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TET2 is required to suppress mTORC1 signaling through urea cycle with therapeutic potential

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Abstract

Tumor development, involving both cell growth (mass accumulation) and cell proliferation, is a complex process governed by the interplay of multiple signaling pathways. TET2 mainly functions as a DNA dioxygenase, which modulates gene expression and biological functions via oxidation of 5mC in DNA, yet whether it plays a role in regulating cell growth remains unknown. Here we show that TET2 suppresses mTORC1 signaling, a major growth controller, to inhibit cell growth and promote autophagy. Mechanistically, TET2 functions as a 5mC "eraser" by mRNA oxidation, abolishes YBX1–HuR binding and promotes decay of urea cycle enzyme mRNAs, thus negatively regulating urea cycle and arginine production, which suppresses mTORC1 signaling. Therefore, TET2-deficient tumor cells are more sensitive to mTORC1 inhibition. Our results uncover a novel function for TET2 in suppressing mTORC1 signaling and inhibiting cell growth, linking TET2-mediated mRNA oxidation to cell metabolism and cell growth control. These findings demonstrate the potential of mTORC1 inhibition as a possible treatment for TET2-deficient tumors.

Introduction

The ten-eleven translocation enzyme TET2 is a DNA dioxygenase, which modulates gene expression by catalyzing the conversion of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC), then to 5-formylcytosine and 5-carboxylcytosine (5caC)[1,2]. 5caC is then demethylated to cytosine via the action of thymine DNA glycosylase[3,4]. Besides being an intermediate during demethylation, existing data indicate that 5hmC per se is an epigenetic mark critical for various biological and pathological processes[5,6] and can be utilized for assessing the efficacy of patients' response to anti-PD-1/PD-L1 immunotherapy[7]. Notably, 5hmC level is significantly reduced across different types of tumors and inversely correlates with tumor cell proliferation[8]. As an epigenetic modifier, TET2 has fundamental roles in cell fate determination[9,10], cell differentiation[11,12] and tumor development[13–19]. Moreover, TET2 is also involved in mRNA stability regulation via inducing its oxidation[20]. These findings suggest diverse functions of TET2 in physiological and pathological processes.

TET2 is a tumor suppressor and loss-of-function mutations of TET2 frequently happen in hematopoietic malignancy[12,21]. Interestingly, a subset of acute myeloid leukemia and glioma patients without TET2 mutations bear isocitrate dehydrogenases 1 and 2 (IDH1/2) mutations, which produce D-2-hydroxyglutarate to competitively inhibit TET2 activity[22,23]. In addition to mutations, TET2 activity is significantly suppressed in multiple tumors by different mechanisms[24–26]. Consistently, restoration of TET2 activity blocks aberrant self-renewal and leukemia progression, further supporting the vital role of TET2 in suppressing tumor development.

The mammalian target of rapamycin (mTOR) is an evolutionarily conserved serine/threonine protein kinase

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