SnapShot: DNA Polymerases II Mammals

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Cell

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Properties of DNA Template-Directed Mammalian DNA Polymerases

Polymerase	Family	Human Gene	Function	Additional Activities	Mutation Rate	Interactions[a]
α	B	*POLA*	Priming	RNA primase	10^{-4}–10^{-5}	SMC1A
β	X	*POLB*	Base excision repair	dRP/AP lyase/terminal transferase	10^{-4}–10^{-5}	TAF1D
γ	A	*POLG*	Mitochondrial maintenance	3′→5′ exonuclease/dRP lyase	10^{-5}–10^{-6}	POLG2, TWINKLE
δ	B	*POLD1*	Replicative polymerase; repair and mutagenesis	3′→5′ exonuclease	10^{-6}–10^{-7}	ABL1, FYN, GRB2, PCNA, POLD2, POLD4, PTP4A3, SRC
ε	B	*POLE1*	Replicative polymerase	3′→5′ exonuclease	10^{-6}–10^{-7}	TOPBP1/RAD17
ζ	B	*REV3L*	Translesion DNA synthesis and chromosome stability		10^{-4}–10^{-5}	MAD2L2, REV1
η	Y	*POLH*	Translesion DNA synthesis		10^{-2}–10^{-3}	PCNA, Ubiquitin, RAD6/18, POLI
θ	A	*POLQ*	Translesion DNA synthesis and chromosome stability	DNA-dependent ATPase/dRP lyase	10^{-2}–10^{-3}	
ι	Y	*POLI*	Translesion DNA synthesis	dRP lyase	10^{-1}	REV1, POLH, PCNA
κ	Y	*POLK*	Translesion DNA synthesis and nucleotide excision repair		10^{-2}–10^{-3}	PCNA, Ubiquitin, REV1
λ	X	*POLL*	Nonhomologous end joining and meiosis	dRP lyase	10^{-4}–10^{-5}	PCNA
μ	X	*POLM*	Nonhomologous end joining	Terminal transferase	10^{-4}–10^{-5}	
ν	A	*POLN*	Translesion DNA synthesis		10^{-3}	
REV1	Y	*REV1*	Translesion DNA synthesis	dCTP transferase		MAD2L2, POLH, POLI, POLK, REV3, Ubiquitin

[a]Interactions from http://www.uniprot.org.

Mammalian Polymerases with Putative Roles in Cancer

Direct Links

Polymerase	Cancer Type	Supporting Evidence
η	Various; Xeroderma pigmentosa variant	Xeroderma pigmentosa variant cells are POLH$^-$ resulting in a greater susceptibility to sunlight-induced carcinomas
κ	Lung	Overexpression attributed to genetic instability
β	Various	Overexpression in various tumor types/increased aneuploidy
θ	Various	Overexpression contributes to tumor progression
ι	Breast, Lung	Overexpression in human breast cancer lines; defective mouse allele results in susceptibility to urethane-induced lung tumors
ζ	Colon	REV3/REV7 expression levels linked to colon cancer
δ	Epithelial	Mouse POLD1 mutation (proofreading deficient) results in several tumor types

Indirect Links

Polymerase	Supporting Evidence
REV1	Colocalizes with FANCD2 in HeLa cells; mutagenesis requires Fanconi anemia core complex
λ	Nonhomologous end-joining defects linked to cancer

Polymerases with other Roles

η	Somatic hypermutation
ζ	Midgestation lethality in REV3L null mice; somatic hypermutation
λ	Mice knockout has immotile cilia syndrome
ι	Controversial role in somatic hypermutation and meiosis
θ	Putative role in somatic hypermutation
γ	Defects in POLG associated with progressive external ophthalmoplegia, Alpers syndrome, ataxia-neuropathy, Charcot-Marie-Tooth disease, idiopathic Parkinson's, and increased toxicity in response to nucleoside reverse transcriptase inhibitors. (For complete list, see: http://tools.niehs.nih.gov/polg/.)

See online version for legend and references.

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DNA polymerases ensure the faithful duplication of genetic information inside the nuclease and mitochondria of eukaryotic cells and the nucleoid of prokaryotic cells. These remarkable enzymes synthesize polynucleotide chains based on the complementarity of an incoming nucleotide to an existing DNA template. DNA polymerases are grouped into six families (A, B, C, D, X, and Y). The previous SnapShot (DNA Polymerases I Prokaryotes) described the structural and functional characteristics conserved across the families, using the DNA polymerases from the bacterium *Escherichia coli* as an example. In this SnapShot, we now highlight DNA polymerases from humans (*Homo sapiens*) and their relationship to human diseases. However, this list is certainly not exhaustive, and the number of putative links between DNA polymerases and diseases continues to grow.

Mammalian DNA Polymerases

Mammalian cells use 14 DNA polymerases from the A, B, X, and Y families to replicate a variety of DNA substrates. These include two polymerases (δ and ε) to replicate the genome; a primase (α) to generate short strands of RNA for the initiation of DNA replication; a mitochondrial polymerase (γ) to replicate the mitochondrial genome; and several other polymerases that are necessary during the repair of damaged DNA (β, λ, and μ) or replication past DNA lesions (θ, ζ, η, ι, κ, ν, and Rev1). Many of these polymerases possess additional enzymatic activities that enhance their ability to perform specialized functions. For example, the replicative polymerases (γ, δ, and ε) contain 3′ to 5′ exonuclease activity. In addition, many of the DNA repair polymerases (β, θ, ι, and λ) help to remove damaged nucleotides during base excision repair (BER) via abasic site lyase (AP lyase) and/or 5′ deoxyribose-5-phosphate lyase (dRP lyase) activities.

DNA Polymerases in Human Disease

Although the health and survival of the organism relies on the proper activity of each DNA polymerase, their specialized functions also come at a potential cost to the organism, including an increased susceptibility to cancer. For example, tumor formation has been associated with the inactivation or overexpression of the Y family of DNA polymerases, η and κ, respectively. These polymerases preferentially catalyze the duplication of damaged substrates, which the replicative polymerases (δ and ε) are unable to copy. To accomplish this task, the Y family polymerases contain an open, spacious active site that makes few contacts with template DNA and incoming nucleotides. This allows bulky DNA lesions to fit inside their active site, but it also results in lower fidelity (mutation rates $\sim 10^{-1}$–10^{-4}) compared to the replicative DNA polymerases δ and ε, which have compact active sites (mutation rates $\sim 10^{-6}$–10^{-7}). Therefore, the cell must tightly regulate the expression and activity of these low-fidelity polymerases (η, ζ, ι, θ, ν, and κ) to ensure that their beneficial activity is directed to the proper substrates during translesion synthesis, somatic hypermutation, and meiosis. Current research is aimed at deciphering the complex regulation of these polymerases, which appears to occur via modulation of protein levels, posttranslational modifications of the enzymes, and a variety of protein-protein interactions. Without these proper controls, cells are more susceptible to tumor formation.

Improper activity of high-fidelity polymerases, such as β and δ from the X and B families, can also result in an increased susceptibility to cancer. Moreover, other types of DNA polymerases are indirectly associated with tumor formation through their critical role in genome maintenance pathways. For example, the nonhomologous end-joining (NHEJ) pathway, which repairs double-stranded breaks in DNA, is associated with cancer, but the polymerases involved in these pathways, such as λ and μ, have not been directly linked. In general, the stability of an organism's genome requires a full complement of properly regulated DNA polymerases to avoid tumor formation.

In addition to preventing cancer, many other aspects of mammalian health depend on the proper function and regulation of DNA polymerases. For example, numerous disorders, such as progressive external ophthalmoplegia and idiopathic Parkinson's disease, result from the improper activity of the mitochondrial DNA polymerase γ. DNA polymerases also have potential links to embryonic development (ζ) and respiratory function (λ).

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