Perspective

Ten-eleven translocation-2 affects the fate of cells and has therapeutic potential in digestive tumors

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Abstract

Ten-eleven translocation (TET) methylcytosine dioxygenases catalyze the oxidative reactions of 5-methylcytosine (5-mC) to 5-hydroxymethylcytosine (5-hmC), 5-formylcytosine (5-fC), and 5-carboxylcytosine (5-caC), which are intermediate steps during DNA demethylation. It is reported that somatic mutations of TET2 gene are identified in a variety of human tumors, especially in hematological malignancies. The tendency and mechanism of cellular differentiation in different systems are affected by TET2 via regulation of associated gene expression or maintenance of demethylated state. TET2 acts as a critical driver of tumorigenesis through the conversion of 5-mC to 5-hmC and successive oxidation products. Sometimes, it requires special interactions and cofactors. Here, we reviewed recent advances in understanding the function of TET2 proteins in regulating cell differentiation, and its role in various tumors focusing on several digestive cancers.

Introduction

During DNA methylation, direct methylation of cytosine in CG dinucleotides, which is one of epigenetic modifications is believed to be an irreversible epigenetic event related to gene repression and tumorigenesis.[1] Ten-eleven translocation (TET) protein family, comprising three members TET1, TET2, and TET3, provided a new perspective about active demethylation mechanism.[2,3] TETs catalyze the oxidation of 5-methylcytosine (5-mC) to 5-hydroxymethylcytosine (5-hmC), 5-formylcytosine (5-fC), and 5-carboxylcytosine (5-caC), and then complete demethylation process with thymine-DNA glycosylase (TDG)-mediated base excision repair mechanism.[4,5] In human mesenchymal stem cells, TET1 and TET2 demethylases epigenetically regulate insulin-like growth factor 2 mRNA binding protein 1 (IGF2BP1) hydroxymethylation status of its promoter and its expression.[6]

TET2 mutations have been reported to be frequently observed in various cancers, such as leucocythemia, including acute myelocytic leukemia (AML), chronic

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myelomonocytic leukemia (CMML), and myelodys-plastic syndrome (MDS).[7–10] TET2 mutations were frequently identified in other hematologic malignancies including angioimmunoblastic T-cell lymphoma and mature lymphoid neoplasms.[11,12] The TET2 functions in mutation-mediated activities are mediated by interactions of TET2 with O-linked N-acetylglucosamine (O-GlcNAc) transferase (Ogt),[13–15] Wilms Tumor 1 (WT1) protein,[16,17] and CXXC finger protein 4 (IDAX).[18] Furthermore, recent studies have demonstrated that TET2 significantly increases in diabetic wound and is associated with insulin sensitivity and pathogenesis of diabetic nephropathy.[19–21] Recent reports suggest that TET2 is the key factor of atherosclerosis, and is involved in regulating the transfer of smooth muscle cell phenotype, ameliorating vascular dysfunction, and inhibiting inflammation.[22] TET2 is involved in clonal hematopoiesis resulting in a marked increase in atherosclerotic plaque size in mice, correlating with the risk of atherosclerotic cardiovascular disease.[23] Another study demonstrated that TET2 played a critical role in immune regulation and DNA repair to promote tolerance or antitumor immunity and maintain genomic stability.[24]

This review summarizes the recent progress in understanding TET2 as an epigenetic regulator, emphasizing its roles in regulation of cellular differentiation and mediation in digestive tumors.

TETs are important molecules for epigenetic regulation

DNA methylation is a reversible epigenetic modification that is not associated with any change in DNA sequence but determines chromatin states. There are mainly two mechanisms of DNA demethylation, passive and active demethylation. One is lost during DNA replication due to the lack of a mechanism for maintenance of methylation modifications. The other is mediated by TET and TDG, in which the demethylase eliminates methylation modification of DNA.[25–30] TET proteins convert 5-mC to 5-hmC, leading to DNA demethylation, which was first reported in 2009.[5] Structural studies suggested that TET proteins contain several parts including a cysteine-rich domain, a conserved double-stranded β-helix (DSBH) domain, and binding sites for the cofactors Fe(II) and 2-oxoglutarate (2-OG), which form the catalytic region in the C terminus binding to cytosine in CpG context. Interestingly, only TET1 and TET3 have an N-terminal CXXC zinc finger domain that can bind DNA but not TET2.[18,31,32] The catalytic domains are the C-termini

with cysteine-rich domain and DSBH domain, catalyzing the oxidation of 5-mC to 5-hmC, and further oxidation of 5-hmC to 5-fC and 5-caC in DNA CpG dinucleotides.[4,33,34]

TET2 regulates cells differentiation and maintains immune homeostasis

T cells differentiation and stability are associated with DNA modification including methylation. It was demonstrated that the loss or mutations of TET2 could have an influence on the differentiation and fate of CD4+ T cell,[35–37] CD8+ T cell,[38] and invariant natural killer T (iNKT) cells.[39] TET2 catalyzes the oxidation of 5-mC to 5-hmC resulting in gene demethylation.[4,40] Treg cell-specific hypomethylation pattern established by TET2 for forkhead box P3 (FOXP3) expression is related to Treg cell differentiation, function, and autoimmune disease.[35] Impaired Treg cell differentiation, reduced FOXP3 expression, and inflammatory disease were found in TET2-knockout mice.[35,36] The loss of TET2 confers abnormal CD4+ T cell proliferation and differentiation.[37] TET2 are guardians of Treg cells stability, which maintains immune homeostasis. In an acute viral infection mice model, TET2 loss stimulated memory CD8+ T cell formation.[38] Moreover, abnormal development and proliferation of invariant natural killer T (iNKT) cells were examined in TET2-TET3 double-knockout mice. TET2 and TET3 regulated iNKT-cell-lineage specification showing a skewing towards NKT17-like phenotype.[39]

In the blood, TET2 regulates erythroid and granular monocyte differentiation of human hematopoietic progenitors and affects human erythropoiesis and terminal myeloid differentiation, with an effect on iron metabolism in erythroblasts.[41–44] In addition, there were some reports that TET2-mediated modification was associated with myoblast differentiation, initiation of adipogenic differentiation, retinal neurogenesis, and conversion of pre-B cells into macrophages.[45–48] For mast cell differentiation and proliferation, and cytokine expression, TET2 also acts as a crucial regulator by oxidizing 5-mC to 5-hmC and via further oxidation products.[49] TET2 is down-regulated in human embryonic stem cell (ESC) lines and up-regulated during hematopoietic differentiation, binding to NANOG promoter and leading to differentiation. Genome-wide analysis revealed an increase in 5-hmC in neuro-ectoderm genes in Sirt6 knockout embryonic stem cells. In TET1/TET2 double-knockdown of ESCs carrying Dox-inducible PRDM14 expression units, the

expression of Klf2 and Tcl1 decreased in the presence of leukemia inhibitory factor suggesting that TET1 and TET2 were important for the maintenance of ESC-pluripotency by PRDM14.[50−52]

The potential role of TET2 in digestive tumors

It was reported that the expression of TET2 was differently dysregulated across digestive tumors. TET2 expression was significantly up-regulated in gastric cancer, hepatocellular carcinoma, and tumor-infiltrating CD4+ T cells colorectal cancer compared to normal tissues, while it was down-regulated in esophageal squamous cell carcinoma.[53−56] There was also a report that TET2 was markedly down-regulated in gastric cancer tissues compared to normal gastric mucosa.[57]

In tumor-infiltrating CD4+ T cells of colorectal cancer patients, signal transducers and activators of transcription 5 (STAT5) and TET2 expression were significantly up-regulated, binding to the transcription factor FOXP3 Treg-specific demethylated region, which contributed to DNA demethylation and mRNA transcription suggesting that STAT5 and TET2 played important roles in the pathogenesis of colorectal cancer.[53] The expression of TET2 was significantly associated with 5-hmC levels in esophageal epithelial cells, subsequently leading to esophageal squamous cell carcinoma development. Notably, it had a key function in oxidation of 5-mC to 5-hmC in esophageal epithelial cells. However, TET2 was not associated with the prognosis of esophageal squamous cell carcinoma patient.[54] mRNA levels of TETs and not TET proteins or 5-hmC levels were significantly higher in gastric cancer than in the corresponding normal tissues In addition, mRNA levels were higher in higher-grade gastric cancers than in lower-grade gastric cancer samples. The increased transcripts were significantly involved in clinicopathological implication including tumor invasion depth, clinical stage, lymph node metastasis, as well as poor overall survival of patients. The knock-down of TET2 inhibited gastric cancer, hepatocellular carcinoma growth, and cell proliferation. TET2 mRNA might play an important oncogenic role independent of the protein in gastric cancer by sequestering the miR-26 resulting in Enhancer of Zeste Homolog 2 (EZH2) overexpression.[55,57] Besides, it was reported that TET2 mRNA levels were associated with cancer stage and prognosis in gastric cancer patients. In this study, worse survival was significantly associated with low level of the oncogenic long noncoding RNA (lncRNA-ANRIL), and TET2 knock-

down markedly up-regulated the expression of lncRNA-ANRIL, inhibitor of cyclin kinase 4a, inhibitor of cyclin kinase 4b, and alternative reading-frame. Therefore, in gastric cancer, lncRNA-ANRIL was correlated with TET2-mediated effects.[57] Subsequently, TET2 repressed E-cadherin expression by interacting with histone deacetylase 1 and reducing the levels of H3K9Ac and H4K16Ac, and attenuated β-catenin transactivation in hepatocellular carcinoma cells.[56]

In terms of potential therapeutic applications in digestive tumors, TET2 may act as a therapeutic target. Down-regulated TET2 may change the hypomethylation state of tumor-infiltrating CD4(+) T cells in colorectal cancer patients.[53] The loss of 5-hmC or TET2 might affect the development of esophageal squamous cell carcinoma and facilitate gastric carcinogenesis.[54,55] Knockdown of TET2 inhibited hepatocellular carcinoma growth *in vitro* and *in vivo*, as well as the invasive potential hepatocellular carcinoma cells.[56] In gastric cancer, TET2 played a tumor suppression role, by inhibiting proliferation and inducing apoptosis of gastric cancer cells. Overexpression of TET2 could restrict the development of cancer.[57] Regarding the role of TET2 in chemotherapy resistance, there has been crucial progress in colon cancer studies. For p53-null tumor cells, TET2 acted as a positive contributor to chemotherapy resistant properties, and the sensitivity of anti-cancer treatment increased after TET2 deletion.[58]

In summary, these findings indicate that the expression pattern and the effect on prognosis of TET2 are the potential mediation mechanisms in digestive tumors and may represent a novel therapeutic target (Table 1).

Frequent mutations of TET2 in other tumors

Mutations of TET2 gene were frequently identified in myeloid malignancies with a frequency of 20% in MDS, 45% in CMML, 20% in AML, and 20% in myeloproliferative neoplasm.[59−62] TET2 mutation showed adverse prognostic effect[63] and inferior overall survival[64,65] in AML patients. Mutated TET2 showed a higher response rate to azacitidine in MDS and low blast count AMLs.[66] TET2 mutations occurred in early disease evolution in MDS.[62,67,68] TET2 mutations were also found in T cell lymphomas[69,70] and diffuse large B-cell lymphoma.[71,72] Interestingly, there were other genes co-mutating with TET2, such as enhancer of zeste 2 polycomb repressive complex 2 (EZH2), additional sex combs like transcriptional regulator 1

Table 1
Role of ten-eleven translocation methylcytosine dioxygenase 2 in digestive tumors.

Cancers	TET2 Expression level	Related genes	Effect on survival or prognosis	Reference
Colorectal cancer	mRNA↑ protein↑ (in CD4+ T cells)	FOXP3	unclear	Ma et al[53]
Esophageal squamous cell carcinoma	5hmC↓ mRNA↓	None	Not associated with prognosis	Murata et al[54]
Gastric cancer	mRNA↑(N = 76) mRNA↓(N = 31) Protein↓	EZH2 lncRNA-ANRIL	Poor overall survival Favorable survival	Deng et al[55] Deng et al[57]
Hepatocellular carcinoma	mRNA↑ protein↑	E-cadherin	Poor overall survival	Yang et al[56]

TET2: Ten-eleven translocation; FOXP3: transcription factor forkhead box P3; EZH2: Enhancer of Zeste Homolog 2; lncRNA-ANRIL: the oncogenic long noncoding RNA.

(ASXL1), isocitrate dehydrogenase 1 and 2 (IDH1/2), and TET1.[73—76] The above gene mutations may together promote the development of various hematological malignancies.[77]

Compared to normal ovarian tissues, a significant reduction in TET2 expression and 5-hmC in epithelial ovarian cancer was discovered.[78] It was reported that a rare variation of TET2 was associated with prostate carcinoma in African-American.[79] Following this discovery, TET2 loss was associated with cancer progression due to change in the expression of some genes.[80] Besides, TET2 interacted with androgen receptor (AR) to influence 5-hmC-mediated tumor progression.[80,81] The specific mechanism of TET2 and the effect on survival and prognosis of these tumors remain to be explored extensively.

Conclusion

The current mechanistic understanding of TET2 mutations in relation to hematological malignancies has been clarified. It is clear that the catalytic function of TETs yields to 5-hmC, 5-fC, and 5-caC. The structures of TET2 had provided insights into the enzymatic activities. Dysregulated function of TET2 mutation induces immunologic derangement and malignant clones. This review focused on the effect of TET2 on FOXP3 expression, hypomethylation pattern establishment, iron metabolism, etc. leading to the differentiation fate of some cells, such as Treg cells, and CD8+ T cells, as well as erythropoiesis. Moreover, in this review, several detailed mediations of TET2 in digestive tumors were obtained to explore the potential mechanisms and therapies. More comprehensive biological functions and conclusions of TET2 and specific elucidation of digestive tumors remain to be identified. Advanced research via systematic genomic approaches will provide further insights into the mechanisms of abnormal TET2 regulation.

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Conflict of interest

None.

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