Enzymatic Removal of Epigenetic Marks from DNA

Alexander C. Drohat[1], Lakshmi Swarna Pidugu[1], Joshua W. Flowers[2], Christopher T. Coey[1], Edwin Pozharski[1], and Marc M. Greenberg[2]

Department of Biochemistry and Molecular Biology,[1] University of Maryland School of Medicine, Baltimore, MD 21201, USA. Department of Chemistry,[2] Johns Hopkins University, Baltimore, MD 21218, USA.

5-methylcytosine (mC) is a prominent DNA modification that signals for transcriptional silencing, and this epigenetic mark is erased through a multi-step pathway involving TET (ten-eleven translocation) and base excision repair (BER) enzymes. Faithful regulation of cytosine methylation is essential for development, and aberrant methylation is implicated in cancer and other diseases. TET enzymes initiate the process of active DNA demethylation, by oxidizing mC to give three potential oxy-mC products, 5-hydroxymethylcytosine (hmC), 5-formylcytosine (fC) and 5-carboxylcytosine (caC). The latter two (fC, caC) are removed by thymine DNA glycosylase (TDG), and subsequent BER enzymes restore a cytosine base, thereby completing demethylation. Structural and biochemical studies illuminate how TDG recognizes and removes fC and caC from DNA. Together with previous findings, the results indicate that an adaptable active site allows TDG to remove a broad variety of nucleobases from DNA.