

par **Sylvie Doublé**  
University of Vermont, Burlington, USA  
Microbiology and Molecular Genetics

## Human DNA polymerase theta (POLQ), double strand break repair and cancer

Human DNA polymerase  $\theta$  (pol  $\theta$ ) is a specialized DNA repair polymerase with homologs in all multicellular organisms. Pol  $\theta$  is a very large protein, which harbors superfamily 2 helicase (SF2) and family A DNA polymerase domains at the N and C-termini, respectively, linked by a large central domain of mostly unknown function. Pol  $\theta$  contributes to radiation resistance in human cells by participating in a Ku-independent DNA end-joining pathway. Higher pol  $\theta$  expression is associated with poor outcome in breast cancer patients. We crystallized an active protein construct comprising the entire C-terminal polymerase domain and its associated N-terminal exonuclease-like domain, in ternary complexes with ddATP opposite an abasic site analog, or with a normal G:C base pair. The overall fold of pol  $\theta$  is reminiscent of bacterial family A polymerases but adorned with 5 unique insertion loops – three in the polymerase domain as expected from sequence alignments and earlier work, and two in the inactivated exonuclease-like domain that could not be predicted based on sequence homology and were brought to light by the crystal structure. The structure further revealed that pol  $\theta$  utilizes an insertion loop located in a specialized thumb subdomain to grasp the primer 3'-end and thus provides a molecular basis for the unprecedented lesion bypass activities catalyzed by this enzyme.

Hôte : Wim Burmeister (IBS/VRM)