Modulation of TET2 expression and 5-methylcytosine oxidation by the CXXC domain protein IDAX.

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Public Summary:
TET (ten-eleven-translocation) proteins are Fe(ii)- and α-ketoglutarate-dependent dioxygenases that modify the methylation status of DNA by successively oxidizing 5-methylcytosine to 5-hydroxymethylcytosine, 5-formylcytosine and 5-carboxycytosine, potential intermediates in the active erasure of DNA-methylation marks. Here we show that IDAX (also known as CXXC4), a reported inhibitor of Wnt signalling that has been implicated in malignant renal cell carcinoma and colonic villous adenoma, regulates TET2 protein expression. IDAX was originally encoded within an ancestral TET2 gene that underwent a chromosomal gene inversion during evolution, thus separating the TET2 CXXC domain from the catalytic domain. The IDAX CXXC domain binds DNA sequences containing unmethylated CpG dinucleotides, localizes to promoters and CpG islands in genomic DNA and interacts directly with the catalytic domain of TET2. Unexpectedly, IDAX expression results in caspase activation and TET2 protein downregulation, in a manner that depends on DNA binding through the IDAX CXXC domain, suggesting that IDAX recruits TET2 to DNA before degradation. IDAX depletion prevents TET2 downregulation in differentiating mouse embryonic stem cells, and short hairpin RNA against IDAX increases TET2 protein expression in the human monocytic cell line U937. Notably, we find that the expression and activity of TET3 is also regulated through its CXXC domain. Taken together, these results establish the separate and linked CXXC domains of TET2 and TET3, respectively, as previously unknown regulators of caspase activation and TET enzymatic activity.

Scientific Abstract:
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