Chapter 3
DNA Repair Polymerases

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Abstract The nuclear and mitochondrial genomes are under constant attack from endogenous (metabolic) and exogenous genotoxins. The resulting genomic insults include damaged bases and nucleotides, deoxyribo- and ribonucleotide misincorporation, intra-strand and interstrand DNA cross-links, and single-strand and double-strand DNA breaks. As expected, efficient recognition and removal of these genotoxic lesions is critical to begin the repair process and restore genome integrity. With the exception of direct reversal mechanisms, repair of both the nuclear and mitochondrial genomes requires DNA synthesis to replace the nucleotides or DNA strands removed during the repair process. Whereas some DNA repair pathways co-opt replicative DNA polymerases to synthesize the DNA in the "repair patch," other DNA repair pathways have dedicated DNA polymerase enzymes. This chapter will detail the DNA polymerases central to the major mammalian DNA repair pathways and, where applicable, highlight the unique roles these DNA polymerases may play in protecting normal cells from mutagenic or genotoxic agents and in providing resistance to genotoxic chemotherapeutic treatments.

Keywords DNA repair • DNA polymerase • Mutation • Genome stability

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Abbreviations

5′dRP	5′-deoxyribose phosphate
8-oxodG	8-oxo-7,8-dihydro-2′-deoxyguanosine
AP	Apurinic/apyrimidinic
APE1	Apurinic/apyrimidinic endonuclease
BER	Base excision repair
dsDNA	Double-stranded DNA
FEN1	Structure-specific flap endonuclease 1
HR	Homologous recombination
KO	Knockout
LigI	DNA ligase I
LigIII	DNA ligase III
MEF	Mouse embryonic fibroblast
MGMT	O^6-methylguanine-DNA methyltransferase
MMR	Mismatch repair
NER	Nucleotide excision repair
NHEJ	Nonhomologous end joining
PARP1	Poly(ADP-ribose)polymerase-1
PARP2	Poly(ADP-ribose)polymerase-2
PCNA	Proliferating cell nuclear antigen
Polκ	DNA polymerase kappa
Polλ	DNA polymerase lambda
Polβ	DNA polymerase beta
Polα	DNA polymerase alpha
Polγ	DNA polymerase gamma
Polδ	DNA polymerase delta
Polη	DNA polymerase eta
Polθ	DNA polymerase theta
Polι	DNA polymerase iota
Polκ	DNA polymerase kappa
Polμ	DNA polymerase mu
RFC	Replication factor C
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SSBs	Single-strand breaks
ssDNA	Single-stranded DNA
TdT	Terminal deoxynucleotidyltransferase
UV	Ultraviolet
WRN	Werner syndrome protein helicase

3.1 Introduction

Human cells repair thousands of DNA lesions per day to prevent the accumulation of DNA mutations or genome aberrations that can impact cellular survival and genomic integrity (Lindahl 1993). These lesions manifest as base (e.g., deamination of cytosine to uracil) or nucleotide modifications (e.g., thymine–thymine dimers), deoxyribo- and ribonucleotide misincorporation (mismatches), intra-strand or inter-strand DNA cross-links, and single-strand or double-strand DNA breaks. These numerous and diverse types of DNA lesions derive from both endogenous and exogenous sources. Base damage can be induced by a variety of reactive oxygen species (ROS), reactive nitrogen species (RNS), and sources of DNA alkylation (Svilar et al. 2011). Such molecules stem from endogenous sources via cellular metabolism and exogenous sources mediated by environmental exposure. Additional modifications include simple and complex DNA adducts (Marnett et al. 2003; Marnett 2000; Knutson et al. 2007, 2009; Otteneder et al. 2006), ultraviolet light-induced pyrimidine dimers (Setlow and Setlow 1962), replication errors that give rise to mutations, deletions, or insertions (Kunkel and Erie 2005), as well as gross modifications such as DNA cross-links (Deans and West 2011) and DNA double-strand breaks (DSBs) from environmental, genetic, and endogenous sources (Friedberg et al. 2006).

To facilitate the repair of these lesions, cells have multiple DNA damage response and DNA repair mechanisms that signal the presence of lesions and promote DNA repair (Jackson and Bartek 2009; Friedberg et al. 2006; Wood et al. 2001, 2005; Hoeijmakers 2001). A general overview of mammalian DNA repair pathways and the lesions each repairs is depicted in Fig. 3.1. With the exception of direct reversal (DR) repair processes, each pathway utilizes one or more DNA polymerases as an integral part of the overall DNA repair pathway. The major DR pathway proteins include O^6-methylguanine DNA methyltransferase (MGMT) and the α-ketoglutarate-dependent dioxygenase enzymes: AlkB homologues 1, 2, and 3 (ALKBH1, ALKHB2, ALKBH3). These proteins directly reverse the damage to the DNA base without the requirement of new DNA synthesis (Fu et al. 2012; Yi and He 2013), each with unique lesion specificity. Further detail on this mode of direct reversal DNA repair can be found elsewhere (Fu et al. 2012; Yi and He 2013).

The remaining DNA repair pathways depicted in Fig. 3.1 utilize DNA polymerases to replace the excised lesion-containing nucleotides. Base lesions and DNA SSBs are primarily repaired by the base excision repair (BER) pathway (Almeida and Sobol 2005, 2007; Svilar et al. 2011). As shown and as will be discussed, BER utilizes specific DNA polymerases depending on the initiating lesion, the subcellular location (nuclear vs. mitochondria), and the BER sub-pathway. Similarly, nonhomologous end joining (NHEJ), a pathway for repair of DNA DSBs, also utilizes specialized DNA polymerases (Lieber 2008; Lange et al. 2011; Ramsden 2011; Ramsden and Asagoshi 2012). Another class of specialized DNA polymerases, translesion DNA polymerases, are discussed in

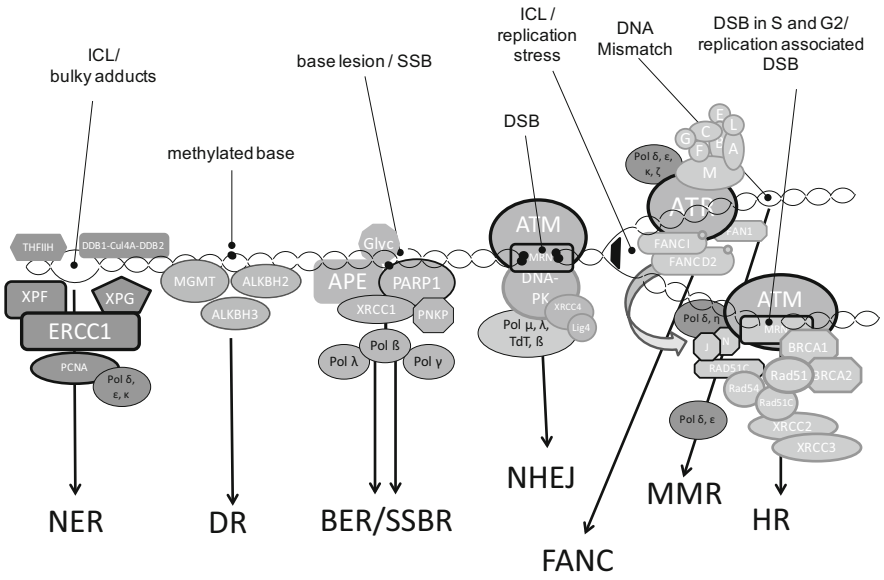

Fig. 3.1 Schematic representation of the mammalian DNA repair pathways. This figure depicts the mammalian DNA repair pathways, the major proteins within each pathway and highlights (*black lettering*) the DNA polymerases involved in each pathway. Adapted from Vens and Sobol (2013)

Chap. 4. The nucleotide excision repair (NER) pathway is a multi-protein, highly complex DNA repair pathway that plays an important role in the repair of DNA lesions induced by many genotoxins and facilitates the removal of bulky DNA adducts that grossly distort the DNA double helix and those that cause a block to transcription (Hoeijmakers 2001; de Laat et al. 1999; Wood 1996; Shuck et al. 2008). As depicted in Fig. 3.1, NER utilizes primarily replicative DNA polymerases but also uses DNA polymerase kappa (Polκ) separate from its role in lesion bypass or translesion DNA synthesis (Ogi et al. 2010). The remaining pathways for the repair of DNA mismatches (MMR), DNA DSBs via homologous recombination (HR), or DNA intra-strand cross-links via the FANC pathway either co-opt replicative DNA polymerases or use specialized polymerases to synthesize DNA after lesion removal or to replicate DNA from the homologous template. The following sections will provide an overview of these DNA repair pathways, emphasizing the role of the DNA polymerases specific to each pathway. Where appropriate, each section will also include relevant discussion on the alterations in these DNA polymerases in cancer since defects in these DNA repair pathways can promote tumorigenesis and are common in human cancers (Hanahan and Weinberg 2011; Harper and Elledge 2007; Curtin 2012; O'Driscoll 2012; Hoeijmakers 2009).

3.2 DNA Polymerases in Base Excision Repair

The proteins of the base excision repair (BER) pathway participate in the repair of dozens of base modifications that result from alkylating agents, reactive nitrogen species, and reactive oxygen species (oxidative DNA damage), among others (Svilar et al. 2011; Almeida and Sobol 2005, 2007). Such damage can arise from numerous exogenous and endogenous sources, resulting in a multitude of detrimental cellular effects, including mutations, genome rearrangements, altered gene expression, and the onset of cell death or senescence (Hoeijmakers 2001; Baute and Depicker 2008; Hegde et al. 2011). The BER pathway model shown in Fig. 3.2 is initiated by a DNA glycosylase such as MYH, a unique glycosylase with specificity for a normal base (adenine) when paired opposite the ROS modified form of deoxyguanosine, 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) (Svilar et al. 2011; David et al. 2007). The remaining ten DNA glycosylases are specific for many types of base lesions, as reviewed elsewhere (Almeida and Sobol 2007; Svilar et al. 2011; Fu et al. 2012). Once the base lesion is removed, the product, an abasic or apurinic/apyrimidinic (AP) site, is a substrate for an endonuclease specific for AP sites, the AP endonucleases APE1 or APE2 (although the majority activity results from APE1) (Almeida and Sobol 2007). There is general consensus that the resulting DNA single-strand break after APE1 (or APE2) cleavage forms a nucleation site for scaffold proteins such as PARP1 and XRCC1 followed by recruitment of the proteins needed to complete repair (not shown in this figure) (Almeida and Sobol 2007). Either DNA polymerase β (Polβ) or DNA polymerase lambda (Polλ) can be recruited to conduct end-trimming and DNA synthesis. Polβ is considered the major end-trimming (5′dRP lyase activity) and DNA polymerase enzyme in BER although, as will be detailed below, Polλ plays a significant role in oxidative damage repair. Alternate DNA polymerases have also been suggested to participate in BER, depending on the base lesion and the subcellular location (nuclear vs. mitochondrial), as will be discussed below. The short-patch BER pathway (Fig. 3.2, left panel) likely contributes 90 % of the repair mediated by BER, but if the 5′ end of the gap is blocked such that end-trimming (5′dRP lyase activity) is attenuated, both Polβ and DNA polymerase δ (Polδ) or DNA polymerase ε (Polε) can extend the repair patch to 2–12 bases, completing a form of BER known as long-patch BER (Fig. 3.2, right panel). Finally, the repair gap is sealed or ligated by either DNA ligase III (LigIII) or DNA ligase I (LigI). Recently, it was suggested that LigI functions as the primary BER DNA ligase in the nucleus with LigIII playing a predominant role in the mitochondria (Gao et al. 2011; Simsek et al. 2011).

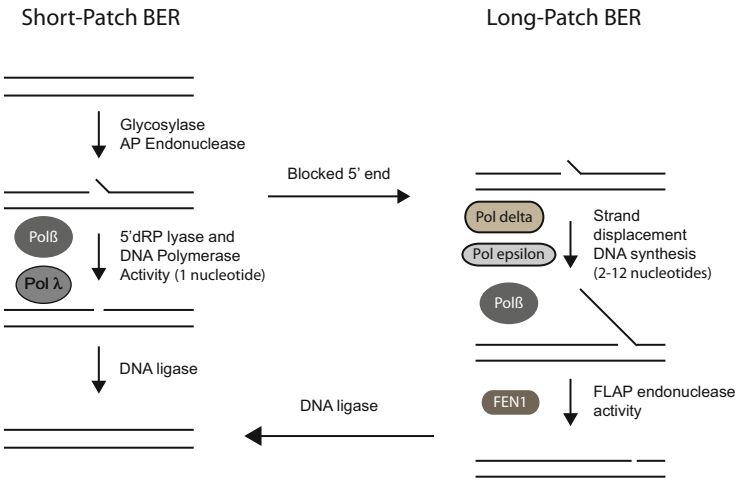

Fig. 3.2 Schematic for short-patch and long-patch BER. Simplified diagram depicting the two sub-pathways for BER: short-patch and long-patch. In short-patch BER, the cleaved AP site can be further processed by the 5′dRP lyase activity of Polβ or Polλ, followed by DNA synthesis and ligation. However, if the 5′ end of the downstream DNA is blocked and cannot be processed, strand-displacement DNA synthesis can proceed. Processing requires FEN1 to remove the 2–12 base flap, followed by DNA ligation

3.2.1 DNA Polβ as the Primary BER Polymerase

DNA polymerase β (Polβ) is a member of the X-family of DNA polymerases (Burgers et al. 2001; Bebenek and Kunkel 2004) and is an essential BER protein, considered the major or primary BER DNA polymerase. At 335 amino acids (39 kDa), Polβ is the smallest of the human DNA polymerases (Beard and Wilson 2006; Lange et al. 2011; Sobol et al. 1996). Polβ has two active sites. The 5′dRP lyase activity is restricted to the 8 kDa N-terminal domain and requires the active site residue K72, whereas the nucleotidyl transferase or DNA polymerase activity resides within the C-terminal domain and requires the aspartate triad D190, D192, and D256, as depicted in Fig. 3.3a. Structurally, the enzyme contains four domains (8K, Fingers, Palm, and Thumb), with the 8K and Fingers domain comprising the dRP lyase activity and the Palm and Thumb domains comprising the majority of the nucleotidyl transferase activity. As depicted in the diagram and structural representation (Fig. 3.3b), the single-stranded DNA (ssDNA) and double-stranded DNA (dsDNA) binding domains reside mostly in the N-terminus, with the enzyme inducing a bend in the DNA upon binding and nucleotide incorporation (Batra et al. 2006).

Since its initial discovery (Weissbach 1977; Weissbach et al. 1975a, b), Polβ was found to be unique in its enzymatic properties (Ono et al. 1979; Tanabe et al. 1979; Yoshida et al. 1979) as compared to the other newly characterized mammalian DNA polymerases alpha (Polα), gamma (Polγ), and delta (Polδ) (Byrnes

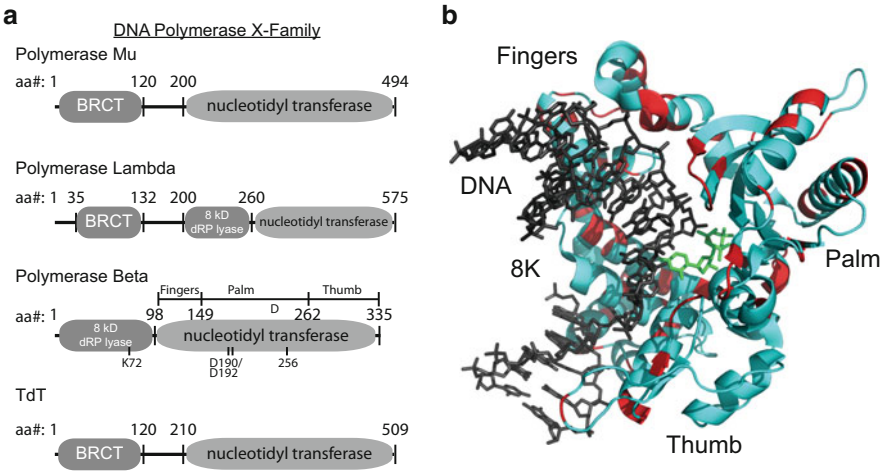

Fig. 3.3 Structural and functional details for DNA Polβ. (**a**) Cartoon depiction of DNA polymerases μ, λ, β, and TdT. For each, the amino acid length is indicated, as well as the domains for protein binding (BRCT), lyase activity (8 kDa lyase), and DNA polymerase activity (nucleotidyl transferase). The amino acid residues spanning each domain are also indicated. A linear depiction of the amino acid residues (1–335) of Polβ is shown, indicating the structural sub-domains as determined by crystallographic analysis (8K, fingers, palm, and thumb), the functional domains (dRP lyase and nucleotidyl transferase), and the essential active site residues (K72 and D190/192/256). (**b**) Ternary structure of DNA Polβ with DNA substrate and incoming nucleotide—structure (pdb2fms) depicting DNA Polymerase β (Polβ) with a gapped DNA substrate and dUMPNPP with magnesium in the catalytic site (Batra et al. 2006). The fingers, palm, and thumb domains of Polβ are indicated. The 8K domain is at the back of the structure facing away from the plane of the image and is shown behind the DNA in this orientation. Amino acids altered by germline or somatic mutations are colored *red* (Sobol 2012b; Donigan et al. 2012)

et al. 1976; Weissbach 1977). Of the four eukaryotic DNA polymerases identified by 1977, Polβ was considered to be "the" DNA repair polymerase (Hubscher et al. 1979; Siedlecki et al. 1980; Waser et al. 1979; Wawra and Dolejs 1979). These early studies defined a role for Polβ in repair using isolated nuclei or nuclear extracts, monitoring the incorporation of radioactive nucleosides following DNA damage (Hubscher et al. 1979; Siedlecki et al. 1980; Waser et al. 1979; Wawra and Dolejs 1979; Mosbaugh and Linn 1983). Although it was subsequently shown that Polα can also carry out gap-filling DNA synthesis in a base excision repair (BER) reaction (Mosbaugh and Linn 1984), the evidence continued to mount in support of Polβ acting as "the" DNA repair polymerase in the nucleus. Studies continued to identify a role for Polβ in the repair of damage induced by many different DNA damaging agents, including bleomycin (Seki and Oda 1986; DiGiuseppe and Dresler 1989), cigarette smoke (Cui et al. 2012), arsenic (Lai et al. 2011), UV-radiation (Orlando et al. 1988), benzo[a]pyrene (Ishiguro et al. 1987), methylmethane sulfonate (Park et al. 1991), ionizing radiation (Price 1993), G-T mis-pairs (Wiebauer and Jiricny 1990), and uracil (Dianov et al. 1992; Nealon et al. 1996; Singhal et al. 1995; Singhal and Wilson 1993). Interestingly, a truncated

version of Polβ expressed in MEFs mediates a dependence of the cells on homologous recombination (HR) and sensitizes cells to radiation (Neijenhuis et al. 2009, 2010). Several groups reported complete BER in vitro with Polβ and additional purified proteins (Singhal et al. 1995; Nealon et al. 1996; Kubota et al. 1996). Like many DNA repair proteins, Polβ has been reported to be modified by and/or regulated by posttranslational modification, including phosphorylation (Tokui et al. 1991; Guo et al. 2008; Phosphosite 2010), acetylation (Hasan et al. 2002), methylation (El-Andaloussi et al. 2006, 2007), as well ubiquitinylation (Parsons et al. 2008, 2009; Sobol 2008). It is not yet clear how these modifications impact overall BER or the role of Polβ in BER as in many cases these observations have been limited to in vitro studies (Sobol 2008; Goellner et al. 2012).

Although it was demonstrated in heterologous systems (*Escherichia coli* and *Saccharomyces cerevisiae*) that Polβ can conduct DNA replication and repair in vivo (Blank et al. 1994; Ohnishi et al. 1990), it was not until a mouse gene knockout (KO) (Gu et al. 1994) was made that the specificity of the repair conducted by Polβ was defined (Sobol et al. 1996).

Characterization of the Polβ KO mouse (Gu et al. 1994; Sugo et al. 2000) and mouse embryonic fibroblasts (MEFs) deficient in Polβ (Sobol et al. 1996) clearly demonstrated a requirement for Polβ in repair of alkylation and oxidative DNA damage (Sobol et al. 1996; Horton et al. 2002) and provided a valuable resource to explore additional functions of Polβ (Esposito et al. 2000; Gonda et al. 2001), to evaluate the impact of Polβ on mutagenesis (Niimi et al. 2005; Cabelof et al. 2003; Sobol et al. 2002; Bennett et al. 2001; Poltoratsky et al. 2005) and mechanisms of genotoxin-induced cell death (Ochs et al. 1999, 2002; Horton et al. 2003, 2005; Le Page et al. 2003; Sobol et al. 2003; Trivedi et al. 2005; Cabelof et al. 2004; Tomicic et al. 2001), to investigate alternate or compensatory repair pathways in the absence of Polβ (Biade et al. 1998; Fortini et al. 1998, 1999; Stucki et al. 1998; Dianov et al. 1999; Braithwaite et al. 2005b), to address structure–function relationships or protein partners of Polβ in vivo (Kedar et al. 2002; Niimi et al. 2005; Sobol et al. 2000) and most recently to evaluate changes of gene expression in response to Polβ depletion (Li et al. 2012a). The most definitive and reproducible endpoint that has been used to evaluate Polβ participation in repair in vivo is survival following DNA damage such as exposure to alkylating agents (Sobol et al. 1996, 2000). Unfortunately, the Polβ mouse knockout is lethal just after birth (neonatal lethality) (Sugo et al. 2000; Gu et al. 1994), complicating efforts to evaluate the role of Polβ in an animal model. Surprisingly, it is the 5′dRP lyase function of Polβ (Matsumoto and Kim 1995) that appears to be essential and sufficient for alkylating agent resistance (Sobol et al. 2000). In the absence of Polβ (in MEFs), cells are unable to efficiently repair the highly toxic 5′dRP moiety and therefore are hypersensitive to different types of alkylating agents such as methylmethane sulfonate, *N*-methyl-*N*-nitrosourea, and *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (Sobol et al. 1996, 2000, 2002, 2003; Trivedi et al. 2005), the thymidine analog 5-hydroxymethyl-2′-deoxyuridine (Horton et al. 2003), as well as the therapeutic agent temozolomide (Trivedi et al. 2005; Horton et al. 2003) and radiation (Neijenhuis et al. 2005, 2009, 2010; Vens and Begg 2010). In human cells, Polβ

is suggested to play a role in the cellular response to cisplatin (Kothandapani et al. 2011) but plays a significant role in the repair of the DNA lesions induced by the clinical alkylating agent temozolomide (Trivedi et al. 2008; Tang et al. 2010, 2011; Goellner et al. 2011; Stachelek et al. 2010), prompting a robust series of investigations to identify specific Polβ inhibitors (Goellner et al. 2012; Wilson et al. 2010; Barakat et al. 2012; Jaiswal et al. 2009).

In mice, an intact 5′dRP lyase domain appears to rescue the neonatal lethality of the Polβ mouse knockout yet does not appear to be sufficient to rescue all of the defects associated with the loss of Polβ in the mouse (Senejani et al. 2012). By expression of a mutant of Polβ deficient in polymerase activity (Y265C) in a Polβ KO background, it was demonstrated that the mice (homozygous for the Y265C mutant Polβ) were born at the expected Mendelian ratios, but loss of the polymerase function in vivo led to the accumulation of repair intermediates and less than 40 % survived 24 h after birth, remaining smaller than the WT littermates even 3 weeks after birth (Senejani et al. 2012).

Dozens of somatic or germline mutations of Polβ have been identified and characterized (Sobol 2012b; Nemec et al. 2012; Donigan et al. 2012), prompting the suggestion that Polβ may be mutated in as much as 30 % of human tumors (Starcevic et al. 2004; Sweasy et al. 2006; An et al. 2011). As depicted in Fig. 3.3b, these mutations are not limited to a single domain or active site and are found throughout the Polβ open reading frame (note the red-shaded regions in the cartoon depicting locations of somatic and germline mutations in the structure of Polβ). In many cases, these mutations show little or no effect but several mutations have significant impact on DNA polymerase activity or 5′dRP lyase activity. For example, the E295K mutant, first identified in gastric cancer (Iwanaga et al. 1999), is defective in nucleotidyl transferase activity, and the resulting protein is defective in BER, inducing cellular transformation when over-expressed (Lang et al. 2007; Li et al. 2012b). Conversely, the L22P cancer mutant is reported to be defective only in 5′dRP lyase activity (Dalal et al. 2008). It has been suggested that tumor-specific defects in BER such as a defect in Polβ may be exploited for selective therapeutic options (Neijenhuis et al. 2010), and so it remains to be determined if the presence of these Polβ mutants can be exploited clinically.

3.2.2 Emerging Role of Polλ in BER of Oxidative Damage

DNA polymerase lambda (Polλ) was first isolated and characterized as a beta-like (Polβ-like) polymerase (Aoufouchi et al. 2000; Garcia-Diaz et al. 2000; Nagasawa et al. 2000). Overall, Polλ is a 575 amino acid enzyme that participates in both BER and nonhomologous end joining (NHEJ). Unique to Polλ is an N-terminal BRCT domain that is essential for its role in NHEJ (see Sect. 3.2 below). Similar to Polβ, Polλ is an X-family polymerase with multiple domains, including both the nucleotidyl transferase activity domain and an 8K domain that contributes the 5′dRP lyase activity important for complete BER (Garcia-Diaz et al. 2001)

(Fig. 3.3a). Although its primary role is likely in NHEJ, the presence of the 5′dRP lyase activity (Garcia-Diaz et al. 2001) has prompted continued investigation into the role of Polλ in BER, even suggesting that in some cases, both Polβ and Polλ compete for repair of the same lesions but may have nonredundant roles in vivo depending on cellular state (Garcia-Diaz et al. 2002). However, it is clear that whether it is a backup or competing player in BER, Polλ has a significant role in BER (Lebedeva et al. 2005; Braithwaite et al. 2005a, b).

Both Polβ and Polλ participate in BER in DT40 cells (Tano et al. 2007) and have redundant as well as independent BER roles in MEFs (Braithwaite et al. 2010). Further, Polλ-deficient cells are sensitive to radiation (Vermeulen et al. 2007a), similar to that found by the same group for Polβ (Vermeulen et al. 2007b). However, the most prominent role for Polλ in BER appears to be in MYH-initiated BER, as depicted in the short-patch BER model shown in Fig. 3.2a. This unique BER process requires the removal of the normal adenine base when opposite the ROS lesion 8-oxodG and insertion of a cytidine opposite 8-oxodG to allow a second round of BER initiated by OGG1 (Sobol 2012a; David et al. 2007). Interestingly, both Polβ and Polλ can fill the gap opposite the 8-oxodG lesion (Brown et al. 2007) although Polλ may be more error prone (Brown et al. 2011). A role for Polλ in MYH-mediated repair has been shown in cells and with purified proteins (van Loon and Hubscher 2009).

Multiple structural studies have been completed for Polλ, specific for the lyase domain (DeRose et al. 2003) or the catalytic core (Garcia-Diaz et al. 2004), providing significant insight with regard to structure and function (Garcia-Diaz et al. 2005). The enzyme is phosphorylated by cdk2 (Frouin et al. 2005; Wimmer et al. 2008) and its stability is regulated by ubiquitylation (Markkanen et al. 2011). Further, the involvement of Polλ in BER of oxidative lesions is regulated by both cdk2-mediated phosphorylation and MULE-mediated ubiquitylation (Markkanen et al. 2012). Most interestingly, there is functional cross talk between these two PTMs in that phosphorylation of Thr553 on Polλ prevents ubiquitylation and proteasome-mediated degradation (Wimmer et al. 2008). More recently, it is suggested that long-patch DNA repair synthesis mediated by Polλ is enhanced by binding to the Werner syndrome protein helicase (WRN) (Kanagaraj et al. 2012).

Only one cancer mutant of Polλ has been characterized, but it appears to have a defect in NHEJ as opposed to BER (Terrados et al. 2009). Polλ inhibitors have also been developed and are suggested to have tenfold greater specificity to Polλ as compared to Polβ (Strittmatter et al. 2011). It remains to be determined if these novel tools can advance our understanding on the role of Polλ in BER.

3.2.3 Alternate or Backup Polymerases in BER

The most relevant or obvious backup DNA polymerases that function in BER (besides Polλ) are those that have been found to participate in the long-patch sub-pathway of BER (Fig. 3.2b). Long-patch BER is initiated similarly to

short-patch BER to produce a nicked DNA intermediate but appears to have different DNA polymerase requirements. Repair completion requires a 3′OH moiety for proper nucleotidyl transfer and chain elongation. In cases where the 5′ moiety within the gap is refractory to Polβ lyase activity (Gary et al. 1999), Polδ, Polε, or Polβ, coupled with proliferating cell nuclear antigen (PCNA) and a variety of other proteins including the flap structure-specific endonuclease 1 (FEN1), poly (ADP-ribose)polymerase 1 (PARP1), and LigI, synthesizes DNA to fill the gap, resulting in a displaced DNA flap of 2–12 bases in length (Fortini et al. 1998; Stucki et al. 1998; Gary et al. 1999; Parlanti et al. 2002; Pascucci et al. 1999; Podlutsky et al. 2001; Matsumoto et al. 1999). DNA synthesis and strand displacement by Polβ is stimulated by the combined presence of FEN1 and PARP1 (Prasad et al. 2000, 2001) or RPA (DeMott et al. 1998). WRN is also observed to stimulate strand-displacement activities of Polβ (Harrigan et al. 2003) to facilitate long-patch BER (Harrigan et al. 2006). FEN1 then catalyzes the removal of the ensuing DNA flap, leaving a nick that has been transferred 2–12 nucleotides downstream of the original damage site. Finally, the intact DNA strand is restored by ligation mediated by LigI (Fig. 3.2b).

Recent studies with purified proteins or in cells (DT40 KO cells, MEF KO cells, or human cells following RNA interference) have implicated additional DNA polymerases that may participate in nuclear BER. DNA polymerase iota (Polι) is a Y-family polymerase and encodes a 5′dRP lyase activity (Bebenek et al. 2001) located in the 40-kDa domain spanning residues M79 to M445 (Prasad et al. 2003). Although Polι is shown to protect cells from oxidative stress suggesting a more prominent role in BER of oxidative damage (Petta et al. 2008), Polι appears to play little or no role in the repair of alkylation damage (Poltoratsky et al. 2008; Sobol 2007). Efforts are continuing to uncover the most significant biological role for Polι (Vidal and Woodgate 2009).

DNA polymerase theta (Polθ), an A-family polymerase, has also been suggested to be involved in BER (Ukai et al. 2006). As with the other BER DNA polymerases, Polθ contains a 5′dRP lyase domain (Prasad et al. 2009) and Polθ KO cells are sensitive to oxidative damage (Goff et al. 2009; Yousefzadeh and Wood 2013), all supportive for a role for Polθ in BER, as well as a role in the response to radiation (Higgins et al. 2010b). Interestingly, Polθ is known to be upregulated in breast cancers and, when over-expressed, correlates with poor prognosis (Higgins et al. 2010a; Lemee et al. 2010; Begg 2010).

3.2.4 Mitochondrial BER

BER has a well-defined role in repair of the mitochondrial genome (Bogenhagen et al. 2001), although recently it has been suggested that other repair pathways function in mitochondria (Kazak et al. 2012). Several nuclear BER enzymes also encode mitochondrial isoforms, i.e., UNG1 (Slupphaug et al. 1993). Additional mitochondrial BER enzymes have been summarized elsewhere (Svilar et al. 2011;

Liu and Demple 2010). The sole polymerase in mitochondria is DNA polymerase γ (Polγ), an A-family DNA polymerase essential for mitochondrial replication (Liu and Demple 2010) and implicated in mitochondrial BER (Stuart et al. 2005; Bogenhagen et al. 2001). The enzyme is comprised of the catalytic subunit (Polγ) and an accessory subunit (POLG2 or POLGB), reported to enhance the BER capacity of Polγ (Pinz and Bogenhagen 2006). As with the other BER DNA polymerases mentioned above, Polγ encodes a 5′dRP lyase activity domain (Longley et al. 1998), supporting its role in the short-patch sub-pathway of BER. Similar to that observed for nuclear BER, Polγ also supports a long-patch BER sub-pathway in mitochondria via both a FEN1-dependent (Liu et al. 2008) and a FEN1-independent (Szczesny et al. 2008) reaction, the latter possibly involving either DNA2 (Zheng et al. 2008) or EXOG (Tann et al. 2011). Interestingly, over 40 disease mutations have been identified in the gene for Polγ (POLG), many of which lead to mitochondrial disorders (Longley et al. 2005). It has yet to be determined if these mutations impact the role of Polγ in BER.

3.3 Unique and Specialized DNA Polymerases in Nonhomologous End Joining

The majority of DNA DSBs are repaired in mammalian cells by the nonhomologous end joining (NHEJ) pathway (Fig. 3.4a) (Lieber 2008; Downs et al. 2007). Primarily, the requisite DNA synthesis associated with NHEJ-mediated repair is via X-family DNA polymerases (Fig. 3.3a). As will be described below, repair of DSBs in the G_2-phase of the cell cycle or during the latter part of the S-phase of the cell cycle is primarily handled by the homologous recombination (HR) pathway (Fig. 3.4b). It is suggested that in G_2-phase and late S-phase, there are numerous factors that contribute to DSB repair pathway choice between HR and NHEJ (Brandsma and Gent 2012). However, in G_0-phase, G_1-phase and in the early part of S-phase, DSBs are repaired primarily by the NHEJ pathway. As depicted in Fig. 3.4a, the DNA ends are recognized by the KU heterodimer (KU70/KU80), a large DNA-binding protein with significant binding affinity to DNA ends (Doherty and Jackson 2001). Bound and activated KU undergoes a conformational change, increasing its affinity (hence recruitment) to the other critical factors required for NHEJ (Lieber 2008), including the nuclease complex Artemis/DNA-PKcs (Gell and Jackson 1999; Rivera-Calzada et al. 2007), the DNA polymerases (primarily Polμ and Polλ) (Ramsden 2011; Ramsden and Asagoshi 2012), and the ligase complex XLF/XRCC4/LigIV (Costantini et al. 2007; Gell and Jackson 1999). This large protein complex subsequently processes the broken, modified DNA ends, resulting in relegation/joining to repair the DSB. The overall process has been extensively reviewed elsewhere (Lieber 2008; Brandsma and Gent 2012; Murray et al. 2012; Boboila et al. 2012; Chapman et al. 2012; Kass and Jasin 2010; Malu et al. 2012; Pawelczak et al. 2011). Note that the recruitment of the

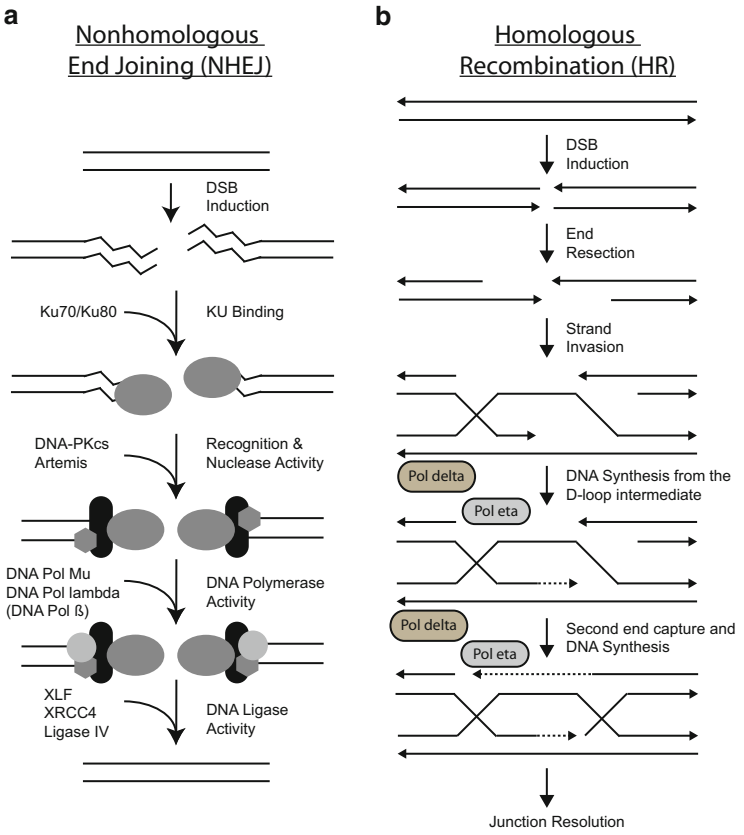

Fig. 3.4 DNA polymerases involved in double-strand break repair. (**a**) Schematic depicting the mechanism of NHEJ functioning in all phases of the cell cycle, showing KU binding to the broken ends of a DNA DSB, followed by nuclease activity to trim the ends, DNA polymerase activity for end processing, and DNA ligase activity to seal the DSB. (**b**) Classical scheme for HR-mediated repair of a DSB, showing DNA synthesis by either Polδ or Polη extending from the D-loop intermediate and followed by second-end capture and coordinated DNA synthesis of the opposite strand

essential polymerases for NHEJ primarily occurs via the BRCT domain of the polymerases (Fig. 3.3a) (DeRose et al. 2007; Matsumoto et al. 2012; Mueller et al. 2008; Gell and Jackson 1999). Details for each of the polymerases involved in mammalian NHEJ are described below.

3.3.1 DNA Polymerase Mu

DNA polymerase μ (Polμ) is an X-family DNA polymerase (Nick McElhinny and Ramsden 2003) with homology to TdT (Dominguez et al. 2000; Ruiz et al. 2001) containing both a BRCT domain in the N-terminus and the nucleotidyl transferase activity in the C-terminus (Fig. 3.3a). A role for Polμ in NHEJ was suggested following the discovery that Polμ interacts with KU and LigIV (Mahajan et al. 2002; Paull 2005). There are known NHEJ-related functional differences between Polμ and the other X-family polymerases (Bertocci et al. 2006). For example, mice deficient for Polμ are defective for immunoglobulin kappa chain rearrangement (Bertocci et al. 2003) but not Ig gene hypermutation (Bertocci et al. 2002). Further, over-expression of Polμ can impact the rate of somatic hypermutation (Ruiz et al. 2004). In addition, Polμ-deficient mice have a defect in hematopoiesis (Lucas et al. 2009). Structural studies have contributed to an in-depth understanding for the role of Polμ in NHEJ, highlighting slight but important differences with other X-family DNA polymerase members that might explain some of the substrate specificity for Polμ as compared to Polλ and Polβ (Moon et al. 2007).

Analysis of Polμ KO MEFs clearly establishes a role for Polμ in DSB repair of a variety of NHEJ substrates (Chayot et al. 2010, 2012; Capp et al. 2007). Similar to that seen for Polλ (see below), gap-filling activities in the NHEJ process mediated by Polμ are dependent on XLF (Akopiants et al. 2009), likely via interaction with the BRCT domain of Polμ (Mueller et al. 2008; DeRose et al. 2007). Polμ is also known to conduct translesion DNA synthesis, as will be discussed elsewhere in this series (Chap. 4). Defects in Polμ with regard to NHEJ can give rise to an increase in genomic abnormalities (e.g., chromosome aberrations) and should be associated with an increase in cancer.

3.3.2 DNA Polymerase Lambda

As described in Sect. 3.1.2, Polλ has a high degree of similarity to Polβ (Garcia-Diaz et al. 2000) and has a significant role in BER, particularly for oxidative damage (Lebedeva et al. 2005; Braithwaite et al. 2005a, b; Markkanen et al. 2012; Kanagaraj et al. 2012). The enzymatic properties of Polλ also suggested a role for this polymerase in NHEJ (Fan and Wu 2004; Lee et al. 2004; Bebenek et al. 2003). As was described above and as shown in Fig. 3.3a, Polλ has an N-terminal BRCT domain that promotes its role in NHEJ (Mueller et al. 2008). Polλ interacts with the XRCC4/LigIV complex via residue R57 in the BRCT domain (Mueller et al. 2008). Polλ-mediated gap filling during NHEJ also requires XLF, a core protein in the NHEJ pathway (Ahnesorg et al. 2006; Buck et al. 2006; Cavero et al. 2007; Revy et al. 2006). By characterizing whole-cell extracts from XLF-deficient human cells, it was determined that XLF is essential for gap filling

by both Polλ and Polμ (Akopiants et al. 2009). It is suggested that XLF may align the DNA ends in the repair reaction, in concert with XRCC4 (Andres et al. 2012), DNA ligase IV (Ropars et al. 2011), KU (Yano et al. 2008, 2011), and APLF (Grundy et al. 2013). Proper polymerase fidelity is also required for Polλ with regard to NHEJ-mediated DNA synthesis, as was discovered by characterizing the single-nucleotide polymorphism (SNP) mutant at codon 438 (R438W) (Terrados et al. 2009). This point mutant of Polλ retains nucleotidyl transferase activity and 5′dRP lyase activity but has a reduction in base substitution fidelity (Terrados et al. 2009). Interestingly, this mutant negatively impacts the role of Polλ in NHEJ, leading to an increase in chromosomal aberrations (Terrados et al. 2009).

3.3.3 TdT

Terminal deoxynucleotidyltransferase (TdT) participates in a very restricted capacity in NHEJ. Expression of TdT is limited to cells productive for V(D)J recombination (Benedict et al. 2000), suggesting that a role for TdT is limited to NHEJ during V(D)J recombination. This unique X-family polymerase catalyzes the addition of nucleotides by a template-independent mechanism, for example, at the junction of rearranged Ig heavy chain and T-cell receptor gene segments during B-cell and T-cell maturation. This activity, even with purified protein, is consistent with a role in NHEJ (Ma et al. 2004). Recently, it has also been shown that TdT can carry out non-template-mediated nucleotide addition at a DSB junction but only in the presence of KU80 and XRCC4 (Boubakour-Azzouz et al. 2012). TdT binds to the essential NHEJ protein KU (Mahajan et al. 1999) as well as the DSB repair protein hPso4 (Mahajan and Mitchell 2003), and its role in V(D)J recombination is suppressed by binding to PCNA (Ibe et al. 2001). As with other X-family polymerases involved in NHEJ, the N-terminal BRCT domain of TdT (Mueller et al. 2008) does have a positive effect on nucleotide addition activity (Repasky et al. 2004). Although TdT shares significant sequence homology with the other X-family polymerase members (Fig. 3.3a), there does not appear to be any significant overlapping function of TdT with Polλ or Polμ (Bertocci et al. 2006). Further activities of TdT are discussed in Chap. 5.

3.3.4 DNA Polymerase Beta

DNA polymerase β (Polβ) is genetically similar to TdT (Anderson et al. 1987) and exhibits strong similarity to Polμ (Ruiz et al. 2001) as well as structural (DeRose et al. 2003) and functional (Ramadan et al. 2003) similarity to Polλ (Fig. 3.3a). In this light, Polβ has long been suggested to have a role, albeit minor, in NHEJ. Although there is evidence of a genetic interaction between Polβ and the NHEJ protein DNA-PKs (Niimi et al. 2005), this by itself does not implicate Polβ in

NHEJ. Mice with a reconstituted lymphoid system using Polβ KO fetal liver cells showed normal patterns of somatic hypermutation, suggesting little role for Polβ in this process (Esposito et al. 2000). Further, the lack of a BRCT domain in Polβ (Fig. 3.3a) would negatively impact its role in NHEJ since this protein–protein interaction domain (Woods et al. 2012) in Polλ, Polμ, and TdT is important for interacting with NHEJ protein partners (Mueller et al. 2008). However, it is possible that Polβ may play a limited role in microhomology-mediated end joining (MMEJ) (Crespan et al. 2012), a sub-pathway of NHEJ that is independent from KU and DNA ligase 4/XRCC4 (McVey and Lee 2008).

3.4 DNA Polymerases Critical to Homologous Recombination Repair of DNA Double-Strand Breaks

The homologous recombination (HR) pathway participates in several critical biological processes, including DNA repair, the rescue of stalled/collapsed DNA replication forks, meiotic chromosome segregation, and telomere maintenance (Sung and Klein 2006; Friedberg et al. 2006; Hoeijmakers 2001). As with NER and MMR, much of the effort in recent years to characterize the proteins involved in HR has focused on the early steps in this pathway including lesion (DSB) recognition, HR protein regulation, DSB repair pathway choice (HR vs. NHEJ), strand exchange processes, as well as the proteins involved in the resolution of holiday junctions (Barzel and Kupiec 2008; Bordeianu et al. 2011; Krejci et al. 2012; Sung and Klein 2006; Symington and Gautier 2011). A classical schematic for the HR pathway is depicted in Fig. 3.4b. Upon recognition of the DSB, the ends are processed through an end resection step, allowing strand invasion of the homologous strand of the sister chromatid, providing the template for HR-directed DNA synthesis from the D-loop and subsequently after second-end capture. Defining the DNA polymerase in this process was first shown in yeast where it was demonstrated that Polδ is preferentially recruited to complete DNA synthesis for HR (Maloisel et al. 2008). There are in fact numerous genetic examples demonstrating that yeast Polδ is involved in HR (Giot et al. 1997; Lydeard et al. 2007; Maloisel et al. 2004, 2008; Wang et al. 2004; Fabre et al. 1991). More recently, using purified proteins, it was shown that yeast Polδ, together with PCNA, is essential for DNA synthesis from the D-loop during HR (Li et al. 2009). In a more recent study, both yeast Polδ and yeast polymerase eta (Polη) contributed equally to DNA synthesis to extend the D-loop (Sebesta et al. 2011).

However, in chicken DT40 cells it was demonstrated that Polη participates in both HR and TLS (Kawamoto et al. 2005). Simultaneously, using purified human proteins and cell lysates, it was shown that human Polη promoted DNA synthesis from the D-loop intermediate (Fig. 3.4b) but this DNA synthesis step could not be conducted by human Polδ or by human polymerase iota (Polι) (McIlwraith et al. 2005). Human Polη, but not human Polδ or human Polι, was also able to

mediate the capture and annealing of the second end of the resected DSB, in concert with RAD52. This was subsequently followed by DNA synthesis from the captured "second" DNA end (McIlwraith and West 2008) (Fig. 3.4b). Of course, some aspects of HR may require a TLS step. This will be discussed elsewhere in this series (Chap. 4).

3.5 DNA Polymerases as Essential Components in Nucleotide Excision Repair

The nucleotide excision repair (NER) pathway plays an important role in the repair of DNA lesions (Kuper and Kisker 2012) induced by many genotoxins and chemotherapeutics including DNA cross-linking agents such as chloroethylating agents, cisplatin, carboplatin, and lesions induced by a host of environmental agents including cigarette smoke (Friedberg et al. 2006) and ultraviolet (UV) light (Wood 1996; de Vries et al. 1995; Yeh et al. 2012). Put simply, NER facilitates the removal of bulky DNA adducts that grossly distort the DNA double helix and those that cause a block to transcription. Overall, the pathway consists of two complementary sub-pathways that have some overlap. These two sub-pathways are referred to as global genome repair (GGR–NER) and transcription-coupled repair (TCR–NER) and facilitate lesion recognition/confirmation and the assembly of the pre-incision complex. Molecular details on the proteins involved in NER can be found in several excellent reviews (Hoeijmakers 2001; de Laat et al. 1999; Wood 1996; Shuck et al. 2008; Hanawalt and Spivak 2008; Gillet and Scharer 2006). The two sub-pathways are distinct regarding the lesion recognition step but converge and utilize the same proteins to remove the ~22–28 base oligonucleotide containing the lesion. Until recently, the molecular details of the later steps in the pathway, the DNA synthesis steps, were not fully characterized (Kunkel and Van Houten 2006). Although much has yet to be worked out, recent studies have provided compelling evidence that the DNA synthesis step of NER involves three DNA polymerases (Fig. 3.5), the replicative DNA polymerases delta (Polδ) and epsilon (Polε) as well as the Y-family DNA polymerase kappa (Polκ) (Kunkel and Van Houten 2006; Ogi et al. 2010; Ogi and Lehmann 2006).

3.5.1 Replicative Polymerases Delta and Epsilon in NER

DNA polymerases δ (Polδ) and ε (Polε) are both B-family DNA polymerases with primary roles in DNA replication (Kunkel and Burgers 2008). The involvement of replicative DNA polymerases in DNA synthesis in human NER evolved from earlier studies with human cell extracts that implicated a requirement for the replication cofactor PCNA (Shivji et al. 1992). Subsequent studies demonstrated

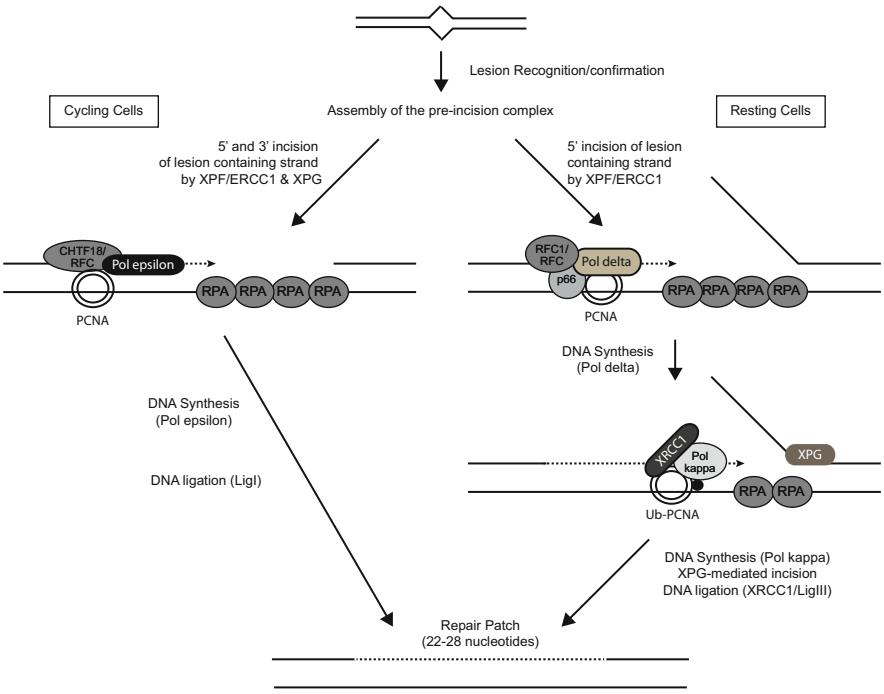

Fig. 3.5 DNA synthesis in NER by Polδ, Polε, and Polκ. Schematic depicting a role for Polδ, Polε, and Polκ in the DNA synthesis step of NER. The diagram shows the NER DNA polymerases in cycling and resting cells (Polδ, Polε, and Polκ) as well as the clamp loaders required for each polymerase (Ogi et al. 2010)

that DNA synthesis during NER was not affected by neutralizing antibodies to polymerase α (Polα) but was blocked by aphidicolin, suggesting a possible role for Polδ and/or Polε (Coverley et al. 1992). Subsequent elegant studies with purified human proteins clearly established the requirement for Polδ and/or Polε in DNA synthesis during NER (Shivji et al. 1995; Aboussekhra et al. 1995), ultimately defining a core set of proteins required for the repair of a cisplatin DNA adduct (Araujo et al. 2000). Replication factor C (RFC) was observed to be required for recruitment of Polδ (Overmeer et al. 2010).

As suggested above, the latest models suggest that Polδ, Polε, and Polκ (see below) are all involved in DNA synthesis during NER (Fig. 3.5) (Lehmann 2011; Ogi and Lehmann 2006; Ogi et al. 2010). Although it is not yet fully resolved as to the conditions or parameters that dictate polymerase choice in NER, several clues have emerged from biochemical studies (Fig. 3.5). Polδ is recruited by RFC1/p66 and loaded onto PCNA. The recruitment of Polκ does not require RFC1 but in fact is mediated by XRCC1 and is loaded onto ubiquitylated PCNA (see below). Conversely, Polε appears to be the polymerase of choice in cycling (dividing) cells in which CHTF18-RFC recruits Polε to load onto PCNA. Recruitment of Polε appears to favor dividing cells with high dNTPs and after dual incision by

XPF/ERCC1 and XPG, whereas Polδ requires RFC and PCNA for recruitment and likely favors nondividing cells (Lehmann 2011).

3.5.2 *A Role for DNA Polymerase Kappa in NER Unrelated to Translesion Synthesis*

DNA polymerase kappa (Polκ) is a Y-family DNA polymerase with a high error rate typical for this family of polymerases (Ohashi et al. 2000). Like other Y-family polymerases, Polκ can participate in DNA synthesis past bulky DNA lesions (translesion DNA synthesis, TLS) (Chap. 4) (Lange et al. 2011; Ziv et al. 2009) and would not be expected to participate in the DNA synthesis step of NER (Kunkel and Van Houten 2006). The low processivity and fidelity of Y-family polymerases (McCulloch and Kunkel 2008) (e.g., synthesis and incorporation of only one to five nucleotides before dissociation from the primer-template) would likely preclude Polκ from participation in NER to fill the gap of 22–28 nucleotides (Friedberg et al. 2006). However, in vitro studies have demonstrated that Polκ polymerizes up to 25 nucleotides before dissociation (Ohashi et al. 2000), supporting a possible role for Polκ in NER gap-filling DNA synthesis.

The first clue that Polκ may participate in NER gap-filling DNA synthesis was the demonstration that Polκ localized to repair foci with PCNA in a pattern that was unlike the other Y-family TLS polymerases eta (Polη) and iota (Polι) (Ogi et al. 2005). In a surprising finding using Polκ-KO MEFs, it was demonstrated that loss of Polκ reduced the level of NER following UV damage. Repair was not completely absent but was significantly reduced and clearly established a novel role for Polκ in NER (Ogi and Lehmann 2006). The same group followed this with a more detailed report implicating Polδ, Polε, and Polκ in NER (Ogi et al. 2010). As described above for Polδ and Polε and in Fig. 3.5, Polκ (in a complex with XRCC1) is recruited to complete DNA repair synthesis by ubiquitylated PCNA following repair DNA synthesis initiated by Polδ (Fig. 3.5, right side). Once repair is completed, the polymerase dissociates (Polκ) and XPG facilitates the 3′ incision to release the flap. This latter step is consistent with the observation that the 5′ incision by XPF/ERCC1 precedes the 3′ incision by XPG and that repair synthesis can proceed in the absence of XPG catalytic activity (Staresincic et al. 2009). Based on this recent model and available biochemical analysis (Fig. 3.5), recruitment and involvement of Polκ in NER requires XRCC1 and ubiquitylated PCNA for recruitment and likely favors low dNTPs and synthesis after 5′ incision by XPF/ERCC1 (Lehmann 2011).

3.6 The Mismatch Repair Pathway as a Replicative Polymerase Fidelity Factor

The DNA mismatch repair (MMR) pathway is involved in numerous processes involving DNA metabolism including repair of damage due to environmental or chemotherapeutic exposures, meiotic recombination, DNA damage signaling, and the correction or repair of numerous base–base mismatches and insertion/deletion loops (Fu et al. 2012; Li 2008; Wyatt and Pittman 2006; Modrich 2006; Jiricny 2006). The latter role of the MMR pathway functions to significantly improve DNA replication fidelity, as much as 1,000-fold, repairing errors made by Polα (Liberti et al. 2013; Nick McElhinny et al. 2010; Niimi et al. 2004), Polδ (Nick McElhinny et al. 2010; Lujan et al. 2012), and Polε (Lujan et al. 2012). Loss of MMR therefore promotes a mutator/genome instability phenotype that can predispose to an increase in mutations and cancer in eukaryotic model systems and humans (Arana and Kunkel 2010; Hubscher 2009; Kunkel 2009; Preston et al. 2010; Reha-Krantz 2010; Albertson et al. 2009).

3.6.1 A Reconstituted Human Mismatch Repair Pathway Utilizes DNA Polymerase Delta

A functional human MMR system has been reconstituted using recombinant proteins and artificial (plasmid) substrates (Modrich 2006). As depicted in the significantly simplified model shown in Fig. 3.6, mismatch recognition is primarily mediated by the heterodimers MUTSα (comprised of the proteins MSH2/MSH6 or MSH2/MSH3) and MUTLα (comprised of the proteins MLH1/PMS1) (Friedberg et al. 2006). Further details on mismatch recognition and MMR can be found in numerous reviews (Fu et al. 2012; Li 2008; Wyatt and Pittman 2006; Modrich 2006; Jiricny 2006). In an elegant series of biochemical studies, a completely reconstituted system was developed that was capable of supporting directional MMR ($3' \geq 5'$ or $5' \geq 3'$) that exploits a previously undiscovered latent endonuclease activity of MUTLα that is both ATP and mismatch dependent (Kadyrov et al. 2006). Together with EXO1, this in vitro system yields the proper substrate for DNA polymerase loading onto PCNA to allow DNA synthesis of the repair patch for MMR, estimated at 1,000 bases (Thomas et al. 1991) but can range from 200 to >2,000 base pairs, depending on the location of the mismatch and the cellular state (Modrich 2006). In this system, purified Polδ was utilized and found to be fully capable of supporting MMR DNA synthesis (Fig. 3.6).

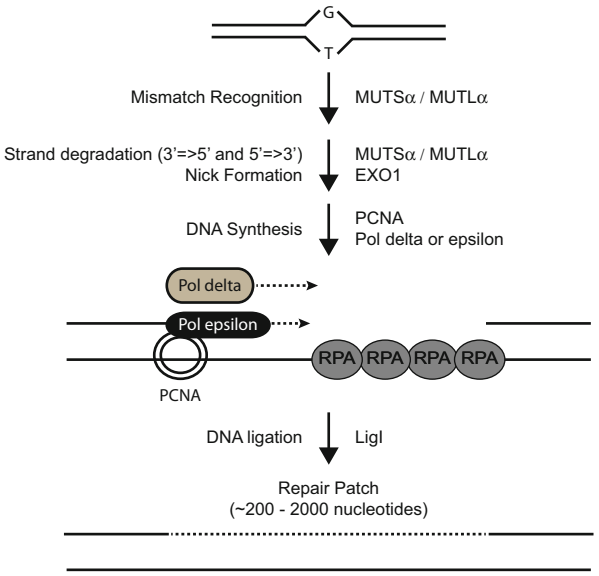

Fig. 3.6 DNA synthesis in human MMR. Schematic depicting a role for Polδ and Polε in the DNA synthesis step of MMR, resulting in a DNA repair patch ranging from 200 to 2,000 bases

3.6.2 Replicative Polymerases Delta and Epsilon in Eukaryotic MMR

Functional (in vivo) studies of eukaryotic MMR and the DNA polymerase requirements for MMR have been limited to *S. cerevisiae* or mouse model systems. As might be expected from the reconstituted system, both replicative polymerases (Polδ and Polε) likely play a role in MMR DNA synthesis. In this model system it is suggested that Polδ, together with Polα, uses the lagging strand as the template for DNA replication whereas Polε uses the leading strand as template (Larrea et al. 2010; Nick McElhinny et al. 2008). It is not yet established if the polymerase used in MMR is also strand specific. Although leading strand (Polε) and lagging strand (Polδ and Polα) fidelity differs, evidence is clear that MMR balances fidelity across both DNA strands (Lujan et al. 2012).

3.7 DNA Polymerase Involved in DNA Cross-link Repair

Characterizing the mechanism or mechanisms that mediate the repair of DNA interstrand cross-links (ICLs) has been a significantly challenging task, complicating the identification of DNA polymerases that may be involved in the repair process. Models have been proposed that depend on replication (Raschle et al. 2008) as well as those that are replication independent (Williams et al. 2012) and involve NER-related transcription-coupled repair or global genome repair and both models (replication dependent and replication independent) involve DNA

translesion synthesis (Enoiu et al. 2012). It is generally accepted that complete repair of an ICL involves proteins from several pathways, including the FANC proteins for ICL recognition and signaling (Kim and D'Andrea 2012), HR and NER proteins for lesion processing (Hinz 2010; Wood 2010), as well as TLS polymerases to synthesize DNA across from the unhooked lesion (Enoiu et al. 2012; Ho et al. 2011; Ho and Scharer 2010; Klug et al. 2012; McHugh and Sarkar 2006; Nojima et al. 2005; Sharma and Canman 2012; Shen et al. 2006). One plausible model for the repair of ICLs is shown in Fig. 3.7. In this model, repair can be achieved by a replication-dependent (right panel) or replication-independent (left panel) process. In the left panel, the replication-independent process utilizes NER proteins to "unhook" the cross-link followed by a translesion DNA polymerase to synthesize DNA across the "lesion." This is followed by a second round of NER-mediated repair and DNA synthesis. The NER proteins involved in ICL repair may vary with the lesion. It was recently reported that cisplatin lesions are repaired in a replication-independent fashion utilizing TCR–NER proteins (Enoiu et al. 2012) whereas MMC and psoralen cross-links are suggested to utilize GGR–NER proteins for ICL repair (Hlavin et al. 2010; Wang et al. 2001; Muniandy et al. 2009). In some cases, BER proteins appear to play a role in ICL repair (Kothandapani et al. 2011; Kothandapani and Patrick 2013). The replication-dependent process utilizes FANC proteins to recognize the ICL and mediate unhooking and induce ICL-associated DSBs, in preparation for HR-mediated repair. Both processes rely heavily on translesion DNA polymerases to synthesize DNA opposite the "unhooked" DNA cross-link (Lange et al. 2011; Sharma and Canman 2012). A separate chapter in this series will discuss translesion DNA polymerases (Chap. 4).

3.8 Summary and Concluding Remarks

There are as many as 15 human DNA polymerases to facilitate DNA replication, DNA repair, and DNA lesion bypass (tolerance) in the nucleus and mitochondrial genomes (Burgers et al. 2001; Bebenek and Kunkel 2004). These are characterized by family or class based upon phylogenetic relationships, as described by Burgers et al. (2001). In most cases, the role of some human DNA polymerases in specific DNA repair pathways is expected, based either on data from *E. coli* or *S. cerevisiae* or on biochemical parameters. The high-processivity, high-fidelity replicative DNA polymerases (Polδ and Polε) are a likely option for synthesis of the longer repair patches needed for NER, MMR, and even long-patch BER, whereas the biochemical parameters of the X-family polymerases suggest they are well suited for DNA synthesis required for the short-patch or minimal DNA synthesis observed in BER and NHEJ. Yet, as the field advances, surprises still abound. For example, the Y-family human DNA polymerase Polκ participates in NER and human Polη but not Polδ or Polι is involved in HR-mediated DNA synthesis from the D-loop

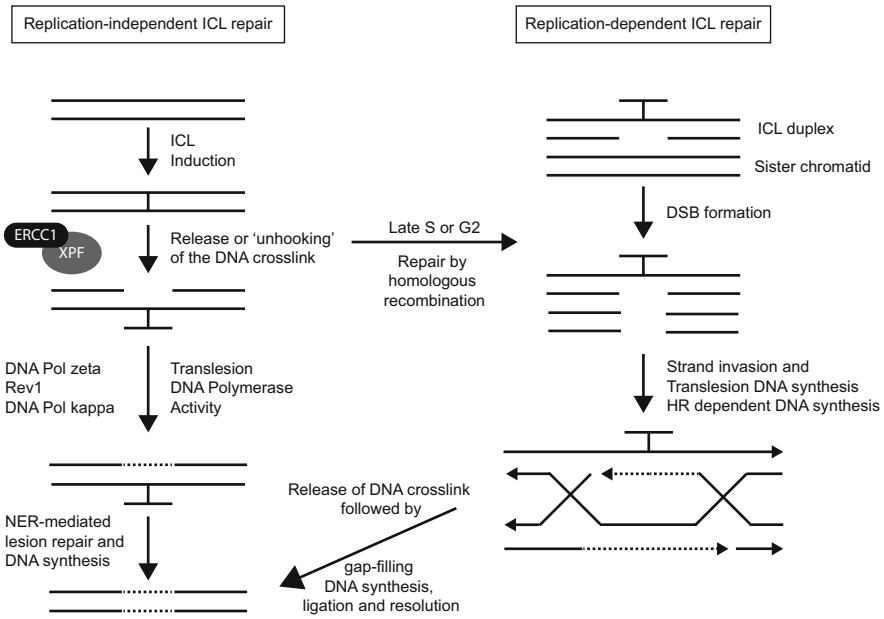

Fig. 3.7 Proposed mechanisms for repair of DNA cross-links. Schematic depicting a current model for the repair of DNA cross-links for cells in the G0/G1 phase of the cell cycle (*left*). Here, repair is mediated by a replication-independent mechanism. Following release or "unhooking" of the lesion (ICL), translesion DNA polymerases can fill the gap across from the lesion, followed by a second lesion removal step and DNA synthesis as in classical NER. On the *right* is a scheme for replication-dependent ICL repair. Here, the repair of DNA cross-links for cells in the late S-phase or G2 phase of the cell cycle would have the availability of the HR pathway to encode the information opposite the unhooked cross-link followed by a second round of DNA synthesis once the lesion (an unhooked cross-link) is removed

intermediate nor involved in second-end capture and the subsequent DNA synthesis step.

Considerable effort is still required to identify and characterize the DNA polymerases involved in many aspects of DNA repair and DNA metabolism. Mutations or defects in DNA polymerases affect response to DNA damaging agents (Sobol et al. 1996, 2000; Trivedi et al. 2005), antibody diversity (Seki et al. 2005), organism survival (Friedberg and Meira 2006), and overall genome maintenance (Prindle and Loeb 2012). The interrelationship between DNA synthesis fidelity and DNA repair is most evident by the cancer predisposition observed when replicative DNA polymerases are mutated in their proofreading domain (Palles et al. 2013). As more details emerge regarding the role of each DNA polymerase in DNA repair, it is expected that we will begin to understand the need for so many different DNA polymerases to maintain genome integrity as well as the multiple roles they may play in the diverse yet interrelated pathways for DNA repair.

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