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 (TET1, TET2, and TET3) [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 TET expression and discussed the feasible mechanism involved in the 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 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 TET1 acted as a suppressor in tumorigenesis, intravasation and metastasis in breast cancer [10,22]. High mobility group AT-hook2 (HMG2), an independent risk factor for triple-negative breast cancer, was verified to be an upstream suppressor of TET1 in breast cancer [23,24]. TET1 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]. TET1 and TET3 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 TET1/TET3 was correlated with poor prognosis in breast cancer. In addition, the hypoxia-induced TET1/TET3 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 TET1, suggesting potential interaction between TET1 with miR-34a in breast cancer [26].

TET and prostate cancer

Reduced TET1 expressions were detected in prostate cancer tissues according to present studies [10,27] and patients with low 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 TET1 gene, suppressing gene expression and inducing tumor vascular invasion [16]. Likewise, the interaction of TET1 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 TET2 expression and 5hmC level were significantly reduced in ESCC than normal tissues [21]. Furthermore, TET2-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].

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TET1 mRNA levels developed higher risk of metastasis. Similarly, to breast cancer, TET1 played a protective role in prostate cancerous cell invasion through TIMP2/3 manner and the overexpression of HMG2A, which promoted prostate intraepithelial neoplasia formation, also suggested latent mechanism between downregulate TET1 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 TET1 and TET2 were downregulated in endometrial cancers, while TET3 was upregulated [28]. They also stated that lower TET1 and TET2 expression correlated with higher risk of lymph node metastasis and tumor stages. In addition, low TET1 levels was identified an independent risk factor for clinical prognosis. The relative molecular mechanism remained unclear.

TET and lung cancer

Present studies suggested TET1 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, misense 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 5mC 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 5mC 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.

References