Molecular Mechanisms of protein-DNA crosslink reversal

DNA strand breaks occur continuously as our cells duplicate their chromosomes, and as a consequence of oxidation or environmental exposure to chemical mutagens and DNA-damaging radiation. Inflammation, cellular respiration, routine DNA metabolism, and xenobiotics including pharmaceutical drugs all lead to the production of cytotoxic DNA strand breaks. Akin to splintered wood, DNA breaks are not "clean." Rather, DNA breaks typically lack DNA 5′-phosphate and/or 3′-hydroxyl moieties required for DNA synthesis and ligation. Failure to resolve damage at DNA ends can lead to abnormal DNA replication and repair, and is associated with genomic instability, mutagenesis, neurological disease, aging and carcinogenesis. A key class of adducted strand breaks are protein-DNA crosslinks linked to metabolic topoisomerase reactions. Eukaryotic Topoisomerase 2 (TOP2) enzymes are vital for life and facilitate key DNA transactions including DNA replication, transcription and recombination, but also pose unique threats to genomic integrity. Pre-existing DNA damage, environmental toxicants and chemotherapeutic drugs poison these enzymes, generating highly genotoxic 5′-TOP2 adducted DNA double strand breaks. This cellular Achilles heel underpins the potency of front-line TOP2-targeting chemotherapeutic agents, and unrepaired TOP2 lesions are linked neurological pathologies. Understanding how TOP2 protein-DNA adducts are resolved is critical not only for unveiling the molecular basis of TOP2-mediated genome organization and dynamics and its impact on neural development and function, but also for driving discovery of new chemotherapeutic approaches and understanding emerging mechanisms of chemotherapy resistance. We have been studying the cellular TOP2 DNA damage clearance apparatus. Our work establishes a novel paradigm for the direct resolution of TOP2-DNA protein crosslinks by the Tyrosyl-DNA phosphodiesterase complex, with implications for cancer therapy chemoresistance. Recent progress in this area will be discussed.