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Regulation Activity of Ten-Eleven Translocation Family in Solid Cancers

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Introduction

The ten-eleven translocation (*TET*) proteins are mammalian paralogs of trypanosome proteins J-binding protein 1 (JBP1) and JBP2, which consist of three members (*TET*1, *TET*2, and *TET*3) [1]. *TET* proteins mediated DNA oxidation by step wisely converting 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC) based on their dioxygenase activity, and aberrant *TET* proteins accompanied with altered 5hmC level have been reported to break the balance between DNA methylation and demethylation and play critical roles in many human malignancies, especially solid tumors [1,2]. In this review, we set out the known solid cancers reported with abnormal *TET* expression and discussed the feasible mechanism involved in the regulation activity of *TET* in these cancers.

TET and digestive system cancers

Colorectal cancer: Many studies demonstrated decreased *TET* and global 5hmC levels in colorectal cancer (CRC) and emphasized that low *TET*2 levels correlated with poor prognosis and loss of *TET*1 associated with higher tumor stages [3-5]. Knappskog et al. reported overexpression of *TET*2-interacting proteins IDAX/CXXC4 and RINF/CXXC5, which negatively influenced stability and function of *TET*2 in colorectal cancer [6]. Ya Wen Cheng et al. found a microRNA-21-5p (miR-21-5p, a diagnostic and prognostic biomarker in CRC)-binding site located in 30-UTR region of *TET*1 genes, suggesting *TET*1-30-UTR luciferase activity might be regulated by miR-21-5p in CRC [7]. However, Yiping Tian et al. observed that patients with low C/N-*TET*1 ratios (the ratio of *TET*1 in CRC tissues to that in adjacent normal tissues) owned better outcomes and *TET*1 promoted cell metastasis and invasion *in vitro* study [5]. Ling Ma et al. study also stated that the hypoxia microenvironment of colorectal cancer could up-regulated *TET*1 levels, which led to the decrease of the hypoxia-responsive elements (HREs)'s CpG methylation levels, drove hypoxia inducible factor-1-alpha (HIF-1α) binding to HREs, and enhanced cell migration [8,9].

Gastric carcinoma: Several studies observed reduced expression levels of *TET*1-3 in gastric cancer tissues compared to nontumoral tissues [9-11,13]. Lowered level of *TET*1 transcripts and proteins, accompanied with lowed level of 5hmC, were thought to associate with tumor size, tumor location, Bormman type, histological grade, tumor invasion, TMN stage, lymph node metastasis and cancer-related death [9,12]. Existed experiment verified that *TET*1 could couple DNA demethylation with inhibition of oncogenic protein EZH2 and activation of p53 though DNA-PK, thus suppressing gastric cancerous progression [10]. By exploring gastric adenocarcinoma with enteroblastic differentiation (GAED), featured by frequent TP53 mutation, researchers found decreased *TET*1 levels in most TP53 promoter methylation cases, which partly resulted in loss of p53 expression [14].

Hepatic carcinoma: Decrease level of *TET*1-3 and 5hmC were reported in hepatocellular cancer (HCC) tissues [10,15,16]. Some articles owed the reduce of 5hmC to the loss of *TET*1, while Sahar Olsadat Sajadian et al. verified the impaired *TET*2 and *TET*3 proteins in HCC also contributed to reduction of 5hmC [17]. Higher recurrence risk and poor outcome might derive from the low level of 5hmC of HCC [18]. *TET* expression could be regulated by a variety of microRNAs in HCC progression. Up-regulated miR-494 in HCC was capable to target the 3'UTR region of *TET*1 gene, suppressing gene expression and inducing tumor vascular invasion [16]. Likewise, the interaction of *TET*1 with miR-29 family and miR-520b were reported adverse impact in HCC development [19,20].

Other: Asuka Murata et al. evaluated the *TET* family expression and 5hmC level in esophageal squamous cell carcinoma (ESCC) tissues and found *TET*2 expression and 5hmC level were significantly reduced in ESCC than normal tissues [21]. Furthermore, *TET*2-reduction related loss of 5hmC was associated with shorter overall survival. Low level of 5hmC was also observed in pancreatic cancer tissues, but its role in tumorigenesis was unclear [10].

TET and breast cancer

Previous studies have confirmed the down-regulated level of *TET* family gene expression in breast cancer and its negative significance in prognosis, since *TET*1 acted as a suppressor in tumorigenesis, intravasation and metastasis in breast cancer [10,22]. High mobility group AT-hook2 (HMGA2), an independent risk factor for triple-negative breast cancer, was verified to be an upstream suppressor of *TET*1 in breast cancer [23,24]. *TET*1 repressed the DNA methylation of tissue inhibitors of metalloproteinase (TIMP) family proteins 2 and 3, which down-regulated matrix metalloproteinase (MMP) proteins, by binding to their CpG-rich regions and induced TIMP2/3 expression, ultimately alleviating cell invasion [1]. *TET*1 and *TET*3 could be regulated by hypoxia in a HIF-1α manner. In contrast to colorectal cancer, the increased DNA hydroxymethylation level result from hypoxia-induced HIF-1α-dependent *TET*1/*TET*3 was correlated with poor prognosis in breast cancer. In addition, the hypoxia-induced *TET*1/*TET*3 proteins regulated cancer stemness by activating TNFα- p38-MAPK pathway [25]. As to microRNA fields, miR-22 was proposed to downregulate *TET* family gene expression and associated with poor prognosis in breast cancer [26-31]. Peng X et al. observed that 3,6-dihydroxyflavone (3,6-DHF) up-regulated tumor suppressor miR-34a in breast carcinogenesis through increasing *TET*1, suggesting potential interaction between *TET*1 with miR-34a in breast cancer [26].

TET and prostate cancer

Reduced *TET*1 expressions were detected in prostate cancer tissues according to present studies [10,27] and patients with low

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*TET*1 mRNA levels developed higher risk of metastasis. Similarly, to breast cancer, *TET*1 played a protective role in prostate cancerous cell invasion through TIMP2/3 manner and the overexpression of HMGA2, which promoted prostate intraepithelial neoplasia formation, also suggested latent mechanism between downregulate *TET*1 expression and prostate cancer progression [25]. Other deductions about the mechanisms of altered *TET* activity in prostate cancer (for instance, the altered transcription factors level of OCT4, SOX2 and MYC detected in prostate cancer might contribute to the aberrant level of *TET*) were still to be corroborated [27].

TET and endometrial cancer

Ciesielski P et al. found that both *TET*1 and *TET*2 were downregulated in endometrial cancers, while *TET*3 was upregulated [28]. They also stated that lower *TET*1 and *TET*2 expression correlated with higher risk of lymph node metastasis and tumor stages. In addition, low *TET*1 levels was identified an independent risk factor for clinical prognosis. The relative molecular mechanism remained unclear.

TET and lung cancer

Present studies suggested *TET*1 acted as inhibitor in lung carcinoma migration and invasion [28,29]. According to Shinsuke Fujii et al. exploration, knocking down *TET* family proteins in NCI-H520 lung squamous cell carcinoma cells could decrease 5hmC levels and facilitate DNA methylation in the 3'- untranslated region (UTR) of ADP-ribosylation factor (ARF)-like 4c (ARL4C) gene to finally relieve the overexpression of ARL4C and the cellular migration it mediated [29].

Conclusion and Perspectives

Mutations of the *TET* genes are not limited to malignant hematopoiesis but have also been observed in a wide variety of human solid tumors, missense and truncating mutations of *TET* genes are observed in nearly all tumor types. But so less is known regarding the role of *TET* enzymes in disease onset and the maintenance of these. Decreased expression of *TET* proteins and lower 5hmC levels are general hallmarks of many cancer types, including gastric, prostate, liver, lung, breast cancer, and glioblastoma or melanoma. Many studies suggest that, a combination of mutations, high proliferation rate, and alterations in regulators of *TET* proteins could result in epigenetic degradation of 5hmC and 5mC patterns. However, this precise impact of altered *TET* activity on the transformation, progression, and maintenance of these tumors is also unknown and remains a topic of active research.

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