers, and crossovers have the potential to generate genomic rearrangements and large-scale loss of heterozygosity (LOH) [107-109]. However, the dissolution of dHJs by BLM-TOPOIIIα into non-crossover products [97, 98] (see above) reaffirms the possibility that dHJs may be an intermediate in DSB repair in somatic cells.

In BIR, the invading strand is postulated to establish a replication fork to copy the entire distal arm of the template chromosome, resulting in LOH (Figure 1, middle) [90, 110]. Hence, the second end is never engaged and the genetic information of that fragment is lost. The contribution of BIR to the repair of interstitial DSBs in wild-type cells is uncertain, but in *rad51* or *mre11* mutants, BIR makes a significant contribution to DSB repair [90, 93, 111]. However, BIR appears to be at least one mechanism responsible for alternative lengthening of telomeres, and both pathways share common genetic requirements [110, 112]. BIR may employ mechanisms similar to the repair of a broken replication fork (Figure 2A, step 3a), involving resection, Rad51 filament formation, and D-loop formation. Therefore, the mechanistic implications are discussed in the following section. The context of a one-sided DSB (S-phase, presence of replication fork components versus an event in G1 or G2) has likely a consequence on repair; e.g., it has been shown that efficient DSB resection is suppressed in budding yeast G1 cells [113].

In conclusion, DSB repair by HR is a group of interrelated conduits that share common core factors in the processing of DSBs, as well as in the assembly and function of the critical Rad51 filament, but that also likely have specific factors that mechanistically differentiate DSBR, SDSA, and BIR.

Homologous recombination and replication fork support

DNA lesions that interfere with the progress of the replicative DNA helicase or DNA polymerases lead to replication fork blockage or demise, producing DNA gaps or one-sided DSBs (Figure 2). Uncoupling of the replicative DNA helicase from the polymerases occurs when a lesion blocks the polymerase but not the helicase. This will generate excessive ssDNA, which could be the target of endonucleoytic processing, resulting in a one-sided DSB. A similar accumulation of unscheduled ssDNA occurs when the coordination of the leading and lagging strand synthesis is lost. In addition, single-stranded breaks induced by endogenous and exogenous sources, including reactive oxygen species [1], IR [80], covalent DNA-type I topoisomerases (see above), or other cellular processes (NER, BER; see chapters by Shuck *et al.*, Hegde *et al.*, and Horton *et al.* in this issue), may lead to the formation of one-sided DSBs due to runoff of the replication fork. Moreover, genetic experiments have identified natural DNA sequences that are difficult to replicate and lead to

fork stalling and fork breakage. These processes have significant ramifications for human disease, as they involve fragile sites, which represent a common form of genomic instability in humans [114]. Specific protein factors like the Rrm3 DNA helicase support replication to successfully pass such obstacles [115]. Aberrant resolution of replication stress is a major cause of genomic instability, and provides a constant impetus for genetic change in highly replicative cancer cells [116].

Multiple pathways are active in the support of DNA replication (Figure 2), including translesion DNA synthesis (TLS; see chapters by Gan *et al.* and Andersen *et al.* in this issue), template switching by fork regression, and HR. Blockage of the replicative polymerase on either the leading or lagging strand can be resolved by a polymerase switch to specialized TLS polymerases that are able to insert bases opposite non-Watson-Crick bases and to extend non-standard primer-templates (Figure 2A, step 3b, and Figure 2B, step 2c). On the basis of genetic and biochemical data, it has been proposed that TLS polymerases are highly specialized in these functions, requiring one polymerase for base insertion and another for extension before a switch back to the replicative polymerase (δ or ε presumably) [117]. Fork regression involves a template switch of the blocked 3′ end to the nascent sister strand, involving the formation of a so-called chicken foot intermediate, a structure that is analogous to a Holliday junction (Figure 2A, steps 3d and 4d). This template switch does not involve strand invasion and is likely independent of Rad51. RPA and DNA annealing by Rad52 protein might be involved, as well as unknown motor proteins that catalyze the formation and dissolution of the chicken foot. Reversal of the chicken foot after template switch and DNA synthesis leads to tolerance of the blocking damage and direct replication restart (Figure 2A, step 5d) [118].

HR is required for gap repair and the repair of one-sided DSBs (Figure 2A, steps 3a-4a-5a, 3c-4c-5c and Figure 2B, steps 2a-3a-4, 2b-3b-4). Reinitiation of DNA synthesis after polymerase blockage can occur on the lagging strand, but was recently also shown to occur on the leading strand [119, 120]. Hence, gaps can occur on both leading and lagging strands. These gaps may also be resolved by TLS polymerases (see chapters by Gan *et al.* and Andersen *et al.* in this issue). Template-switching by HR can be envisioned to occur in two ways (Figure 2B, steps 2a-3a or 2b-3b), depending on which strand invades the undamaged template. The outcome of both mechanisms, lesion bypass and damage tolerance (Figure 2B, step 4), is the same, but the intermediates involved and the enzymatic functions differ. First, the uninterrupted strand can serve as a template for Rad51 filament formation and invade the sister chromatid (Figure 2A, steps 3c-4c-5c and Figure 2B, 2a-3a-4). The displaced strand of the D-loop would serve as template for the blocked 3′-OH end. This mechanism involves the formation of a paranemic joint, where the paired strands cannot truly intertwine due of the lack of an end. These joints are known to be unstable [121] and may require specific cofactors for Rad51. Alternatively, a 5′-3′DNA helicase could dislodge the blocked strand, leading to Rad51 filament assembly on the interrupted strand and formation of a D-loop (Figure 2B, steps 2b-3b). It is not known which helicase might participate in this reaction, but the RecQ-like helicases are excluded, because they unwind DNA in the opposite, 3′-5′ direction [122].

One-sided DSBs may originate from direct endonucleolytic action at stalled forks or indirectly when the fork encounters a nick in the DNA. In the repair of one-sided DSBs, HR appears to be the only pathway leading to their productive resolution (Figure 2A, steps. 2a-3a-4a-5a). Formally analogous to BIR (Figure 1, right), the DSB is resected to form a 3′-tailed end for Rad51 filament assembly and DNA strand invasion. Work in bacteria established that the critical step in replication fork restart (and by implication BIR) is reloading of the replicative helicase [118]. The PriA 3′-5′ helicase is critical for loading of the replicative helicase at D-loops, but the mechanisms and proteins involved in this step in eukaryotes are not known. Another mechanistic aspect of one-sided DSB repair by HR is the formation of a single Holliday junction (Figure 2A, steps 4a-5a), which requires resolution prior to chromosome segregation.

The presumptive mechanisms of replication fork support by HR require additional factors that are not required in DSB repair. As depicted in Figure 2, different sets of junctions are formed and processed. Additionally, Rad51 filaments may form at a gap rather than a tailed DSB. Several genes have been identified in yeast that genetically map into the *RAD52* (HR) epistasis group, but the corresponding mutants did not display sensitivity to DSBs, the hallmark phenotype of an HR defect in this organism. Interestingly, such mutants are sensitive to agents that stall replication forks and may represent examples of context-specific HR proteins acting primarily during replication fork support. The budding yeast Shu1-Psy3-Shu2-Csm2 complex falls into this category (Table 1). The members of this complex have been identified as suppressors of the slow growth caused by a mutation in the *TOP3* gene [123]. Genetic analysis suggests that the Shu complex is involved in the formation of recombination intermediates that require processing by Sgs1-Top3-Rmi1 [124]. Members of the Shu complex display functional and structural homology to mammalian Rad51 paralogs (Table 1; Shu1 to Xrcc2, Psy3 to Rad51D) [125]. This suggests that the Shu complex may have a specialized role in Rad51 filament formation

during replication fork support.

Also the Mus81-Mms4 complex (Table 1) appears to be a replication context-specific cofactor of HR (reviewed in [126, 127]). Cells deficient for the complex are not sensitive to DSBs induced by HO endonuclease or IR, but display sensitivity to fork-stalling agents like methylmethane sulfonate (MMS), UV, and the ribonucleotide reductase inhibitor hydroxyurea as well as the topoisomerase I inhibitor camptothecin [128, 129]. The *mus81 mms4* mutants are epistatic with the *RAD52* group for these phenotypes. Mus81-Mms4 is a structure-selective DNA endonuclease that cleaves a number of substrates *in vitro*, including replication fork-like substrates, nicked Holliday junctions, D-loops, and 3′-flaps (reviewed in [126, 127]). A number of potential Mus81-Mms4 substrates are envisioned to arise during the processing of stalled replication forks (Figure 2). The *in vivo* substrate(s) of Mus81-Mms4 remain to be determined. Mus81-Mms4 has also been identified to be involved in ICL repair in mammalian cells (see below).

In sum, a complex web of pathways support stalled or broken replication forks. The data suggest that use of TLS, HR, and template switching by fork regression may entail a regulated hierarchy, likely involving the mono- and poly-ubiquitylation of PCNA [130-132]. HR-independent template switching (chicken foot formation) is actively repressed by DNA damage checkpoints at forks stalled by depleting nucleotides by addition of hydroxyurea [133]. HR is actively counteracted during S-phase through the recruitment of the Srs2 anti-recombinase by K164-sumoylated PCNA [134, 135]. Srs2 DNA helicase exerts its anti-recombinogenic function by dissociating Rad51 from ssDNA, opposing the formation of the presynaptic filament necessary for DNA strand invasion [104, 136]. In addition, efficient HR after replication fork stalling requires activating phosphorylation of the Rad55-Rad57 mediator complex by DNA damage checkpoint kinases [137]. These data suggest that TLS is the preferred option at stalled forks, but this choice may be affected by the chromosomal context or by the specific way the fork was stalled or broken. In conclusion, HR in replication fork support requires not only the core program of Rad51 filament formation and DNA strand invasion but also context-specific factors, such as Mus81-Mms4, that may have little or no role in HR during DSB repair.

Homologous recombination and DNA interstrand crosslink repair

DNA ICLs are one of the most deleterious DNA lesions. By covalently linking the Watson and Crick strands of the double helix, ICLs obstruct DNA replication and transcription (reviews in refs. [138, 139]). ICL-inducing agents usually generate multiple types of DNA damage besides ICLs, such as DNA mono-adducts, intrastrand crosslinks, and DNA-protein crosslink. Although ICLs comprise only a small fraction of the induced damage, these are the most cytotoxic and genotoxic lesions produced. ICL-inducing agents exist in natural sources like certain medicinal and edible plants, as well as some endogenously produced metabolites. Malondialdehyde, a metabolite of lipid peroxidation and prostaglandin biosynthesis, preferentially crosslinks two deoxyguanosine residues on the opposite strands of the sequence d(CpG). Studies in human cells show that malondialdehyde is highly mutagenic, suggesting that malondialdehyde may be an endogenous source of ICLs [140]. Due to their high toxicity and selectivity against proliferating cells, a variety of ICL-inducing agents, including psoralens, cis-platinum, and mitomycin C, are widely utilized in cancer chemotherapy [138, 139, 141]. Sensitivity to ICL agents is a hallmark of mammalian HR defects and of cells derived from FA patients [12, 13] (see below).

NER, HR, and TLS pathways participate in ICL repair in eukaryotes [138, 139]. Recognition of ICL lesions likely involves the formation of stalled replication forks (Figure 3, step 2), yet the detailed mechanism is unknown. In eukaryotes, DSBs near the ICL site have been observed as a pivotal intermediate of ICL repair [142, 143]. Ensuing repair of the one-sided DSB by HR may involve lesion processing by NER (Figure 3 left, steps 4a and 8) and TLS polymerases (steps 5a and 7a). A more complex scheme (Figure 3 right, steps 4b-7b) involves D-loop formation and DNA synthesis on the undamaged homolog prior to DNA strand invasion on the sister chromatid downstream of the blocking lesion, leading to damage tolerance.

In mammalian cells, the hMus81-Eme1 structure-selective endonuclease was recently identified to be required for DSB formation after mitomycin C and cis-platinum treatment [144]. Replication fork-like structures are an excellent substrate for the enzyme *in vitro* (reviewed in [126, 127]) (Figure 3, step 2). Unhooking of the lesion for repair (Figure 3, steps 4a and 8) has been proposed to be accomplished by the XPF-Ercc1 endonuclease, a key factor in NER [145]. Mus81-Mms4/Eme1 and XPF-Ercc1 are related endonucleases, but neither appears to be required for DSB formation during ICL repair in yeast (see ref. [139]). A third nuclease with a specific function in ICL repair is Pso2/Smn1. The protein exhibits a 5′-3′ DNA exonuclease activity, which is required after DSB formation [146-148]. Unlike mammalian Mus81 or XPF-deficient cells that are sensitive to several ICL-inducing agents [144, 145], mouse *smn1*$^{-/-}$ cells were sensitive only to mitomycin C but not other ICL agents [149]. In yeast, however, *pso2/smn1* mutants display sensitivity to a spectrum of ICL agents [139]. The

difference between these organisms is further accentuated by the existence of the FA pathway that is critical for ICL repair in humans but absent in yeast (an exception being the FANCM homolog Mph1) [12, 13].

FA is a rare, recessive chromosomal-instability disorder, and cells from FA patients display a diagnostic sensitivity to DNA crosslinking agents. The genes for 13 known FA complementation groups (called *FANC* genes) groups have now been identified [12, 13, 150-152]. A nuclear E3 mono-ubiquitin ligase core complex consisting of FANCA, B, C, E, F, G, L, M, and FAAP24 ubiquitylates the FANCD2-FANCI complex upon encountering stalled replication forks. This modification leads to colocalization of FANCD2-FANCI with HR proteins in DNA damage-induced foci together with BRCA2 (corresponding to FANCD1) possibly in conjunction with its interacting partner FANCN (PALB2). FANCJ has previously been identified as the DNA helicase BACH1/BRIP and also functions downstream of FANCD2 ubiquitylation. The molecular impact of FANCD2 ubiquitylation on BRCA2-FANCN or FANCJ function is not known. Here, we focus the discussion on FANCM-FAAP24, FANCJ and FANCD1 (BRCA2), because these proteins interact directly with DNA. FANCN co-localizes with BRCA2 in foci and is required for BRCA2 focus formation, but its mechanistic role is unknown [54].

FANCM and FAAP24 are required for activation of the core complex to ubiquitylate FANCD2-FANCI. Although FANCM is a member of the DNA helicase superfamily 2, it is unable to catalyze strand separation and is rather a dsDNA translocase [153]. Studies in chicken DT40 cells showed that the motor domain is critical for its biological function [153, 154]. FANCM-FAAP24 form an XPF family heterodimer that lacks nuclease activity but has dsDNA translocase activity, as inferred from the activity of FANCM in the absence of FAAP24 [153, 155]. FANCM is proposed to be a sensor for stalled forks, and this specificity could be provided by FAAP24 that preferentially binds to splayed DNA [153, 155]. Based on the ability of other superfamily 2 dsDNA translocases to remodel protein-dsDNA complexes [156] (e.g. Rad54 [67]; see above), it could be speculated that FANCM-FAAP24 remodels stalled forks to allow their processing. FANCJ (= BACH1/BRIP1) is a DNA helicase, capable of strand separation with a 5′-3′ polarity [157]. Together with BRCA2, in conjunction with the BRCA2-binding partner FANCN, they are the only FANC proteins to function downstream of FANCD2, suggesting that these proteins might function in concert. The role of BRCA2 in Rad51 filament formation has been discussed above (see also [6]). The physical interaction of FANCJ with RPA [158] is consistent with a possible role in an early step in HR leading to the formation of the presynaptic Rad51 filament on ssDNA. Despite the remarkable progress in identifying the FANC genes, the mechanistic role of the FANC core ubiquitylation complex and how FANCD2-FANCI ubiquitylation impacts ICL repair remain unknown.

In conclusion, ICL repair is very complex, involving proteins from the NER, HR and TLS pathways. Substantial mechanistic differences appear to exist between yeast and mammalian ICL repair, although the pathways are incompletely understood at present. In addition, mammals contain a new suite of genes, the FA pathway, which appear to be critical for the recruitment of Rad51-mediated HR during ICL repair.

Conclusion

At the nexus of DNA repair and DNA replication, HR constitutes a key pathway to maintain genomic stability. HR supports DNA replication and aids replication restart after fork stalling or breakage. DNA replication in turn affords the ideal damage recognition process, checking the entire genome, base by base, for lesions that interfere not only with replication, but also with other DNA functions such as transcription. The human tumor suppressor protein BRCA2 highlights the connection between HR and cancer predisposition, and it is likely that mutations in other HR proteins will be shown to influence cancer risk. BRCA2 also epitomizes the intersection between HR and FA, but the mechanisms involved in ICL repair and the specific contributions of BRCA2 and the other *FANC* genes to this process remain to be elucidated. In the past, DNA repair pathways have been neatly separated on the basis of genetic and biochemical criteria. Now it has become apparent that many DNA metabolic processes are intertwined. One of the consequences of this functional integration between DNA replication and the various DNA damage repair/tolerance pathways is the added complexity brought about by regulatory decisions governing how a specific lesion is processed. Hence, besides the need to elucidate the process of HR in repair and replication fork support, more attention will focus on these regulatory mechanisms in the future.

Acknowledgments

The support of our research by the National Institutes of Health, the Susan G Komen Breast Cancer Foundation, and University of California BioStar program (USA) is gratefully acknowledged. We thank all members of the Heyer lab for discussion and critical comments on the manuscript. We offer our sincere apologies for omitting all the references and great work that could not be discussed here due to space limitations.

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