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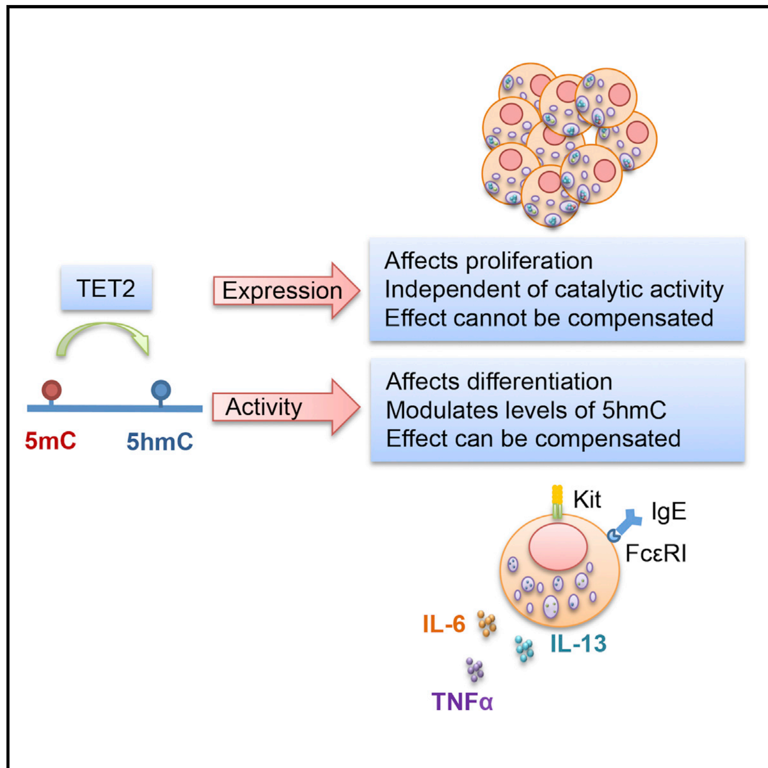
TET2 Regulates Mast Cell Differentiation and Proliferation through Catalytic and Non-catalytic Activities

Graphical Abstract



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In Brief

The impact of TET enzymes on gene expression and cell function is incompletely understood. Montagner et al. investigate the TET-mediated regulation of mast cell differentiation and function, uncover transcriptional pathways regulated by TET2, and identify both enzymatic activity-dependent and -independent functions of TET2.

Highlights

- TET2 regulates mast cell differentiation, cytokine production, and proliferation
- Lack of TET2 leads to extensive changes in transcriptome and 5hmC landscape
- Cell differentiation defects can be compensated for by other TETs
- Cell proliferation depends on TET2 expression, independent of its enzymatic activity

Accession Numbers

GSE77845

Montagner et al., 2016, Cell Reports *15*, 1566–1579
May 17, 2016 © 2016 The Author(s)
http://dx.doi.org/10.1016/j.celrep.2016.04.044

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TET2 Regulates Mast Cell Differentiation and Proliferation through Catalytic and Non-catalytic Activities

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http://dx.doi.org/10.1016/j.celrep.2016.04.044

SUMMARY

Dioxygenases of the TET family impact genome functions by converting 5-methylcytosine (5mC) in DNA to 5-hydroxymethylcytosine (5hmC). Here, we identified TET2 as a crucial regulator of mast cell differentiation and proliferation. In the absence of TET2, mast cells showed disrupted gene expression and altered genome-wide 5hmC deposition, especially at enhancers and in the proximity of downregulated genes. Impaired differentiation of *Tet2*-ablated cells could be relieved or further exacerbated by modulating the activity of other TET family members, and mechanistically it could be linked to the dysregulated expression of C/EBP family transcription factors. Conversely, the marked increase in proliferation induced by the loss of TET2 could be rescued exclusively by re-expression of wild-type or catalytically inactive TET2. Our data indicate that, in the absence of TET2, mast cell differentiation is under the control of compensatory mechanisms mediated by other TET family members, while proliferation is strictly dependent on TET2 expression.

INTRODUCTION

DNA methylation at promoters is traditionally considered a stable modification linked to gene silencing and with pivotal regulatory roles in mammalian development. The Ten-Eleven-Translocation (TET) 1–3 proteins are α-ketoglutarate and Fe^{2+}-dependent enzymes able to epigenetically alter DNA by oxidizing 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) and further oxidation products (Ito et al., 2011; Tahiliani et al., 2009). Oxidized cytosines serve as intermediates in the process of DNA demethylation, enabling the dynamic turnover of this modification. Moreover, due to the existence of 5mC- and 5hmC-selective or preferential binders, including a broad panel of adapters and chromatin regulators (Pastor et al., 2013), TET activity also directly controls the recruitment of proteins or complexes to methylated DNA.

Different TET family members can have unique and non-overlapping functions, as highlighted by the phenotypes displayed by TET-deficient animals. While the phenotype of mice lacking TET1 is quite mild, mice lacking TET2 display late-onset hematological abnormalities and lack of TET3 is embryonic lethal (reviewed in Pastor et al., 2013). In hematopoietic stem cells (HSCs), lack of TET2 leads to decreased global genomic levels of 5hmC, increased size of the progenitor pool, and enhanced multi-lineage repopulating ability, with a developmental skewing toward the monocyte/macrophage lineage (An et al., 2015; Ko et al., 2011, 2015). A division of labor between the different TET family members in controlling 5hmC distribution is suggested by the observation that, in mouse embryonic stem cells (mESCs), TET1 is primarily responsible for 5hmC modifications at the level of promoter regions and transcriptional start sites (TSSs), whereas TET2 mostly regulates levels of 5hmC at enhancers and in gene bodies (Hon et al., 2014; Huang et al., 2014; Williams et al., 2011). In addition, TET proteins can play unique roles partly due to their specific interactions with co-regulators, allowing them to modulate gene expression independently of DNA hydroxymethylation. For example, TET2 and TET3 interact with the enzyme *O*-linked β-*N*-acetylglucosamine (O-GlcNAc) transferase (OGT) to facilitate its activity (Chen et al., 2013; Deplus et al., 2013), and TET2 was shown to interact with HDAC2, thus modulating transcription of the *Il6* gene (Zhang et al., 2015). TET2 also can also contribute to gene silencing by facilitating the recruitment of the Polycomb Repressive Complex 2 to CpG dinucleotide-rich gene promoters (Wu et al., 2011). Conversely, TET1 (but not TET2) can be incorporated into the SIN3A co-repressor complex, resulting in transcriptional effects independent of 5hmC (Williams et al., 2011).

As an important link of these protein activities to disease, *TET2* frequently acquires loss-of-function mutations in different types of cancers, notably myeloid neoplasms (Ko et al., 2010), while *TET1* and *TET3* are rarely mutated in hematological malignancies (Abdel-Wahab et al., 2009; Huang and Rao, 2014). In

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