DNA Repair 12 (2013) 1–9

Contents lists available at SciVerse ScienceDirect

DNA Repair

journal homepage: www.elsevier.com/locate/dnarepair

Mini review

DNA polymerase POLQ and cellular defense against DNA damage

Matthew J. Yousefzadeh[a,b], Richard D. Wood[a,b,*]

[a] Department of Molecular Carcinogenesis, The University of Texas MD Anderson Cancer Center, P.O. Box 389, Smithville, TX 78957, USA
[b] The Graduate School of Biomedical Sciences at Houston, USA

ARTICLE INFO

Article history:
Received 12 October 2012
Accepted 15 October 2012
Available online 4 December 2012

Keywords:
DNA polymerase
POLQ
Translesion synthesis
Thymine glycol
Abasic site
Genomic instability
Ionizing radiation

ABSTRACT

In mammalian cells, POLQ (pol θ) is an unusual specialized DNA polymerase whose *in vivo* function is under active investigation. POLQ has been implicated by different experiments to play a role in resistance to ionizing radiation and defense against genomic instability, in base excision repair, and in immunological diversification. The protein is formed by an N-terminal helicase-like domain, a C-terminal DNA polymerase domain, and a large central domain that spans between the two. This arrangement is also found in the *Drosophila* Mus308 protein, which functions in resistance to DNA interstrand crosslinking agents. Homologs of *POLQ* and *Mus308* are found in multicellular eukaryotes, including plants, but a comparison of phenotypes suggests that not all of these genes are functional orthologs. Flies defective in *Mus308* are sensitive to DNA interstrand crosslinking agents, while mammalian cells defective in POLQ are primarily sensitive to DNA double-strand breaking agents. Cells from *Polq*$^{-/-}$ mice are hypersensitive to radiation and peripheral blood cells display increased spontaneous and ionizing radiation-induced levels of micronuclei (a hallmark of gross chromosomal aberrations), though mice apparently develop normally. Loss of POLQ in human and mouse cells causes sensitivity to ionizing radiation and other double strand breaking agents and increased DNA damage signaling. Retrospective studies of clinical samples show that higher levels of *POLQ* gene expression in breast and colorectal cancer are correlated with poorer outcomes for patients. A clear understanding of the mechanism of action and physiologic function of POLQ in the cell is likely to bear clinical relevance.

Contents

1. Introduction

The functions of the 15 known mammalian DNA polymerases are currently being explored [1,2]. DNA polymerases (pols) play pivotal roles not only in DNA replication (pols α, δ, ε), but also in base excision repair (pol β), mitochondrial replication and repair (pol γ), non-homologous end-joining and immunological diversity (pols λ, μ, and terminal-deoxynucleotidyl transferase), and DNA damage tolerance including translesion synthesis (η, κ, ζ, Rev1). Some DNA polymerases have roles in more than one pathway of DNA processing.

Identification of mammalian POLQ initially arose from interest in the Mus308 gene product of the fruit fly *Drosophila melanogaster*.

* Corresponding author.
E-mail address: rwood@mdanderson.org (R.D. Wood).

1568-7864/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.dnarep.2012.10.004

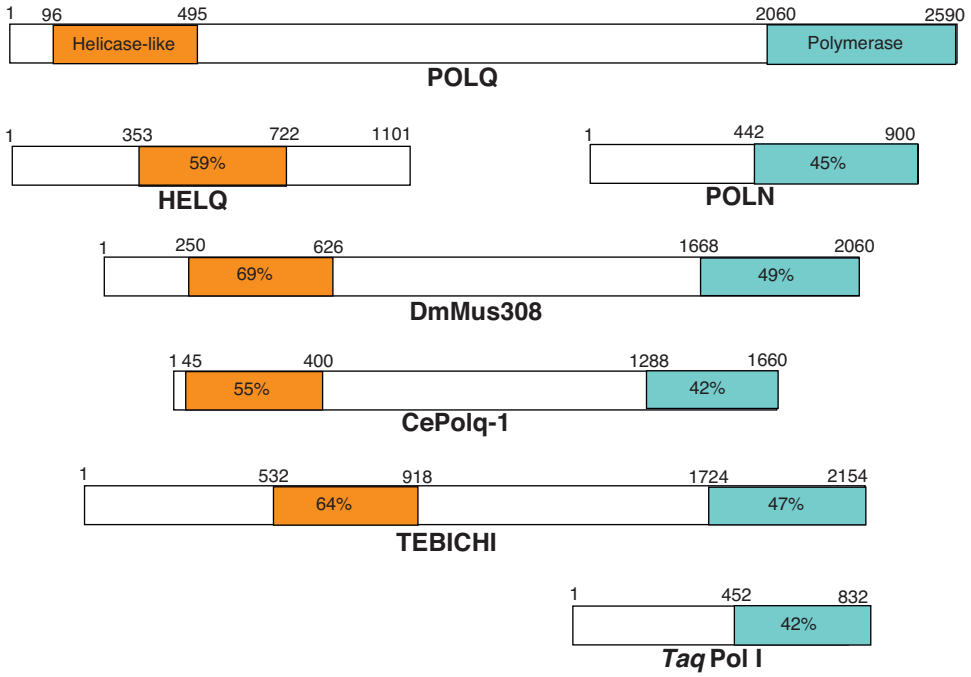

Fig. 1. Structural comparison and related grouping of *POLQ* gene family members. The orange and blue shaded regions are affiliated with the respective helicase and polymerase domains of the proteins. Numbers above the proteins indicate amino acid lengths. Percentages indicating the individual % similarity between the helicase-like and polymerase domains of human POLQ were generated in MacVector.

Mus308 mutants are hypersensitive to agents that cause DNA interstrand cross-links (ICL), with only modest sensitivity to monofunctional alkylating agents [3]. This suggested that Mus308 might play a specific role in repair of ICLs in DNA. Characterization of the *Mus308* gene showed that it encodes an unusual domain configuration, with the C-terminal part of the protein encoding a DNA polymerase, and the N-terminal part of the protein encoding a DNA helicase [4] (Fig. 1).

A cDNA encoding the DNA polymerase domain of a homologous enzyme, designated DNA polymerase θ (POLQ), was identified by Sharief et al. [5]. The predicted protein of 1762 amino acids did not include a helicase-like domain, and is now recognized to correspond to the C-terminal portion of full-length POLQ. Independently, Abbas and Linn assembled a larger 9.1 kb cDNA encoding both polymerase and helicase domains and predicted it to encode a protein of 2724 amino acids [6]. Seki et al. independently isolated the first complete and functional POLQ cDNA, showing that it encodes a 2590 amino acid protein with both a DNA polymerase and helicase-like domain [7]. An orthologous mouse POLQ of 2544 amino acids was predicted from the genomic sequence by Shima et al. [8].

The polymerase domains of POLQ and Mus308 belong to the "A" family of DNA polymerases, showing sequence similarity to *E. coli* DNA polymerase I [4,9]. As described in more detail below, however, the polymerase domain of POLQ contains three unique "insert" regions within the DNA polymerase sequence (Fig. 2A and B) which determine some of its biochemical properties [10]. While much is known about the enzymatic properties of POLQ *in vitro*, further study is needed to better determine its functions in cells. Here we review data on the roles of POLQ in the defense against DNA damage.

1.1. *POLQ* gene family distribution in nature

Genes with similarity to *POLQ* and *Mus308* are present in plants, protists, and multicellular eukaryotes (Fig. 1), but not in yeast or other fungi. It remains to be determined whether the POLQ-like genes are true orthologs, as it appears that there are functional differences between species. Mutations in the *polq-1* gene of *C. elegans* confer sensitivity to ICL-inducing agents [11]. TEBICHI, a POLQ-like protein found in *Arabidopsis*, is important for normal plant development and contributes to alleviating DNA replication stress and perhaps recombination. *Tebichi* mutant plants are sensitive to both the ICL-inducing agent mitomycin C (MMC) and to the monofunctional alkylating agent methyl methane sulfonate (MMS) [12,13].

As described below, there are apparent functional differences in POLQ/Mus308 related genes from different species. The availability of numerous high quality sequences allows comparison by primary alignment, revealing several evolutionary patterns in the POLQ family. The length of the central domain of POLQ is about 1500-1600 amino acids long in vertebrates, but comprises only about 800 residues in plant homologs and 800-1000 in invertebrate animals (Table 1A). Further, the positions of the polymerase domain "inserts" are conserved within the entire POLQ family, but the inserts are much shorter in the non-vertebrate family members (Table 1B). Expansion of the size of the central domain and the inserts apparently arose contemporaneously in a common vertebrate ancestor. The variations in the central domain and polymerase domain insert lengths may account for some of the differences in damage sensitivities associated with defects in POLQ family genes in different organisms (Table 1A and B, Fig. 2C).

Two other genes in multicellular eukaryotes show significant and intriguing relationships with POLQ. HELQ (formerly HEL308) is a DNA repair helicase with amino acid sequence similarity to the helicase-like domain of POLQ. HELQ homologs are found in both animals [14] and archaea [15] but not in fungi or bacteria. POLN is a 900 amino acid protein in human cells, harboring an A-family DNA polymerase domain related to that of Mus308 and POLQ [9,16,17]. In contrast with POLQ, the phylogenetic distribution of POLN appears to be limited to the deuterostome lineage of eukaryotes, including vertebrates. Phylogenetic analysis suggests that POLN and POLQ were divergent from one another before the onset of the vertebrate lineage (Fig. 2C).