“DNA ligase complexes in replication and repair”

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Abstract: DNA joining events are required to complete DNA replication, genetic recombination and almost all DNA repair pathways. In human cells, there are three genes LIG1, LIG3, and LIG4, that encode DNA ligases. Each of the ATP-dependent DNA ligase polypeptides encoded by the human LIG genes share a related catalytic region that recognizes and encircles nicked DNA. A major goal of the Tomkinson laboratory has been to determine the cellular functions of these enzymes by complementary genetic and biochemical approaches. These studies have shown that specific protein-protein interactions involving regions adjacent to the catalytic region dictate the cellular functions of the DNA ligases.

Using the atomic resolution structure of human DNA ligase I complexed with nicked DNA, the Tomkinson laboratory identified small molecule inhibitors of human DNA ligases by molecular modelling followed by biochemical and cell-based screening. These inhibitors have been utilized as probes of DNA ligase function in normal and cancer cells, leading to the identification of an abnormality in the repair of DNA double strand breaks (DSB)s in cancer cell lines and samples from cancer patients. Recent studies in which the processing and joining of DNA strand breaks have been reconstituted and the multiprotein complexes formed by DNA ligases characterized by biophysical approaches will be described.

Bio: My research interests are focused on the molecular mechanisms of DNA replication, repair, and recombination pathways that maintain genome stability. There are two compelling reasons for studying these processes. Firstly, abnormalities in these processes result in genome instability that in turn leads to increased cancer formation. Secondly, because of the differences in these processes between normal and cancer cells, a better understanding of these processes and how they are altered in cancer cells will provide a framework for developing improved and novel cancer therapies. Finally, there is mounting evidence that abnormalities in DNA repair are a causative factor in neurodegeneration. As a postdoctoral fellow in the laboratories of Stuart Linn and Tomas Lindahl, I received training in the purification and characterization of proteins involved in DNA replication, repair, and recombination. Upon becoming an independent investigator, I expanded the range of experimental approaches to include molecular biology, gene cloning, yeast genetics, and structural biology. My lab has focused on delineating the cellular functions of eukaryotic DNA ligases that are key enzymes in DNA replication, repair, and recombination using a combination of in vitro and in vivo approaches. Specifically, we have identified DNA ligase–interacting proteins and characterized these interactions. These studies have been continuously funded by the National Institutes of Health (NIH) for more than 25 years. These studies have provided mechanistic insights into known and novel DNA repair pathways. As a participant in a multi-institutional NCI P01 program project focused on the structural biology of DNA repair for more than 15 years, I have greatly benefited from the collaborations fostered by this program. In collaborative work with Dr. Tom Ellenberger, we have determined the structure of human DNA ligases I and III complexed with nicked DNA. More recently, in collaboration with Drs. Yuan He and Susan Lees-Miller, we determined the structures of key protein complexes involved in the repair of DNA double strand breaks by non-homologous end joining by cryo-electron microscopy.