ROLLING WITH THE PUNCH: FUNCTION AND CONTROL OF TRANSLESION SYNTHESIS DNA POLYMERASES

Sharotka M. Simon[1], Francisco J. R. Sousa[2], Daniel F. Jarosz[1], Veronica Godoy[1], Lauren S. Waters[1], Ronaldo Mohana-Borges[2], G.C. Walker[1].

[1]Department of Biology, Massachusetts Institute of Technology, Cambridge, MA 02139. [2]Laboratório de Genômica Estrutural, Instituto de Biofísica Carlos Chagas Filho, Universidade Federal do Rio de Janeiro, 21941-590, Rio de Janeiro, RJ, Brazil

The importance of Family Y translesion DNA polymerases in helping organisms coping with damage to their DNA caused by endogenous and exogenous agents has only been appreciated relatively recently. *Escherichia coli* possesses two Family Y DNA polymerases, which are encoded by the SOS-regulated *umuDC* and *dinB* genes. The UmuD protein is similarly cleaved to LexA when it interacts with RecA/ssDNA nucleoprotein filaments to generate UmuD'. The cleaved form of the *umuD* gene product interacts with UmuC (DNA pol V), a DNA polymerase that is responsible for much of UV and chemical mutagenesis because of its ability to polymerize over a variety of lesions. The presumed biological function that has led to DinB being the most conserved subfamily of Family polymerases had not been obvious. Our observation that *dinB* mutants are sensitive to nitrofurazone led us to the discovery that *E. coli* DinB (DNA pol IV), as well as the mammalian ortholog (DNA pol kappa) are much better polymerases opposite N^2-furfuryl-dG than opposite ordinary dG. Our additional discovery that a single mutation can eliminate DinB's ability to carry out this type of translesion synthesis without affecting its ability to copy ordinary DNA suggests that the biological role of the DinB family is to carry out relatively accurate DNA synthesis over a common class of N2-dG adducts common to all three domains of life. Recent unexpected results have shown that, like UmuC, the functions of DinB are controlled by the products of the *umuD* and *recA* genes. UmuD and its cleavage product UmuD' undergo strikingly specific interactions with several proteins including UmuC, DinB, RecA, ClpX, and the catalytic, proofreading, and processivity subunits of the replicative DNA polymerase, DNA pol III. Our discovery that $UmuD_2$ and $UmuD'_2$ are members of the class of proteins referred to as intrinsically disordered is offering insights into how they may be able to coordinate DNA polymerase action by making these multiple highly specific contacts. The *Saccharomyces cerevisiae* Rev1 protein is a Family Y DNA polymerase that lies at the root of mutagenesis in eukaryotes, carrying out limited translesion synthesis itself, but more importantly, serving as a scaffold to recruit other translesion DNA polymerases. We have discovered that Rev1 levels vary strikingly during the cell cycle, being very low in G1, and then peaking at 50-fold higher levels during G2/M. Our studies lead us to suggest that most mutagenic translesion synthesis, which is carried out predominantly by Rev1 and Rev3/Rev7 (DNA pol zeta), takes place later in the cell cycle at single strand gaps that were left behind when replication forks encountered lesions.

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