Chemical Biology of DNA Damages and Damage Tolerance Pathways

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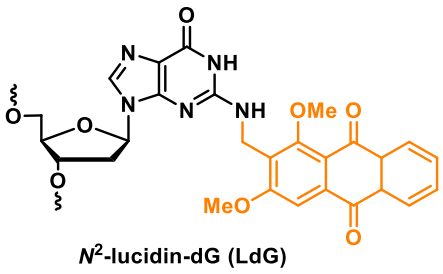
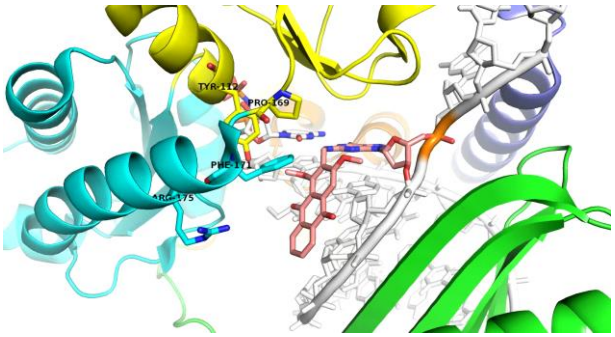
DNA is in continuous contact with damaging agents and their various reactive metabolites, which lead to the formation of covalent modifications (lesions or adducts). These adducts can stall the DNA synthesis by replicative polymerases, and if the common DNA repair pathways do not remove them, it can result in genomic instability, which generally leads to the death or oncogenic transformation of the cell. An important mechanism to overcome this problem is Translesion Synthesis (TLS), a bypass mechanism, which involves the tolerance of DNA damages with the help of TLS polymerases. To understand the structural and functional requirements of TLS polymerases, we have utilized a chemical biology approach. In this direction, we have developed robust protocols to synthesize the N^2-furfuryl dG (fdG) and N^2-lucidin (LdG) damaged DNAs. The fdG is a lethal DNA damage caused by furfuryl alcohol, a carcinogen, as well as a structural analog of the damage induced by the antibiotic nitrofurazone. Lucidin, a coloring agent, is a metabolite of a Lucidin-3-*O*-primeveroside, which is present in the roots of *Rubia tinctorum L* (madder root). Primer extension studies revealed that TLS polymerases such as Pol IV (*E. Coli*) and polκ (human) could bypass this adduct in an error-free manner with high efficiency. Crystal structures of these damaged DNAs in complex with Pol IV/pol κ and incoming dCTP reveal the formation of a hydrophobic pocket in the active site of the enzyme to accommodate these lesions, thereby facilitating TLS. These results have implications in understanding the origin of antibiotic resistance in bacteria and opens up avenues to develop new antibiotics/anticancer agents.



N^2-lucidin-dG (LdG)



Active site of pol polκ with LdG

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