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POLD1: Central mediator of DNA replication and repair, and implication in cancer and other pathologies

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ABSTRACT

The evolutionarily conserved human polymerase delta (*POLD1*) gene encodes the large p125 subunit which provides the essential catalytic activities of polymerase δ (Polδ), mediated by 5′–3′ DNA polymerase and 3′–5′ exonuclease moieties. POLD1 associates with three smaller subunits (POLD2, POLD3, POLD4), which together with Replication Factor C and Proliferating Nuclear Cell Antigen constitute the polymerase holoenzyme. Polδ function is essential for replication, with a primary role as the replicase for the lagging strand. Polδ also has an important proofreading ability conferred by the exonuclease activity, which is critical for ensuring replicative fidelity, but also serves to repair DNA lesions arising as a result of exposure to mutagens. Polδ has been shown to be important for multiple forms of DNA repair, including nucleotide excision repair, double strand break repair, base excision repair, and mismatch repair. A growing number of studies in the past decade have linked germline and sporadic mutations in *POLD1* and the other subunits of Polδ with human pathologies. Mutations in Polδ in mice and humans lead to genomic instability, mutator phenotype and tumorigenesis. The advent of genome sequencing techniques has identified damaging mutations in the proofreading domain of *POLD1* as the underlying cause of some inherited cancers, and suggested that mutations in *POLD1* may influence therapeutic management. In addition, mutations in *POLD1* have been identified in the developmental disorders of mandibular hypoplasia, deafness, progeroid features and lipodystrophy and atypical Werner syndrome, while changes in expression or activity of POLD1 have been linked to senescence and aging. Intriguingly, some recent evidence suggests that POLD1 function may also be altered in diabetes. We provide an overview of critical Polδ activities in the context of these pathologic conditions.

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Contents

Abbreviations: ATR, Ataxia Telangiectasia and Rad3-related protein; AWS, atypical Werner syndrome; BER, base excision repair; BIR, break-induced recombination; bMMRD, biallelic mismatch repair deficiency; CIA, cytosolic iron–sulfur protein assembly; CRC, colorectal cancer; DSB, double strand break; EDMC, endometrial cancer; ISC, iron sulfur cluster; lncRNA, long non-coding RNA; LS, Lynch syndrome; MDPL, mandibular hypoplasia, deafness, progeroid features and lipodystrophy; miR, microRNA; MMEJ, microhomology-mediated end joining; MMR, mismatch repair; ncRNA, non-coding RNA; NER, nucleotide excision repair; NHEJ, nonhomologous end joining; NoDS, nucleolar detention sequence; OMIM, Online Mendelian Inheritance in Man; PCNA, proliferating cell nuclear antigen; PIP, PCNA-interacting protein; PKA, protein kinase A; Polα, polymerase alpha; POLD1, human polymerase delta subunit 1; Polδ, polymerase delta; Polε, polymerase epsilon; PRMT7, protein arginine methyltransferase 7; RFC, Replication Factor C; sLS, suspected cases of Lynch syndrome; Sp1, specificity protein 1; Sp3, specificity protein 3; SSB, single-strand break; TCGA, The Cancer Genome Atlas; TLS, translesion synthesis; WS, Werner syndrome.

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1. Introduction

Replication of DNA is a fundamental property of all living organisms, from single celled prokaryotes through metazoans. The core protein machinery that mediates replication of nuclear DNA in humans is evolutionarily ancient, with polymerases (pols) alpha (α), delta (δ), and epsilon (ε) conserved from humans through yeast (Pol1-3) (Makarova et al., 2014). Polα functions as a DNA primase, while Polε synthesizes the leading strand and most current studies indicate that Polδ predominantly synthesizes the lagging strand. Single-celled eukaryotes often undergo very rapid replication cycles, with complete cell doubling occurring within 90 min, and can exist in both haploid and diploid forms. These constraints mandate a replicative process of high integrity under tight time constraints, which is addressed in part by the presence of robust proofreading functions encoded within the δ and ε polymerases. In more complex multicellular organisms with long lifespans, the integration of replicative activity with these proofreading functions is increasingly appreciated as essential for normal development, and as contributing to protection against disorders of aging.

Over the past decade, a growing body of information on the genomic and transcriptomic landscape of human diseases has implicated defects in the proofreading/exonuclease and DNA replicative function of δ and ε polymerases in developmental disorders and cancer; in response to therapeutics; and more speculatively, in the process of aging and metabolic disorders. In this review, we focus primarily on POLD1, the catalytic subunit of Polδ, based on a number of recent studies that have emphasized key roles for this protein in human disease. We first summarize the basic gene and protein structures, and biological activities of POLD1 in the context of the polymerase holoenzyme. We then discuss evidence indicating that germline lesions in *POLD1* are the etiologic basis of two genetic diseases: mandibular hypoplasia, deafness, progeroid features and lipodystrophy (MDPL) and a subtype of Werner syndrome not linked to the canonical WRN gene. We also discuss evidence linking defects in POLD1 to inherited risk for cancer, providing supporting evidence from mouse models and cell culture experiments. Finally, we discuss several studies that potentially link changes in POLD1 function to additional biological syndromes.

In the present review, the main emphasis is on the regulation of the *POLD1* gene, its protein product, and functions in relationship to defects that have been observed in patients. On other complementary aspects of the process of the replication, we direct the reader to recent reviews listed in Table 1.

2. POLD1 gene

The *POLD1* gene, also known as *CDC2*, *MDPL*, *POLD*, and *CRCS10*, is located on chromosome 19 (Chung et al., 1991) at q13.3–q13.4 (Kemper et al., 1992) and is approximately 34 kb long. The major transcript (NM_002691.3) has 27 exons, which translate into a 1107 amino acid protein called the p125 subunit or A unit of Polδ (Fig. 1A). A longer isoform with a 26 amino acid in-frame insertion after amino acid 592 (NP_001295561.1) is also reported in multiple databases, although at present no publication addresses the biological activity of this protein. A pseudogene (LOC100422453) is located on chromosome 6.

As is the case for many housekeeping genes, the *POLD1* promoter is GC rich and does not contain a TATA box (Chang et al., 1995). Transcription of *POLD1* is regulated during the cell cycle, with the highest level of expression observed in late G1/S phase when cellular DNA is replicated in preparation for mitosis. Fig. 1B summarizes elements of the promoter that have been studied. Several defined elements in the *POLD1* promoter connect expression of this gene to the activity of proteins that regulate the cell cycle. Two 11-bp direct repeats which can be bound by the transcription factors specificity protein 1 (Sp1) and specificity protein 3 (Sp3), and an E2F-like sequence also located immediately upstream of the major transcription site, are involved in the induction of POLD1 by serum stimulation (Zhao and Chang, 1997). An Sp1 site is located between the two halves of a p53 site. By competing for binding to these sequences p53 (encoded by the *TP53* tumor suppressor) represses Sp1-stimulated *POLD1* promoter activity (Li and Lee, 2001). Competitive displacement of Sp1 by p53 from *POLD1* promoter is proposed as the mechanism for the inhibition of POLD1 expression upon cadmium treatment (Antoniali et al., 2015).

A cell cycle element/cell cycle gene homology region (CDE/CHR), known to be important for transcription in G2/M (Muller et al., 2014), is located within 50 bp downstream of the start site (Song et al., 2009). Mutations in this element affect the regulation of the *POLD1* promoter by E2F1 and p21 (Song et al., 2009). A recent study by Fischer and colleagues confirmed earlier observations of p53 repression of *POLD1*,

Table 1
List of references for recent reviews on replication, to guide further study.

Topic	References
Replication initiation and nuclear organization	Marks et al. (2016)
Asymmetry of nuclear DNA replication—fidelity in replication of the leading and lagging strands	Lujan et al. (2016b)
Role of polymerase epsilon in DNA replication and genome stability	Henninger and Pursell (2014)
Quality of nucleotide pools and accuracy of DNA replication	Waisertreiger et al. (2012)
Regulation of deoxynucleotide metabolism in cancer	Kohnken et al. (2015)
Correction of the rare mismatches that escape proofreading by mismatch repair	Kunkel and Erie (2015)
Translesion synthesis and damage tolerance	Hedglin and Benkovic (2015); Jansen et al. (2015b)
Checkpoint signal at the replication block-Chk1 activation	Gonzalez Besteiro and Gottifredi (2015)
Oncogene-induced replication stress	Hills and Diffley (2014)
Replication stress response	Berti and Vindigni (2016); Munoz and Mendez (2016); Roos et al. (2016)
Transcription as a source of replication stress	Gaillard and Aguilera (2016)
Replication stress and cancer therapy	Kotsantis et al. (2015)
Ribonucleotide incorporation during DNA replication	Lujan et al. (2016b)
Ribonucleotide triggered DNA damage and cellular response to damage	Wallace and Williams (2014)
Long range coordination and regulation of replication and repair events by Fe–S clusters	Fuss et al. (2015)
Role of PCNA in DNA replication and repair	Park et al. (2015)

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