Review

Pathways for mitotic homologous recombination in mammalian cells

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Abstract

Homologous recombination (HR) is essential for cellular survival in mammals. In this review, the substrates for HR, the pathways of repair, and their end products (i.e. sister chromatid exchange (SCE), gene conversion, deletions or tandem duplications) are discussed. HR is involved in the repair of DNA double-strand breaks (DSBs) and DNA lesions that occur at replication forks. A classical DSB may result in deletions, tandem duplications or gene conversion following two-end recombination repair. In contrast, a SCE may be the result of one-end recombination repair at a collapsed replication fork, i.e. a single-strand break converted into a DSB at a replication fork. Recombination repair at a stalled replication fork may occur in the absence of a DSB intermediate and may result in either SCE or gene conversion. Finally, substrates and pathways involved in spontaneous HR are discussed.
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1. Introduction

Homologous recombination (HR) is a process for genetic exchange between DNA sequences that share homology. This process is conserved from bacteria to man and recent observations suggest that mitotic HR is essential for faithful replication in vertebrate cells.

Cells deficient in HR were first identified owing to their hypersensitivity to X-rays [1–3], which indicated that DNA double-strand breaks (DSBs) are substrates for mitotic homologous recombination repair (HRR). Only later was it shown that a specific endonuclease-induced DSB potently induces HR [4]. The lesion formed following this treatment is a classic DSB leaving two free ends that need repairing (Fig. 1a).

A DSB may also arise if a replication fork collides with an unrepaired DNA single-strand break (SSB), giving rise to a collapsed replication fork (Fig. 1b). These replication-fork-associated DSBs also trigger HRR in mammalian cells [5], even though they only have one free DNA end to initiate the repair.

Recently, HRR has been implicated in the repair of stalled replication forks, which may also occur in the
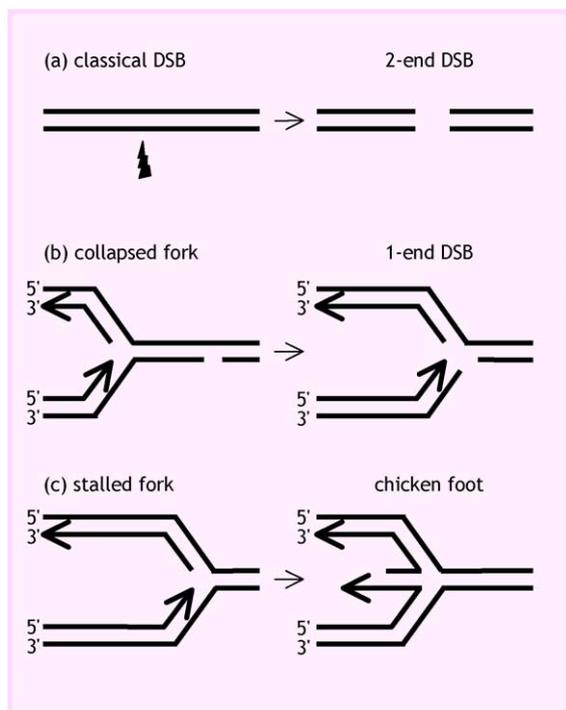
Fig. 1. Structure of substrates for recombination in mammalian cells. (a) A classical DSB cuts the DNA strand leaving two free DNA ends that both may initiate recombination. (b) A persisting SSB may be converted into a DSB during replication that collapses the replication fork, leaving one free DNA end that is a substrate for recombination. (c) A replication fork may encounter roadblocks on the template DNA that stall the replication fork. Under such conditions the replication fork may reverse to form a chicken-foot intermediate that may serve as a substrate for recombination.

absence of detectable DSBs [6]. In this case, we know less about the substrates that initiate HR. However, it has been shown in bacteria that nascent DNA strands may anneal and reverse stalled replication forks to form a chicken-foot structure that may serve as a substrate for HR (Fig. 1c; see also [7] for a review).

This review describes the current models for the homology mediated repair of these three different DNA lesions in mammalian cells.

2. Recombination in repair of a DSB—two-end repair

A classical two-ended DSB is repaired by either non-homologous end joining (NHEJ) or HR, and

several comprehensive reviews on this topic are available [8–15].

2.1. NHEJ in two-end repair

DSBs may be repaired by either a slow or a fast pathway. The fast repair involves NHEJ (Fig. 2a [16,17]) and often results in a deletion at the breakage site. Occasionally, insertion of foreign DNA may accompany the deletion [18], however, the mechanism for insertion of this extra DNA is unknown.

Environmental agents such as γ-rays induce DSBs either directly or indirectly as a result of the action of free radical intermediates. In any case, the ends of these DSBs are likely to be accompanied by additional DNA damage to bases or even DNA cross-links. These dirty ends need cleaning before they can be further processed. This might be executed by the Mre11/RAD50/Nbs1 (MRN) protein complex that localises to sites of DSBs and has exonuclease as well as endonuclease activity [19]. The same complex may also be involved in signalling of the DSB to downstream DNA response proteins (see [19] for a review). The RAD50 component of the MRN complex, has two highly flexible intramolecular coiled coils, producing two long arms from the core protein, which can dimerize using a Zn^{2+} ion [20–22]. These arms suggest an additional role for the MRN complex in NHEJ, such as facilitating the two ends of the DSB finding each other. The chance that two free ends would find each other is greatly increased with long RAD50 arms as it would increase the search radius. A doubling of the search radius at free DNA ends would increase the chance of them finding each other by at least 16-fold.

NHEJ is initiated at a DSB by binding of the Ku70 and Ku80 heterodimer to the free DNA end. This heterodimer binds as a ring surrounding the broken DNA end and structurally supports it to facilitate re-joining [23]. To bring the ends together, the DNA–PK catalytic subunit binds to the Ku70–Ku80 heterodimer and catalyzes joining of the two DNA ends, with inositol-6-phosphate acting as a co-factor [24–26]. The DNA–PK appears to have the additional role of being a sensor to signal transducer molecules as being discussed elsewhere [13,27].

Again, the DNA ends may need trimming before ligation, a reaction catalysed by the protein Artemis. It
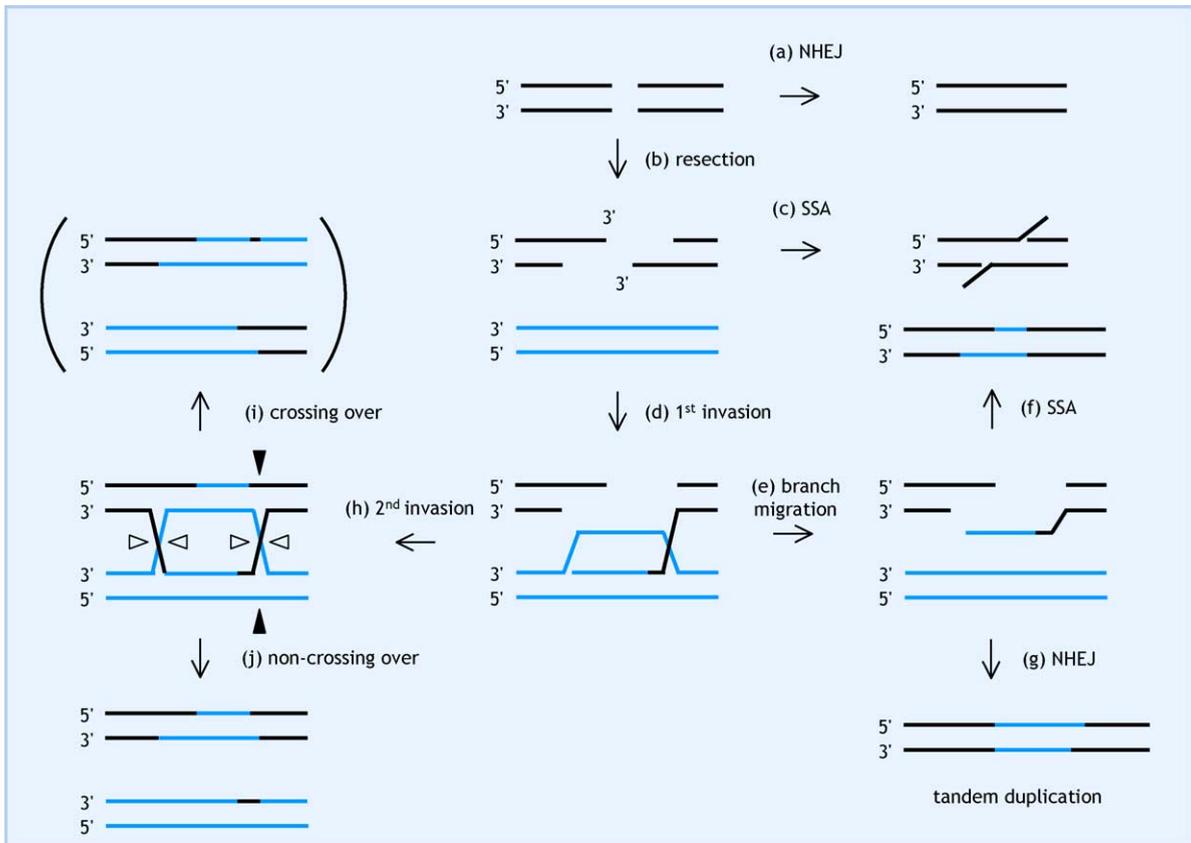
Fig. 2. Recombination repair of a two-end DSB. (a) NHEJ is involved in a fast, but often inaccurate repair of a two-end DSB that may result in deletions. Sometimes these deletions are accompanied by the insertion of foreign DNA. (b) DNA ends may be resected by exonucleases leaving 3′ ssDNA overhangs. (c) Repeated regions may be uncovered which can be used in SSA, causing deletion of the DNA that separated the repeats. (d) Strand invasion of a homologous DNA sequence (blue) may be initiated by one of the ssDNA ends. The invading strand is elongated past the site of breakage. (e) Branch migration of the HJ may release the invading strand, unveiling homologous DNA sequences to the ssDNA overhang on the opposite DNA end. (f) Synthesis-dependent SSA may use this homology in repair, which causes a gene conversion with no deletion. (g) Synthesis-dependent NHEJ rejoins the extended DNA end without using the sequence homology. This will cause tandem duplications, giving a longer product than following synthesis-dependent SSA. (h) Strand invasion by the second DNA end may occur if the invading strand is not released by branch migration; this causes a double HJ (see [66] for a review). In mammalian cells, these HJs are probably not resolved by crossing over (i; filled arrowheads) since crossing over products are suppressed in mitotic mammalian cells [52,67]. Instead the HJs may be resolved by non-crossing over (j; open arrowheads), causing a gene conversion event [53].

binds DNA–PK and has endonuclease activity, which opens up hairpins and other structures that cannot easily be religated [28]. If small homologies are present at the DNA ends, these may assist in alignment. When ends are aligned, ligatable 3′-OH and 5′-phosphate moieties have to be produced for efficient ligation; addition of phosphate to 5′-OH groups is catalysed by polynucleotide kinase (PNK) [29]. The ends are finally sealed by ligase IV, which exists in complex with XRCC4 [30,31]. More proteins are likely to be involved in NHEJ, as an additional factor in NHEJ, yet uncharacterised, has recently been identified [32].

2.2. HR in two-end repair

HR is an important repair pathway of DSBs in mammalian cells [4]. In contrast to NHEJ, it not only utilizes homologous DNA sequences (making this process conservative and in most cases error-free), but it is also a slow repair component. A reason as to why

NHEJ predominates in mammalian cells, even though it produces deletions, could be that it is a fast process and does not require an intact homologous DNA template.

The initial step in HR is thought to be a 5′ to 3′ exonuclease resectioning of the DNA end to produce a 3′ single-stranded DNA (ssDNA) overhang (Fig. 2b). As in NHEJ, the MRN complex is believed to be responsible for the initial cleaning up of DNA ends and for the 5′ to 3′ exonuclease activity [33]. However, no direct evidence has been presented to confirm this hypothesis.

2.2.1. Single-strand annealing in two-end repair

If repeated sequences are uncovered within the resected 3′ ssDNA overhangs, RAD52 and replication protein A (RPA) may initiate single-strand annealing (SSA) repair between the repeated sequences (Fig. 2c). The RAD52 protein binds 3′ ssDNA ends [34,35], whereas the RPA protein binds tightly to the 3′ ssDNA overhang [36]. When these repeats are annealed, the regions in between the repeats will be flipped out on either side. These are substrates for the ERCC1/XPF endonuclease that seems to play a role in SSA [37,38]. The final ssDNA gap is ligated by an enzyme that has not yet been identified.

Work in mammalian cells suggests that SSA is a frequent repair event between repetitive sequences [4]. The product formed by SSA is a deletion, making this pathway error-prone. Since a large proportion of mammalian genomes consists of repetitive sequences, e.g. Alu sequences, SSA may frequently be recruited in the repair of DSBs with two ends.

2.2.2. Strand invasion in two-end repair

The key protein required for strand invasion in mammalian cells is RAD51, the eukaryotic homologue to RecA in *Escherichia coli*. The RAD51 protein, like RecA, forms a nucleoprotein filament on ssDNA regions [39] and catalyses the search for homologous sequences, strand pairing and strand exchange [40,41]. While the *RAD52* knockout mice are alive and healthy [42], a knockout of the *RAD51* gene is embryonic lethal [43,44]. Similarly, knockouts in other genes involved in HR (i.e. *XRCC2* [45], *RAD51B* [46], *RAD51D* [47], *RAD50* [48], *Mre11* [49,50], or *Nbs1* [51]) are lethal, implying that the intact HR pathway is vital.

A homologous DNA sequence is required for RAD51-dependent strand invasion (Fig. 2d). The sister chromatid which is present in late S or G2 phases of the cell cycle participates in this event at least 100-fold more frequently than the homologous chromosome [52–54]. This is not surprising, given that the homologous chromosome is further away than the sister chromosome and that repair on the homologous chromosome would result in loss of heterozygosity. Loss of heterozygosity could potentially inactivate tumour suppressor genes and subsequently result in cancer (see [55] for a review).

For invasion to occur RAD51 must displace the RPA protein on the 3′ ssDNA overhang. This might not be easy, given that RPA has a high affinity for ssDNA and RAD51 has a low one. Replacement of RPA with RAD51 may be catalysed by the RAD51 paralogs [56]. The RAD51 paralog complex, which includes RAD51B, RAD51C, RAD51D and XRCC2 can also facilitate formation of RAD51 filaments on gapped DNA sequences [57]. This is a very interesting observation suggesting that strand invasion can be initiated without a free DNA end. The BRCA2 protein may also play a role in loading RAD51 onto ssDNA [58]. BRCA2 (FANCD1) is in turn regulated by BRCA1, FANCD2 and other proteins in the Fanconi anaemia protein family (see [59] for a review).

Strand invasion is further stimulated by the RAD54 protein [60]. This protein forms negative supercoils in duplex DNA, which may increase accessibility for strand invasion [61,62]. For a more detailed review of proteins involved in HR see [15].

Following invasion of the homologous DNA molecule by HR (Fig. 2d), DNA synthesis is initiated at the DNA 3′ end by a DNA polymerase. The synthesis is likely to proceed beyond the site of the original DSB. A Holliday Junction (HJ) is left at the site of invasion, which may branch migrate in either direction. If the HJ migrates in the direction of replication (Fig. 2e) it may reverse the invasion, leaving a DNA end that has been extended beyond the original DSB. This ssDNA end will share homology with the other end and may be repaired by SSA (Fig. 2f). The end product following synthesis-dependent SSA will not contain any deletion, while regular SSA, using repeated sequences, will (Fig. 2c). However, synthesis-dependent SSA results in gene conversion,

Table 1
Summary of recombination substrates and products

Agents	Recombinogenic lesion	Recombination pathway	Recombination products	References
γ-Rays, restriction endonucleases	Two-end DSB	NHEJ, HR	Deletion, gene conversion, tandem duplication	[53,63]
Topoisomerase I inhibitors (e.g. camptothecin)	One-end DSB	NHEJ, HR	SCE, deletion	[5,77,123,124]
Hydroxyurea, thymidine	Stalled fork	HR	Gene conversion, SCE	[6]

which is an error-free repair pathway although it may result in loss of heterozygosity.

Alternatively, the extended DNA end may be repaired by NHEJ (Fig. 2g). This synthesis-dependent NHEJ will result in a tandem duplication at the site of the DSB [63]. Tandem duplications of this sort represent 2% of all spontaneous gene mutations in the *hprt* gene in Chinese hamster cells [64], showing that coupling of NHEJ and HR is important in the repair of spontaneous DSBs [65].

As an alternative to the release of the invading end, the second DNA end may invade the same homologous DNA molecule (Fig. 2h). This will result in a double HJ structure that may be resolved either by crossing over (Fig. 2i) or non-crossing over (Fig. 2j) (see [66] for a review). Crossing-over events are probably rare in mammalian cells, since HRR using a sequence on another chromosome does not result in translocation [52,67] and a SCE event has never been observed when analysing the HR products following repair of an induced DSB [53]. However, little is known about the relative frequency of non-crossing over, since synthesis dependent SSA can also account for these products. Nevertheless, the product formed following resolution of double HJ structures by non-crossing over will always be a gene conversion. In conclusion, the products following two-end HR are deletions, gene conversions or tandem duplications (Table 1).

2.3. NHEJ versus HR in repair of a classical two-end DSB

It is clear that both NHEJ and HR are important in the repair of DSBs in mammalian cells [53]. In contrast to NHEJ-deficient cells, cells deficient in HR are not impaired in repair of γ-ray-induced DSBs and show less γ-ray sensitivity than NHEJ-deficient cells [16,17]. Furthermore, the majority of DSBs introduced in the genome are repaired by NHEJ [68], which suggests that NHEJ has a more important role than HR in two-end DSB repair.

The most likely explanation for the overlapping role of NHEJ and HR in the repair of DSBs is the context in which the DSB occurs. HR is probably favoured in the late S and G2 phases of the cell cycle when a sister chromatid is present; while NHEJ is favoured in G1 phase, when the homologous chromosome is far away and would result in loss of heterozygocity [69,70]. In yeast, the NEJ1 protein, specifically expressed in haploids, has been reported to promote NHEJ repair [71]. It is likely therefore that there are also proteins that regulate the onset of NHEJ or HR in mammalian cells.

3. Recombination in repair of a collapsed replication fork—one end repair

HR has been shown to be important in repair of damage during replication in all cellular organisms [6,72–75]. It has been difficult to establish the importance of RAD51 and other HR proteins in replication as most HR knockout mice are embryonic lethal [43–51]. However, a conditional knockout $RAD51^{-/-}$ chicken cell line has been established. It has been reported to accumulate chromosome breaks during the first round of replication and arrests in the G2/M phase before entering apoptosis [75], suggesting that HR is involved in repair of naturally occurring DSBs arising during the S phase of the cell cycle. DSBs may be generated following replication by conversion of persisting SSBs into DSBs, resulting in a collapsed replication fork (Fig. 1b). This collapsed fork may trigger
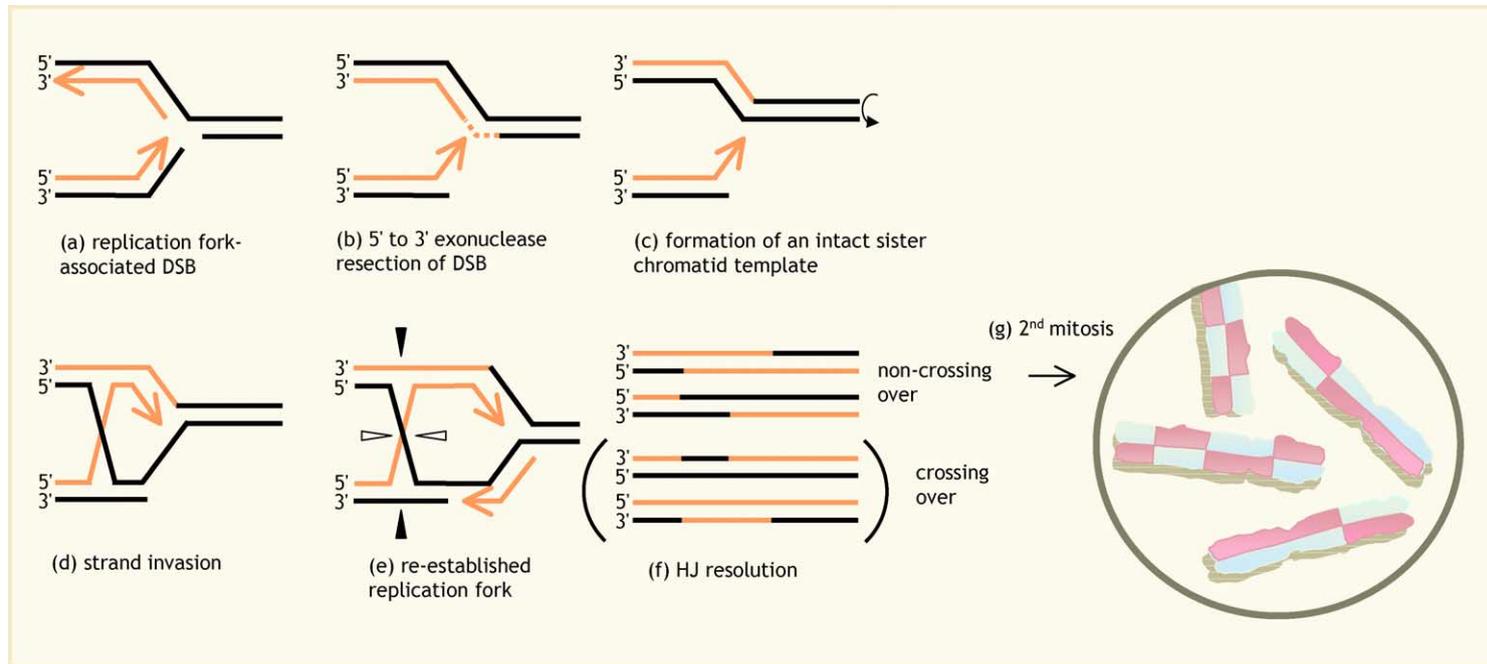
Fig. 3. HRR of a collapsed replication fork, i.e. one-end repair. (a) A replication fork-associated DSB has one free end to initiate exonuclease resectioning. (b) The $3'$ ssDNA overhang is coated with RAD51 and other HR proteins involved in strand invasion. (c) The single-strand gap on the template DNA will be filled in advance of (d) strand invasion. Leading strand synthesis may continue on the invaded template DNA, and a replication fork is re-established (e). This re-established replication fork will have swapped the leading and lagging strand synthesis; compare (a) and (e). (f) A single HJ is left behind the replication fork, this is probably resolved by non-crossing over since crossing over is an unlikely event [52,67]. Since template DNA and newly synthesised DNA are fused following non-crossing over (follow lines in f), SCE will be visualised following a second mitosis (g). Arrows indicate the directions of DNA synthesis; black lines designate template DNA and orange lines newly synthesized DNA; open arrowheads designate non-crossing over and filled arrowheads indicate crossing over.

break-induced replication (BIR) via HR, as suggested by Haber [73,76].

The experimental evidence for the BIR model in mammalian cells is that stabilised SSBs (produced by camptothecin) are converted into DSBs by a "run off" mechanism [77]. These replication-associated DSBs have been shown to induce HR by a SCE type of mechanism in Chinese hamster cells [5]. For a more detailed review on replication-mediated DSBs induced by camptothecin see [78] this issue.

The most important difference between a classical DSB and a replication-associated DSB at collapsed forks is that there is only one end to initiate HR (Fig. 3b). After the single-stranded gap in the template DNA strand has been filled (Fig. 3c), the free DNA end may invade this intact DNA molecule (Fig. 3d) and resume replication (Fig. 3e). Following this recombination event, the leading strand of replication will now occur on the opposite side and a single HJ will be left behind the replication fork [79]. A SCE event will subsequently be produced with no gene conversion, since non-cross-over of a HJ is preferred in mammalian mitotic recombination [52,67] (Fig. 3f). This SCE is visualised since newly synthesised DNA are ligated to template DNA (follow lines in Fig. 3f). Following a second mitosis, this break site may be clearly scored as a SCE by cytological methods (Fig. 3g).

Further evidence that SCEs originate from persisting SSBs comes from cells with a defect in SSB repair, i.e. XRCC1 or PARP-1 deficient cells, which show increased levels of spontaneous SCE [80–83].

4. Recombination in repair of a stalled replication fork

It is clear that HR also has an important role in the repair of stalled replication forks in mammalian cells [6]. In addition to the fact that a deficiency in HR is embryonic lethal in mice [43–51], Chinese hamster cells deficient in HR show delayed progress through the cell cycle [2,84,85], hypersensitivity to agents that stall replication [6], increased levels of spontaneous apoptosis [86], chromosome instability [87,88], and increased mutation rates [2,89]. Furthermore, agents that inhibit replication are potent inducers of HR [90,91] and RAD51 focus formation [6,90,92].

RAD51 foci have been shown to form in postreplicative DNA [93] and at sites of stalled replication forks [94]. It has also been suggested that p53 may control HR and RAD51 foci specifically at stalled replication forks ([95,96], Kumari, Schultz and Helleday, submitted), possibly by interaction with RAD51 and the BLM protein, mutated in Bloom's syndrome [94].

Emerging evidence from bacteria shows that stalled replication forks may reverse to form an intermediate chicken-foot structure that may be repaired by trans-lesion synthesis or recombination (see [7,72,74,97,98] for reviews). It is possible that stalled replication forks may also reverse to form chicken-foot structures in mammalian cells, although there is no direct evidence thus far. Some mammalian cell lines treated with hydroxyurea, an agent that blocks replication by depletion of several nucleotides [99], accumulate DSBs at or near replication forks [6]. Both NHEJ and HR have been shown to be involved in the repair of hydroxyurea-induced damage [6,90]. In contrast, DSBs are not observed in mammalian cells treated with thymidine [6], which depletes only the dCTP pool levels and slows the progression of the replication fork [100]. In this case, HR alone is involved in the repair [6], suggesting that NHEJ is only involved in repair of blocked replication forks that have been processed into a DSB. More importantly, it indicates that HR repairs lesions at stalled replication forks that do not appear as detectable DSBs. The conclusion from these and other experiments is that HR repairs a broader spectrum of lesions that occur at stalled replication forks, while NHEJ only repairs DSBs [6,92]. The fact that HR is potently induced at stalled forks in mammalian cells in the absence of DSBs supports the bacterial model that recombination intermediates, such as the chicken foot, are also substrates for HR in mammalian cells.

The current and unproved model for bypass and restoration of stalled replication forks involves fork reversion, possibly caused by positive torsional strain in the DNA [101] or enzymatic action (Fig. 4). First, one strand will reverse to form a "half chicken foot" (Fig. 4b). This and other early intermediary structures formed at stalled replication forks are the substrates for the human Mus81-Eme1 endonuclease complex [102] that is induced when cells are treated with inhibitors of replication [103]. Cleavage of this structure produces a one-ended DSB identical to that
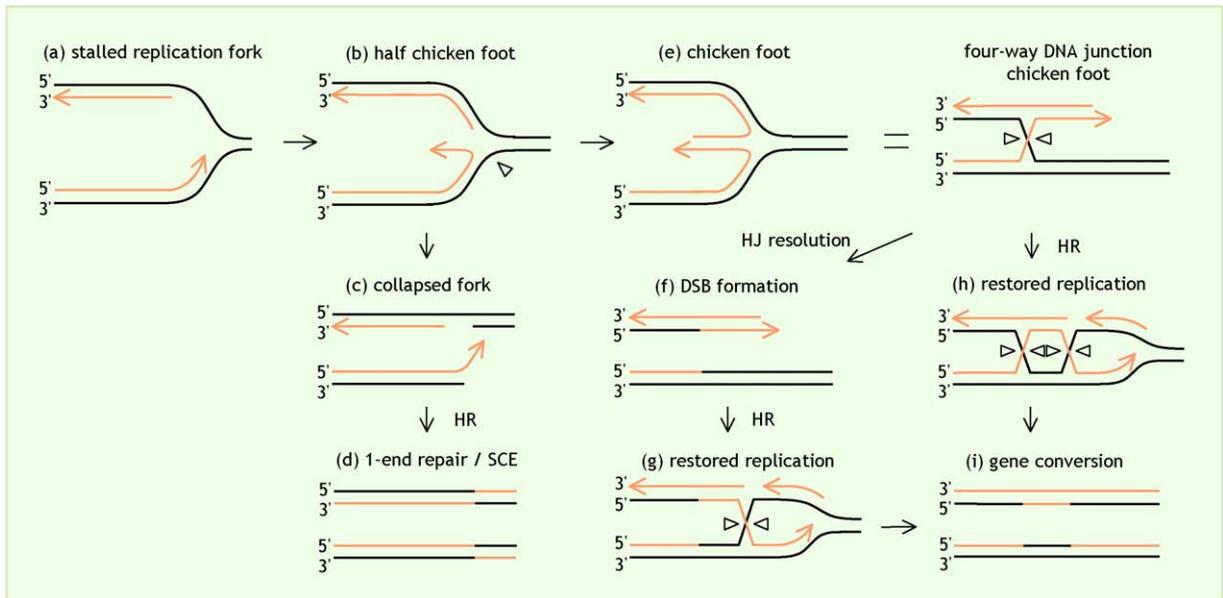
Fig. 4. HRR at a stalled replication fork. (a) A replication fork may stall owing to obstacles on the template DNA. (b) A stalled replication fork may reverse because of positive torsional strain in the DNA [101] or enzymatic action. A half chicken foot is an early intermediary structure, formed only when one strand has reversed. (c) This and other early intermediary structures may be cleaved by endonucleases, causing a collapsed replication fork with one free end. (d) This can be repaired with HR as shown in Fig. 3 and will result in a SCE. (e) The replication fork may also reverse to form a full chicken foot that includes a HJ. Here, the chicken foot is represented as a reversed fork or as a recombination intermediate, which are identical. (f) The HJ may be cleaved to form a one-end DSB that can be repaired by HR to restore replication (g). Alternatively, the free DNA end sticking out from the Chicken foot may be used directly by HR to restore replication (h). This avoids the formation of a DSB. (i) Resolution of the HJ with non-crossing over results in gene conversion, since two HJ are cleaved as in the Szostak model [66]. Arrows indicate the directions of DNA synthesis; black lines designate template DNA and orange lines newly synthesized DNA; open arrowheads designate non-crossing over; crossing over is not shown.

produced at a collapsed replication fork (Fig. 4c). This HRR event will result in a SCE as suggested above (Fig. 4d). However, the replication fork may continue to reverse and produce a chicken foot structure that includes a HJ at the four-way junction (Fig. 4e). Following synthesis at the protruding DNA end and/or repair, this HJ may branch migrate back and resume replication without recombination. This process may involve the BLM and WRN proteins or other human RecQ homologues [104,105] that localise to sites of stalled replication forks [94,104]. However, the HJ within the chicken foot might be cleaved by a resolvase yet to be determined and form a DSB (Fig. 4f). HR could then repair this DSB with the same mechanism as seen in one-end repair and thus resume replication (Fig. 4g). Alternatively, HR may be activated at the protruding DNA end before the HJ is cleaved and restore replication (Fig. 4h). It

is easy to imagine that the latter would be favoured in mammalian cells, since even a single DSB may be lethal [106].

It is likely that the result of HRR at a chicken foot is always a gene conversion event, since it involves resolution of two HJ intermediates as in the Szostak model [66] and HJ are preferentially resolved by non-crossing over in mitotic mammalian cells [52,67] (Fig. 4i). A summary of the products following HRR of a DSB with one and two ends or at a stalled replication fork is presented in Table 1.

5. Additional substrates for HR?

The dogma is that HR is primarily involved in the repair of DSBs. However, it may now be necessary to revise this. All DSB-inducing agents trigger both HR

and NHEJ [4,68,107,108]. However, more agents trigger HR than NHEJ [108–110], implying that a different lesion is produced and is causing HR. Indeed many different types of agents induce SCE and HR in mammalian cells, these include; alkylating agents [108], heavy metals [110], agents that forms bulky adducts (e.g. benzo[a]pyrene) [111], cross-linkers [91], and UV-light [108], as well as many environmental contaminants (e.g. PCB and brominated flame retardants) [109,112]. Given what is known about their varied mechanisms of action, it seems unlikely that all of these unrelated agents induce DSBs. What then is the lesion that causes HR?

One hypothesis is that they all interfere with DNA replication, which in turn triggers HR. Clearly, if HR plays an important role besides repair of mitotic DSBs in mammalian cells, future experiments should be aimed at understanding how HR recognises and repairs DNA damage other than DSBs.

6. Spontaneous HR

The embryonic lethality of HR knockouts shows that spontaneous HR, via strand invasion, is critical for survival in mammals [43–51], while NHEJ is generally not [113–116]. This is likely to be related to the role of HR in the repair of obstacles encountered during normal DNA replication [75]. Patients with a defect in a protein involved in HR are predisposed to cancer [117] or premature aging [118], indicating that HR is vital in the control of these human diseases. Furthermore, aberrant HRR underlies genetic rearrangements often found in cancers [55,119–121]. Nevertheless, the spontaneous lesions that trigger HR and the pathways involved in the subsequent repair are unknown.

Spontaneous HR occurs at a rate of 10^{-6} to 10^{-5} per cell cycle between repeated DNA sequences in mammalian cells. An average recombination substrate is about 1–5 kb, which means that about 10 spontaneous HR events occur in each cell per cell cycle. This rate of HR is probably dependent on the genome position, length of the repeated sequences and the distance between them [108]. The number of spontaneous SCEs visualised by cytological methods in mammalian cells is also about 10 SCEs per cell. It is reasonable to suppose that a majority of the spontaneous HR events taking place in mammalian cells are SCEs, since they are

mediated by HR [122]. However, this is still unproven, and little is known about the spontaneous lesion that triggers these SCEs.

7. Concluding remarks

Emerging evidence suggests that HR is vital in the repair of damage that occurs during DNA replication, while NHEJ may be more important in the repair of classical DSBs with two DNA ends [68]. The outcome following HRR of a one- or two-ended DSB differs significantly, and HRR at a stalled replication fork represents yet another pathway for repair. Probably, there are specific proteins involved in each of these pathways. Future work should identify these proteins and their biochemical roles within these pathways. Apart from the three HR pathways described here, more pathways may exist, given that HRR is involved in repair following treatment by agents that produces a wide variety of DNA damage. Future work should be aimed at understanding these additional repair pathways. More importantly, though, is to understand the pathways of spontaneous HR and what triggers these events, since they may participate in two of the most common causes of human death, i.e. aging and cancer.

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