INTRODUCTION

Epigenetic modifiers that regulate DNA cytosine methylation and histone methylation/acetylation are recurrent targets of genetic aberrations in hematological malignancies. Ten-eleven translocation 2 (TET2) is one of the TET family proteins that either catalyzes serial oxidation of 5-methylcytosine (5mC) or mediates histone modifications. Genomic studies have uncovered recurrent TET2 loss-of-function mutations in various hematological malignancies as well as in clonal hematopoiesis of indeterminate potential (CHIP), suggesting a critical role for TET2 in both normal and malignant hematopoiesis. In this review, we will summarize the most recent updates regarding TET2 biology, focusing on its key roles in hematopoietic stem cell (HSC) self-renewal/differentiation, inflammatory response, and leukemogenesis.
The TET family of proteins was first reported with the cloning of TET1 as a fusion partner of MLL1 in patients with t(10;11)(q22;q23) acute myeloid leukemia (AML). TET proteins (TET1-3) are Fe(II)- and α-ketoglutarate (α-KG)-dependent mammalian DNA oxidases that catalyze the conversion of 5mC to 5-hydroxymethylcytosine (5hmC) (Figure 1A). The discovery of this new modification on DNA methylcytosine has provided a novel insight into DNA demethylation pathways. The TET enzymes can further oxidize 5hmC to 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC), which can be directly recognized and repaired by thymine DNA glycosylase (TDG)-mediated base-excision repair (BER) to generate unmethylated cytosines, leading to active DNA demethylation (Figure 1A). Alternative active DNA demethylation through the activation-induced cytidine deaminase (AID)-APOBEC DNA repair pathway has also been reported. The first step of this pathway is the conversion of 5hmC to 5-hydroxymethyluracil (5hmU) by AID/APOBEC, followed by TDG- or single-strand-selective monofunctional uracil DNA glycosylase (SMUG1)-mediated BER to generate unmethylated cytosines (Figure 1A). Conversely, 5hmC might also lead to passive DNA demethylation, as DNMT1, a maintenance methyltransferase that methylates unmethylated cytosines in the daughter strand upon DNA replication, cannot recognize 5hmC.

**FIGURE 1** DNA demethylation and histone modification by ten-eleven translocation 2 (TET2). A, The biochemical process of DNA methylation/demethylation and the enzymes involved in each step are shown. Cytosine can be methylated into 5-methylcytosine (5mC) by DNA methyltransferases (DNMTs) and 5mC can be iteratively oxidized into 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC), and 5-carboxylcytosine (5caC) by TETs. 5caC can be converted to unmethylated cytosine by the thymine DNA glycosylase (TDG)-mediated base-excision repair (BER) pathway. Alternatively, 5hmC can be deaminated into 5-hydroxymethyluracil (5hmU) by activation-induced cytidine deaminase (AID)/APOBEC, followed by TDG- or SMUG1-mediated BER to generate unmethylated cytosine. α-KG, α-ketoglutarate. B, TET2 interacts with β-N-acetylglucosamine (O-GlcNAc) transferase (OGT), tethering OGT to the target gene promoters and regulating gene transcription through histone H2B-O-GlcNAcylation or H3K4 trimethylation mediated by proteolytic activation/O-GlcNAcylation of host cell factor 1 (HCF1), an integral component of H3K4 methyltransferase complex SET1/COMPASS. TET2 also recruits histone deacetylase 2 (HDAC2) to inactivate interleukin-6 (IL-6) transcription through histone deacetylation.
Recent studies have also uncovered a novel role of TET proteins in histone modifications. Several groups have reported that TET2 interacts with O-linked β-N-acetylglucosamine (O-GlcNAc) trans-ferase (OGT), tethering OGT to the target gene promoters and regulating gene transcription through histone H2B O-GlcNAcyla-tion or O-GlcNAcylate/protolytic activation of HCF1, an integral component of H3K4 methyltransferase complex SET1/COMPASS (Figure 1B). Notably, TET2 was shown to enhance catalytic activity of OGT. However, Tet2 has been shown to recruit histone deacetylase 2 (Hdac2) to the interleukin-6 (Il-6) promoter and repress trans-cription of Il-6 through histone deacetylation (Figure 1B). These data indicate that TET2 modifies both chromatin landscape and DNA methylation, thereby regulating gene transcription.

3 | TET2 MUTATIONS IN CHIP AND HEMATOLOGICAL MALIGNancies

TET2 is one of the major epigenetic modifiers recurrently mutated in individuals with CHIP. Previous studies using high throughput genome-wide sequencing have also identified somatic deletions and loss-of-function mutations in the TET2 gene in 10%-20% of patients with myelodysplastic syndromes/myeloproliferative neoplasms (MDS/MPN), in 10%-20% of patients with AML, and in 40%-50% of patients with chronic myelomonocytic leukemia. Additionally, TET2 mutations are also reported in lymphoid malignancies, especially at high frequency in angioimmunoblastic T-cell lymphoma. These data clearly suggest a common key role for TET2 as a tumor suppressor in hematological malignancies.

4 | PLEIOTROPIC EFFECTS OF TET2 LOSS ON HSC HOMEOSTASIS

A number of studies have explored the functional role of TET2 in hematopoiesis and leukemogenesis. Initial study on TET2 mutations in myeloid malignancies has shown enhanced repopulating capacity of HSCs derived from TET2-mutated MPN patients in xenograft assay. Tet2-silenced murine bone marrow (BM) hematopoietic stem/progenitor cells (HSPCs) showed preferential differentiation toward myeloid lineage in vitro. Consistent with murine data, TET2 silencing in human cord blood CD34+ cells led to skewed differentiation toward CD14+ monocytic lineage in ex vivo culture. In addition, Aid-deficient mice as well as Aid-silenced human BM CD34+ cells showed myeloid skewing. These data suggest that active DNA demethylation mediated by the TET2/AID pathway functions as a safeguard mechanism against aberrant HSC self-renewal and their perturbation skews differentiation toward myeloid lineage (Figure 2).

In line with the above observations, several groups have generated mouse models of germline or conditional Tet2 loss and reported common features in these mice, including disrupted hematopoietic differentiation, expansion of HSPC (LSK; Lin- Sca-1+ c-Kit+) compartment and enhanced HSC self-renewal. Furthermore, some Tet2-null mice eventually developed myeloid malignancies in vivo. Of note, Tet2-disrupted fetal liver common myeloid progenitors showed enhanced replating capacity in vitro, implying that Tet2 loss could potentially transform more differentiated myeloid progenitors. Additionally, microRNA-22 (miR-22), which targets TET2, was reported to be upregulated in MDS patient samples. Mice conditionally expressing miR-22 displayed increased HSC self-renewal with defective hematopoietic differentiation and developed MDS similar to Tet2-deficient mice, confirming the functional relevance of the miR-22/TET2 regulatory network in myeloid transformation. Interestingly, a recent study using transcriptomic/epigenomic profiling and mathematical modeling has shown that TET2 loss in human AML cell lines increases stem-like signatures and that TET2 loss of function alters the cellular switching dynamics between stem-like and differentiated cell states, thereby enhancing population fitness during drug treatment. TET2 deficiency is also associated with disordered erythropoiesis in both human and mouse models. Together, these data clearly show that Tet2 regulates both myeloid/
erythroid differentiation and clonal hematopoietic expansion, and thereby functions as a tumor suppressor (Figure 2).

Recent studies have also uncovered novel aspects of Tet2 biology in blood homeostasis and hematopoietic transformation. Ito et al.37 analyzed Tet2 catalytic-mutant and KO mice and reported that Tet2 enzymatic activity is critical for myelopoiesis, whereas noncatalytic activity is mainly associated with augmented HSC self-renewal and aberrant lymphopoiesis. Intriguingly, loss of Tet2 in BM mesenchymal stromal cells increased their proliferation, self-renewal, and osteoblast differentiation potential, which in turn accelerated Tet2-deficiency-mediated myeloid malignancy progression in vivo.38 Notably, Tet2 loss leads to hypermutagenicity in HSPCs, as TET2-mutated myeloid tumors had significantly more mutational events than the tumors with WT TET2, particularly at the genomic loci enriched in 5hmC.39 Consistent with this notion, a recent study has shown that TET2 mutant HSPCs are highly sensitive to topoiso-merase 1 (TOP1)-targeted drugs and poly(ADP-ribose) polymerase 1 (PARP1) inhibitors due to low levels of tyrosyl-DNA phosphodiesterase and inability to remove TOP1 cleavage complexes, leading to DNA double-strand breaks and cell death.40 These data suggest a novel functional relevance of noncatalytic activity and cell-extrinsic effect and a role for genome stability of TET2 in HSC homeostasis and myeloid transformation.

5 | TET2 MEDIATES ANTILEUKEMIC ACTIVITY OF ASCORBATE

Ascorbate is a cofactor for several α-KG-dependent dioxygenases, including TET oxidases.41 Importantly, ascorbate is enriched in HSCs to promote Tet2 activity in vivo, limiting HSC frequency and suppressing leukemogenesis.42 Of note, vitamin C treatment mimics Tet2 restoration to block leukemia progression and enhances sensitivity of leukemia cells to PARP inhibition.43 These data suggest that TET2 mediates antileukemic activity of ascorbate in HSCs.

6 | TET2 MODIFICATION LINKS TO ONCOGENESIS AND ERYTHROPOIESIS

Two recent studies shed light on the functional link between TET2 modification and oncogenesis. Epidemiologically, diabetes is
associated with increased risk of cancer.\textsuperscript{44} Wu et al have shown that hyperglycemic conditions impede AMP-activated kinase (AMPK)-mediated phosphorylation of TET2 at serine 99, leading to its destabilization. This leads to dysregulation of both 5hmC and the tumor-suppressive function of TET2, mechanistically linking diabetes with cancer (Figure 3A).\textsuperscript{45} Treatment with the anti-diabetic drug metformin protects AMPK-mediated phosphorylation of TET2 at serine 99, thereby increasing TET2 stability and 5hmC levels (Figure 3A).\textsuperscript{45}

Modification of TET2 is also involved in JAK2-mediated erythropoietin signaling as well as oncogenic JAK2\textsuperscript{V617F} signaling. Jeong et al\textsuperscript{46} have reported that cytokine receptor-associated JAK2 phosphorylates TET2 at tyrosines 1939 and 1964 upon erythropoietin stimulation. Phosphorylated TET2 interacts with the erythroid transcription factor (TF), KLF1, thereby promoting transcription of erythroid genes and differentiation of erythroid progenitors (Figure 3B).\textsuperscript{46} Interestingly, CD34\textsuperscript{+} cells derived from MPN patients with activating JAK2\textsuperscript{V617F} mutation and murine HSPCs expressing Jak2\textsuperscript{V617F} showed increased TET2 activity and cytosine hydroxymethylation as well as genome-wide loss of cytosine methylation, leading to increased expression of several oncogenic transcripts, such as Meis1 and Hoxa9 (Figure 3C).\textsuperscript{46}

These results underscore a critical role for TET2 modification in oncogenesis and erythropoiesis.

**FIGURE 3**

Inflammatory signals drive ten-eleven translocation 2 (TET2)-loss-driven clonal expansion and preleukemic myeloproliferation. TET2-null hematopoietic stem/progenitor cells (HSPCs) show hyperactivation of interleukin-6 (IL-6)/Shp2/Stat3/Morrbid pathway, which reduces apoptosis and promotes cell survival, clonal expansion, and preleukemic myeloproliferation of TET2-deficient cells under basal conditions as well as inflammation. In addition, noncanonical nuclear factor-κB signaling mediated by Toll-like receptor (TLR)-TRAF6-A20 axis protects TET2-deficient HSPCs from chronic inflammation and drives competitive advantage of these cells in an inflammatory milieu. BM, bone marrow; LPS, lipopolysaccharide

**FIGURE 4**

Inflammatory signals drive ten-eleven translocation 2 (TET2) loss-driven clonal expansion and preleukemic myeloproliferation. TET2 loss itself might also enhance Morrbid expression. As Morrbid is a prosurvival, long noncoding RNA that selectively suppresses BIM transcription, TET2 loss-induced enhanced expression of Morrbid led to reduced apoptosis and promoted survival of TET2\textsuperscript{−/−} HSPCs under basal conditions as well as inflammation (Figure 4).\textsuperscript{48} Of note, MORRBID is overexpressed in murine TET2\textsuperscript{−/−} Flt3\textsuperscript{ITD} AML and a subset of human AML with TET2 mutation.\textsuperscript{49} These results together
suggest that Tet2 loss confers HSPCs with survival advantage during inflammation in an IL-6-dependent manner.

Similar to IL-6, cell-intrinsic noncanonical nuclear factor-κB signaling protects MDS HSPCs, including Tet2-deficient HSPCs, from chronic inflammatory stress driven by LPS (Figure 4). In addition, both Tet2-deficient murine and Tet2-mutant human HSPCs showed clonal advantage in an in vitro environment containing the proinflammatory cytokine, tumor necrosis factor-alpha (TNF-α). These observations clearly depict emerging roles of inflammatory signals in Tet2 loss-mediated myeloproliferation and clonal expansion.

8 | TARGETS OF TET2-MEDIATED CYTOSINE MODIFICATION AND ITS FUNCTIONAL RELEVANCE

Exploring the exact genetic loci of Tet2-mediated cytosine modification has been a focus of intense study for more than a decade. Recent study using a mammalian two-hybrid screen has revealed that SMAD nuclear interacting protein 1 (SNIP1) recruits Tet2 to the promoters of c-MYC target genes, including those involved in DNA damage response and cell viability, thereby connecting epigenetic control to maintenance of genome stability.

Ostrander et al. compared functional difference between Dnmt3a-null and Tet2-null HSPCs and found that Tet2 loss induced profound myeloid lineage skewing, whereas Dnmt3a loss conferred limitless self-renewal to HSCs. RNA sequencing (RNA-seq) and assay for transposase-accessible chromatin-sequencing (ATAC-seq) deciphered divergent transcriptomes and chromatin accessibility underlying these functional differences. Genome-wide mapping of Tet2 binding sites through ChIP and sequencing, together with ATAC-seq and RNA-seq, uncovered that Tet2 localizes to regions of open chromatin and cell type-specific enhancers. Following loss of Tet2, chromatin binding of the members of basic helix-loop-helix (bHLH) TF family was attenuated in multipotent progenitors as well as in fully transformed AML cells. More recently, single-cell analyses for RNA-seq, DNA methylation, and ATAC-seq have shown that Tet2 loss drives methylation of accessible TF binding sites, such as those of erythroid TFs. This leads to attenuated binding of erythroid TFs, including Klf1 and Tal1, to CpG-rich erythroid motifs, which then induces block of erythroid differentiation and skewed differentiation to myelomonocytic lineage in Tet2-null HSCs (Figure 5). Together, these data suggest that Tet2 loss-mediated disruption of DNA methylation in gene promoters as well as in TF binding sites alters the landscape of hematopoietic differentiation and promotes hematopoietic transformation.

9 | COOPERATIVITY AND EXCLUSIVITY OF MUTATED TET2 WITH OTHER DISEASE ALLELES IN LEUKEMOGENESIS

Recent genomic studies have uncovered mutual exclusivity and cooperativity with other disease alleles in Tet2-mutant hematological malignancies.

Isocitrate dehydrogenase 1 and 2 (IDH1/2) and Wilms tumor 1 (WT1) mutations, recurrently seen in AML patients, are known to be mutually exclusive with Tet2 mutations in AML. Interestingly, all these mutations are associated with global reductions in 5hmC levels in primary AML samples, suggesting a functional link between IDH1/2, WT1, and Tet2 in DNA hydroxymethylation. Consistent with this notion, oncometabolite 2-hydroxyglutarate, produced by IDH1/2 mutations, inhibits Tet2 function as well as other α-KG-dependent oxygenases. In addition, WT1 physically interacts with and recruits Tet2 to regulate its target gene expression. Furthermore, AML-derived Tet2 mutations disrupt its binding to WT1, and in turn, WT1 mutations lead to impaired Tet2 function and decreased 5hmC levels. These studies revealed that IDH1/2 mutations and WT1 mutations share, at least partially, common epigenetic pathogenesis in AML with Tet2 mutations through altered DNA hydroxymethylation (Figure 6A).
Tet2 mutations frequently cooccur with various other mutations, and functional cooperativity between these alleles in inducing hematological malignancies has been rigorously tested in mouse models.

Signaling molecules are frequently comutated with TET2 in myeloid neoplasms, and studies have indicated epigenetic remodeling by TET2 mutation synergizes with enhanced signaling to drive myeloid malignancies. A recent study has reported the cooperative function of Tet2 loss and Flt3ITD mutation to induce AML in vivo through synergistic remodeling of DNA methylation by both mutations, resulting in reduced expression of Gata2 by promoter methylation.60 Concurrent Tet2 loss and NrasG12D expression in hematopoietic cells induced lethal chronic myelomonocytic leukemia-like disease in vivo through decrease in negative regulators of MAPK signaling, including Spry2, thereby causing synergistic activation of MAPK signaling.61 Concurrent Tet2 loss and KitD814V expression in hematopoietic cells induced mastocytosis-like MPN in vivo, partially due to PI3K activation.62 Furthermore, studies from two independent groups have shown that combination of Tet2 loss and Jak2V617F resulted in aggressive MPN phenotype through both clonal HSC dominance and expansion of downstream precursor populations.63,64

Mutations in epigenetic modifiers, such as the members of polycomb group complex, are another well-known partner for TET2 mutation. In agreement with cooccurrence of TET2 and EZH2 mutations in MDS and MDS/MPN patients, concurrent depletion of Tet2 and Bcor insufficiency, which developed MDS or MDS/MPN, further confirming functional cooperativity of these two alleles in myeloid transformation.65,66 Concordant with this, Tet1/2 double-KO mice developed lethal B cell malignancies and Tet2 loss combined with Dnmt3a mutation caused T-cell lymphoma/leukemia in vivo, possibly due to dysregulated Bcl6/Myc and Notch pathways, respectively.67,68,69 Although TET3 mutations are infrequent in hematological malignancies, its expression declines with age in mouse HSCs as well as in human peripheral blood T cells.70 Consistent with this observation, both TET2−/− and TET2−/− × Tet3−/− mice developed lethal AML in vivo with spontaneous inactivation of residual nontargeted Tet2 or Tet3 allele, respectively, suggesting that this phenomenon is a recurrent genetic event during myeloid transformation with Tet insufficiency.71
TET2 loss was also shown to cooperate with spliceosome factor mutations in MDS pathogenesis. The combination of the \(538\) mutation and TET2 deletion causes an early onset of MDS characteristics and rescues the competitive disadvantage of stem cells in vivo.\(^7^4\) Oncogenic fusion gene associated with chromosomal translocation also cooperates with TET2 mutation. Combined TET2 loss with AML1-ETO expression leads to fully penetrant AML in vivo, partially due to hypermethylation of enhancer regions, thereby silencing tumor suppressors.\(^7^5,7^6\)

Collectively, these data suggest that functional convergent cooperativity of TET2 mutations and cooccurring disease alleles drives hematopoietic transformation (Figure 6B).

10 | CONCLUSION

Biochemical analyses have revealed fundamental roles of TET2 in active/passive DNA demethylation processes and in histone modification, thereby regulating expression of target genes. Previous genomics studies have identified somatic deletions and loss-of-function mutations in the TET2 gene in various hematological malignancies. Since the first report of TET2 mutations in myeloid malignancies in 2009, a number of groups have explored the functional relevance of TET2 loss in normal and malignant hematopoiesis. These studies uncovered pleiotropic effects of TET2 on HSC self-renewal, myeloid/erythroid differentiation, genome instability, and inflammation. Recent seminal studies have identified gene promoters as well as TF binding sites as key genetic loci in which disruption of DNA methylation can significantly alter the hematopoietic differentiation landscape and promote hematopoietic transformation. Finally, mutations in signaling factors, epigenetic modifiers, and spliceosome factors have been shown to cooperate with TET2 loss in the pathogenesis of hematological malignancies. Deeper insights into the molecular basis of stem cell and immune regulation by TET2 loss will allow us to decipher the exact pathophysiology and molecular vulnerabilities of TET2-mutant hematological malignancies.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

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