The TET-TDG Axis in Active DNA Demethylation

Abstract: Despite intense research efforts, the mechanisms of active DNA demethylation have remained a subject of speculation and controversy for decades. The recent discovery of enzymes capable of oxidizing 5-methylcytosine (5mC) in DNA, however, has provided a plausible concept for the biochemistry of such a processs. Today, it is generally accepted that TET catalyzed oxidation of 5mC coupled to TDG dependent base excision repair constitutes a major pathway of active DNA demethylation in cells. Yet, while the biochemistry of the process is well-established, its mode and purpose of action in living cells poses questions. The phenotypes observed upon TET and/or TDG inativation in mouse embryonic cells, for instance, implicate that the TET-TDG system operates in continuous cycles of methylation and demethylation at specific genomic loci determined by cell-type of differentiation state. This apparently futile mode of action suggests a biological function the this demethylation pathway beyond the simple replacement of a methylated with an unmethylated cytosine. I will present and discuss data implicating a role of DNA repair mediated DNA demethylation in the establishment of epigenetic plasticity.