4

DNA Replication in Repair

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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, polϒ. 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. polθ 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 polα, polδ, and polε. polα with its accompanying primase is responsible for initiation of DNA synthesis (Harrington & Perrino 1995). polδ and polε cooperate to accomplish leading and lagging strand DNA synthesis (Chilkova *et al.* 2007). polδ and polε are also involved in Homologous Recombination Repair (HRR) of DNA (Asturias *et al.* 2006; Kelman 1997; Maloisel *et al.* 2008). Another B Family member, polζ, 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 polβ, polσ, polλ, and polμ, as well as terminal deoxynucleotidyl transferase (TdT). Some of the X Family members, including polβ and polλ, 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 where it plays a critical role in V(D)J Recombination, a specific type of NHEJ (Mahajan *et al.* 1999). polλ and polμ are required for NHEJ (Fan & Wu 2004; Mahajan *et al.* 2002). polσ works in concert with polε in sister chromatid cohesion and HRR (Edwards *et al.* 2003).

The Y Family of polymerases, including polη, polι, polκ, and REV-1 are involved in TLS. Each polymerase in this family has a different bypass preference. For example, polη will bypass cyclothymine dimers (CTD), inserting two adenines opposite the lesion in an error free manner. Loss of polη 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). polι 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 polκ cannot insert bases opposite damage as polηand 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
	polκ	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 O^6-alkylguanine DNA alkyltransferase (AGT), 1-alkyladenine 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, polβ 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 polβ binding (a common step in the recruitment of many polymerases to damaged sites) and polβ 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.

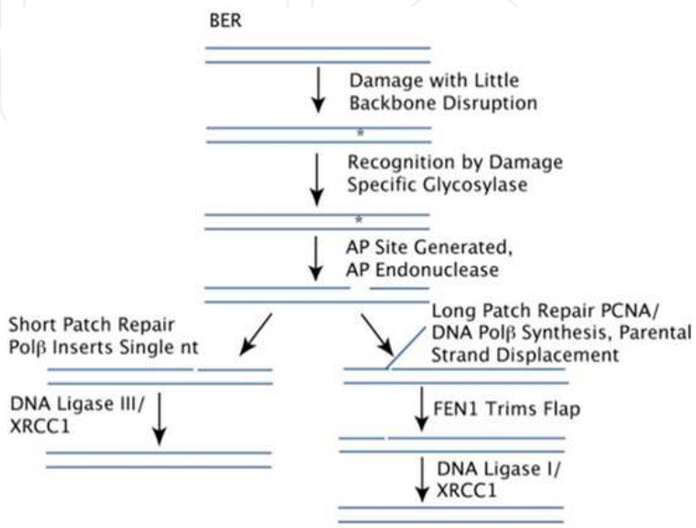

Fig. 1. The generalized steps of BER

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 dimmers and 6-4 photoproducts (Mellon *et al.* 1987; Ng *et al.* 2003)) or N-acetoxy-2acetyl-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).

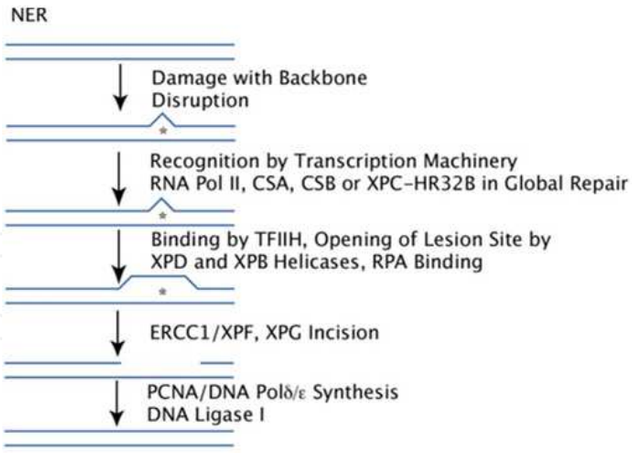

Fig. 2. Generalized Steps of NER

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 polδ and polε will syntheize 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), polκ 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 (polη, ι, κ and Rev1) also known as UmuC/DinB/Rev1/Rad30 superfamily, in addition to a member of the B-family of polymerases, polζ (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 monoubiquitnated, sumoulated, 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, polη, polι, and polκ, 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 polζ. polζ 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 polλ 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 then 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 in known that PARP-1 interacts with DNA polα, suggesting possible involvement in this pathway (Dantzer et al. 1998).

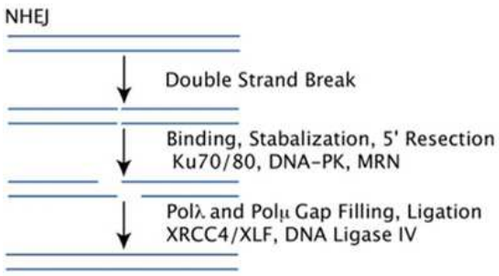

Fig. 3. Generalized steps of NHEJ

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 polε 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.

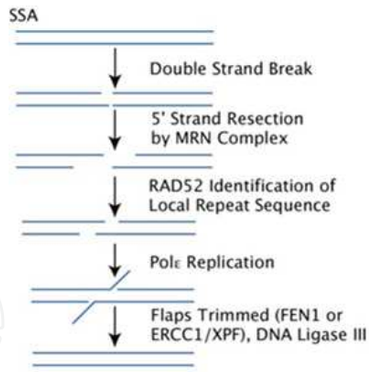

Fig. 4. Generalized Steps of SSA

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 CtlP, 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)).

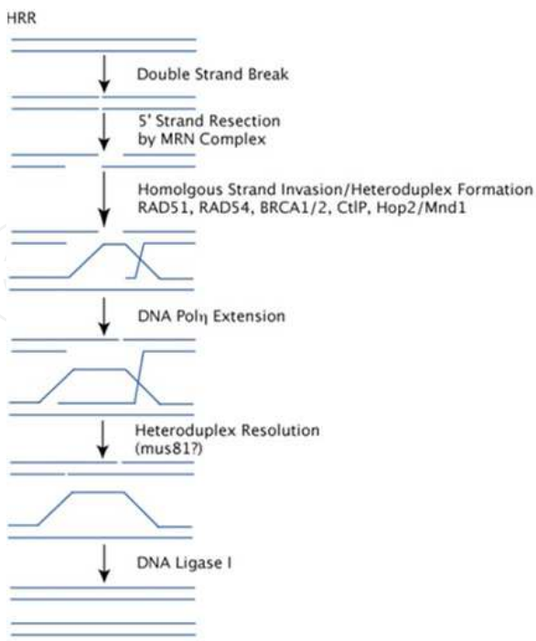

Fig. 5. Generalized Steps of HRR

DNA polη 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 polα primase is required for initiation of replication by polδ (Maloisel *et al.* 2008). polε 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 hololog ous 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 psorlen (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 polζ or polη might replicate past the ICL following DSB formation (reviewed in (Dronkert & Kanaar 2001)). However, polη 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 monoubiqitination 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 monoubiqitination, suggesting BLM functions in this pathway downstream of core complex signaling for activation of the FA pathway (Meetei *et al.* 2003). FANCJ 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).

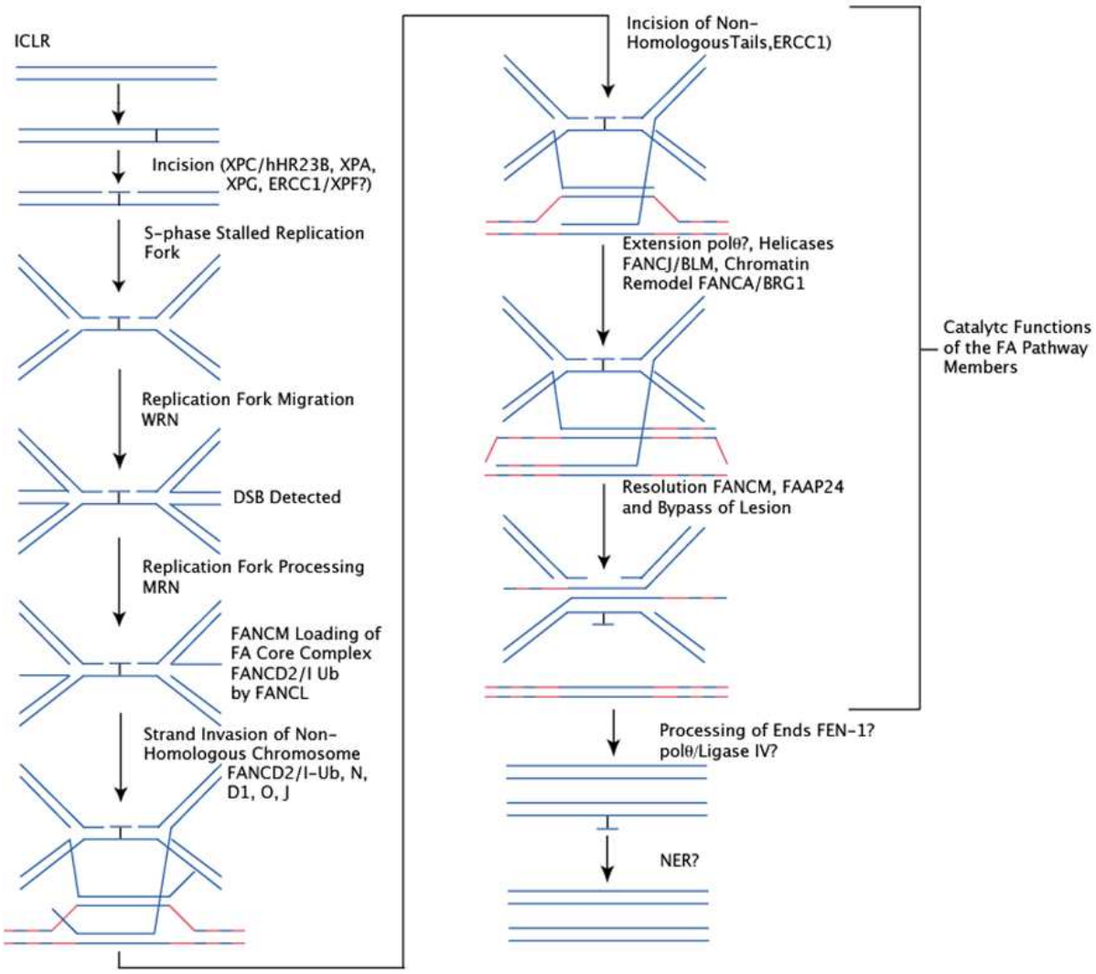

Fig. 6. Hypothetical Steps of ICLR

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 polθ/Ligase IV, (Chan *et al.* 2010)), and subsequent resolution of the recombination intermediate (Figure 6).

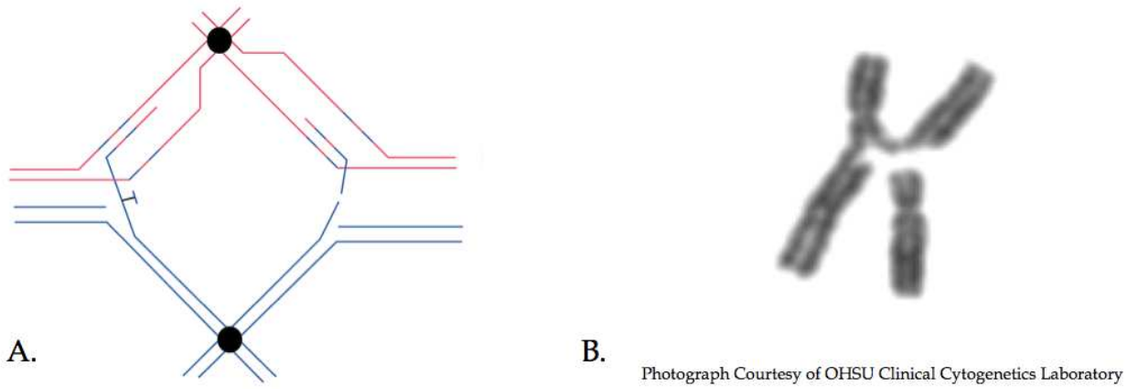

Fig. 7. A. Reorganization of non-homologous chromosome recombination intermediates from the model in Figure 6 into a chromosomal context (large circles represent centromeres) demonstrates the possibility for intermediates from this mechanism to yield radials. B. Portion of a metaphase spread of ICL treated 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 indispensible 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 polε, because of its processivity (Asturias *et al.* 2006). BIR requires the normally dispensable polδ subunit, pol32, to facilitate replication restart in response to this specific recombination based repair mechanism (Lydeard *et al.* 2007). The importance of polη 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 indispensible facet of life, as we know it.

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6. References

Aboussekhra, A., Biggerstaff, M., Shivji, M. K., Vilpo, J. A., Moncollin, V., Podust, V. N., Protic, M., Hubscher, U., Egly, J. M. and Wood, R. D. (1995). Mammalian DNA nucleotide excision repair reconstituted with purified protein components. *Cell* 80, (6):859-68.

Al-Minawi, A. Z., Saleh-Gohari, N. and Helleday, T. (2008). The ERCC1/XPF endonuclease is required for efficient single-strand annealing and gene conversion in mammalian cells. *Nucleic Acids Res* 36, (1):1-9.

Araujo, S. J., Tirode, F., Coin, F., Pospiech, H., Syvaoja, J. E., Stucki, M., Hubscher, U., Egly, J. M. and Wood, R. D. (2000). Nucleotide excision repair of DNA with recombinant human proteins: definition of the minimal set of factors, active forms of TFIIH, and modulation by CAK. *Genes Dev* 14, (3):349-59.

Araujo, S. J. and Wood, R. D. (1999). Protein complexes in nucleotide excision repair. *Mutat Res* 435, (1):23-33.

Asturias, F. J., Cheung, I. K., Sabouri, N., Chilkova, O., Wepplo, D. and Johansson, E. (2006). Structure of Saccharomyces cerevisiae DNA polymerase epsilon by cryo-electron microscopy. *Nat Struct Mol Biol* 13, (1):35-43.

Aylon, Y., Liefshitz, B. and Kupiec, M. (2004). The CDK regulates repair of double-strand breaks by homologous recombination during the cell cycle. *EMBO J* 23, (24):4868-75.

Baker, T. A. and Bell, S. P. (1998). Polymerases and the replisome: machines within machines. *Cell* 92, (3):295-305.

Banerjee, A., Santos, W. L. and Verdine, G. L. (2006). Structure of a DNA glycosylase searching for lesions. *Science* 311, (5764):1153-7.

Birger, Y., West, K. L., Postnikov, Y. V., Lim, J. H., Furusawa, T., Wagner, J. P., Laufer, C. S., Kraemer, K. H. and Bustin, M. (2003). Chromosomal protein HMGN1 enhances the rate of DNA repair in chromatin. *EMBO J* 22, (7):1665-75.

Bloom, L. B., Chen, X., Fygenson, D. K., Turner, J., O'Donnell, M. and Goodman, M. F. (1997). Fidelity of Escherichia coli DNA polymerase III holoenzyme. The effects of beta, gamma complex processivity proteins and epsilon proofreading exonuclease on nucleotide misincorporation efficiencies. *J Biol Chem* 272, (44):27919-30.

Bohr, V. A., Smith, C. A., Okumoto, D. S. and Hanawalt, P. C. (1985). DNA repair in an active gene: removal of pyrimidine dimers from the DHFR gene of CHO cells is much more efficient than in the genome overall. *Cell* 40, (2):359-69.

Bruner, S. D., Norman, D. P. and Verdine, G. L. (2000). Structural basis for recognition and repair of the endogenous mutagen 8-oxoguanine in DNA. *Nature* 403, (6772):859-66.

Bryans, M., Valenzano, M. C. and Stamato, T. D. (1999). Absence of DNA ligase IV protein in XR-1 cells: evidence for stabilization by XRCC4. *Mutat Res* 433, (1):53-8.

Burgers, P. M., Koonin, E. V., Bruford, E., Blanco, L., Burtis, K. C., Christman, M. F., Copeland, W. C., Friedberg, E. C., Hanaoka, F., Hinkle, D. C., Lawrence, C. W., Nakanishi, M., Ohmori, H., Prakash, L., Prakash, S., Reynaud, C. A., Sugino, A., Todo, T., Wang, Z., Weill, J. C. and Woodgate, R. (2001). Eukaryotic DNA polymerases: proposal for a revised nomenclature. *J Biol Chem* 276, (47):43487-90.

Cantor, S., Bell, D. W., Ganesan, S., Kass, E. M., Drapkin, R., Grossman, S., Wahrer, D. C., Sgroi, D. C., Lane, W. S., Haber, D. A. and Livingston, D. M. (2001). BACH1, a novel helicase-like protein, interacts directly with BRCA1 and contributes to its DNA repair function. *Cell* 105, (1):149-60.

Cantor, S., Drapkin, R., Zhang, F., Lin, Y., Han, J., Pamidi, S. and Livingston, D. M. (2004). The BRCA1-associated protein BACH1 is a DNA helicase targeted by clinically relevant inactivating mutations. *Proc Natl Acad Sci U S A* 101, (8):2357-62.

Cary, R. B., Peterson, S. R., Wang, J., Bear, D. G., Bradbury, E. M. and Chen, D. J. (1997). DNA looping by Ku and the DNA-dependent protein kinase. *Proc Natl Acad Sci U S A* 94, (9):4267-72.

Chan, S. H., Yu, A. M. and McVey, M. (2010). Dual roles for DNA polymerase theta in alternative end-joining repair of double-strand breaks in Drosophila. *PLoS Genet* 6, (7):e1001005.

Chen, L., Nievera, C. J., Lee, A. Y. and Wu, X. (2008). Cell cycle-dependent complex formation of BRCA1.CtIP.MRN is important for DNA double-strand break repair. *J Biol Chem* 283, (12):7713-20.

Chilkova, O., Stenlund, P., Isoz, I., Stith, C. M., Grabowski, P., Lundstrom, E. B., Burgers, P. M. and Johansson, E. (2007). The eukaryotic leading and lagging strand DNA polymerases are loaded onto primer-ends via separate mechanisms but have comparable processivity in the presence of PCNA. *Nucleic Acids Res* 35, (19):6588-97.

Dantzer, F., Nasheuer, H. P., Vonesch, J. L., de Murcia, G. and Menissier-de Murcia, J. (1998). Functional association of poly(ADP-ribose) polymerase with DNA polymerase alpha-primase complex: a link between DNA strand break detection and DNA replication. *Nucleic Acids Res* 26, (8):1891-8.

Davies, A. A., Masson, J. Y., McIlwraith, M. J., Stasiak, A. Z., Stasiak, A., Venkitaraman, A. R. and West, S. C. (2001). Role of BRCA2 in control of the RAD51 recombination and DNA repair protein. *Mol Cell* 7, (2):273-82.

Dronkert, M. L. and Kanaar, R. (2001). Repair of DNA interstrand cross-links. *Mutat Res* 486, (4):217-47.

Duncan, T., Trewick, S. C., Koivisto, P., Bates, P. A., Lindahl, T. and Sedgwick, B. (2002). Reversal of DNA alkylation damage by two human dioxygenases. *Proc Natl Acad Sci U S A* 99, (26):16660-5.

Edwards, S., Li, C. M., Levy, D. L., Brown, J., Snow, P. M. and Campbell, J. L. (2003). Saccharomyces cerevisiae DNA polymerase epsilon and polymerase sigma interact physically and functionally, suggesting a role for polymerase epsilon in sister chromatid cohesion. *Mol Cell Biol* 23, (8):2733-48.

Ellis, N. A., Groden, J., Ye, T. Z., Straughen, J., Lennon, D. J., Ciocci, S., Proytcheva, M. and German, J. (1995). The Bloom's syndrome gene product is homologous to RecQ helicases. *Cell* 83, (4):655-66.

Engelward, B. P., Weeda, G., Wyatt, M. D., Broekhof, J. L., de Wit, J., Donker, I., Allan, J. M., Gold, B., Hoeijmakers, J. H. and Samson, L. D. (1997). Base excision repair deficient mice lacking the Aag alkyladenine DNA glycosylase. *Proc Natl Acad Sci U S A* 94, (24):13087-92.

Fan, W. and Wu, X. (2004). DNA polymerase lambda can elongate on DNA substrates mimicking non-homologous end joining and interact with XRCC4-ligase IV complex. *Biochem Biophys Res Commun* 323, (4):1328-33.

Ferguson, D. O. and Holloman, W. K. (1996). Recombinational repair of gaps in DNA is asymmetric in Ustilago maydis and can be explained by a migrating D-loop model. *Proc Natl Acad Sci U S A* 93, (11):5419-24.

Fishman-Lobell, J., Rudin, N. and Haber, J. E. (1992). Two alternative pathways of double-strand break repair that are kinetically separable and independently modulated. *Mol Cell Biol* 12, (3):1292-303.

Folias, A., Matkovic, M., Bruun, D., Reid, S., Hejna, J., Grompe, M., D'Andrea, A. and Moses, R. (2002). BRCA1 interacts directly with the Fanconi anemia protein FANCA. *Hum Mol Genet* 11, (21):2591-7.

Fousteri, M. and Mullenders, L. H. (2008). Transcription-coupled nucleotide excision repair in mammalian cells: molecular mechanisms and biological effects. *Cell Res* 18, (1):73-84.

Frankenberg-Schwager, M., Gebauer, A., Koppe, C., Wolf, H., Pralle, E. and Frankenberg, D. (2009). Single-strand annealing, conservative homologous recombination, nonhomologous DNA end joining, and the cell cycle-dependent repair of DNA double-strand breaks induced by sparsely or densely ionizing radiation. *Radiat Res* 171, (3):265-73.

Garcia-Diaz, M., Bebenek, K., Kunkel, T. A. and Blanco, L. (2001). Identification of an intrinsic 5'-deoxyribose-5-phosphate lyase activity in human DNA polymerase lambda: a possible role in base excision repair. *J Biol Chem* 276, (37):34659-63.

Garcia-Higuera, I., Taniguchi, T., Ganesan, S., Meyn, M. S., Timmers, C., Hejna, J., Grompe, M. and D'Andrea, A. D. (2001). Interaction of the Fanconi anemia proteins and BRCA1 in a common pathway. *Mol Cell* 7, (2):249-62.

Goetz, J. D., Motycka, T. A., Han, M., Jasin, M. and Tomkinson, A. E. (2005). Reduced repair of DNA double-strand breaks by homologous recombination in a DNA ligase I-deficient human cell line. *DNA Repair (Amst)* 4, (6):649-54.

Gotte, M., Li, X. and Wainberg, M. A. (1999). HIV-1 reverse transcription: a brief overview focused on structure-function relationships among molecules involved in initiation of the reaction. *Arch Biochem Biophys* 365, (2):199-210.

Gottlich, B., Reichenberger, S., Feldmann, E. and Pfeiffer, P. (1998). Rejoining of DNA double-strand breaks in vitro by single-strand annealing. *Eur J Biochem* 258, (2):387-95.

Greider, C. W. and Blackburn, E. H. (1989). A telomeric sequence in the RNA of Tetrahymena telomerase required for telomere repeat synthesis. *Nature* 337, (6205):331-7.

Grossmann, K. F., Ward, A. M., Matkovic, M. E., Folias, A. E. and Moses, R. E. (2001). S. cerevisiae has three pathways for DNA interstrand crosslink repair. *Mutat Res* 487, (3-4):73-83.

Guo, C., Fischhaber, P. L., Luk-Paszyc, M. J., Masuda, Y., Zhou, J., Kamiya, K., Kisker, C. and Friedberg, E. C. (2003). Mouse Rev1 protein interacts with multiple DNA polymerases involved in translesion DNA synthesis. *EMBO J* 22, (24):6621-30.

Haracska, L., Johnson, R. E., Unk, I., Phillips, B., Hurwitz, J., Prakash, L. and Prakash, S. (2001a). Physical and functional interactions of human DNA polymerase eta with PCNA. *Mol Cell Biol* 21, (21):7199-206.

Haracska, L., Kondratick, C. M., Unk, I., Prakash, S. and Prakash, L. (2001b). Interaction with PCNA is essential for yeast DNA polymerase eta function. *Mol Cell* 8, (2):407-15.

Haracska, L., Prakash, S. and Prakash, L. (2003). Yeast DNA polymerase zeta is an efficient extender of primer ends opposite from 7,8-dihydro-8-Oxoguanine and O6-methylguanine. *Mol Cell Biol* 23, (4):1453-9.

Harrington, C. and Perrino, F. W. (1995). Initiation of RNA-primed DNA synthesis in vitro by DNA polymerase alpha-primase. *Nucleic Acids Res* 23, (6):1003-9.

Henning, K. A., Li, L., Iyer, N., McDaniel, L. D., Reagan, M. S., Legerski, R., Schultz, R. A., Stefanini, M., Lehmann, A. R., Mayne, L. V. and Friedberg, E. C. (1995). The Cockayne syndrome group A gene encodes a WD repeat protein that interacts with CSB protein and a subunit of RNA polymerase II TFIIH. *Cell* 82, (4):555-64.

Hirsch, B., Shimamura, A., Moreau, L., Baldinger, S., Hag-alshiekh, M., Bostrom, B., Sencer, S. and D'Andrea, A. D. (2004). Association of biallelic BRCA2/FANCD1 mutations with spontaneous chromosomal instability and solid tumors of childhood. *Blood* 103, (7):2554-9.

Hubscher, U., Maga, G. and Spadari, S. (2002). Eukaryotic DNA polymerases. *Annu Rev Biochem* 71, 133-63.

Hussain, S., Wilson, J. B., Medhurst, A. L., Hejna, J., Witt, E., Ananth, S., Davies, A., Masson, J. Y., Moses, R., West, S. C., de Winter, J. P., Ashworth, A., Jones, N. J. and Mathew, C. G. (2004). Direct interaction of FANCD2 with BRCA2 in DNA damage response pathways. *Hum Mol Genet* 13, (12):1241-8.

Iliakis, G. (2009). Backup pathways of NHEJ in cells of higher eukaryotes: cell cycle dependence. *Radiother Oncol* 92, (3):310-5.

Ishino, Y., Komori, K., Cann, I. K. and Koga, Y. (1998). A novel DNA polymerase family found in Archaea. *J Bacteriol* 180, (8):2232-6.

Johnson, R. E., Kondratick, C. M., Prakash, S. and Prakash, L. (1999a). hRAD30 mutations in the variant form of xeroderma pigmentosum. *Science* 285, (5425):263-5.

Johnson, R. E., Prakash, S. and Prakash, L. (1999b). Efficient bypass of a thymine-thymine dimer by yeast DNA polymerase, Poleta. *Science* 283, (5404):1001-4.

Johnson, R. E., Washington, M. T., Haracska, L., Prakash, S. and Prakash, L. (2000). Eukaryotic polymerases iota and zeta act sequentially to bypass DNA lesions. *Nature* 406, (6799):1015-9.

Kalle, W. H., Hazekamp-van Dokkum, A. M., Lohman, P. H., Natarajan, A. T., van Zeeland, A. A. and Mullenders, L. H. (1993). The use of streptavidin-coated magnetic beads and biotinylated antibodies to investigate induction and repair of DNA damage: analysis of repair patches in specific sequences of uv-irradiated human fibroblasts. *Anal Biochem* 208, (2):228-36.

Kao, G. D., McKenna, W. G. and Yen, T. J. (2001). Detection of repair activity during the DNA damage-induced G2 delay in human cancer cells. *Oncogene* 20, (27):3486-96.

Kawasaki, Y. and Sugino, A. (2001). Yeast replicative DNA polymerases and their role at the replication fork. *Mol Cells* 12, (3):277-85.

Kelman, Z. (1997). PCNA: structure, functions and interactions. *Oncogene* 14, (6):629-40.

Khanna, K. K. and Jackson, S. P. (2001). DNA double-strand breaks: signaling, repair and the cancer connection. *Nat Genet* 27, (3):247-54.

Kim, S. T., Malhotra, K., Smith, C. A., Taylor, J. S. and Sancar, A. (1993). DNA photolyase repairs the trans-syn cyclobutane thymine dimer. *Biochemistry* 32, (28):7065-8.

Kitao, H. and Takata, M. (2011). Fanconi anemia: a disorder defective in the DNA damage response. *Int J Hematol* 73(4):417-24.

Klungland, A., Rosewell, I., Hollenbach, S., Larsen, E., Daly, G., Epe, B., Seeberg, E., Lindahl, T. and Barnes, D. E. (1999). Accumulation of premutagenic DNA lesions in mice defective in removal of oxidative base damage. *Proc Natl Acad Sci U S A* 96, (23):13300-5.

Kubota, Y., Nash, R. A., Klungland, A., Schar, P., Barnes, D. E. and Lindahl, T. (1996). Reconstitution of DNA base excision-repair with purified human proteins: interaction between DNA polymerase beta and the XRCC1 protein. *EMBO J* 15, (23):6662-70.

Kuchta, R. D., Benkovic, P. and Benkovic, S. J. (1988). Kinetic mechanism whereby DNA polymerase I (Klenow) replicates DNA with high fidelity. *Biochemistry* 27, (18):6716-25.

Kuchta, R. D., Mizrahi, V., Benkovic, P. A., Johnson, K. A. and Benkovic, S. J. (1987). Kinetic mechanism of DNA polymerase I (Klenow). *Biochemistry* 26, (25):8410-7.

Kulaksiz, G., Reardon, J. T. and Sancar, A. (2005). Xeroderma pigmentosum complementation group E protein (XPE/DDB2): purification of various complexes of XPE and analyses of their damaged DNA binding and putative DNA repair properties. *Mol Cell Biol* 25, (22):9784-92.

Lamers, M. H., Georgescu, R. E., Lee, S. G., O'Donnell, M. and Kuriyan, J. (2006). Crystal structure of the catalytic alpha subunit of E. coli replicative DNA polymerase III. *Cell* 126, (5):881-92.

Lawley, P. D. and Phillips, D. H. (1996). DNA adducts from chemotherapeutic agents. *Mutat Res* 355, (1-2):13-40.

Li, L., Lu, X., Peterson, C. A. and Legerski, R. J. (1995a). An interaction between the DNA repair factor XPA and replication protein A appears essential for nucleotide excision repair. *Mol Cell Biol* 15, (10):5396-402.

Li, L., Peterson, C. A., Lu, X. and Legerski, R. J. (1995b). Mutations in XPA that prevent association with ERCC1 are defective in nucleotide excision repair. *Mol Cell Biol* 15, (4):1993-8.

Lord, R. V., Brabender, J., Gandara, D., Alberola, V., Camps, C., Domine, M., Cardenal, F., Sanchez, J. M., Gumerlock, P. H., Taron, M., Sanchez, J. J., Danenberg, K. D., Danenberg, P. V. and Rosell, R. (2002). Low ERCC1 expression correlates with prolonged survival after cisplatin plus gemcitabine chemotherapy in non-small cell lung cancer. *Clin Cancer Res* 8, (7):2286-91.

Lydeard, J. R., Jain, S., Yamaguchi, M. and Haber, J. E. (2007). Break-induced replication and telomerase-independent telomere maintenance require Pol32. *Nature* 448, (7155):820-3.

Machida, Y. J., Machida, Y., Chen, Y., Gurtan, A. M., Kupfer, G. M., D'Andrea, A. D. and Dutta, A. (2006). UBE2T is the E2 in the Fanconi anemia pathway and undergoes negative autoregulation. *Mol Cell* 23, (4):589-96.

Mahajan, K. N., Gangi-Peterson, L., Sorscher, D. H., Wang, J., Gathy, K. N., Mahajan, N. P., Reeves, W. H. and Mitchell, B. S. (1999). Association of terminal deoxynucleotidyl transferase with Ku. *Proc Natl Acad Sci U S A* 96, (24):13926-31.

Mahajan, K. N., Nick McElhinny, S. A., Mitchell, B. S. and Ramsden, D. A. (2002). Association of DNA polymerase mu (pol mu) with Ku and ligase IV: role for pol mu in end-joining double-strand break repair. *Mol Cell Biol* 22, (14):5194-202.

Maloisel, L., Fabre, F. and Gangloff, S. (2008). DNA polymerase delta is preferentially recruited during homologous recombination to promote heteroduplex DNA extension. *Mol Cell Biol* 28, (4):1373-82.

McCabe, K. M., Hemphill, A., Akkari, Y., Jakobs, P. M., Pauw, D., Olson, S. B., Moses, R. E. and Grompe, M. (2008). ERCC1 is required for FANCD2 focus formation. *Mol Genet Metab* 95, (1-2):66-73.

McCabe, K. M., Olson, S. B. and Moses, R. E. (2009). DNA interstrand crosslink repair in mammalian cells. *J Cell Physiol* 220, (3):569-73.

McIlwraith, M. J., Vaisman, A., Liu, Y., Fanning, E., Woodgate, R. and West, S. C. (2005). Human DNA polymerase eta promotes DNA synthesis from strand invasion intermediates of homologous recombination. *Mol Cell* 20, (5):783-92.

McKinnon, P. J. and Caldecott, K. W. (2007). DNA strand break repair and human genetic disease. *Annu Rev Genomics Hum Genet* 8, 37-55.

Meetei, A. R., Sechi, S., Wallisch, M., Yang, D., Young, M. K., Joenje, H., Hoatlin, M. E. and Wang, W. (2003). A multiprotein nuclear complex connects Fanconi anemia and Bloom syndrome. *Mol Cell Biol* 23, (10):3417-26.

Mellon, I., Spivak, G. and Hanawalt, P. C. (1987). Selective removal of transcription-blocking DNA damage from the transcribed strand of the mammalian DHFR gene. *Cell* 51, (2):241-9.

Meselson, M. and Stahl, F. W. (1958). The Replication of DNA in Escherichia Coli. *Proc Natl Acad Sci U S A* 44, (7):671-82.

Mitchell, J. R., Hoeijmakers, J. H. and Niedernhofer, L. J. (2003). Divide and conquer: nucleotide excision repair battles cancer and ageing. *Curr Opin Cell Biol* 15, (2):232-40.

Mladenov, E. and Iliakis, G. (2011). Induction and repair of DNA double strand breaks: The increasing spectrum of non-homologous end joining pathways. *Mutat Res* 711(1-2):61-72.

Mol, C. D., Hosfield, D. J. and Tainer, J. A. (2000). Abasic site recognition by two apurinic/apyrimidinic endonuclease families in DNA base excision repair: the 3' ends justify the means. *Mutat Res* 460, (3-4):211-29.

Moser, J., Kool, H., Giakzidis, I., Caldecott, K., Mullenders, L. H. and Fousteri, M. I. (2007). Sealing of chromosomal DNA nicks during nucleotide excision repair requires XRCC1 and DNA ligase III alpha in a cell-cycle-specific manner. *Mol Cell* 27, (2):311-23.

Nakanishi, K., Taniguchi, T., Ranganathan, V., New, H. V., Moreau, L. A., Stotsky, M., Mathew, C. G., Kastan, M. B., Weaver, D. T. and D'Andrea, A. D. (2002). Interaction of FANCD2 and NBS1 in the DNA damage response. *Nat Cell Biol* 4, (12):913-20.

Nakatsu, Y., Asahina, H., Citterio, E., Rademakers, S., Vermeulen, W., Kamiuchi, S., Yeo, J. P., Khaw, M. C., Saijo, M., Kodo, N., Matsuda, T., Hoeijmakers, J. H. and Tanaka, K. (2000). XAB2, a novel tetratricopeptide repeat protein involved in transcription-coupled DNA repair and transcription. *J Biol Chem* 275, (45):34931-7.

Nevaldine, B., Longo, J. A. and Hahn, P. J. (1997). The scid defect results in much slower repair of DNA double-strand breaks but not high levels of residual breaks. *Radiat Res* 147, (5):535-40.

Newell, A. E., Akkari, Y. M., Torimaru, Y., Rosenthal, A., Reifsteck, C. A., Cox, B., Grompe, M. and Olson, S. B. (2004). Interstrand crosslink-induced radials form between non-homologous chromosomes, but are absent in sex chromosomes. *DNA Repair (Amst)* 3, (5):535-42.

Ng, J. M., Vermeulen, W., van der Horst, G. T., Bergink, S., Sugasawa, K., Vrieling, H. and Hoeijmakers, J. H. (2003). A novel regulation mechanism of DNA repair by damage-induced and RAD23-dependent stabilization of xeroderma pigmentosum group C protein. *Genes Dev* 17, (13):1630-45.

O'Donovan, A., Davies, A. A., Moggs, J. G., West, S. C. and Wood, R. D. (1994). XPG endonuclease makes the 3' incision in human DNA nucleotide excision repair. *Nature* 371, (6496):432-5.

Ogi, T. and Lehmann, A. R. (2006). The Y-family DNA polymerase kappa (pol kappa) functions in mammalian nucleotide-excision repair. *Nat Cell Biol* 8, (6):640-2.

Ohashi, E., Murakumo, Y., Kanjo, N., Akagi, J., Masutani, C., Hanaoka, F. and Ohmori, H. (2004). Interaction of hREV1 with three human Y-family DNA polymerases. *Genes Cells* 9, (6):523-31.

Ohmori, H., Friedberg, E. C., Fuchs, R. P., Goodman, M. F., Hanaoka, F., Hinkle, D., Kunkel, T. A., Lawrence, C. W., Livneh, Z., Nohmi, T., Prakash, L., Prakash, S., Todo, T., Walker, G. C., Wang, Z. and Woodgate, R. (2001). The Y-family of DNA polymerases. *Mol Cell* 8, (1):7-8.

Otsuki, T., Furukawa, Y., Ikeda, K., Endo, H., Yamashita, T., Shinohara, A., Iwamatsu, A., Ozawa, K. and Liu, J. M. (2001). Fanconi anemia protein, FANCA, associates with BRG1, a component of the human SWI/SNF complex. *Hum Mol Genet* 10, (23):2651-60.

Parsons, B. L. (2003). MED1: a central molecule for maintenance of genome integrity and response to DNA damage. *Proc Natl Acad Sci U S A* 100, (25):14601-2.

Patel, S. S., Wong, I. and Johnson, K. A. (1991). Pre-steady-state kinetic analysis of processive DNA replication including complete characterization of an exonuclease-deficient mutant. *Biochemistry* 30, (2):511-25.

Pellegrini, L., Yu, D. S., Lo, T., Anand, S., Lee, M., Blundell, T. L. and Venkitaraman, A. R. (2002). Insights into DNA recombination from the structure of a RAD51-BRCA2 complex. *Nature* 420, (6913):287-93.

Prasad, R., Dianov, G. L., Bohr, V. A. and Wilson, S. H. (2000). FEN1 stimulation of DNA polymerase beta mediates an excision step in mammalian long patch base excision repair. *J Biol Chem* 275, (6):4460-6.

Prasad, R., Longley, M. J., Sharief, F. S., Hou, E. W., Copeland, W. C. and Wilson, S. H. (2009). Human DNA polymerase theta possesses 5'-dRP lyase activity and functions in single-nucleotide base excision repair in vitro. *Nucleic Acids Res* 37, (6):1868-77.

Rass, E., Grabarz, A., Plo, I., Gautier, J., Bertrand, P. and Lopez, B. S. (2009). Role of Mre11 in chromosomal nonhomologous end joining in mammalian cells. *Nat Struct Mol Biol* 16, (8):819-24.

Reid, S., Schindler, D., Hanenberg, H., Barker, K., Hanks, S., Kalb, R., Neveling, K., Kelly, P., Seal, S., Freund, M., Wurm, M., Batish, S. D., Lach, F. P., Yetgin, S., Neitzel, H., Ariffin, H., Tischkowitz, M., Mathew, C. G., Auerbach, A. D. and Rahman, N. (2007). Biallelic mutations in PALB2 cause Fanconi anemia subtype FA-N and predispose to childhood cancer. *Nat Genet* 39, (2):162-4.

Richardson, C. and Jasin, M. (2000). Frequent chromosomal translocations induced by DNA double-strand breaks. *Nature* 405, (6787):697-700.

Robu, M. E., Inman, R. B. and Cox, M. M. (2001). RecA protein promotes the regression of stalled replication forks in vitro. *Proc Natl Acad Sci U S A* 98, (15):8211-8.

Rogakou, E. P., Boon, C., Redon, C. and Bonner, W. M. (1999). Megabase chromatin domains involved in DNA double-strand breaks in vivo. *J Cell Biol* 146, (5):905-16.

Rosidi, B., Wang, M., Wu, W., Sharma, A., Wang, H. and Iliakis, G. (2008). Histone H1 functions as a stimulatory factor in backup pathways of NHEJ. *Nucleic Acids Res* 36, (5):1610-23.

Ryu, J. S., Hong, Y. C., Han, H. S., Lee, J. E., Kim, S., Park, Y. M., Kim, Y. C. and Hwang, T. S. (2004). Association between polymorphisms of ERCC1 and XPD and survival in non-small-cell lung cancer patients treated with cisplatin combination chemotherapy. *Lung Cancer* 44, (3):311-6.

Scharer, O. D. (2005). DNA interstrand crosslinks: natural and drug-induced DNA adducts that induce unique cellular responses. *Chembiochem* 6, (1):27-32.

Sharan, S. K., Morimatsu, M., Albrecht, U., Lim, D. S., Regel, E., Dinh, C., Sands, A., Eichele, G., Hasty, P. and Bradley, A. (1997). Embryonic lethality and radiation hypersensitivity mediated by Rad51 in mice lacking Brca2. *Nature* 386, (6627):804-10.

Sijbers, A. M., de Laat, W. L., Ariza, R. R., Biggerstaff, M., Wei, Y. F., Moggs, J. G., Carter, K. C., Shell, B. K., Evans, E., de Jong, M. C., Rademakers, S., de Rooij, J., Jaspers, N. G., Hoeijmakers, J. H. and Wood, R. D. (1996). Xeroderma pigmentosum group F caused by a defect in a structure-specific DNA repair endonuclease. *Cell* 86, (5):811-22.

Singh, T. R., Bakker, S. T., Agarwal, S., Jansen, M., Grassman, E., Godthelp, B. C., Ali, A. M., Du, C. H., Rooimans, M. A., Fan, Q., Wahengbam, K., Steltenpool, J., Andreassen, P. R., Williams, D. A., Joenje, H., de Winter, J. P. and Meetei, A. R. (2009). Impaired FANCD2 monoubiquitination and hypersensitivity to camptothecin uniquely characterize Fanconi anemia complementation group M. *Blood* 114, (1):174-80.

Singh, T. R., Saro, D., Ali, A. M., Zheng, X. F., Du, C. H., Killen, M. W., Sachpatzidis, A., Wahengbam, K., Pierce, A. J., Xiong, Y., Sung, P. and Meetei, A. R. (2010). MHF1-MHF2, a histone-fold-containing protein complex, participates in the Fanconi anemia pathway via FANCM. *Mol Cell* 37, (6):879-86.

Smith, K. N. and Nicolas, A. (1998). Recombination at work for meiosis. *Current Opinion in Genetics & Development* 8, (2):200-211.

Smogorzewska, A., Matsuoka, S., Vinciguerra, P., McDonald, E. R., 3rd, Hurov, K. E., Luo, J., Ballif, B. A., Gygi, S. P., Hofmann, K., D'Andrea, A. D. and Elledge, S. J. (2007). Identification of the FANCI protein, a monoubiquitinated FANCD2 paralog required for DNA repair. *Cell* 129, (2):289-301.

Sobeck, A., Stone, S. and Hoatlin, M. E. (2007). DNA structure-induced recruitment and activation of the Fanconi anemia pathway protein FANCD2. *Mol Cell Biol* 27, (12):4283-92.

Solinger, J. A., Lutz, G., Sugiyama, T., Kowalczykowski, S. C. and Heyer, W. D. (2001). Rad54 protein stimulates heteroduplex DNA formation in the synaptic phase of DNA strand exchange via specific interactions with the presynaptic Rad51 nucleoprotein filament. *J Mol Biol* 307, (5):1207-21.

Srivastava, D. K., Berg, B. J., Prasad, R., Molina, J. T., Beard, W. A., Tomkinson, A. E. and Wilson, S. H. (1998). Mammalian abasic site base excision repair. Identification of the reaction sequence and rate-determining steps. *J Biol Chem* 273, (33):21203-9.

Stasiak, A. Z., Larquet, E., Stasiak, A., Muller, S., Engel, A., Van Dyck, E., West, S. C. and Egelman, E. H. (2000). The human Rad52 protein exists as a heptameric ring. *Curr Biol* 10, (6):337-40.

Stauffer, M. E. and Chazin, W. J. (2004). Physical interaction between replication protein A and Rad51 promotes exchange on single-stranded DNA. *J Biol Chem* 279, (24):25638-45.

Steitz, T. A. (1998). A mechanism for all polymerases. *Nature* 391, (6664):231-2.

Sugawara, N., Ira, G. and Haber, J. E. (2000). DNA length dependence of the single-strand annealing pathway and the role of Saccharomyces cerevisiae RAD59 in double-strand break repair. *Mol Cell Biol* 20, (14):5300-9.

Sung, P. and Robberson, D. L. (1995). DNA strand exchange mediated by a RAD51-ssDNA nucleoprotein filament with polarity opposite to that of RecA. *Cell* 82, (3):453-61.

Szostak, J. W., Orr-Weaver, T. L., Rothstein, R. J. and Stahl, F. W. (1983). The double-strand-break repair model for recombination. *Cell* 33, (1):25-35.

Tantin, D. (1998). RNA polymerase II elongation complexes containing the Cockayne syndrome group B protein interact with a molecular complex containing the transcription factor IIH components xeroderma pigmentosum B and p62. *J Biol Chem* 273, (43):27794-9.

Tantin, D., Kansal, A. and Carey, M. (1997). Recruitment of the putative transcription-repair coupling factor CSB/ERCC6 to RNA polymerase II elongation complexes. *Mol Cell Biol* 17, (12):6803-14.

Tischkowitz, M., Xia, B., Sabbaghian, N., Reis-Filho, J. S., Hamel, N., Li, G., van Beers, E. H., Li, L., Khalil, T., Quenneville, L. A., Omeroglu, A., Poll, A., Lepage, P., Wong, N., Nederlof, P. M., Ashworth, A., Tonin, P. N., Narod, S. A., Livingston, D. M. and Foulkes, W. D. (2007). Analysis of PALB2/FANCN-associated breast cancer families. *Proc Natl Acad Sci U S A* 104, (16):6788-93.

Tissier, A., Kannouche, P., Reck, M. P., Lehmann, A. R., Fuchs, R. P. and Cordonnier, A. (2004). Co-localization in replication foci and interaction of human Y-family members, DNA polymerase pol eta and REV1 protein. *DNA Repair (Amst)* 3, (11):1503-14.

Trincao, J., Johnson, R. E., Escalante, C. R., Prakash, S., Prakash, L. and Aggarwal, A. K. (2001). Structure of the catalytic core of S. cerevisiae DNA polymerase eta: implications for translesion DNA synthesis. *Mol Cell* 8, (2):417-26.

Van Dyck, E., Stasiak, A. Z., Stasiak, A. and West, S. C. (1999). Binding of double-strand breaks in DNA by human Rad52 protein. *Nature* 398, (6729):728-31.

Vignard, J., Siwiec, T., Chelysheva, L., Vrielynck, N., Gonord, F., Armstrong, S. J., Schlogelhofer, P. and Mercier, R. (2007). The interplay of RecA-related proteins and the MND1-HOP2 complex during meiosis in Arabidopsis thaliana. *PLoS Genet* 3, (10):1894-906.

Wang, H., Perrault, A. R., Takeda, Y., Qin, W. and Iliakis, G. (2003). Biochemical evidence for Ku-independent backup pathways of NHEJ. *Nucleic Acids Res* 31, (18):5377-88.

Wang, H., Zeng, Z. C., Bui, T. A., Sonoda, E., Takata, M., Takeda, S. and Iliakis, G. (2001a). Efficient rejoining of radiation-induced DNA double-strand breaks in vertebrate cells deficient in genes of the RAD52 epistasis group. *Oncogene* 20, (18):2212-24.

Wang, H., Zeng, Z. C., Perrault, A. R., Cheng, X., Qin, W. and Iliakis, G. (2001b). Genetic evidence for the involvement of DNA ligase IV in the DNA-PK-dependent pathway of non-homologous end joining in mammalian cells. *Nucleic Acids Res* 29, (8):1653-60.

Wang, M., Wu, W., Rosidi, B., Zhang, L., Wang, H. and Iliakis, G. (2006). PARP-1 and Ku compete for repair of DNA double strand breaks by distinct NHEJ pathways. *Nucleic Acids Res* 34, (21):6170-82.

Washington, M. T., Johnson, R. E., Prakash, L. and Prakash, S. (2002). Human DINB1-encoded DNA polymerase kappa is a promiscuous extender of mispaired primer termini. *Proc Natl Acad Sci U S A* 99, (4):1910-4.

Washington, M. T., Johnson, R. E., Prakash, S. and Prakash, L. (2000). Accuracy of thymine-thymine dimer bypass by Saccharomyces cerevisiae DNA polymerase eta. *Proc Natl Acad Sci U S A* 97, (7):3094-9.

Washington, M. T., Prakash, L. and Prakash, S. (2001). Yeast DNA polymerase eta utilizes an induced-fit mechanism of nucleotide incorporation. *Cell* 107, (7):917-27.

Waters, L. S., Minesinger, B. K., Wiltrout, M. E., D'Souza, S., Woodruff, R. V. and Walker, G. C. (2009). Eukaryotic translesion polymerases and their roles and regulation in DNA damage tolerance. *Microbiol Mol Biol Rev* 73, (1):134-54.

Wibley, J. E., Pegg, A. E. and Moody, P. C. (2000). Crystal structure of the human O(6)-alkylguanine-DNA alkyltransferase. *Nucleic Acids Res* 28, (2):393-401.

Windhofer, F., Wu, W. and Iliakis, G. (2007). Low levels of DNA ligases III and IV sufficient for effective NHEJ. *J Cell Physiol* 213, (2):475-83.

Wold, M. S. (1997). Replication protein A: a heterotrimeric, single-stranded DNA-binding protein required for eukaryotic DNA metabolism. *Annu Rev Biochem* 66, 61-92.

Wong, I., Patel, S. S. and Johnson, K. A. (1991). An induced-fit kinetic mechanism for DNA replication fidelity: direct measurement by single-turnover kinetics. *Biochemistry* 30, (2):526-37.

Wu, W., Wang, M., Mussfeldt, T. and Iliakis, G. (2008). Enhanced use of backup pathways of NHEJ in G2 in Chinese hamster mutant cells with defects in the classical pathway of NHEJ. *Radiat Res* 170, (4):512-20.

Xia, B., Dorsman, J. C., Ameziane, N., de Vries, Y., Rooimans, M. A., Sheng, Q., Pals, G., Errami, A., Gluckman, E., Llera, J., Wang, W., Livingston, D. M., Joenje, H. and de

Winter, J. P. (2007). Fanconi anemia is associated with a defect in the BRCA2 partner PALB2. *Nat Genet* 39, (2):159-61.

Xia, B., Sheng, Q., Nakanishi, K., Ohashi, A., Wu, J., Christ, N., Liu, X., Jasin, M., Couch, F. J. and Livingston, D. M. (2006). Control of BRCA2 cellular and clinical functions by a nuclear partner, PALB2. *Mol Cell* 22, (6):719-29.

Yamasaki, K., Urushibata, Y., Yamasaki, T., Arisaka, F. and Matsui, I. (2010). Solution structure of the N-terminal domain of the archaeal D-family DNA polymerase small subunit reveals evolutionary relationship to eukaryotic B-family polymerases. *FEBS Lett* 584, (15):3370-5.

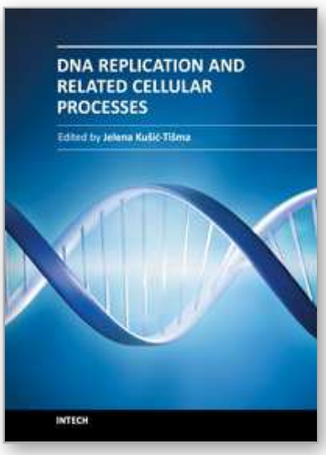
Yan, Z., Delannoy, M., Ling, C., Daee, D., Osman, F., Muniandy, P. A., Shen, X., Oostra, A. B., Du, H., Steltenpool, J., Lin, T., Schuster, B., Decaillet, C., Stasiak, A., Stasiak, A. Z., Stone, S., Hoatlin, M. E., Schindler, D., Woodcock, C. L., Joenje, H., Sen, R., de Winter, J. P., Li, L., Seidman, M. M., Whitby, M. C., Myung, K., Constantinou, A. and Wang, W. (2010). A histone-fold complex and FANCM form a conserved DNA-remodeling complex to maintain genome stability. *Mol Cell* 37, (6):865-78.

Yano, K., Morotomi-Yano, K., Wang, S. Y., Uematsu, N., Lee, K. J., Asaithamby, A., Weterings, E. and Chen, D. J. (2008). Ku recruits XLF to DNA double-strand breaks. *EMBO Rep* 9, (1):91-6.

Yokoi, M., Masutani, C., Maekawa, T., Sugasawa, K., Ohkuma, Y. and Hanaoka, F. (2000). The xeroderma pigmentosum group C protein complex XPC-HR23B plays an important role in the recruitment of transcription factor IIH to damaged DNA. *J Biol Chem* 275, (13):9870-5.

Zhao, B., Xie, Z., Shen, H. and Wang, Z. (2004). Role of DNA polymerase eta in the bypass of abasic sites in yeast cells. *Nucleic Acids Res* 32, (13):3984-94.

Zhao, X., Liu, J., Hsu, D. S., Zhao, S., Taylor, J. S. and Sancar, A. (1997). Reaction mechanism of (6-4) photolyase. *J Biol Chem* 272, (51):32580-90.



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