TET Loss-of-Function in Malignant Hematopoiesis

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The methylation of cytosine followed by subsequent oxidation constitutes a fundamental epigenetic modification in mammalian genomes, and its abnormalities are intimately coupled to the onset and progression of cancer. Proteins of the TET family (TET1, TET2 and TET3) are dioxygenases that utilize -ketoglutarate, reduced iron and molecular oxygen to catalyze iterative oxidation of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) and subsequent oxidized products. Besides being transient intermediates in the reversal of cytosine methylation, these oxidized 5-methylcytosine derivatives represent stable epigenetic marks that fundamentally influence chromatin organization and gene expression. Of note, loss of TET function is commonly observed in a wide spectrum of cancers and often leads to marked disruption of DNA methylation and hydroxymethylation profiles in mammalian genome. Particularly, TET loss-of-function is strongly associated with hematologic malignancies of lymphoid and myeloid origin as well as diverse solid cancers and the molecular mechanism underlying oncogenesis driven by loss of TET function has been being unraveled. Here, I will introduce previous key observations on the role of TET proteins in normal and malignant hematopoietic development, with an emphasis on the pivotal functions of TET proteins in controlling genome-wide DNA methylation patterns, cell lineage commitment and genome integrity during hematopoiesis. Understanding the impact of TET dysregulation during oncogenesis may provide novel avenues to develop effective epigenetic therapy applicable to cancers.