

DNA Replication in Repair

Kevin M. McCabe
University of Colorado at Boulder
United States of America

1. Introduction

All living organisms face a constant barrage of DNA damage from anthropogenic and naturally occurring external and endogenous sources, yet DNA provides the blueprint for all other cellular structures. Unlike these other structural and functional molecules, DNA is not turned over in a cycle of breakdown and rebuild; DNA, by the nature of its function as an informational macromolecule and its double stranded structure, is faithfully repaired and copied to maintain the encoded information. In the case of multicellular organisms, the focus of this review, fidelity of information prevents disease, both heritable (e.g. genetic disorders), and within an individual (e.g. cancer). However, errors in DNA replication and repair serve as the grist of evolution; in some sense, these errors are essential to life as we know it.

With few exceptions, the repair of DNA damage requires the action of one or more DNA polymerases. In many cases, these are specialized polymerases, recruited to the site of damage for their specific biochemical properties. In this literature review, I will present different types of DNA damage, the biochemical systems utilized in the repair of this damage, the role of various enzymes in this repair - emphasizing the role of specific DNA polymerases - and the outcome of repair - including the resulting mutation spectrum - where relevant.

2. DNA polymerases

DNA polymerases are responsible for the replication of DNA. They perform this function by adding free deoxynucleotides to the 3' end of a DNA strand or RNA primer and extending the strand in the 5' direction; they are not able to synthesize DNA *de novo* without this 3' hydroxyl (Baker & Bell 1998; Hubscher *et al.* 2002). They are typically composed of several subunits, but an in depth discussion of polymerase components is beyond the scope of this chapter; please see Kawasaki and Sugino for a more in depth discussion of polymerase subunits (Kawasaki & Sugino 2001). The mechanism of nucleotide insertion by a polymerase is a process consisting of 6 steps binding of the DNA template, binding of the incoming dNTP, undergoing a change in conformation to become more catalytically effective, formation of the phosphodiester bond, release of the pyrophosphate group, and translocation to the next template base or dissociation from DNA (Kuchta *et al.* 1988; Kuchta *et al.* 1987; Patel *et al.* 1991; Washington *et al.* 2000; Washington *et al.* 2001; Wong *et al.* 1991). The structure of a polymerase is similar to that of a right human hand grasping a DNA strand, and is thus described as having finger, palm and thumb subdomains (Steitz 1998). Synthesis is carried out using the opposite strand as a template—the semi-conservative model of DNA synthesis (Meselson & Stahl 1958).

2.1 DNA polymerase families

Polymerases are organized into 7 families by their sequence, structure, and function. These polymerase families are: A, B, C, D, X, Y and RT. Each family has different properties and roles. For example, A Family polymerases are responsible for the bulk of S-phase DNA synthesis, and Y Family polymerases are responsible for Translesion Synthesis (TLS) and the bypass of some DNA lesions. A brief discussion of bacterial polymerase families follows, as does a more detailed discussion of multicellular eukaryotic polymerase families, representative members, and roles (summarized in Table 1).

A Family polymerases are replicative and repair polymerases that include the *E. coli* replicative polymerase polI, *T. aquaticus* polI, and the human mitochondrial polymerase, pol γ . This family also includes the *E. coli* T7 polymerase, one of the most studied polymerases. Orthologues of this family include members of the B Family of eukaryotic polymerases (Hubscher *et al.* 2002). The tight active site and 3' primer interactions prevent base pair mismatches, and thus these polymerases have a low error rate. pol θ is a low fidelity A Family member with roles in repair, possibly including Base Excision Repair (BER) and Interstrand Crosslink Repair (ICLR) (Chan *et al.* 2010; Prasad *et al.* 2009).

The B Family of polymerases is closely related to the A Family in structure and function. They are DNA directed DNA polymerases and this family includes the eukaryotic replicative and repair polymerases pol α , pol δ , and pol ϵ . pol α with its accompanying primase is responsible for initiation of DNA synthesis (Harrington & Perrino 1995). pol δ and pol ϵ cooperate to accomplish leading and lagging strand DNA synthesis (Chilkova *et al.* 2007). pol δ and pol ϵ are also involved in Homologous Recombination Repair (HRR) of DNA (Asturias *et al.* 2006; Kelman 1997; Maloisel *et al.* 2008). Another B Family member, pol ζ , is involved in TLS (Haracska *et al.* 2003).

C Family polymerases represent the main bacterial chromosomal synthetic polymerases (Lamers *et al.* 2006). They are fast moving, have proofreading capability, and are structurally and possibly evolutionarily distinct from the other polymerase families (Bloom *et al.* 1997; Lamers *et al.* 2006). Another distinct family are the D Family polymerases. They are archaeal polymerases that are assumed to function as replicative polymerases (Ishino *et al.* 1998; Yamasaki *et al.* 2010).

X Family polymerases are extensively involved in a variety of DNA repair mechanisms. This family includes pol β , pol σ , pol λ , and pol μ , as well as terminal deoxynucleotidyl transferase (TdT). Some of the X Family members, including pol β and pol λ , can cleave a 5' abasic deoxyribose sugar, a critical function in BER and possibly required for Non-Homologous End Joining (NHEJ) (Fan & Wu 2004; Garcia-Diaz *et al.* 2001). TdT expression is limited to developing leukocyte lineages where it plays a critical role in V(D)J Recombination, a specific type of NHEJ (Mahajan *et al.* 1999). pol λ and pol μ are required for NHEJ (Fan & Wu 2004; Mahajan *et al.* 2002). pol σ works in concert with pol ϵ in sister chromatid cohesion and HRR (Edwards *et al.* 2003).

The Y Family of polymerases, including pol η , pol ι , pol κ , and REV-1 are involved in TLS. Each polymerase in this family has a different bypass preference. For example, pol η will bypass cyclothymines dimers (CTD), inserting two adenines opposite the lesion in an error free manner. Loss of pol η because of its involvement in CTD bypass gives a Xeroderma pigmentosum variant phenotype as with many Nucleotide Excision Repair (NER) enzymes (Johnson *et al.* 1999b; Washington *et al.* 2000). pol ι is not able to replicate past a CTD, however, it is involved in the nucleotide incorporation opposite an abasic site and the 3' thymine of a (6-4) photoproduct (Johnson *et al.* 2000). Although it can insert bases opposite

the lesion, this polymerase cannot extend the nascent DNA strand. While polk cannot insert bases opposite damage as polη and polι can, it does extend opposite the 3' end of the lesion (Washington *et al.* 2002). REV-1 is thought to play a supporting role as well, triggering synthesis of the other Y family members at these lesions (Guo *et al.* 2003; Ohashi *et al.* 2004; Tissier *et al.* 2004). The roles of polymerases in TLS are discussed in more detail below.

Polymerase Family	Polymerase	Role in DNA Replication	DNA Repair Pathway Participation
A	polθ	N/A	BER?, ICLR?
B	polα	Initiation of Replication	N/A
	polδ	Processive Synthesis	HRR
	polε	Processive Synthesis	Long Range HRR DNA Synthesis, SSA
	polζ	N/A	TLS, HRR?
X	polβ	N/A	BER
	polλ	N/A	NHEJ
	polμ	N/A	NHEJ
	polσ	N/A	Stimulates polε
	TdT	N/A	V(D)J Recombination
Y	polη	N/A	TLS past CTD
	polι	N/A	TLS past abasic and 6-4 photoproduct
	polk	N/A	Extension from 3' of bypass by polη and polι
	REV-1	N/A	Triggering Synthesis by the Other Y Family Members

Table 1. DNA Polymerases Involved in DNA Repair and Their Roles

The RT Family of polymerases includes RNA-directed DNA polymerases that use RNA primers or are involved in viral reverse transcription, like the eukaryotic polymerases responsible for telomere maintenance, telomerase (Gotte *et al.* 1999; Greider & Blackburn 1989). RT stands for Reverse Transcriptase, the primary function of members of this polymerase family.

3. DNA repair

The goal of all DNA repair is to maintain the integrity of the genome with minimal, and ideally no changes to the original DNA sequence. In the case of single strand damage, such as spontaneous depurination, oxidation, alkylation, and ultraviolet (UV) light photoproducts, this is readily achieved by Direct Reversal Repair (DRR), in which an enzyme directly returns the lesion to its former, undamaged state, or utilizing the

antiparallel DNA strand as template, as in TLS, or following excision of the damage as in BER and NER. However, when both strands are damaged, repair mechanisms including Double Strand Break Repair (DSBR) and Interstrand Crosslink Repair (ICLR) are utilized, and repair becomes increasingly complicated and in many cases mutagenic.

The type of DNA damage incurred dictates the mechanism(s) of DNA repair. Initial recognition of the lesion directly recruits, or signals for the recruitment of repair factors. The exact repair mechanism implemented for a specific type of lesion may vary, depending upon available factors or cell cycle status.

3.1 Direct reversal repair

DRR represents a set of enzymes that catalyze direct repair of the damaged base/s, returning the DNA to its previous, undamaged configuration and sequence. Examples of DNA damage and their repair proteins would include *O*⁶-alkylguanine being repaired by AlkB dioxygenase human homologues AHB2 and AHB3, cyclopyrimidine dimers (CPD) being repaired by DNA photolyase and 6-4 photoproducts being repaired by 6-4 photolyase (Duncan *et al.* 2002; Kim *et al.* 1993; Wibley *et al.* 2000; Zhao, X. *et al.* 1997). As these specific enzyme mechanisms execute a direct catalytic repair of DNA damage, they do not require DNA synthesis in repair. However, some of these same forms of DNA damage, for example CPD, can be repaired through alternate, DNA polymerase requiring mechanisms, such as NER.

3.2 Base excision repair

BER is utilized in the repair of DNA damage incurred on a single strand, where there is little structural alteration of the DNA backbone. This damage includes apurinic sites resulting from spontaneous depurination, oxidized or alkylated bases, or base mismatches resulting from 5-methylcytosine deamination (T/G mismatch) or polymerase errors. Because there is little backbone distortion, these lesions tend not to block replicative polymerases, and as a result, this damage can be highly mutagenic if not detected and repaired. For example, an unrepaired 8-oxoguanine at DNA synthesis will lead to G:C to T:A transversions common to many solid tumors (Bruner *et al.* 2000).

3.2.1 Steps of BER

In BER, specific glycosylases recognize and bind specific lesions (Banerjee *et al.* 2006; Bruner *et al.* 2000; Engelward *et al.* 1997; Klungland *et al.* 1999; Parsons 2003) with the assistance of accessory proteins such as MutM (Banerjee *et al.* 2006) (Figure 1). Examples include 8-oxoguanine DNA glycosylase recognizing and binding 8-oxoguanine (Bruner *et al.* 2000) or alkyladenine DNA glycosylase recognizing and binding alkyladenine (Engelward *et al.* 1997). The damaged base is flipped out and cleaved by the glycosylase (Banerjee *et al.* 2006) generating an abasic site. Apurinic-apyrimidinic endonuclease (APE1) will then nick or break the DNA backbone (Mol *et al.* 2000; Srivastava *et al.* 1998) (Figure 1).

At this point, two possible pathways, Short Patch Repair (SPR) and Long Patch Repair (LPR), diverge (Kubota *et al.* 1996). In SPR, pol β will cleave the 5' abasic sugar and replace the missing nucleotide (Garcia-Diaz *et al.* 2001). X-ray Repair Cross Complementing Protein 1 (XRCC1), along with its binding partner, DNA Ligase III will seal the backbone nick. In LPR, Replication Factor C (RFC) loads Proliferating Cell Nuclear Antigen (PCNA) at the

incision (Kelman 1997). PCNA will facilitate pol β binding (a common step in the recruitment of many polymerases to damaged sites) and pol β will synthesize a stretch of DNA, creating a 5' flap (Srivastava *et al.* 1998). This flap is trimmed by Flap Endonuclease 1 (FEN1), and DNA Ligase I seals the remaining nick or break in the DNA backbone (Prasad *et al.* 2000; Srivastava *et al.* 1998) (Figure 1). In both cases, the DNA is repaired in an error-free manner, if the damage is recognized before S-phase and DNA synthesis.

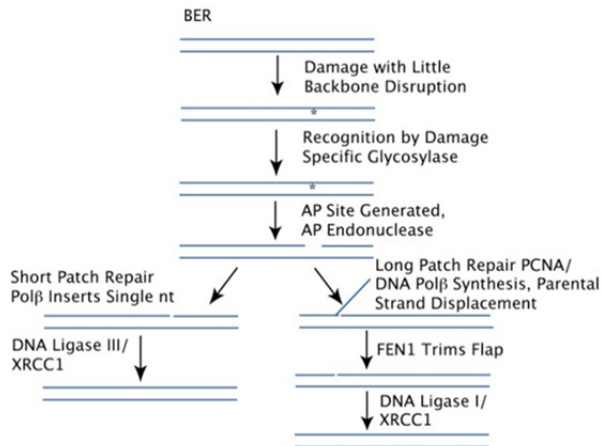


Fig. 1. The generalized steps of BER

3.3 Nucleotide excision repair

Whereas the damage to which BER responds does not significantly distort the DNA backbone, NER explicitly recognizes this backbone distortion utilizing two different systems—Transcription Coupled Repair (TCR, (Bohr *et al.* 1985; Mellon *et al.* 1987)) and Global Genome Repair (GGR, (Aboussekhra *et al.* 1995; Araujo *et al.* 2000)). The types of damage recognized by these systems primarily consist of bulky adducts, including UV photoproducts (cyclopyrimidine dimers and 6-4 photoproducts (Mellon *et al.* 1987; Ng *et al.* 2003)) or N-acetoxy-2-acetyl-aminofluorene induced adducts (Ng *et al.* 2003). These bulky adducts will stall DNA polymerases as well as transcription machinery, and are therefore less mutagenic than the types of damage repaired by BER, but they can be cytotoxic (Mitchell *et al.* 2003).

3.3.1 Steps of NER

TCR is activated by the stalling of RNA polymerase II upon encountering a bulky adduct. This recruits Cockayne Syndrome Proteins A and B (CSA and CSB, (Henning *et al.* 1995)), Xeroderma Pigmentosum Protein A (XPA), Binding Protein 2 (XAB2, (Nakatsu *et al.* 2000)), and High Mobility Group Nucleosome Binding Protein 1 (HMGN1, (Birger *et al.* 2003)) to the site of damage. This system for sensing DNA damage can only function on actively transcribed genes. With GGR, the bulky adducts are recognized by the Xeroderma Pigmentosum Protein C (XPC)-Homologue of RAD23 B (HR23B) complex (Figure 2), with help from Xeroderma Pigmentosum Protein E (XPE, also known as Damaged DNA Binding Protein 2 (DDB2)) in the case of photodimers (Kulaksiz *et al.* 2005; Yokoi *et al.* 2000).

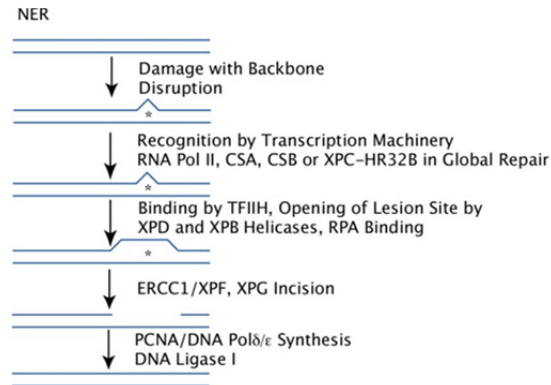


Fig. 2. Generalized Steps of NER

Following damage recognition, these two repair systems utilize the same enzymes to catalyze repair. These include the basal transcription factor (TFIIH), with the helicases Xeroderma Pigmentosum Protein B (XPB, 3' to 5' helicase) and Xeroderma Pigmentosum Protein D (XPD, 5' to 3' helicase), as well as Xeroderma Pigmentosum Protein A (XPA) and Xeroderma Pigmentosum Group G (XPG) (Tantin 1998; Tantin *et al.* 1997). Once bound, the TFIIH complex opens the lesion. XPA recruits Replication Protein A (RPA), which stabilizes the single stranded DNA (ssDNA) (Li *et al.* 1995a; Li *et al.* 1995b). The Excision Repair Cross Complementation Group 1–Xeroderma Pigmentosum Group F (ERCC1-XPF) heterodimer then incises the DNA backbone 5' of the damage, while XPG incises the backbone on the 3' side of the adduct (O'Donovan *et al.* 1994; Sijbers *et al.* 1996).

With 25–30nt surrounding the lesion removed, RFC loads PCNA, as in BER (Kelman 1997). At this stage, variations in the final steps may be observed with dividing and non-dividing cells (Fousteri & Mullenders 2008). In the case of dividing cells, DNA pol δ and pol ϵ will synthesize DNA across the gap, and DNA Ligase I will seal the resulting nick (Aboussekhra *et al.* 1995; Araujo *et al.* 2000; Araujo & Wood 1999). In the DNA of non-dividing cells (out of S-phase), pol κ might instead be utilized to bridge the gap, with XRCC1-DNA Ligase III sealing the nick (Moser *et al.* 2007; Ogi & Lehmann 2006). Again, as with BER, the utilization of the undamaged strand results in error-free repair.

3.4 Translesion synthesis

The DNA lesions produced in cells by a variety of chemical or physical agents can sometimes escape the repair mechanisms of the cells, including NER. Because these lesions distort the structure of the DNA, the high-fidelity polymerases are no longer able to bind and replicate past the lesions. Other polymerases, the low-fidelity, TLS polymerases, are recruited at the replication fork and are involved in replication past the DNA damage (Burgers *et al.* 2001; Ohmori *et al.* 2001). As noted above, the most significant classes of TLS enzymes encountered in eukaryotes are the members of the Y-family of DNA polymerases (pol η , ι , κ and Rev1) also known as UmuC/DinB/Rev1/Rad30 superfamily, in addition to a member of the B-family of polymerases, pol ζ (Ohmori *et al.* 2001; Zhao, B. *et al.* 2004).

3.4.1 Steps of TLS

The first step in DNA repair is the recruitment of TLS polymerases at the stalled replication fork by a monoubiquitinated, sumoylated, or otherwise modified PCNA (Haracska *et al.* 2001a; Haracska *et al.* 2001b; Waters *et al.* 2009). Rev-1 is suspected to act as a trigger in mobilizing the other polymerases, pol η , pol ι , and pol κ , to insert a base or bases opposite the damaged nucleotide/s (Guo *et al.* 2003; Ohashi *et al.* 2004; Tissier *et al.* 2004). After bringing the polymerases to the lesion site during the repair process, the same Rev-1 will bind pol ζ . pol ζ is a member of the B-family of polymerases that is not very efficient in inserting the nucleotides opposite lesions, but can extend the primer termini (Haracska *et al.* 2003). Once this polymerase binds, it will begin to synthesize a stretch of DNA opposite the damage site, completing the bypass of the lesion. Two generalized models for TLS include polymerase switching, in which a replicative polymerase stalls, PCNA is modified, and a TLS polymerase extends from the lesion, and once bypassed, replication resumes. The other model is gap filling, in which a gap is left following replication fork stalling at a damaged site, and TLS fills this gap. These models are reviewed in Waters *et al.* (Waters *et al.* 2009).

3.5 Double strand break repair

Unlike the damage repaired by DRR, BER, and NER, DSB involve both strands of DNA. This eliminates the ability of DSBR to utilize DNA's built in backup, the opposing DNA strand, as it too is damaged. This damage is typically caused by ionizing radiation, neighboring single strand breaks, natural processes such as V(D)J recombination, meiotic and mitotic crossing over, yeast mating type switching, and the collapse or stalling of replication forks (Khanna & Jackson 2001; Sugawara *et al.* 2000).

There are three main pathways for the repair of DSB:— Single Strand Annealing (SSA), NHEJ, and HRR. Local differences in DNA sequence, the availability of repair factors, the availability of a homologous sequence, and cell cycle status affect which mechanism of DSBR is utilized. NHEJ, of which there are two alternate biochemical pathways, the primary, Ligase IV dependent NHEJ (D-NHEJ) and the backup, Ligase III dependent NHEJ (B-NHEJ), is utilized for most DSB in mammalian cells (Mladenov & Iliakis 2011). SSA can occur where there are direct repeats in DNA sequence, and there are lower levels of NHEJ components (Fishman-Lobell *et al.* 1992). HRR functions predominantly in S and G2 phases of the cell cycle, when homologous substrates are readily available (Aylon *et al.* 2004).

3.5.1 Steps of NHEJ

DSBR by NHEJ can follow a main D-NHEJ (named for the requirement of DNA-PKcs) pathway responsible for the bulk of DSBR in mammalian cells, or a Backup B-NHEJ. Both pathways repair DSB in similar manners, but utilize different proteins at each step (Mladenov & Iliakis 2011). For simplicity, Figure 3 will only list D-NHEJ, but B-NHEJ follows similar catalytic steps, as discussed below.

In mammalian D-NHEJ, the DSB is recognized and bound by Ku70/Ku80 heterodimer. This leads to binding of the DNA Dependent Protein Kinase catalytic subunit (DNA-PKcs) yielding a functional DNA-PK holoenzyme (Cary *et al.* 1997). The ends are modified by polynucleotide kinase (PNK) and terminal deoxynucleotide transferase (TDT), also, an as yet unidentified endonuclease (possibly Artemis, a substrate of DNA-PK) will then resect the 5' ends leaving 3' ssDNA. These ends will be filled by DNA pol λ and μ , and joined by the DNA Ligase IV-XRCC4 complex, enhanced by XRCC4 Like Factor (XLF) (Bryans *et al.* 1999; Fan & Wu 2004; Mahajan *et al.* 2002; Yano *et al.* 2008) (Figure 3).

Less is known about B-NHEJ than D-NHEJ, but B-NHEJ seems to act more slowly than D-NHEJ, though it can ultimately achieve the same ends, the repair of DSB (Iliakis 2009; Wang, H. et al. 2003; Wang, M. et al. 2006; Wu et al. 2008). This alternate pathway was identified in cell lines deficient in many of the D-NHEJ proteins (Nevaldine et al. 1997; Wang, H. et al. 2001a; Wang, H. et al. 2001b). In B-NHEJ, Poly [ADP-ribose] polymerase 1 (PARP-1), usually associated with single strand break repair, is responsible for end recognition and binding (McKinnon & Caldecott 2007; Wang, M. et al. 2006). A role for the MRN complex in processing of the break has been suggested based upon reduced end joining in D-NHEJ deficient cells when Mre11 is inhibited (Rass et al. 2009). DNA Ligase III and XRCC1 are regulated by PARP-1, and a role for Ligase III has been demonstrated in NHEJ (McKinnon & Caldecott 2007; Windhofer et al. 2007). Enhancement of Ligase III activity by Histone H1, suggests a role in B-NHEJ as well (Rosidi et al. 2008). No direct evidence for the role of a specific polymerase has been identified in B-NHEJ, however, it is known that PARP-1 interacts with DNA pol α , suggesting possible involvement in this pathway (Dantzer et al. 1998).

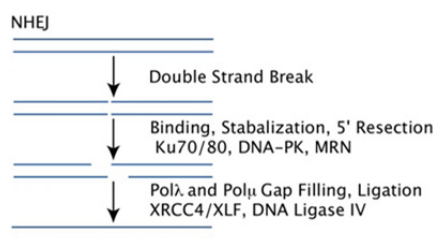


Fig. 3. Generalized steps of NHEJ

If the two ends that are joined by NHEJ are from a single double strand break, the outcome can be conservative or lead to deletions of varying sizes, depending upon the extent of processing of the ends. If, however, the two ends that are rejoined were from separate DSBs, the result will be a translocation. While NHEJ is quite proficient at rejoining DSB ends and eliminating this highly cytotoxic DNA damage, it does not involve a mechanism to choose which ends to rejoin, and is, thus, considered to be a non-conservative mechanism for DNA repair.

3.5.2 Steps of SSA

SSA requires a more specific set of conditions than NHEJ, specifically neighboring repeats either side of the DSB, and will predominantly occur in S-phase (Frankenberg-Schwager *et al.* 2009; Sugawara *et al.* 2000). At the site of the DSB, there is a 5' to 3' resection, likely by the MRN complex, that leaves 3' tails. RAD52 binds the 3' ends, and these tails are stabilized by the ssDNA binding protein, RPA (Stasiak *et al.* 2000; Van Dyck *et al.* 1999; Wold 1997). These factors are sufficient for annealing of the repeat sequences. FEN1 or ERCC1/XPF then trim the 3' overhangs (Al-Minawi *et al.* 2008; Gottlich *et al.* 1998). The remaining gaps are filled and ligated by DNA pol α and DNA Ligase III (Gottlich *et al.* 1998) (Figure 4).

As neighboring repeats are annealed, sometimes at distances of 40bp to 1-2kb apart, SSA results in deletions of varying sizes (Gottlich *et al.* 1998; Richardson & Jasin 2000). With multiple genomic DSB, SSA has also been demonstrated to yield translocations (Richardson & Jasin 2000). Presumably, these result from homologous sequences on non-homologous chromosomes annealing and being joined by the SSA machinery.

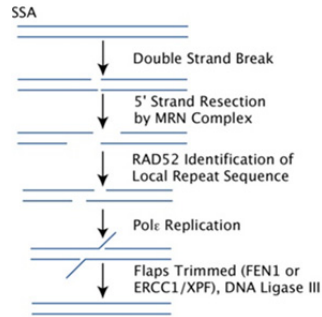


Fig. 4. Generalized Steps of SSA

3.5.3 Steps of HRR

Like SSA, HRR requires a homologous sequence, typically a sister chromatid; thus most HRR occurs in late S or G2 phases of the cell cycle. Following DSB formation, there is a 5' resection leaving 3' tails. Rad51 recombinase (made up of Rad51B and Rad51C) binds these single stranded regions, a homologous region is identified, and a D-loop is formed (Sung & Robberson 1995). This complicated process utilizes a number of other proteins, including the MRN complex which, along with BRCA1 and CtIP, again serves a role in resection; BRCA2, which facilitates Rad51 loading and facilitates recombination; RPA, which acts to stabilize the ssDNA and promote strand exchange with Rad51; Rad54, which aids in chromatin remodeling; and Hop2-Mnd1, which help promote D-loop capture and processing (Chen *et al.* 2008; Pellegrini *et al.* 2002; Solinger *et al.* 2001; Stauffer & Chazin 2004; Sung & Robberson 1995; Vignard *et al.* 2007). (Other protein systems are responsible for meiotic recombination and are not discussed in detail here, but are reviewed in (Smith & Nicolas 1998)).

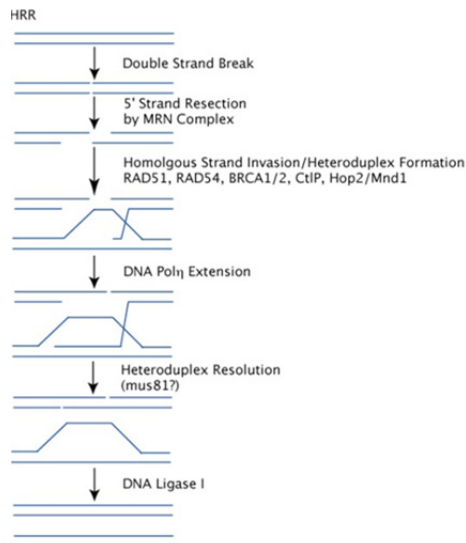


Fig. 5. Generalized Steps of HRR

DNA pol η will then extend from the 3' end of the invading strand, elongating the D-loop (McIlwraith *et al.* 2005). The invading strand is then displaced and anneals with the second DSB end, being ligated by DNA Ligase I (Goetz *et al.* 2005) (Figure 5). This mechanism of repair avoids the formation of a Holiday junction and the risk of crossover (referred to as Synthesis Dependent Strand Annealing or SDSA) (Ferguson & Holloman 1996). However, where the goal is crossover, as in meiotic recombination, the extended D-loop will bind the second DSB end creating a Holiday junction, leading to crossover and non-crossover products (referred to as the DSBR pathway) (Szostak *et al.* 1983).

A specialized version of HRR, called Break Induced Replication (BIR), acts to preserve single DSB ends such as those at chromosomal termini, or, as we will discuss in ICLR, at stalled replication forks. In BIR similar factors are utilized to process the ends, invade a homologous or repeat sequence, extend, and resolve the lesion. Of note, the pol α primase is required for initiation of replication by pol δ (Maloisel *et al.* 2008). pol ϵ is required for long-range synthesis, and, unique to BIR, Pol32 is required but does not function in other HRR pathways (Asturias *et al.* 2006; Lydeard *et al.* 2007).

HRR is the only truly conservative repair mechanism for double strand breaks, with both SDSA and DSBR, when a homologous chromosome provides the template for repair. Unlike NHEJ and SSA, it does not typically lead to translocations or deletions, but DSBR can lead to crossing over of chromatids. In BIR, if the substrate for recombination is a homologous chromatid, repair is conservative; however, if a repeat from a non-homologous sequence is utilized, a translocation may result.

3.6 Interstrand crosslink repair

There are certain chemicals, endogenous and exogenous, that covalently link both strands of a DNA molecule together; these agents include malondialdehyde, mitomycin C, or psoralen (Scharer 2005). With an ICL, much like a DSB, the anti-parallel strands can no longer be used as template for one another. ICLs covalently link both strands of DNA together preventing strand separation required for transcription and replication, making ICL inducing agents particularly potent killers of cycling cells (Dronkert & Kanaar 2001). For this reason, many ICL inducing agents are used as chemotherapeutic agents in the treatment of cancer (Lawley & Phillips 1996; Lord *et al.* 2002; Ryu *et al.* 2004). Stalled replication forks will also utilize ICLR under certain circumstances (McCabe *et al.* 2008).

The genetic disorder Fanconi Anemia (FA) is intimately associated with ICLR, much the way Xeroderma Pigmentosum is associated with NER. There are currently 15 FA groups, representing defects in 15 proteins involved in ICL repair. These genes are, FANCA, B (Fanconi Anemia Associated Protein of 95kDa, FAAP95), C, D1 (BRCA2), D2, E, F, G, I, J (BRCA1 Interacting Protein C-terminal Helicase 1, BRIP1), L, M (Fanconi Anemia Associated Protein of 250KD, FAAP250), N (Partner and Localizer of BRCA2, PALB2), O (Rad51C), and P (SLX4) (Kitao & Takata 2011). The numerous proteins involved in ICLR reflect the complexity of repairing this type of damage. The model presented here (Figure 6) is speculative; it is based upon published biochemical functions of the proteins involved and the formation of recombination intermediates in FA cells between non-homologous chromosomes (Newell *et al.* 2004). The ICLR pathway likely represents a last ditch mechanism of repair for this extremely cytotoxic damage where there are no homologous substrates for HRR of these lesions (McCabe *et al.* 2009). TLS is one other option for damage bypass, but does not constitute repair.

3.6.1 TLS in response to ICL

If there are incisions on both sides of an ICL on one strand, TLS has been proposed to replicate past the lesion, reducing its cytotoxicity and permitting continuation of the cell cycle. TLS utilizing error prone pol ζ or pol η might replicate past the ICL following DSB formation (reviewed in (Dronkert & Kanaar 2001)). However, pol η mutants show normal sensitivity to ICL, suggesting no role for this polymerase in repair (Grossmann *et al.* 2001). Little is known about this pathway compared to NER and HR repair; however, it is thought that this pathway helps the cells to bypass an ICL to reduce cytotoxicity as opposed to actually repairing the lesion (Dronkert & Kanaar 2001). Further, the severity of the FA phenotype with respect to ICL damage suggests TLS is, at most, a minor mechanism of ICL repair.

3.6.2 Steps of ICLR

It has been suggested that the distortion created by the ICL or the ensuing chromatin change could be one of the initial signals for repair (Dronkert & Kanaar 2001). DSB signaling, including ATM kinase activity, also plays a clear role in ICLR, as DSB are an important intermediate in repair, though data suggests that DSB do not activate the FA pathway (Rogakou *et al.* 1999; Sobeck *et al.* 2007). The collapsed replication fork at the site of ICL damage, or in response to hydroxyurea treatment, collapses and regresses with the help of RECA (Robu *et al.* 2001). This leads to loading of the FA core complex via the DNA translocase activity of FANCM/MHF complex (Singh *et al.* 2010; Yan *et al.* 2010). The FA core complex is comprised of FANCA, B, C, E, F, G, L and M, and is required for monoubiquitination of FANCD2 by the E3 ligase FANCL, in concert with the E2 subunit UBE2T (Machida *et al.* 2006) (Figure 6).

Central to the FA pathway are FANCD2 and its paralog FANCI (Smogorzewska *et al.* 2007). FANCD2 monoubiquitination is traditionally looked upon as the marker of activation of the FA pathway. Monoubiquitination is required for FANCD2 and FANCI localization to chromatin (Garcia-Higuera *et al.* 2001; Smogorzewska *et al.* 2007). Monoubiquitinated FANCD2/FANCI colocalizes with BRCA1 in response to DNA damage and at synaptonemal complexes (Garcia-Higuera *et al.* 2001). Additionally, FANCD2 has been shown to interact in a constitutive manner with FANCD1/BRCA2 and co-localizes with RAD51 in nuclear foci (Hussain *et al.* 2004). FANCD2 also interacts with the MRN complex, which may serve a role in processing a recombination intermediate (Nakanishi *et al.* 2002). FANCA, a core complex component, has been shown to interact with several other proteins. Independently of the other FA proteins, FANCA interacts directly with BRCA1 without the requirement for DNA damage, suggesting a constitutive interaction (Folias *et al.* 2002). Additionally, FANCA has been suggested to aid in the recruitment of the SWI/SNF complex subunit, brahma-related gene 1 (BRG1), and may be involved in chromatin remodeling at the site of action of the FA pathway (Otsuki *et al.* 2001).

Biochemical studies have identified several proteins forming large complexes with the FA proteins. Included in the BRAFT complex are five FA proteins (FANCA, C, E, F, and G), the Bloom syndrome helicase (BLM), replication protein A (RPA) and topoisomerase IIIa (Topo3a). This complex has a DNA duplex unwinding capability that requires BLM, but not FANCA. However, BLM is not required for FANCD2 monoubiquitination, suggesting BLM functions in this pathway downstream of core complex signaling for activation of the FA pathway (Meetei *et al.* 2003). FANCI is a BRCA1 interacting protein that functions as an ATP-dependent 5'-3' helicase (Cantor *et al.* 2001; Cantor *et al.* 2004). Combined with the

interaction of FA proteins with BLM, a 3'-5' helicase, these data suggest the ability of FA complexes to open stretches of DNA in both directions (Ellis *et al.* 1995).

The discovery of FANCD1 as BRCA2 directly linked the FA pathway and HRR pathway (Hirsch *et al.* 2004). BRCA2 is known to regulate RAD51 controlling the formation of the RAD51/ssDNA nucleoprotein filament required for strand pairing during HRR in DSBR (Davies *et al.* 2001; Sharan *et al.* 1997). In addition, BRCA2 binds FANCD2 and G placing the core complex and FANCD2 at sites of homologous recombination repair (Hussain *et al.* 2004). Another recombination and FA was uncovered with the identification of FANCN as the partner and localizer of BRCA2 (PALB2) (Reid *et al.* 2007; Tischkowitz *et al.* 2007; Xia *et al.* 2006). As its name suggests, PALB2 interacts with BRCA2 and is responsible for its localization to chromatin; thus, PALB2 is required for BRCA2's function in homologous recombination repair and cell cycle checkpoints (Xia *et al.* 2007; Xia *et al.* 2006). FANCM, in addition to its early binding role, also serves a catalytic function in the processing or resolution of the recombination intermediate, as cells from a FANCM patient form radials in response to ICL inducing agents, but the FANCM defect does not impact FANCD2 monoubiquitination (Singh *et al.* 2009).

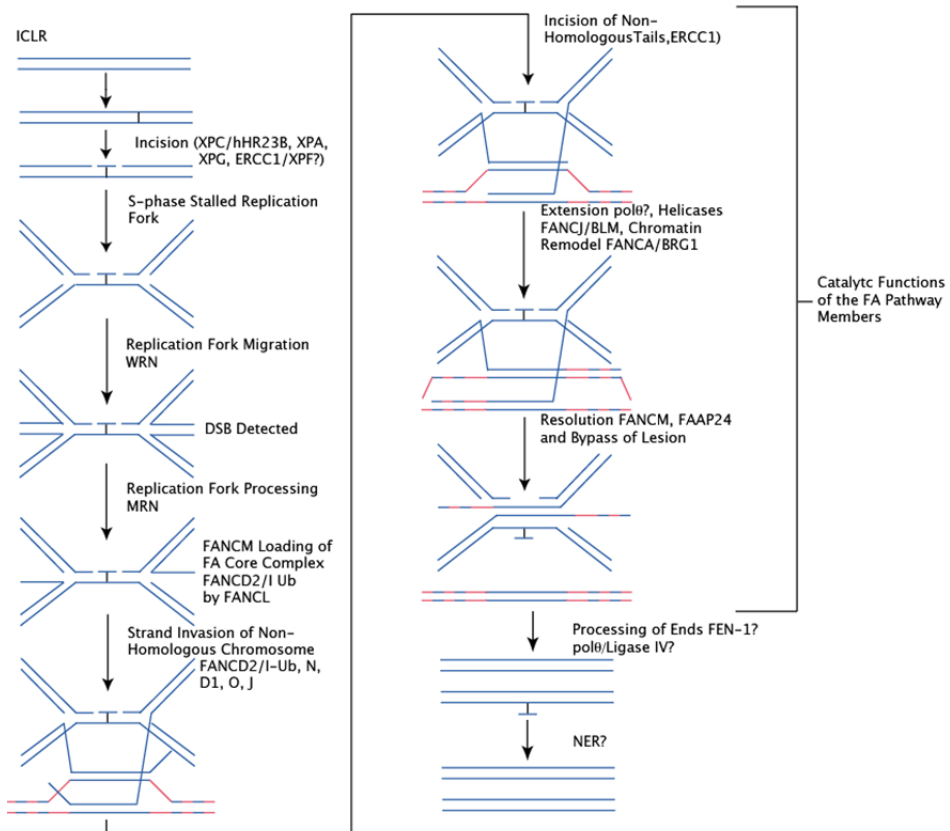


Fig. 6. Hypothetical Steps of ICLR

All of this suggests the next step in repair involves a HRR or HRR like repair mechanism, likely similar to BIR with a non-homologous substrate, as failure to complete repair yields a radial formation (Figure 7), and these radials are between non-homologous chromosomes (Newell *et al.* 2004). It would seem the variety of functions pulled together for ICLR serve to stabilize the stalled replication fork, initiate recombination in the absence of an available direct homologue by identifying repeats or microhomology suitable for recombination on non-homologous chromosomes, synthesis along this sequence past the region affected by the ICL (possibly involving pol θ /Ligase IV, (Chan *et al.* 2010)), and subsequent resolution of the recombination intermediate (Figure 6).

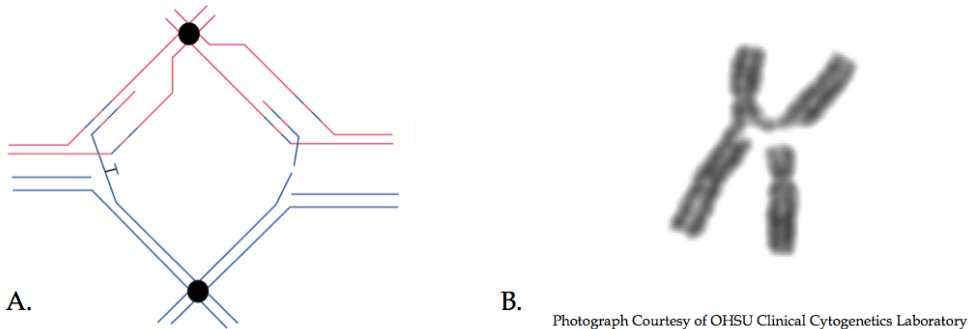


Fig. 7. A. Reorganization of non-homologous chromosome recombination intermediates from the model in Figure 6 into a chromosomal context (large circles represent centromeres) demonstrates the possibility for intermediates from this mechanism to yield radials. B. Portion of a metaphase spread of ICL treated FA mutant cells and a radial formation.

4. Discussion

With the exception of DRR and possibly a small subset of NHEJ, DNA damage repair requires DNA replication. BrdU incorporation, a general marker of DNA synthesis, has been successfully used as a surrogate marker for DNA damage repair (Kalle *et al.* 1993; Kao *et al.* 2001). The requirement of replication for repair relates to the double stranded structure of DNA, and the idea of having a built in backup copy of information on the opposing strand. To a certain extent, this holds true even in the case of double stranded damage, though the backup may be a repeat sequence on the same stretch of DNA or on a non-homologous chromosome, in the case of SSA and ICLR respectively.

Different types of DNA damage will utilize any of a variety of DNA polymerases, based upon the structure/function of this polymerase. The evolution of various DNA polymerase families with specific roles supports the importance of replication as an indispensable tool in the repair of DNA damage. TLS utilizes polymerases with open active sites to permit synthesis past an adduct (Trincao *et al.* 2001). Long-range synthesis in HRR requires pol ϵ , because of its processivity (Asturias *et al.* 2006). BIR requires the normally dispensable pol δ subunit, pol32, to facilitate replication restart in response to this specific recombination based repair mechanism (Lydeard *et al.* 2007). The importance of pol η in NER, is demonstrated by the similarity of disease spectrum present in XP variant and the XP group genes constituting catalytic functions in the repair of bulky adducts (Johnson *et al.* 1999a).

The evolutionary persistence of many of these polymerases demonstrates that this intimate involvement of DNA replication in repair is an indispensable facet of life, as we know it.

5. Acknowledgements

I would like to thank Alina M. Handorean, PhD for her contributions to the sections on Translesion Synthesis and Y Family Polymerases. The photo of the metaphase chromosomes in a radial formation was generously provided by Susan Olson, PhD and Amy Hanlon-Newell, PhD of the Oregon Health and Science University Clinical Cytogenetics Laboratories.

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