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The Emerging Role of Ten-Eleven Translocation 1 in Epigenetic Responses to Environmental Exposures

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ABSTRACT: Mounting evidence from epidemiological studies and animal models has linked exposures to environmental factors to changes in epigenetic markers, especially in DNA methylation. These epigenetic changes may lead to dysregulation of molecular processes and functions and mediate the impact of environmental exposures in complex diseases. However, detailed molecular events that result in epigenetic changes following exposures remain unclear. Here, we review the emerging evidence supporting a critical role of ten-eleven translocation 1 (TET1) in mediating these processes. Targeting TET1 and its associated pathways may have therapeutic potential in alleviating negative impacts of environmental exposures, preventing and treating exposure-related diseases.

KEYWORDS: Ten-eleven translocation 1 (TET1), DNA demethylation, 5-hydroxymethylcytosine (5hmC), 5-methylcytosine (5mC), chromatin, environmental epigenetics, exposures

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Introduction

Epigenetics is defined as the study of heritable changes in gene function without alteration of DNA sequence.[1,2] Epigenetic marks primarily include DNA methylation, histone marks, noncoding RNA (ncRNA), and chromatin remodeling. Many studies have linked epigenetic modifications to both short-term and long-term environmental exposures in plants and animals (recently reviewed in Cavalli and Heard[3]). Therefore, the epigenome is proposed as an interface for gene-environment interactions. DNA methylation is the most studied epigenetic modification in relationship to environmental exposures in human populations and animal models. The cycle of methylation and demethylation of cytosine is modulated by DNA methyltransferases (DNMTs) and ten-eleven translocation (TET) methylcytosine dioxygenases. Accumulating research has shown that TET1 can be regulated by many environmental factors, including observations from our group.[4] The goal of this review is to discuss current evidence of interactions between environmental exposures and DNA demethylase TET1 in mammalian species and suggest possible roles of TET1 in mediating the effects of environmental exposures on disease pathogenesis.

DNA Methylation

Although other forms of modifications exist, DNA methylation often refers to chemical modification of cytosine via the covalent addition of a methyl group to its 5′ carbon (5-methylcytosine), which occurs mostly in the context of CpG dinucleotide. 5-Methyl-cytosine (5mC) regulates the transcription of the target genes, and it is essential for normal development and many diseases.[5,6] DNMTs, DNMT1, DNMT3A, and DNMT3B, contribute substantially to methylation maintenance and *de novo* DNA methylation. DNMT3A and DNMT3B, *de novo* methyltransferases, are responsible for DNA methylation at the early embryonic stage. The main role of DNMT1 is to maintain CpG methylation patterns during cell division; DNMT1 preferentially methylates hemimethylated CpG through interacting with its partner UHRF1 (reviewed in Xie and Qian[7]). Recently, some studies showed that DNA methylation also occurs at non-CpG sequences (non-CpG methylation). Non-CpG methylation is prevalent in human embryonic stem cells (ESCs) and in the central nervous system.[8] However, the function of non-CpG methylation remains unclear. Whether DNA methylation activates or suppresses gene expression is dependent on the location of its occurrence and the combinatorial presence of other epigenetic marks and binding of transcription factors.[5,9] 5-Methyl-cytosine is maintained through mitosis through binding of UHRF1 to the hemimethylated DNA, to H3K9me2/3, or to ubiquitylated H3K23.[10-12] Despite the dynamic changes in DNA methylation during germ cell development and the differentiation of the fertilized zygote,[13] there is evidence supporting the inheritance of DNA methylation patterns (epigenetic inheritance) through generations in mammals. Examples of this heritability include genomic imprinting[14] and the agouti allele.[15] However, a recent study suggests that the transgenerational inheritance of agouti allele methylation is one unique case instead of a common mechanism applicable to other variably methylated intracisternal A particles.[16] The underpinning mechanisms for transgenerational inheritance of DNA methylation remain unclear.

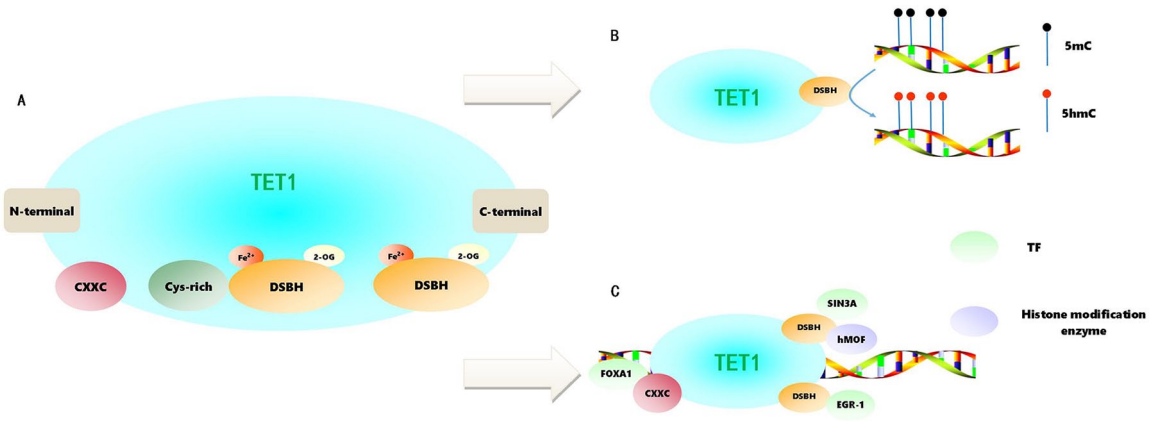

Figure 1. Structure and function of TET1. (A) The structure of TET1. The C-terminal end contains 2 DSBH domains and a cysteine-rich region. A CXXC domain is on the N-terminal end. (B) DNA demethylation. DSBH domain, the catalytic center, is responsible for oxidizing 5mC into 5hmC. The main function of the cysteine-rich region is to stabilize TET-DNA interaction. A CXXC domain can recognize and bind to unmethylated CpG sites. (C) TET1 can directly interact with TFs and histone modification enzymes to regulate gene expression. DNA indicates deoxyribonucleic acid; DSBH, double-stranded β-helix domain; Fe^{2+}, $Iron^{+2}$; 2-OG, 2-oxoglutarate; TET, ten-eleven translocation; TF, transcription factor.

TET1 and DNA Demethylation

Structure of TET1

Ten-eleven translocation methylcytosine dioxygenases in mammalian cells are composed of 3 members, TET1, TET2, and TET3, which are $iron^{+2}$ and α-ketoglutarate (αKG) dependent.[17] TET1 was first identified as a mixed lineage leukemia (MLL) translocation partner gene in acute myeloid leukemia (AML).[18] The full structure of TET1 includes a double-stranded β-helix (DSBH) domain, a cysteine-rich domain, and a CXXC domain (Figure 1A). The dioxygenase activity of DSBH is dependent on Fe^{2+} and 2-oxoglutarate (2-OG). Double-stranded β-helix is the catalytic active subunit, which oxidizes the methyl group attached to the 5′ position of C. The function of the cysteine-rich domain is to stabilize the TET-DNA interaction.[19,20] The CXXC domain recognizes and binds to unmethylated CpG sites.[19,20] Besides DNA, TET1 also binds to transcription factors. It is reported that TET1 binds to Egr-1 at its C-terminal region (containing the DSBH domain),[21] interacts with hMOF and SIN3A via the DSBH domain,[22] and interacts with FOXA1 through the CXXC domain.[23] Besides the highly conserved C-terminal catalytic domain, TET2 and TET3 have different protein structures than TET1 (reviewed in Pastor et al[24]). Specifically, compared to TET1 and TET3, TET2 lacks the CXXC domain in the N-terminus as a result of a chromosomal inversion.[25] This domain is encoded by a separate gene, *Idax*, in mammals. In addition, each *TET* gene has unique regulatory promoter and enhancer sequences, suggesting different regulatory mechanisms underlying their expression (reviewed in Melamed et al[19]).

Function of TET1

Together with TET2 and TET3, TET1 catalyzes the hydroxylation of DNA methylcytosine (5mC) into 5-hydroxymethylcytosine (5hmC), and it can further oxidize 5hmC into 5-formylcytosine (5fC) and 5-carboxycytosine (5caC) (Figure 1B). However, 5fC and 5caC are mostly unstable, as they can be rapidly excised by thymine DNA glycosylase (TDG) in active demethylation state. Subsequently, 5fC and 5caC are replaced by unmodified cytosines through base excision repair (BER) mechanisms.[26] Some studies confirmed that 5fC and 5caC were found at 100 to 1000 times lower abundance than 5hmC,[27] including one study on mouse embryonic stem cells (mESCs).[27] These studies indicate that DNA methylation is reversible and different states/forms of cytosine modifications are present in a dynamic balance. Imbalance of DNA methylation and demethylation are associated with pathological states, including alcohol and cocaine addiction, cardiac fibrosis, cancer, asthma, and diabetes.[4,26,28-34] Although all 3 TET enzymes have similar catalytic activity, there are many differences among them, including cell-/tissue-specific expression patterns and cellular functions,[35-37] suggesting that TET2 and TET3 may regulate different cellular processes than TET1.

Sometimes independent of its catalytic activity, TET1 directly interacts with transcription factors and histone modification enzymes to regulate gene expression (Figure 1C). For instance, Tanaka et al[38] found that ETV2 directly interacts with TET1 and TET2. ETV2 is an E26 transformation-specific (ETS) family transcription factor that can bind to ETS motifs in the Robo4 promoter and activate its expression. Robo4 is a transmembrane protein that stabilizes vasculature in pathological angiogenesis[39] and regulates the interaction between endothelial cells and immune cells.[40] The authors showed that the ETV2/TET1 and ETV2/TET2 complexes bind to the Robo4 promoter, demethylate the promoter, and induce Robo4 expression in human dermal fibroblasts. Importantly, the binding of TET1/TET2 to the promoter is dependent on the co-expression of ETV2. In addition, Yang et al[23] showed that FOXA1 (a transcriptional factor that regulates lung morphogenesis and cell differentiation during formation of the lung[41]) induces the expression of TET1 by binding to an enhancer at the TET1 locus in human prostate cell lines.

Through interaction with FOXA1, TET1 promotes DNA demethylation and subsequently H3K4 methylation and H3K27 acetylation at FOXA1-target enhancers, which facilitates FOXA1 recruitment and forms a positive feedback loop. Another example is Egr1, which is a transcription factor important for memory formation. EGR1-TET1 complex was found in neurons in mouse frontal cortices by co-immunoprecipitation (Co-IP) assays; this complex contributed substantially to the demethylation in EGR1-target genes, such as *Galnt9* and *Npas4*.[21] TET1 also interacts with MOF (hMOF, also known as KAT8); hMOF specifically modifies H4K16 residue to generate H4K16ac. H4K16ac marks active promoters and enhancers, regulates chromatin accessibility, and promotes gene transcription.[42,43] Zhong et al[22] reported that a TET1-hMOF-SIN3A complex was found in HEK293T cells through Co-IP and pull-down assays. They also found that TET1 modulated the auto-acetylation of hMOF, promoting chromatin affinity and enzymatic activity of hMOF against acetylation of H4K16 residue.[22] Meanwhile, our studies in human bronchial epithelial cells (HBECs) suggest that TET1 may interact with histone modification enzymes EZH2 and transcription factors to regulate expression of genes in the interferon signaling pathway.[44]

Environmental Epigenetics and TET1

Environmental epigenetics refers to the study of interactions between environmental exposures and epigenetic changes. The significance of the environment in defining phenotypes can be most appreciated in studies of identical twins. These twins share the same genomic DNA sequence; however, they are unique individuals with significant phenotypic differences. Some of these differences are induced by distinct gene expression programs impacted by epigenetic factors. Behaviors, lifestyle, nutrition, chemicals, and industrial pollutants are the most common environmental factors with epigenetic effects.[45] For instance, smoking, an environmental exposure and lifestyle associated with lung cancer and chronic obstructive pulmonary disease (COPD), may impact health by influencing epigenetic marks.[46-49] In addition to smoking, other environmental exposures, either prenatally, perinatally, or after birth, have been associated with changes in DNA methylation in various tissues. However, the role of environmental exposures in generating epigenetic variation and the underlying molecular mechanisms remain unclear. Given the distinct protein structures, expression patterns, and functions among TET1-3, we will primarily focus on TET1 and discuss the evidence supporting the involvement of TET1 in responding to environmental cues (Table 1).

Food/nutrition and TET1

Food and nutrition are critical for embryonic development. Several studies have revealed that abnormal nutrition exposure may harm the fetus by impairing the balance of epigenome modifications in the processes of organism development, which increases disease risk in later life. Li et al[50] showed that maternal food intake restriction during late gestation in goats resulted in a reduction of fetal weight, fetal heart, and liver weight. Concomitantly, *TET1* and methyl-CpG-binding domain protein 2 (*MBD2*) had significantly increased expression in fetal heart and liver when there was maternal food intake restriction, while DNMT1, 3a, and 3b remained unchanged. Spearman et al[34] showed that exposure to an adverse maternal environment (AME) during the last third of pregnancy (from embryonic day 13 until offspring birth) in combination with perinatal exposure to Western diet (WD) induced cardiac fibrosis in male offspring of pregnant mice. The expression of TET1-3, together with DNMT3a, was noticeably suppressed by AME in the heart of the offspring, suggesting a role of these epigenetic modifiers in mediating susceptibility to fibrosis.

Some food components and nutrition may trigger epigenetic modifications in different organs, and these modifications can be associated with pathological conditions. Spallotta et al[64] found that high-fat diet (HFD) and streptozotocin (STZ) impaired thymine DNA glycosylase (TDG) function, TET1 nuclear localization, and TET/TDG association through the reduction of intracellular αKG synthesis in cardiac mesenchymal cells (CMSCs) from mice. 5hmC and 5fC prevalence and TDG and TET1 protein levels in human diabetic CMSCs (D-CMSCs) were lower than in human nondiabetic CMSCs (ND-CMSCs) due to the presence of αKG. Furthermore, the authors also showed that a small-molecule inhibitor of αKG dehydrogenase, (S)-2-[(2,6-dichlorobenzoyl)amino]succinic acid (AA6), could improve glucose uptake and insulin response by restoring DNA demethylation through the activation of TET/TDG complex formation and function in the heart in mice. These results directly support the key role of the TET1-associated demethylation pathway in regulating glucose uptake and insulin response of the heart in diabetes. There has also been evidence linking vitamins and TET function. Chen et al[66] showed that vitamin C regulates the impact of TET1 on the reprogramming of mouse embryonic fibroblast to induced pluripotent stem cell (iPSC), which is different from the consistent positive role of TET2 in the regulation of iPSC reprogramming. Gradual increase of vitamin C converts TET1 from a positive regulator of reprogramming to a negative regulator, through the regulation of 5hmC levels at loci critical for mesenchymal to epithelial transition. Blaschke et al[67] also showed that vitamin C induces TET1-/TET12-dependent changes in 5mC and 5hmC in cultured ESCs. This is likely due to the observations that vitamin C can potentiate TET activity by reducing Fe^{3+} to Fe^{2+}.[68] Collectively, these studies suggested that TET1 plays a hub role in responses to nutrition levels and that nutritional intervention is a potential way to prevent and treat certain diseases, such as diabetes.

Alcohol and TET1

Studies from human specimens, cell culture, and animal models have linked alcohol use with changes in TET1 and changes

Table 1. The impact of different environmental factors on TET1.

FACTORS	CATEGORY	IMPACT ON TET1	ORGANS, TISSUES, AND CELLS	EXPOSED SPECIES/ SUBJECTS
Maternal feed intake restriction[50]	Food and nutrition	Upregulation	Fetal heart and liver	Goats
Ethanol exposure[51]	Food and nutrition	Upregulation	Embryonic stem cells (ESCs)	Mice
Ethanol exposure[52]	Food and nutrition	Upregulation	Primary fetal cerebral cortical neuroepithelial stem cells	Mice
Chronic intermittent ethanol (CIE)[53]	Food and nutrition	Upregulation	Nucleus accumbens (NAc)	Mice
Diesel exhaust particles (DEP) and house dust mite (HDM) exposure[4,54]	Pollution and allergen	Time- and dose-dependent regulation	Human bronchial epithelial cells (HBECs)	Human
Voluntary physical exercise[55]	Lifestyle and exercise	Upregulation	Hippocampus	Adult rats
Age[56]	Other	Downregulation	Hippocampus	Aged mice
Voluntary physical exercise[56]	Lifestyle and exercise	Upregulation	Hippocampus	Aged mice
Prenatal restraint stress (PRS)[57]	Behavior	Upregulation	Frontal cortex and hippocampus	Mice
Ionizing radiation (IR)[58]	Radiation	Upregulation	TK6 cells and WTK1 cells	Human
Radiation[59]	Radiation	Upregulation	Hippocampus	Mice
Ultraviolet B (UVB)[60]	Radiation	Upregulation	HaCaT cells	Human
Adverse maternal environment (AME)[34]	Behavior	Downregulation	Heart	Adult male mice
Alcohol use disorders (AUD)[34]	Food and nutrition	Down-regulation	Cerebellum	Human
Psychosis[32]	Disease	Upregulation	Prefrontal cortex (PFC) layer II	Patients with psychosis
Alcohol abuse[32]	Food and nutrition	Downregulation	Prefrontal cortex (PFC) layer II	Patients with psychosis
Late gestational sleep fragmentation (SF)[61]	Behavior	Downregulation	Visceral white adipose tissue (VWAT)	Mice
Chronic restraint stress (CRS)[62]	Behavior	Down-regulation	Prefrontal cortex (PFC)	Mice
Repeated cocaine administration[33]	Cocaine	Downregulation	Nucleus accumbens (NAc)	Mice
Electromagnetic fields (EMF) exposure[63]	Occupation	No impact	Plasma	Human males
High-fat diet (HFD) and streptozotocin (STZ)[64]	Food and nutrition	Inactivation of TET/TDG complex formation and TET1 nuclear localization	Cardiac mesenchymal cells (CMSCs)	Human
Inhibitor of αKG dehydrogenase, (S)-2-[(2,6-dichlorobenzoyl)amino] succinic acid (AA6)[64]	Food and nutrition	Activation of TET/TDG complex formation and function	Cardiac mesenchymal cells (CMSCs)	Human
Hydroquinone[65]	Pollution and allergen	Upregulation	HEK293 cells	Human

Abbreviations: TDG, thymine DNA glycosylase; TET1, ten-eleven translocation 1.

in DNA methylation. Using postmortem tissues, Gatta et al[31] demonstrated that the reduction of the δ subunit GABAA receptor (GABRD) expression was correlated with increased methylation of *GABRD* promoter in the cerebellum from alcohol use disorders (AUD) subjects. DNMT1, DNMT3A, and DNMT3B mRNA expressions were not affected by AUD. However, the mRNA expression of *TET1* in AUD patients was noticeably lower than in controls, suggesting that AUD-induced increased methylation of GABRD promoter in the cerebellum may be due to the downregulation of TET1. Guidotti et al[32] showed that DNMT1 and TET1 mRNA was significantly increased in the prefrontal cortex (PFC) layer II from postmortem tissues of psychotic (PS) patients. However, DNMT1 and TET1 mRNA in PFC layer II in PS patients with a history of alcohol abuse were lower than PS patients without alcohol abuse. Ten-eleven translocation 2 (TET2) and TET3 mRNA levels were not affected by psychosis or a history of alcohol abuse.

Veazey et al[51] revealed that the TET1 and TET2 expression levels were upregulated after ethanol exposure in a dose-dependent manner in murine ESCs. Another study from the same group demonstrated that 3 days of ethanol exposure followed by 4 days of rest significantly increased the expression of *Tet1*, *Dnmt1*, and *Uhrf1* in primary murine fetal cerebral cortical neuroepithelial stem cells.[52] There were some measurable changes in 5mC in selected genes and loci immediately after the ethanol exposure, including the 5′ untranslated region (UTR) of *Gf* and the regulatory region of *Sycp3*. However, no significant alterations in 5hmC were observed, possibly due to the limitation of study methods. Interestingly, significant changes in histone modifications (histone 3 lysine 9 dimethylation, lysine 9 acetylation, and lysine 27 trimethylation) were observed, consistent with time-specific changes in histone modification enzymes including Ehmt2, Setdb1, Kdm1a, Kdm4c, Eed, and Ezh2. The authors also observed similar changes in histone modifications in the fetal cortex from C57BL/6J pups exposed to ethanol in utero, supporting the relevance of the in vitro studies. Finegersh et al[53] found that chronic intermittent ethanol (CIE) enhanced the expression of TET1 in nucleus accumbens (NAc) but not PFC in C57BL/6J (B6) mice. Meanwhile, CIE also induced significantly histone modifications in the cerebral cortex, NAc, and PFC in mice. Whether there were changes in 5mC and 5hmC is unknown.

Taken together, alcohol intake can lead to DNA methylation/demethylation imbalance. The role of alcohol in the regulation of TET1 and DNMTs is organ- and tissue-dependent. Other epigenetic modifications, including histone marks, are also involved in the pathophysiology of alcohol toxicity. These findings indicate that TET1 is a promising target of treating alcohol toxicity–related diseases that need further investigation.

Lifestyle (exercise, stress, and substance use) and TET1

It is well-known that appropriate physical exercise is good for health, particularly for the heart and lungs. Moreover, recent studies found that physical exercise also plays a positive role in brain function, such as learning and memory. Sølvsten et al[55] showed that 2 weeks of voluntary physical exercise increased TET1 and decreased Dnmt3b mRNA expression in the hippocampi of rats. This study suggests the involvement of epigenetics as a mediator of the beneficial effects of physical exercise. Aging-induced reduction of TET1 and TET2 expression in the hippocampus was blunted by voluntary exercise in aged mice.[56] Furthermore, hippocampal 5hmC content in the promoter region of miR-137 was elevated and memory was improved by voluntary exercise.[56] Zhou et al[69] identified extensive epigenetic reprogramming by HFD in mouse liver and potential beneficial effects of exercise through the epigenome. However, whether TET1 is involved remains unexplored.

In addition, sleep disorder and abnormal stress are critical regulators of TET1 in several organs and tissues. Khalyfa et al[61] found that late gestational sleep fragmentation (SF) exposures in pregnant mice induced metabolic dysfunction; increased food intake/body weight/visceral white adipose tissue (VWAT) mass, and insulin resistance; and reduced adiponectin (AdipoQ) expression in VWAT in 24-week-old male offspring mice. Upregulation of DNMT3a and DNMT3b increased global DNA methylation, and downregulation of histone acetyltransferase activity (HAT) and TET1-3 was detected in VWAT of SF offspring. The decrease in 5hmC and H3K4m3 and increase in 5mC and H3K9m2 in the promoter and enhancer regions of AdipoQ were observed in adipocytes from VWAT, correlating with AdipoQ mRNA expression. Cheng et al[62] revealed that chronic restraint stress (CRS) induced depression-like behavior in mice and 5hmC reduction in the PFC. The interaction between TET1 and HIF1α was substantially enhanced by CRS and loss of TET1 led to resistance to CRS, suggesting that TET1 regulates response to stress through interactions with HIF1α. Dong et al found that prenatal restraint stress (PRS) upregulated Dnmt1 and Tet1 expression and led to the enrichment of 5mC and 5hmC at neocortical GABAergic and glutamatergic gene promoters in the frontal cortex and hippocampus. Prenatal restraint stress also induced schizophrenia (SZ)-like behavior in mice, which was consistent with the findings in postmortem chronic SZ patients.[57,70] Cocaine administration–induced brain dysfunction has also been associated with aberrant TET1 expression. Feng et al[33] found that TET1 in NAc was noticeably downregulated after repeated cocaine exposure in both mice and humans. Knocking out TET1 by shRNA in NAc increased preference for cocaine in mice, while promoting TET1 expression in NAc by adeno-associated virus (AAV)-TET1 significantly reduced cocaine preference. Repeated cocaine exposure induced differential

levels of 5hmC in 11 511 regions in NAc. These differences are preferentially located at flanking exon boundaries, which are involved in mRNA alternative splicing of corresponding genes. Significant correlations between cocaine-induced increases in 5hmC at gene bodies and enhanced gene expression were observed after 4 and 24 hours of withdrawal from cocaine exposure. These genes were mainly associated with processes involved in drug addiction, including long-term plasticity, synaptic transmission, and glutamate neurotransmitter. At last, they showed that some of these expression changes (such as Adcy1, Hrk, and Ntrk2), together with increases in 5hmC, can last more than 1 month.

Lifestyle, therefore, is deeply implicated in the regulation of DNA methylation/demethylation. Unhealthy lifestyles, such as SF and substance use, are the potential etiologies of many metabolic disorders and neurological diseases. Current evidence strongly suggests that TET1 is involved in lifestyle-regulated organ function and induced pathological states, such as metabolic dysfunction, mental disorder, and substance addiction.

Air pollution, allergen exposure, and TET1

Air pollution, one of the most important pollution sources, is a major risk factor of many diseases, including cardiovascular diseases and respiratory diseases such as asthma. Changes in DNA methylation associated with air pollution have been identified in many studies,[26,71-73] suggesting that DNA methylation/demethylation imbalance may play a critical role in air pollution–induced injury in cells and organs. In our previous study, we noticed that hypomethylation of a CpG site in the *TET1* promoter (cg23602092) and the increased global 5hmC in nasal mucosa were associated with childhood asthma.[54] Meanwhile, traffic-related air pollution (TRAP) was associated with increased *TET1* promoter (cg23602092) methylation in the nasal mucosa in both asthmatic and nonasthmatic subjects. Furthermore, our results showed that *TET1* mRNA and global 5hmC levels were regulated by diesel exhaust particles (DEP) exposure in HBECs. Subsequently, we confirmed that TET1, DNMT1, and DNMT3A expressions were regulated by DEP in HBECs in a dose- and time-dependent manner.[4] Our data also showed that genome-wide 5mC + 5hmC, 5mC, and 5hmC modifications were markedly changed, particularly at genes and pathways associated with oxidative stress responses, epithelial function, and immune cell responses. Remarkably, these changes were shared after exposures to DEP and house dust mite (HDM), which provides a possible epigenetic mechanism explaining the interaction between indoor dust mite exposure and outdoor particulate matter exposure. Other groups have also linked exposure to benzene and benzene metabolites (toxicants found in cigarette smoke and petroleum products) to global increases in 5hmC levels and TET1 activity,[74,65] lending further evidence that TET1 plays a vital role in responding to pollutants.

Subsequently, we recently showed that Tet1 inhibits asthma-related phenotypes including airway hyperresponsiveness (AHR) and lung eosinophilia in mice.[44] In this HDM-induced allergic airway model, we found that Tet1, Tet2, and Tet3 were downregulated while Dnmt1, Dnmt3a, and Dnmt3b remain unchanged following the last intratracheal instillation of HDM. These changes in DNA methylation machinery are associated with DNA methylation changes in pathways such as Epithelial Adherens Junction Signaling and Leukocyte Extravasation Signaling (Zhang X and Ji H, unpublished data). Consistent with its role in DNA demethylation, loss of Tet1 in mouse lungs results in an increase in DNA methylation across the genome.[44] In addition, computational analysis of Tet1-regulated genes in airway epithelial cells also indicate that Tet1 may interact with transcriptional factors and histone-modifying enzymes to regulate gene expression. Taken together, these studies indicate that DEP and HDM may contribute to asthma development through regulation of Tet1, and TET1 may be a potential target to mitigate the negative impact of air pollution and allergen exposure.

Radiation and TET1

Radiation can upregulate TET1 in different types of tissues and cells. Initially, Chaudhry and Omaruddin[58] found that ionizing radiation (IR) could increase DNMT3A, DNMT3B, and TET1 expression and significantly change genomic DNA methylation patterns in both radiation-sensitive (TK6 cells) and radiation-resistant cells (WTK1 cells). Acharya et al[59] showed that radiation-induced upregulation of Dnmt3a, Tet1, and Tet3 increased 5mC and 5hmC in mouse hippocampus. Wang et al[60] showed that ultraviolet B (UVB) exposure increased 5hmC in a dose-dependent manner, without 5mC changes, and upregulated TET1, TET2, and TET3 expression in keratinocytes (HaCaT cells). Ionizing radiation–induced aberrant cell cycle and apoptosis processes were intensified by TET1 deficiency in A172, U373, HEK293, and glial-derived 10B1 cells, indicating TET1 was essential for the regulation of genomic stability.[75,76] However, Zhong et al[22] found that TET1 depletion led to an accumulation of DNA damage and genomic instability in mice embryonic fibroblast (MEF) cells and augmented X-ray-induced deterioration of the coat (fur and skin) in mice. They further showed that TET1 promoted chromatin affinity and increased H4K16ac level by enhancing auto-acetylation of hMOF, which was independent of its DNA demethylation activity. Loss of TET1 results in severe DNA damage, deficiency in DNA repair, and increased genomic instability. Taken together, TET1 is essential for DNA damage response, genomic stability, and cell cycle maintenance following radiation, which is dependent on its DNA demethylation and transcription regulation activities.

In addition, Wang et al[63] carried out a cross-sectional study to explore the role of electromagnetic fields (EMFs) exposure on TET1, hormonal and inflammatory molecules in plasma through

enzyme-linked immunosorbent assay (ELISA). They showed that compared with the control group (77 health male with low EMFs exposure, 44.5 ± 6.3 years old), the levels of testosterone, testosterone/estradiol (T/E2) ratio, and nuclear factor (NF)-κB in plasma were significantly lower in male with high electric and magnetic fields (EMF) exposure (n = 77, 45.0 ± 7.9 years old). However, no differences in estradiol, melatonin, HSP70, HSP27, and TET1 in plasma were found between the 2 groups. While these results suggest that the protein level of TET1 in blood was not influenced by EMFs exposure, the impacts of EMFs exposure on other organs, particularly the nervous system and immune system, are still unknown. As the impacts of radiation are probably organ- and tissue-specific and time- and dosage-dependent, future experiments considering all these variables are needed to fully understand the health effects of different types of radiation and the role of Tet1 in these processes.

Future Insights. The balance of the DNA methylation/demethylation is critical for homeostasis and health. Ten-eleven translocation 1 (TET1), a key DNA demethylase, is expressed in almost all tissues in humans (https://www.proteinatlas.org/ENSG00000138336-TET1/tissue) and is present in many mammalian species.[77] Imbalance in the DNA methylation/demethylation system can lead to organ dysfunctions and diseases. Growing evidence indicates that TET1 plays a hub role in responding to environmental exposures, including behaviors, lifestyle, nutrition, chemicals, air pollutants, and allergen exposure. These exposures are linked to many pathological conditions, such as asthma, diabetes, and cardiovascular and neurological diseases. However, the underlying mechanisms and signal pathways through which TET1 interacts with environment factors and generates downstream molecular responses are still unclear and warrant further investigation.

Analyses of TET1 function have primarily focused on bulk samples containing multiple cell types. One notable exception to this was a study examining the role of TET1 in human bone marrow–derived mesenchymal stem/stromal cells, where the authors discovered that TET1 is a repressor of osteogenesis and adipogenesis in these cells.[78] These findings illustrate that TET1 has multiple functional roles and that many of them may be cell-type specific. Single-cell sequencing, therefore, will be critical for elucidating the role of TET1 in shaping the epigenome in response to environmental exposures. Combining multiple single-cell profiles (ie, transcriptomes, methylomes, chromatin accessibility) would be especially informative. For example, single-cell RNA sequencing on TET1-deficient and wild-type individuals following an environmental exposure (eg, DEP or HDM) could reveal cell-type-specific differentially expressed genes. Single-cell bisulfite sequencing and assay for transposase-accessible chromatin with sequencing (ATAC-sequencing) on these samples would reveal how the presence or absence of TET1 affects the transcriptional availability of genes in individual cell types. This will also help to understand the mechanisms of co-regulation of other protein involved in the balance of DNA methylation/demethylation following environmental exposures, such as DNMT1. As the response of TET1 and other enzymes to environmental exposures may also be time-dependent,[4] single-cell analysis in a time-course experiment would reveal step-wise cellular events following exposures. Together, these analyses would give an overview of how TET1 affects the epigenome following environmental exposures and how these epigenetic changes ultimately influence transcription in individual cell types. In vivo animal models with tissue-specific transgenic or knockout of Tet1 or in vitro models (air-liquid interface cell culture or organoid) will enable the functional validation of these findings and evaluate the role of Tet1 in the context of disease development.

Intervention targeting TET1 and its associated regulatory factors has the potential for prevention and treatment for specific diseases influenced by environmental factors. For instance, integration of nutrition and physical exercise to alleviate the negative impact of certain environmental exposures in the prevention and treatment of asthma and metabolic disorder is promising,[79,80] and several clinical trials on vitamin D supplementation in asthmatic patients are in progress. In addition, Jiang et al[81] showed that NSC-311068, NSC-370284, and UC-514321; selective *tet1* transcription suppressive drugs; and attenuated acute myelogenous leukemia (AML) progression improved the median survival in TET1-high AML mice. Li et al[82] found that serum protein levels of ErbB4, BDNF, and TET1 were independent predictors of SZ. The sensitivity, specificity, and Youden index of TET1 were 0.830, 0.667, and 0.497 (with the cutoff value of 65.75 pg/mL) in 53 patients with SZ. These studies indicate TET1 is a potential and promising therapeutic target of AML treatment and a promising predictor of SZ. More studies in relevant animal models, followed by clinical trials in carefully selected patients, are needed to fully evaluate the value of these strategies in mitigating the negative impact of environmental exposures and reducing disease burden.

Author Contributions

HJ conceived the study. TZ performed primary literature search and drafted the manuscript in discussion with HJ and APB. TZ, APB, and HJ revised the manuscript. All authors read and approved the final version of the manuscript.

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