**Molecular mechanisms of alkylation- and platination-induced mutagenesis**

**Seongmin Lee**

The genomic DNA is persistently attacked by endogenous and exogenous alkylating agents (e.g., S-adenosyl methionine, cisplatin), which gives rise to a wide variety of alkylated DNA lesions such as N7-MeG, N3-MeA, O6-MeG, and cisplatin-GG intrastrand cross-links. These lesions, if not removed by DNA repair pathways, can be bypassed by error-prone translesion synthesis DNA polymerases, which could cause mutations and cancers. The structural basis for promutagenic replication past these lesions remains elusive. To elucidate the alkylation-induced mutagenesis mechanism, we conducted kinetic and structural studies of the bypass of these lesions by various human DNA polymerases. N7-MeG formed a Watson-Crick-like base pair, rather than a wobble base pair, with thymine, suggesting promutagenicity of N7-MeG. N3-MeA formed a Watson-Crick base pair with thymine but strongly deterred nucleotide incorporation opposite the lesion. O6-MeG formed a Watson-Crick-like base pair with thymine, which was consistent with the reported high mutagenicity and carcinogenicity of O6-MeG. Cisplatin-GG intrastrand cross-links engage in favorable interactions with adenine in non-instructional fashion, suggesting that the predominant cisplatin-induced G to T mutations may follow an ?A-rule?. Taken together, these studies revealed the features of promutagenic base pairings of N7-MeG, O6-MeG and cisplatin-GG cross-links, thereby providing new insights into the molecular mechanisms of alkylated-induced mutagenesis and carcinogenesis.