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Communication between DNA synthesis and proofreading in mitochondrial DNA polymerase

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Like all high-fidelity DNA polymerases, human mitochondrial DNA polymerase, Pol- γ contains polymerization (pol) activity for DNA synthesis and proofreading exonuclease (exo) activity for error correction. Pol- γ is a holoenzyme consists of a catalytic subunit Pol- γ A and accessory subunit Pol- γ B. Pol- γ A contains all enzymatic activity including pol, exo and deoxyribose phosphate (dRP) lyase, Pol- γ B contains no enzymatic activity of its own but regulates all Pol- γ A activates, consequently, the holoenzyme has higher processive and elevated dRP lyase activity. We determined crystal structures of Pol- γ ternary complex with primer/template DNA and an incoming nucleotide to understand how the two active sites communicate with each other. The ternary complex reveals a β -hairpin situated between the two active sites in Pol- γ A could transfer the information of nucleotide misincorporation in the pol site to the exo site 40Å away for excision. Our enzymatic studies indicate that Pol- γ variants in the β -hairpin completely abolish pol activity while retains full exo activity. Additionally, we performed molecular simulation and found the hairpin region are energetically destabilized with perturbation of Pol- γ variants in either pol or exo active sites, revealing for the first time that the two active sites are energetically coupled and DNA strand shuttling is accompanied by destabilization of the path connecting the pol and exo sites.

Biography

Whitney Yin is an Assistant Professor for University of Texas Medical Branch, USA. She has received Doctoral degree (PhD) in Department of Pharmacology and Toxicology. She is the Editorial Board Member of many peer reviewed journals and has many publications in national and international journals to her credit. She is committed to highest standards of excellence and it proves through her authorship of many books.

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