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“DNA repair mechanisms involved in bacterial resistance to genotoxic natural products”

DNA is susceptible to alkylation from environmental toxins and endogenous metabolites, which create chemically diverse aberrant nucleotides that interfere with DNA replication and other nucleic acid processes. Consequently, DNA alkylation damage is a leading cause of genome instability and heritable disease, and is the basis for the use of alkylating agents in cancer chemotherapy. All organisms have multiple enzymatic pathways that function to repair these DNA lesions in order to maintain genome integrity and allow for faithful genome duplication. Over the past several years, two distinct families of unique DNA glycosylases have been identified in the biosynthetic gene clusters of bacterial secondary metabolites that form highly cytotoxic DNA adducts as a stress response. These enzymes provide self-resistance to the antibiotic producing organisms by repairing these lesions. I will discuss our work to understand the structures and chemical mechanisms of these newly discovered bacterial repair enzymes, which have the potential to enable discovery of new bioactive natural products.