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Cellular Roles of DNA Polymerase Beta

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Since its discovery and purification in 1971, DNA polymerase ß (Pol ß†) is one of the most well-studied DNA polymerases. Pol ß is a key enzyme in the base excision repair (BER) pathway that functions in gap filling DNA synthesis subsequent to the excision of damaged DNA bases. A major focus of our studies is on the cellular roles of Pol ß. We have shown that germline and tumor-associated variants of Pol ß catalyze aberrant BER that leads to genomic instability and cellular transformation. Our studies suggest that Pol ß is critical for the maintenance of genomic stability and that it is a tumor suppressor. We have also shown that Pol ß functions during Prophase I of meiosis. Pol ß localizes to the synaptonemal complex and is critical for removal of the Spo11 complex from the 5' ends of double-strand breaks. Studies with Pol ß mutant mice are currently being undertaken to more clearly understand the function of Pol ß during meiosis. In this review, we will highlight our contributions from our studies of Pol ß germline and cancer-associated variants.

INTRODUCTION

DNA polymerase beta (Pol ß) was originally purified from rabbit bone marrow by Chang and Bollum and characterized as a low molecular weight DNA polymerase [1]. Several years later, Abbotts and Wilson subcloned the cDNA of both human and rat Pol ß and successfully expressed this protein in *Escherichia coli* [2], permitting large quantities of active enzyme to be purified and studied.

Pol ß is a 39 kDa protein with DNA polymerase and deoxyribose phosphatase (dRP lyase) activities [2-4]. It belongs to the X family of DNA polymerases. DNA polymerase β is expressed in all stages of the cell cycle and in all of the analyzed tissues [5,6]. Since the time of its cloning and purification, Pol ß has become one of the

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†Abbreviations: BER, base excision repair; Pol ß, DNA polymerase beta; dRP lyase, deoxyribose phosphatase; dRP, 5'deoxyribose phosphate; MEFs, mouse embryo fibroblasts; JS, Joann Sweasy; MMS, methyl methanesulfonate; MNU, *N*-methyl-*N*-nitrosourea.

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most highly studied DNA polymerases. In this overview, we will discuss our contributions to elucidating the mechanism of DNA synthesis of Pol ß with particular regard to variants of this enzyme identified in the germlines of humans in tumors.

Joann Sweasy (JS) performed her graduate work with Evelyn Witkin on the roles of *E. coli* recA mutants in SOS mutagenesis and the restart of DNA synthesis cultivated an interest in the study of DNA polymerases [7-9]. This led her to join Lawrence Loeb's laboratory, where she began research on Pol ß. To understand the mechanisms of substrate choice by Pol ß, JS set out to characterize mutator variants of Pol ß. Identification of mutator variants in human or mouse cells would be difficult, so, drawing upon her previous experience as a graduate student, she decided to develop a complementation system in *E. coli*, and, using the Pol ß cDNA clone generously given to the laboratory by Dr. Samuel Wilson, showed that rat Pol ß could substitute for *E. coli* Pol I in the joining of Okazaki fragments during DNA replication [10]. This permitted JS to use *E. coli* mutation reporters to identify Pol ß mutator mutants [11]. JS carried a box full of Pol ß mutator variants [12] with her to her new faculty position in the Department of Therapeutic Radiology at Yale School of Medicine, a department with an incredible history of research in DNA repair that she was very enthusiastic to join. Since that time, JS's laboratory has characterized many of these mutator variants of Pol ß, showing how amino acid residues of Pol ß distant from the active site are critical for accurate DNA synthesis. In addition to this work, JS became interested in understanding the cellular roles of Pol ß and initiated work in this area using polymorphic and cancer-associated variants of Pol ß, and this is the focus of this overview.

POL ß AND BASE EXCISION REPAIR

Pol ß functions in base excision repair (BER), a major genome maintenance pathway in mammalian cells that is responsible for removal and repair of at least 20,000 DNA lesions per cell per day [13]. The simplest and most common form of BER is short patch BER, which can be initiated by one of several different DNA glycosylases, each having preferences for specific types of lesions [14]. Monofunctional DNA glycosylases recognize DNA lesions and catalyze the hydrolysis of the N-glycosylic bond to generate an abasic site. The abasic site is nicked at its 5' side by the APE1 endonuclease, leaving a 3'OH and a 5'deoxyribose phosphate (dRP). Pol ß fills in the single nucleotide gap and catalyzes removal of the dRP group. Bifunctional glycosylases, which usually recognize oxidative lesions, generate an abasic site and then catalyze its removal via ß-elimination to generate a 3'dRP and 5'phosphate. APE1 then removes the 3'dRP, leaving a 3'OH, to which Pol ß can bind and fill in the resulting single nucleotide gap. In both cases, the XRCC1/Ligase IIIα or XRCC1/Ligase I complex catalyzes ligation of the resulting ends. An alternative BER pathway that does not depend on APE1 is utilized when the NEIL glycosylases initiate repair [15]. NEIL 1, 2, and perhaps 3 catalyze excision of the damaged base via ß,δ elimination, leaving a 3'phosphate and a 5'phosphate. The 3'phosphate is removed by polynucleotide kinase, leaving a gap that is most often filled by Pol ß, followed by ligation. Therefore, Pol ß is required for all forms of BER.

GERMLINE VARIANTS OF POL ß

Five hundred sixty-seven SNPs have been identified in the 33 Mb POLB gene, of which only 22 are found within the coding region [16,17]. Two missense germline variants of Pol β have been identified in the human population. These are R137Q (rs12678588) and P242R (rs3136797), which have been reported to be present in 0.6 percent and 2.4 percent, respectively, of the human population [18]. The P242R variant was specifically identified in Keralites and Europeans. The R137Q Pol ß variant has reduced polymerase activity and an impaired interaction with PCNA. When expressed in

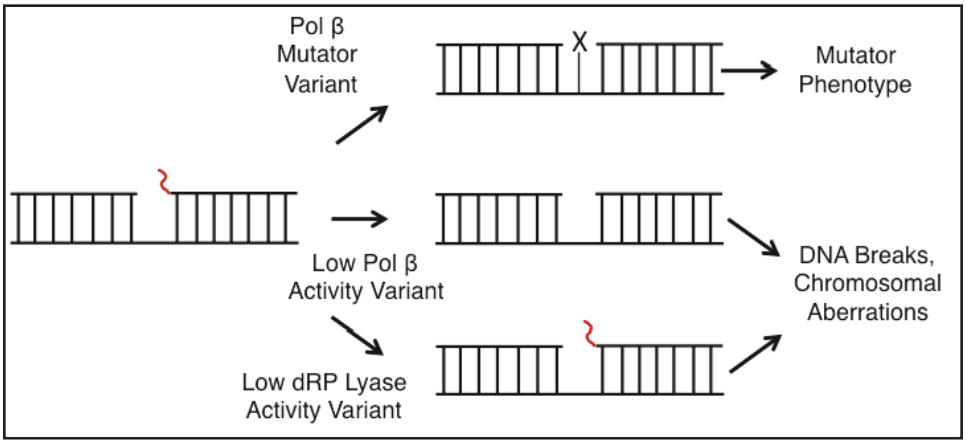

Figure 1. Mechanisms of genomic instability generated by Pol ß variant proteins. The DNA substrate for Pol ß is usually a single nucleotide gap with a 5'dRP group (red) that is generated upon excision of a damaged base. A mutator variant of Pol ß will remove the dRp group using its dRp lyase activity and fill in the gap in an error-prone manner, inducing mutations (denoted by X). A Pol ß variant with slow polymerase activity (low activity variant) will remove the dRp group, but not fill in all gaps in the cell, leading to the accumulation of BER intermediates and eventually to genomic instability. Failure to remove the dRp group by a Pol ß variant with slow dRp lyase activity will also result in the accumulation of BER intermediates and genomic instability.

Pol β-deficient MEFs, R137Q confers sensitivity to the DNA damaging agents methyl methanesulfonate (MMS) and *N*-methyl-*N*-nitrosourea (MNU) [19]. Pol β P242R also catalyzes DNA synthesis with a reduced rate [20]. In human mammary epithelial cells, P242R Pol β induces chromosomal aberrations and cellular transformation, suggesting a putative role for P242R Pol β as a cancer driver [20]. The mechanistic basis underlying the generation of chromosomal aberrations is the slow BER gap filling catalyzed by P242R. Unfilled gaps in the proximity of the replication fork lead to the induction of double-strand breaks and can result in chromosomal aberrations, as shown in Figure 1. The studies on Pol β R137Q and P242R suggest that individuals with these variants have an increased risk of developing cancer. This hypothesis is currently being tested using mouse models.

TUMOR-ASSOCIATED POL ß VARIANTS

Small-scale sequencing studies have revealed that *POL B* is mutated in 30 percent to 40 percent of human tumors, including colon, gastric, and prostate carcinomas [21,22]. Interestingly, the resulting amino acid alterations are not localized to one particular domain of Pol β but are widespread across the protein [22].

Colon Tumor-Associated Pol ß Variants

The K289M Pol ß variant was identified in a colon carcinoma [23]. We showed that K289M is a sequence context-dependent mutator in mouse cells and that it induced mutations at a 16-fold greater frequency within a sequence nearly identical to a highly mutated sequence in the APC gene, the mutation of which results in colon cancer [24]. Work from our laboratory also demonstrated that expression of K289M in immortal but non-transformed mouse cells induces cellular transformation through a mutational process as shown in Figure 1 [25].

Given this result, our laboratory sequenced the exons 5' and 3' UTRs of the *POL B* gene from colon tumors and found that 40 percent of these tumors carried a mutation in the coding region of *POL B* that was not found in normal tissue [22]. A subset of these variants that were predicted by mathematical algorithms to be damaging exhibited reduced DNA polymerase activity.

We showed that two of these variants, G231D and E295K, which was also identified in a gastric carcinoma [26], induce chromosomal aberrations and cellular transformation [27,28]. The G231D variant has a low affinity for the incoming nucleotide due to a disordered active site once bound to DNA [27]. E295K appears to lack DNA polymerase activity as a result of its inability to assume an active polymerase conformation [28,29]. During BER, neither of these variants fills single nucleotide gaps in an efficient manner, leading to the accumulation of BER intermediates and resulting in an increase in double-strand breaks and genomic instability (Figure 1). The E288K variant was also identified in a colon carcinoma [22]. Interestingly, this variant is a sequence context-dependent mutator and prefers to misincorporate nucleotides opposite template A, which could result in a mutator phenotype in human cells [30].

Gastric Carcinoma-Associated Pol ß Variants

In addition to E295K, Pol β L22P, Y265C, and D160N were identified in human gastric carcinomas [26]. L22P has low affinity for DNA and very low dRP lyase activity [31]. The expression of L22P in Pol β deficient mouse embryo fibroblasts (MEFs) results in sensitivity to MMS and cellular transformation in immortalized mouse cells, likely as a result of the accumulation of BER intermediates [31]. Y265C catalyzes DNA synthesis at a significantly slower rate than WT Pol ß and is also a mutator polymerase [11,32,33]. In mouse LN12 cells, expression of Y265C leads to an 8-fold increase in mutation frequency, and the types of mutations induced include point mutations and small deletions [32]. Y265C has normal dRP lyase activity [34]. We recently constructed the Y265C Pol β knock-in mouse model [34]. The homozygous mutant animals are born at the expected Mendelian ratio; however, they are small and 60 percent die within a few hours post birth. The *POL B* $^{Y265c/c}$ E11 and E14 embryos and newborn mice are 33 percent smaller ($p < 0.0001$) than their wild-type and heterozygous littermates [34]. We showed that MEFs isolated from these mice exhibit slow proliferation. Significantly higher levels of apoptosis were observed in the *POL B* $^{Y265c/c}$ MEFs versus MEFs from wild-type mice. In combination, these results indicate that both slow proliferation and increased cell death contribute to the small size of the c/c mice [34]. We showed that BER intermediate substrates accumulate in the *POL B* $^{Y265c/c}$ MEFs in the form of unfilled gaps and that these substrates resulted in increased levels of chromosomal aberrations. The D160N variant, also identified in a gastric carcinoma, induces complex tandem mutations that appear to be template-dependent [35]. We suggest that the active site of this variant exists in a conformation that can accommodate movement of the DNA substrate, permitting complex mutations to be generated.

Prostate Cancer-Associated Pol ß Variant

The I260M prostate cancer-associated variant is a sequence context-dependent base substitution mutator [36] that also induces insertions of dinucleotide repeats within runs of the same types of repeats. Expression of I260M in immortal but non-transformed mouse epithelial cells results in cellular transformation by a mutational mechanism [25] (Figure 1, mutator phenotype).

In summary, Pol ß variants have the potential to drive cancer by induction of a mutator phenotype or genomic instability, as shown in Figure 1. Our results suggest that during the gap filling step of BER, which occurs at least 20,000 times per cell per day, some of the Pol ß variants, including I260M, insert the incorrect nucleotide, eventually resulting in a mutation. Should the mutation occur within key growth control genes, it could lead to cancer. For example, we showed that expression of I260M in mouse epithelial cells led to mutation of PPARγ, resulting in global alterations in gene expression [37]. Interestingly, PPARγ. has been suggested to function as a tumor suppressor. In contrast, many of the Pol ß variants fill single nucleotide gaps less efficiently than WT Pol ß, leading to accumulation of BER

intermediates that result in chromosomal aberrations and cellular transformation. BER is a highly coordinated process, and our results suggest that imbalances in this repair pathway have the potential to lead to cancer. In combination, our results suggest that Pol β is critical for the repair of endogenous DNA damage and the maintenance of genomic stability.

ROLE OF DNA POLYMERASE β IN MEIOSIS

Meiosis involves a highly orchestrated process of cell division wherein diploid cells undergo two successive divisions to produce four haploid germ cells. Meiotic recombination involves physical interaction between homologous chromosomes, which form chiasmata and lead to crossover products [38]. The meiotic recombination pathway is induced by formation of DNA double strand breaks (DSBs) by the meiosis-specific Spo11 complex, a relative of archeal topoisomerase VI [39], during the leptotene substage of Prophase I [40]. DSBs are marked by formation of γH2AX foci, a phosphorylated version of H2A. DSBs are repaired through the pachytene substage of Prophase I in processes resulting in crossover and non-crossover products [39]. Synapsis occurs between chromosomes and genetic exchange is facilitated by synaptonemal complex (SC) formation. Upon introduction of DSBs, Rad51, a RecA homolog in eukaryotes promotes homology search and DNA strand invasion. Dmc1, a meiosis-specific protein, also promotes homology-directed DNA strand exchange that leads to crossover products. The homologs synapse in the zygotene substage of Prophase I [41]. During the diplotene substage, the homologs desynapse and crossovers are formed which are an essential outcome of meiotic recombination [41]. The crossovers are observed as chiasmata [42,43]. The enzymes involved in the catalysis of DNA synthesis during meiosis are not well characterized.

DNA polymerases are known to function in DNA replication, repair, and recombination. Interestingly, expression of DNA Pol β is highest in mouse testis, suggesting that it may have a role in meiosis [44]. Recently it has also been shown that overexpression of Pol β stimulates Rad51-dependent homologous recombination in mammalian cells [45].

We initiated our studies of Pol ß in meiosis in collaboration with Terry Ashley and attempted to localize Pol ß to the SC. We showed that Pol ß foci were present on the SC during Prophase I of meiosis in a pattern consistent with the idea that this enzyme functions in DSB repair during this process [44]. Deletion of the *POL B* gene in mice leads to lethality, thus to characterize the role of Pol β in meiosis, we employed the Cre-loxP gene targeting system to delete the *POL B* gene specifically in primordial germ cells. Synapsis is defective in spermatocytes and oocytes isolated from these mice. Importantly, Pol β-deficient spermatocytes have persistent Spo11-induced γH2AX DSBs and a significantly reduced level of Spo11-complex removal from the 5' end of the DSB. Thus Pol β has a very critical role in meiosis that is associated with the removal of the Spo 11 complex [41]. We suggest that Pol ß can act as a "landing platform" for other proteins that are required for Spo 11 removal. Alternatively, Pol ß could facilitate formation of a DNA structure, which is conducive to removal of Spo11. Additional experiments are being conducted to more clearly define the role of the Pol ß protein in Prophase I of meiosis.

CONCLUSIONS AND OUTLOOK

Experiments from our laboratory have shown that Pol ß functions in DNA repair and during Prophase I of meiosis. Pol ß functions to maintain genomic stability during DNA BER. Both germline and cancer-associated variants lead to aberrant DNA repair that is either error-prone or inefficient, resulting in the accumulation of BER intermediates. Therefore, Pol ß somatic and germline variants have the potential to be cancer drivers and to impact cancer therapy. We have also shown that Pol ß functions during Prophase I of meiosis, although its precise role during this process is not

known. This has led us to characterize meiosis in mice that express various Pol ß variants and these experiments are currently under way.

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