Effects of DNA polymerase eta regulation by post translational modifications on genome stability.

DNA replication is a highly processive and accurate process, but DNA damage is an extraordinary challenge and if left unrepaired can lead to increased mutagenesis, replication fork stalling and subsequent cell death. At the organism level these deficiencies can lead to cancerogenesis, neurodegeneration and immune defect. A tolerance mechanism called Post Replication Repair (PRR) can efficiently bypass unrepaired damage and allows completion of replication. The main interest of our research is a specialized DNA polymerase called pol eta that is a fundamental player in such DNA damage tolerance mechanism. A deficiency in pol eta is the cause of the genetic disease XPV. XPV patients present with abnormal pigmentation of the skin and are highly prone to sunlight-induced skin cancers, such as basal and squamous cell carcinomas and malignant melanomas. In particular we focus on the characterization on how pol eta is regulated by post-translational modifications (Ubiquitination, phosphorylation and SUMO), in the context of the cellular repair mechanisms and DNA damage checkpoints. We tackle these questions via a multidisciplinary approach ranging from cell biology to protein biochemistry in human cell lines. Work in the lab is aimed to provide insights into the way that polη assists in the maintenance of genome stability as a barrier for cancer development, potentially providing diagnostic biomarkers for atypical XPV diagnosis and, in the long-term, hopefully contribute to the design of rational cancer therapies.