Clinical Epigenetics

REVIEW

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TET2 mutation in acute myeloid leukemia: biology, clinical significance, and therapeutic insights

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Abstract

TET2 is a critical gene that regulates DNA methylation, encoding a dioxygenase protein that plays a vital role in the regulation of genomic methylation and other epigenetic modifications, as well as in hematopoiesis. Mutations in *TET2* are present in 7%–28% of adult acute myeloid leukemia (AML) patients. Despite this, the precise mechanisms by which *TET2* mutations contribute to malignant transformation and how these insights can be leveraged to enhance treatment strategies for AML patients with *TET2* mutations remain unclear. In this review, we provide an overview of the functions of *TET2*, the effects of its mutations, its role in clonal hematopoiesis, and the possible mechanisms of leukemogenesis. Additionally, we explore the mutational landscape across different AML subtypes and present recent promising preclinical research findings.

Keywords *TET2*, Acute myeloid leukemia, DNA methylation, Mechanisms, Therapeutic insights

Introduction

Acute myeloid leukemia (AML) is a heterogeneous malignant clonal disorder that arises from myeloid blast proliferation with expansion and a block in differentiation, characterized by multiple somatically acquired mutations in genes of different functional categories, a complex clonal architecture, and disease evolution over time [1, 2]. *TET2* is one of the ten–eleven translocation (TET) family genes encoding DNA dioxygenases, regulates the process of genome demethylation, and is also involved in histone modification [3, 4]. Due to its role in epigenetic regulation, somatic *TET2* mutations are frequently detected in the elderly and are one of the most prominent genetic mutations in clonal hematopoiesis [5, 6]. Mutations in *TET2* are present in 7%–28% of adult AML patients [7–10]. *TET2* mutations result in a loss of function of the TET2 enzyme, leading to altered DNA methylation patterns [11]. This epigenetic dysregulation affects the proliferation and differentiation of hematopoietic stem and progenitor cells (HSPCs), potentially contributing to clonal hematopoiesis and abnormal hematopoietic stem and progenitor cell (HSPC) differentiation [12, 13]. However, as an epigenetic regulator, *TET2* mutations are infrequently associated with other clinical characteristics and have limited prognostic value, although they demonstrate a significant correlation with age [9, 14, 15]. There have been some explorations of therapeutic approaches targeting *TET2* mutations, with noteworthy findings emerging in the context of cellular immunotherapy.

In this review, we provide an overview of the functions of *TET2*, the effects of its mutations, its role in clonal

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hematopoiesis, and the possible mechanisms of leukemogenesis. Additionally, we explore the mutational landscape across different AML subtypes and present recent promising preclinical research findings, with the aim of elucidating the current understanding of *TET2* in AML and identifying potential areas for future research and therapeutic development.

Structure and functions of *TET2* gene

The *TET2* gene is located on chromosome 4q24, with a length of 133.9 kb, and encodes a full-length TET2 protein of 2,002 amino acids. *TET2* mutations are frequently identified in hematologic malignancies [4]. *TET2* is ubiquitously expressed in the hematopoietic compartment, including in all HSPC (hematopoietic stem/progenitor cell) subsets and mature myeloid and lymphoid cells [13].

As a member of the TET, TET2 is involved in regulating the active demethylation process of DNA. The *TET* family contains three similar genes encoding DNA dioxygenase: *TET1*, *TET2*, and *TET3*. At the C-termini, they share a conserved dioxygenase domain composed of a cysteine (Cys)-rich domain CRD and a double-stranded β-helix fold (DSBH) domain. The DSBH domain consists of 3 Fe^{2+}-binding sites and one α-ketoglutarate (α-KG)-binding site which are necessary for the catalytic function [4, 16] (Fig. 1A). TETs mediate the first step in the demethylation process, catalyzing 5-methylcytosine (5mC) into 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC), and 5-carboxycytosine (5caC). The thymine DNA glycosylase (TDG) catalyzes the excision of 5fC and 5caC to generate an apyrimidinic site (AP site), and then, the demethylation process is completed by base excision repair (BER) (Fig. 1B) [16]. The functional redundancy

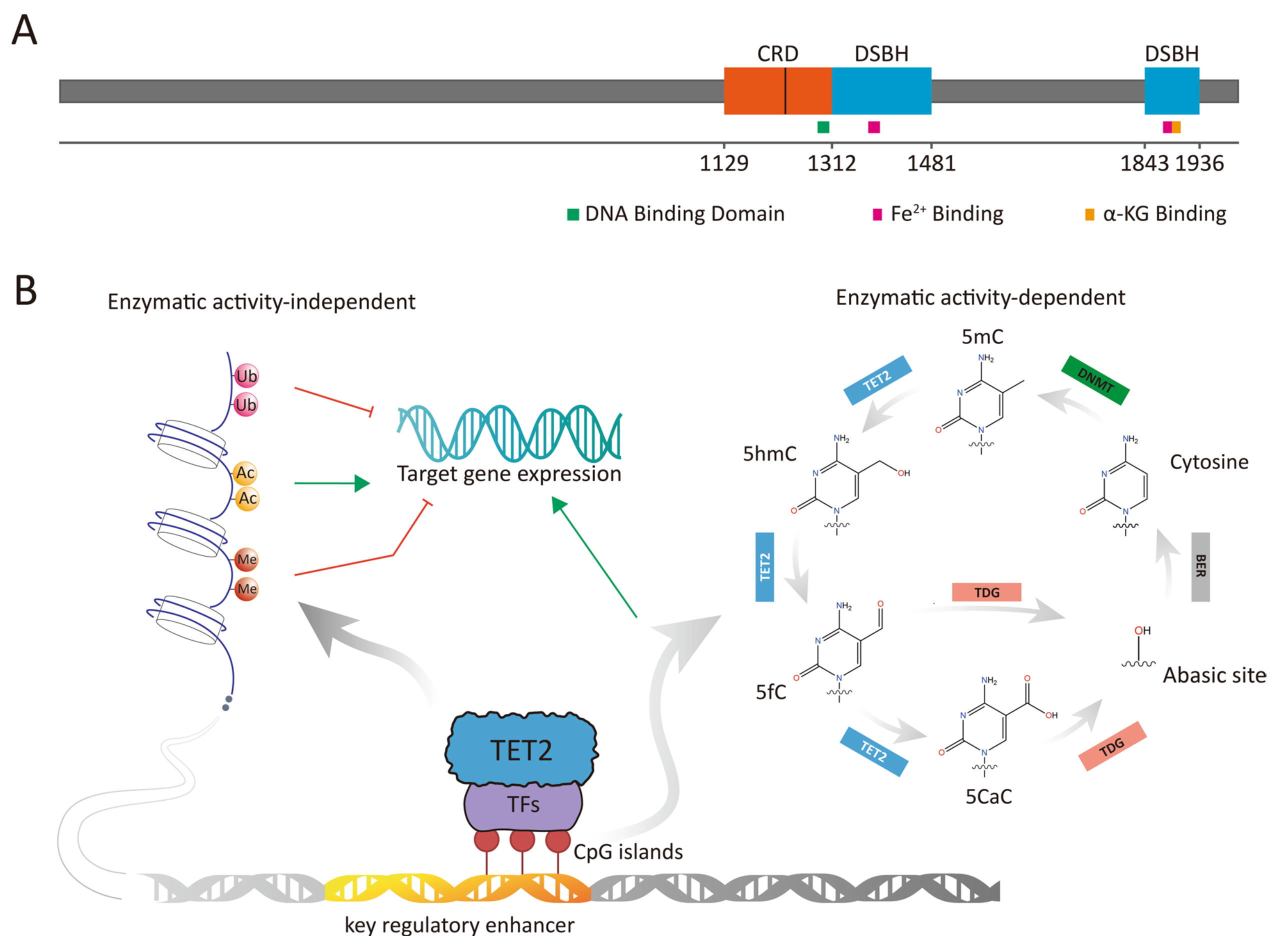


Fig. 1 Structure and functions of TET2 protein. **A** This schematic diagram shows the functional domains of the TET2 protein and the binding region of cofactors. TET2 protein contains a conserved dioxygenase domain, which is composed of a Cys-rich domain (CRD) and a double-stranded β helix (DSBH) domain. **B** TET mediates the first step of the demethylation process, catalyzing the conversion of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC), and 5-carboxylcytosine (5caC). It can regulate histone modifications independently of enzyme activity

of the three genes makes it possible that *TET1* and *TET3* are involved in the pathogenesis of *TET2*-mutated disease by partially compensating for the loss of *TET2* [17]. Gene expression can be regulated by altering DNA methylation. *TET2* does not contain the CXXC domain shared by *TET1* and *TET3*, which is located in the amino-terminal region and is involved in binding to CpG dinucleotides. So it has to collaborate with DNA-binding proteins (such as transcription factors) to regulate sequence-specific DNA methylation [4]. Master epigenetic pioneer transcription factors (TFs) recruit *TET2* to the regulatory regions, especially the enhancers, to reshape the genomic landscape of 5mC and 5hmC which determines the accessibility of the key TFs to the genomic motifs.

TET proteins can also regulate histone modifications independent of their enzymatic activities, by collaborating with lineage-specific TFs (Fig. 1B). Recent studies have demonstrated that TET2 can catalyze the hydroxymethylation of RNA to perform post-transcriptional regulation [4].

Studies of AML patients and TET2-deficient animal models have shown that the primary effect of *TET2* loss in preleukemia hematopoietic cells is widespread DNA hypermethylation [3, 18, 19]. These methylation sites are enriched in non-CpG islands containing hematopoietic-specific enhancers and transcription factor (TF)-binding sites [3, 18, 20]. Deregulated TET2-mediated demethylation results in genome-wide changes in 5mC/5hmC profiles, and the DNA hypermethylation of active enhancers inhibits the access of the key TFs for lineage commitment and differentiation. These changes in the gene expression profiles lead to enhanced proliferation, self-renewal of cells, and alterations in the differentiation process [17].

The role of TET2 in hematopoiesis and leukemogenesis

Somatic *TET2* mutations and clonal hematopoiesis

Somatic *TET2* mutations are relatively common in healthy people, especially in the elderly. The expansion of the *TET2* mutated clone was observed in 10% of persons older than 65 years of age but in only 1% of those younger than 50 years of age [5]. This phenomenon of clonal expansion driven by somatic genetic alternations in normal adults is now referred to as clonal hematopoiesis (CH) [21]. Clonal hematopoiesis of indeterminate potential (CHIP) is a subset of CH referring to the presence of expanded somatic blood cell clones carrying mutations in leukemia driver genes at a variant allele frequency (VAF) $\geq$ 2% [6, 22]. *TET2* is one of the most common mutated genes (*DNMT3A*, *TET2,* and *ASXL1*) in CH and is more strongly associated with age [5, 6]. Clones with *TET2* mutations emerged across all ages and expanded at approximately 10% per year on average [15, 23].

CH is an initial event in the progression toward hematological malignancies, though the majority of individuals with this condition do not go on to develop blood cancer. However, it is associated with an increase in all-cause mortality and a marked rise in the incidence of hematological cancers, as well as a higher prevalence of age-related diseases [21].

Mechanistic studies have revealed the reasons why TET2-deficient cells gain a selective advantage over other HSPCs. All of the HSPCs express high levels of TET2 proteins, especially in lineage-negative (Lin^-) $Sca\text{-}1^+$ $c\text{-}Kit^+$ multipotent progenitors (LSK) [13]. The absolute number of LSK and Lin^- Sca^- $c\text{-}kit^+$ (LK) was greater in $TET2^{-/-}$ mice compared with controls, indicating that *TET2* defects lead to compensatory enlargement of the HSPC pool. Within the LK compartment, the absolute number of common myeloid progenitors was increased in $TET2^{-/-}$ mice compared with WT controls, suggesting that TET2 restrains the expansion of the HSPC compartment in the BM. The chimeric mice reconstituted with $TET2^{-/-}$ bone marrow also displayed an increase in the frequency and absolute number of LSK and LK cells, supporting that TET2 deficiency augments the size of the HSPC pool in a cell-autonomous manner. Competitive reconstitution assays revealed that $TET2^{-/-}$ LSK cells had an increased hematopoietic repopulating capacity and exhibited a greater cloning efficiency than that of $TET2^{\pm}$ and WT cells, indicating that TET2 deficiency resulted in enhanced proliferative capacity [13].

Currently, this proliferative advantage is found to be associated with DNA damage repair, inflammatory pathways, and the migration of hematopoietic cells.

Mouse models have demonstrated that DNA damage resulting from *TET2* mutations in HSPCs activates the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway, which plays a pivotal role in the development of CH. This pathway is crucial in mediating the effects of TET2 deficiency on dysregulated hematopoiesis. The DNA damage in TET2-deficient HSPCs triggers the cGAS-STING pathway, enhancing self-renewal and contributing to the progression of CH. Pharmacological inhibition or genetic deletion of STING effectively suppresses *TET2* mutation-induced aberrant hematopoiesis, underscoring the therapeutic potential of targeting this pathway in mitigating *TET2*-associated hematologic disorders [24]. Research on primary AML cells has highlighted the impact of TET2 on cell homing and migration, which may also be a mechanism of CH. TET2 deficiency leads to the accumulation of methyl-5-cytosine (m5C) modification in *TSPAN13* mRNA, which is specifically recognized by YBX1, thereby increasing the stability and expression of *TSPAN13* transcripts and activating the CXCR4/CXCL12 signaling

pathway. This, in turn, enhances the homing and migration of leukemia stem cells (LSCs) into the bone marrow niche, promoting their self-renewal and proliferation [25]. In TET2-deficient zebrafish models, it has been observed that stress-induced hematopoiesis caused by external stimuli such as infection and cytokines leads to excessive proliferation of TET2-deficient HSPCs. This indicates that external stimuli may promote the development of CH.

In addition, inflammatory cytokines may promote the development of TET2-deficient CH. TET2-deficient murine bone marrow progenitors exhibit a proliferative advantage under TNF-α and IFN-γ stress compared to their wild-type counterparts [26]. Furthermore, administration of IL-1 to mice with CHIP promotes IL-1 receptor 1 (IL-1R1)-dependent expansion of *TET2*$^{\pm}$ HSPCs and mature blood cells. IL-1α-treated *TET2*$^{\pm}$ HSPCs show enhanced DNA replication and repaired transcriptomic signatures, and reduced susceptibility to IL-1α-mediated downregulation of self-renewal genes. Genetic deletion of IL-1R1 in *TET2*$^{\pm}$ HSPCs or pharmacological inhibition of IL-1 signaling impairs clonal expansion [27]. Moreover, elevated IL1β levels in CHIP patients correlate with expansion of proinflammatory monocytes/macrophages, coinciding with dysregulation in demethylation of lymphoid and erythroid lineage enhancers and transcription factor binding sites in a mouse model of TET2-deficient CHIP [28]. These findings underscore the critical role of inflammatory cytokines in driving proliferative advantages in TET2-deficient CH.

CH detection is becoming increasingly prevalent due to ubiquitous next-generation sequencing testing. However, prospective data for CH are limited and there are no effective risk prediction tools and management strategies for CH [29, 30].

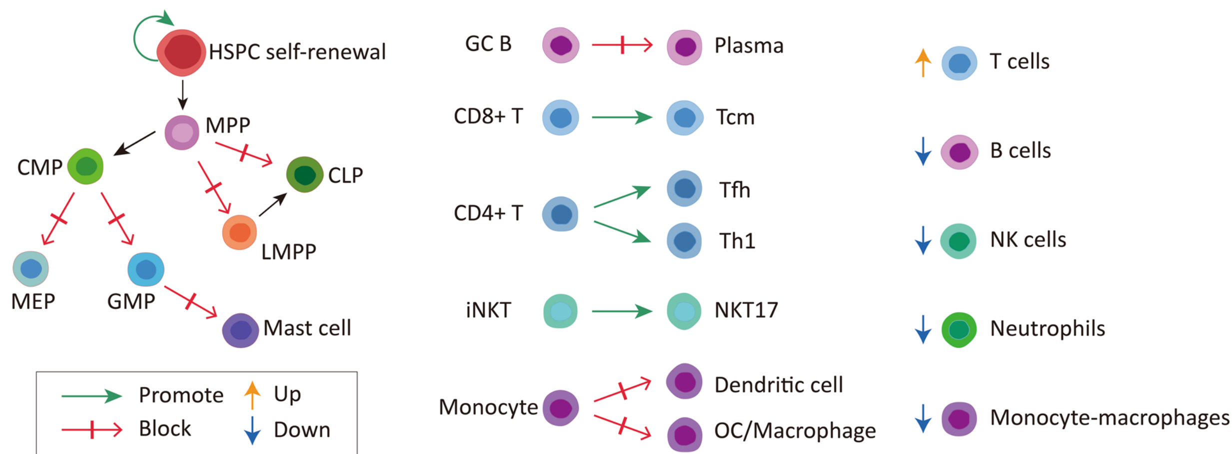
TET2 defects in HSPC result in abnormal differentiation changes

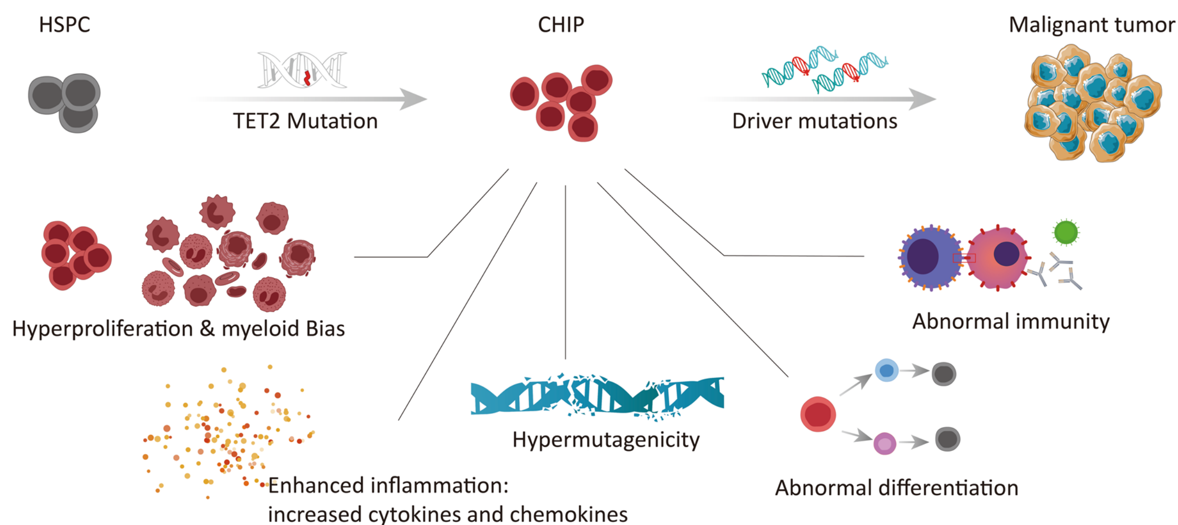
Knockout mouse studies have shown that TET2 regulates the differentiation and lineage commitment of HSPCs by controlling the methylation of active enhancers, which allows key TFs to access the genome. By collaborating with master epigenetic pioneer TFs like Pu.1 and Runx1, TET2 reshapes the genomic landscape of 5-methylcytosine (5mC) and 5-hydroxymethylcytosine (5hmC), influencing gene expression related to HSPC differentiation. Summarizing the knockout mouse experiments conducted by various groups, the absence of TET2 generally leads to HSPCs differentiating toward the myeloid lineage at the expense of lymphoid and erythroid cells [12, 13]. Mechanistic studies explain that TET2 regulates lineage commitment by inhibiting the genomic accessibility of myeloid monocytic TFs like Irf8 and Pu.1, while promoting the accessibility of erythroid TFs such as Gata1, Scl, and Klf1 [17]. In-depth mechanistic studies have clarified how TET2 influences the differentiation and function of cells across different lineages, as will be elaborated subsequently (Fig. 2A).

TET2 is required for the humoral immune response. It is involved in the regulation of the proliferation of germinal centers (GC), class switch recombination (CSR), and terminal differentiation of B cells. The loss of *TET2* disrupts the transit of B cells through GC, causing GC hyperplasia, impaired CSR, blockade of plasma cell differentiation, and a preneoplastic phenotype [31, 32]. TET2 also has an important function in T cell differentiation. Two antagonistic transcriptional repressors, Blimp-1 and Bcl-6, are known to direct CD8 + T cell memory differentiation. *TET2* loss leads to hypermethylation of the *PRDM1* genomic locus, and alters the relative expression of Blimp-1 and Bcl-6. *TET2* loss promotes early acquisition of a memory CD8^{+} T cell fate and increases the frequency of central memory T cells, enhancing their proliferation in response to antigen-presenting cells without disrupting effector function [33–35]. TET2 coordinates with multiple transcription factors including Foxo1 and Runx1, to regulate the epigenetic landscape of CD4^{+} T cells, thereby controlling differentiation toward T helper 1 cell (Th1) and T follicular helper (Tfh) cells. Naïve antigen-specific CD4^{+} T cells proliferate and differentiate into Th1 and Tfh subsets. TET2 is necessary for full Th1 lineage commitment. TET2-deficient CD4^{+} T

(See figure on next page.)

Fig. 2 Role of TET2 in hematopoiesis and leukemogenesis. **A** *TET2* deficiency affects the differentiation of multiple lineages of hematopoietic stem and progenitor cells (HSPCs) and has complex effects on the function of immune cells. Key abbreviations: CLP (common lymphoid progenitors), CMP (common myeloid progenitors), GMP (granulocyte and monocyte progenitors), LMPP (lymphoid-primed multipotent progenitors), MEP (megakaryocyte-erythroid progenitors), MPP (multi-potent progenitors), OC (osteoclasts), Tcm (central memory T cell), Tfh (T follicular helper cell), Th1 (T helper 1 cell). **B** *TET2* is one of the most commonly mutated genes in clonal hematopoiesis. *TET2* mutations lead to clonal hematopoiesis with some important phenotypic changes, including enhanced self-renewal capacity and myeloid bias, abnormal differentiation, enhanced inflammatory response and immune function, and increased mutation incidence. The generation of driver gene mutations is an important event in the occurrence of malignant tumor transformation. **C** Strategies for inhibiting TET2 mutant clones. The left panel presents drugs that exhibit targeted lethal effects on TET2 mutant clones, along with their mechanisms of promoting apoptosis. The right panel illustrates the inhibition of mutant clones by restoring TET protein function or by directly facilitating DNA demethylation to restore the normal 5mC/5hmC spectrum





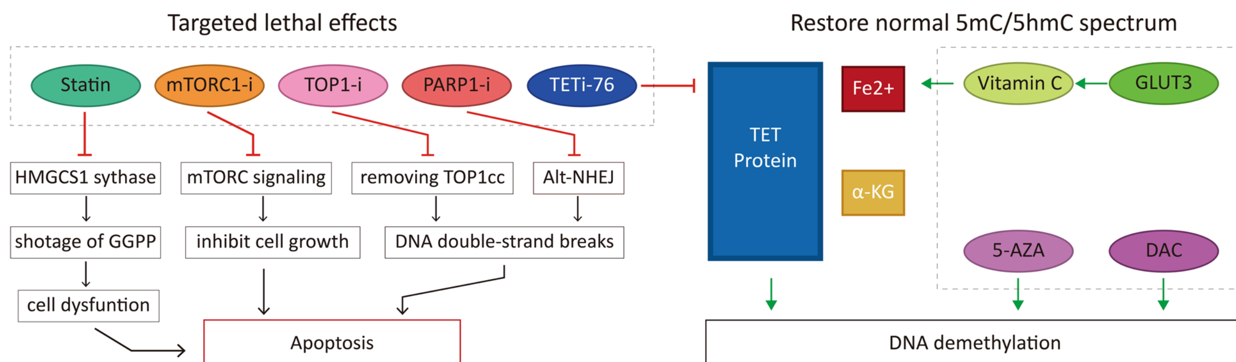


Fig. 2 (See legend on previous page.)

cells showed less differentiation to Tfh and preferentially differentiate into highly functional germinal center Tfh cells that provide enhanced help for B cells [36, 37]. *TET2* knockout reshapes chromatin accessibility and enhances the transcription of tumor-suppressive genes in tumor-infiltrating lymphocytes (TILs). These changes help the binding of TF associated with $CD8^+$ T cell activation. The assay for transposase-accessible chromatin with high-throughput sequencing (ATAC-seq) analysis shows that differentially accessible regions are mainly enriched in the bZIP and ETS motifs. The ETS family of TF, including ETS1 and ELFs, were enriched in $TET2^{MT}$ cells and contributed to augmented $CD8^+$ T cell function following *TET2* depletion. Single-cell RNA-sequencing analysis suggested that TET2-deficient TILs exhibit effector-like features and their antitumor activity was significantly enhanced [38]. Simultaneous deletion of *TET2* and *TET3* impaired the expression of key lineage-specifying factors T-bet and ThPOK, leading to dysregulated development of invariant natural kill T cells (iNKT cells) skewing toward the NKT17 lineage. These iNKT cells displayed an uncontrolled expansion dependent on the nonclassical major histocompatibility complex (MHC) [39, 40]. Experiments based on samples from myelodysplastic syndrome (MDS) patients found that *TET2* mutations lead to phenotypic defects in circulating NK cells. *TET2* mutations lead to hypermethylation of key genes for cytotoxicity and cytokine release by NK cells, reducing the expression of Killer Immunoglobulin-like receptors (*KIR*), perforin, and TNF-α. In vitro, inhibition of *TET2* in NK cells of healthy donors also reduces their cytotoxicity [41].

TET2 is essential for the maintenance of myeloid cell function. Transcriptional analysis reveals that the inflammatory response pathway is aberrantly upregulated in *TET2* mutant leukemic cells. MHC II^{hi} inflammatory monocytes are part of the leukemic infiltrate but lack leukemia-initiating capacity, which can be detected in old $TET2^{MT}$ mice. *TET2* loss results in the skewing of myelopoiesis toward the production of proinflammatory MHC II^{hi} monocytes. Inflammatory signals such as LPS can accelerate the production of MHC II^{hi} monocytes in $TET2^{MT}$ mice [42–44]. Neutrophils with *TET2* mutations are characterized by low granule content and low density, with hypermethylated and more compacted chromatin. They shift toward more primitive transcriptional stages and possess a higher repopulating capacity. Their phagocytic capacity and the neutrophil extracellular traps (NETs) produced by $TET2^{MT}$ neutrophils had a significantly smaller area. These differences result in the heterogeneity of neutrophils in tissues and blood, leading to exacerbated inflammatory responses but suppressed antimicrobial effector functions [45, 46].

In addition, *TET2* mutations can lead to ineffective erythropoiesis. *TET2* defects in stem cells lead to increased phosphorylation of c-Kit and decreased expression of its negative regulator SHP-1. At later stages, TET2-deficient progenitors expressed normal surface markers but exhibited stem cell factor (SCF)-dependent hyperproliferation and impaired differentiation of human colony-forming unit-erythroid (CFU-E) cells. AXL expression was increased in these abnormal progenitor cells with increased activation of AKT and ERK. They exhibited impaired differentiation which resulted in ineffective erythropoiesis [47, 48].

Overall, the loss of *TET2* leads to a general differentiation bias toward the myeloid lineage. However, the function of various myeloid cell lineages is suppressed, weakening the phagocytic functions of monocyte-macrophages and neutrophils, leading to ineffective erythropoiesis. At the same time, it also inhibits the functions of B lymphocytes and NK cells. Interestingly, it promotes various functions of T cells by enhancing memory differentiation and activation. Therefore, TET2 deficiency leads to abnormal differentiation and functional changes in HSPCs, affecting the complex crosstalk between immunity and tumorigenesis.

Germline *TET2* mutations cause spontaneous tumor and immune deficiency

Experiments with germline *TET2* knockout mice by several different groups have shown that mice with defects in the *TET2* gene were more likely to die early in life. These mice showed a predominance of erythroid or myeloid cells, as well as multiple characteristics of chronic myelomonocytic leukemia (CMML). Subsequent tests found that these moribund/deceased $TET2^{-/-}$ mice developed a wide spectrum of lethal myeloid malignancies, including MDS with erythroid predominance, CMML, MPD-like myeloid leukemia, and myeloid leukemia with maturation [13, 18, 49]. These results demonstrate that deletion of *TET2* is sufficient to cause myeloid malignancies in mice.

However, the presence of asymptomatic carriers of *TET2* mutation, such as patients with CHIP, suggests that a *TET2* mutation alone is not sufficient to cause a tumor though it can cause tumor predisposition including advantages in self-renewal and proliferative ability. A significant increase in mutations in other genes was detected in *TET2* knockout mice that developed spontaneous tumors, suggesting that *TET2* mutation leads to a higher mutation burden. Exome sequencing and single-cell sequencing show that these mutations enrich at genome sites that gained 5-hydroxymethylcytosine, suggesting that the absence of *TET2* leads to genomic instability, which predisposes cells to accumulate other

mutations [18]. From these results, it can be inferred that additional mutations are required for malignant transformation.

Experimental studies in lineage-specific *TET2*-knockout mice have provided further insights into the role of *TET2* in hematopoiesis and leukemia. Specifically, inactivation of TET2 in HSPCs, but not in more differentiated cells, can induce myeloid malignancies. This indicates that the loss of TET2 function in early hematopoietic cells is critical for the development of these malignancies [50].

Patient case reports are consistent with the results of these mouse experiments. In de novo AML, the mutation profiles of *TET2* mutant ($TET2^{MT}$) and *TET2* wild-type ($TET2^{WT}$) cases differ significantly. $TET2^{MT}$ cases exhibit higher frequencies of mutations in genes such as *NPM1*, *DNMT3A*, *CEBPA*, *ZRSR2*, *ASXL1*, and *NRAS*. This distinction highlights the unique molecular landscape of $TET2^{MT}$ AML compared to $TET2^{WT}$ AML. Furthermore, the prevalence of certain mutations varies across different tumor types. For example, mutations in *NPM1*, *FLT3-ITD*, *CBL*, *c-KIT*, and specific isolator mutations are more common in AML compared to MDS and MDS/MPN. These mutations are frequently observed in AML, indicating that concomitant mutations might influence tumor type and progression [17].

The extensive literature on human TET2 deficiency focuses exclusively on the more frequent somatic variations, mainly in the context of CHIP, myeloid, and lymphoid malignancies [51]. Recent reports of autosomal recessive germline TET2 deficiency showed phenotype changes consistent with the above mouse experiments (Fig. 2B). These patients with biallelic or monoallelic germline mutations are susceptible to lymphoid and myeloid malignancies, and it should be noted that they unusually have clinically varying degrees of immunodeficiency and an autoimmune lymphoproliferative syndrome (ALPS) [51, 52]. Similarly, a prior history of thyroid disorders was noticed in a family line of patients with germline *TET2* mutations [53]. Impaired lymphocyte function may explain these immune abnormalities. Patient-derived induced pluripotent stem cells showed a skewed and boosted clonogenic potential toward the myeloid lineage and impaired differentiation of erythroid cells [51]. Their T cells showed expanded double-negative T cells, depleted follicular helper T cells, and impaired apoptosis. TET2-deficient B cells showed defective CSR and impaired B-cell terminal differentiation. These findings explain the occurrence of immunodeficiency. The clinically relevant autoimmunity is found to be associated with impaired T cell apoptosis [51]. In addition, some of these patients showed signs of an enhanced monocyte- and macrophage-mediated inflammatory response associated with increased activation of NLRP3 inflammasomes with atherosclerotic plaque formation. These results are consistent with the enhanced monocyte–macrophage-mediated inflammatory response in previous mouse experiments [54].

These findings support the hypothesis that dysregulation of inflammatory pathways and immune environment disruptions contribute to tumor susceptibility, while subsequent oncogenic mutations drive malignant transformation (Fig. 2B). Inflammatory pathways are involved in the mechanism of CH, suggesting that inflammation may play a role in tumorigenesis by creating and maintaining a proinflammatory environment. *TET2*-knockout HSPCs show abnormal immune cell differentiation and function. Additionally, immunodeficiencies and autoimmune syndromes observed in patients with germline *TET2* mutations indicate that impaired antitumor immunity contributes to tumor development.

In summary, TET2 deficiency enhances self-renewal and proliferative advantage, along with genetic instability, facilitating the acquisition of additional mutations. These factors collectively lead to increased tumor susceptibility (Fig. 2B). Malignant transformation is likely driven by subsequent genetic events, particularly aggressive oncogenic mutations. Thus, *TET2* mutations can be seen as catalysts in tumorigenesis and significant risk factors. While not necessary for cancer development, nor do they invariably lead to cancer, *TET2* mutations significantly promote its occurrence.

TET2 Mutation landscapes and clinical features of AML

TET2 Mutation landscapes of AML

TET2 gene mutation is a common genetic variation in AML. In several different AML cohorts, *TET2* mutations were identified in 7%–28% of adult patients, right behind the most common mutated genes (*FLT3*, *NPM1*, *DNMT3A*, and *NRAS*) [7–10]. *TET2* mutations, like mutations in other epigenetic regulator genes, often arise as ancestral events in pre-leukemic stem cells [2]. Cross-sectional analysis based on VAF indicated that $TET2^{MT}$ are first hits in 40% of $TET2^{MT}$ cases [14]. Over 40% of patients had more than one *TET2* mutation, and *TET2* mutations were concomitantly observed with mutations in *ASXL1*, *SRSF2*, *NPM1*, *FLT3*, *RUNX1*, *CEBPA*, *CBL*, *KRAS* and *DNMT3A* [8, 14]. Interestingly, *TET2* mutations were mutually exclusive of *IDH1/2* mutations [8]. Mutations of *TET2* were distributed all over the gene and most commonly affected the largest exon 3 and exon 11 [7, 8]. Frameshift and nonsense mutations resulting in protein truncation and missense mutations in CRD or DSBH domain almost all lead to the loss of function of TET2 dioxygenase [11].

As described earlier, this leads to abnormal changes in DNA methylation profiles and subsequent complex effects.

Correlation between *TET2* mutation and clinical features of AML

In clonal hematopoiesis, *TET2* mutations were closely associated with higher age, and the VAFs of $TET2^{MT}$ increased with patient age [9, 14, 15]. AML patients with *TET2* mutations had significantly higher white blood cell counts, and in some studies, lower platelet counts and higher blast counts [7, 8, 55]. Analyses of patient chromosome data revealed that *TET2* mutations were associated with normal karyotype and enriched in intermediate-risk cytogenetics or CN-AML patients [8, 55]. The clinical data of these cohorts did not show significant differences in other clinical and laboratory characteristics.

The prognostic role of *TET2* mutations in AML is limited. In most AML cohorts, event-free survival (EFS), incidence of relapse, and overall survival (OS) showed no significant differences between patients with *TET2* mutations and those without it [7, 14, 55, 56]. Mutations in *TET2* are enriched in cytogenetically defined intermediate-risk AML or CN-AML where the frequency of *TET2* mutations is 18%–23% [57]. Survival analyses of this subtype found that *TET2* mutations were associated with reduced OS, shorter EFS, and a higher probability of relapse, but these differences were not consistent and statistically significant in different cohorts [7, 8].*TET2*-mutated patients within the favorable-risk group had a shorter EFS and a higher probability of relapse [8]. However, in some studies, the prognostic effect of *TET2* mutations in these AML subtypes is also not supported [7]. When the VAF of *TET2* mutations was considered, survival was worse in patients with larger VAF of $TET2^{MT}$ [14, 58]. In addition to the mutation itself, several studies have focused on the prognostic effects of *TET2* transcripts and the demethylation of its target genes. Although *TET2* transcripts have a limited prognostic effect, patients with low levels of TET2-specific differentially methylated CpGs had markedly longer OS [59].

The results of these studies did not support the presence of *TET2* mutation as a robust molecular prognostic marker. CHIP-associated mutations including *TET2* often persist at high levels even at cytological remission of AML, and relapsed samples could be devoid of the original *TET2* mutations at diagnosis [55, 60, 61]. So it is not correlated with the incidence of relapse and may not be a good marker for monitoring minimal residual disease.

Therapeutic values of *TET2* mutations in AML

As previously mentioned, the *TET2* mutation has a high variant frequency as a founder mutation, and the population carrying this mutation may persist from diagnosis through remission or relapse. *TET2* mutations give mutant cell clones a survival advantage by enhancing cell self-renewal and proliferation, reducing the effect of drugs, and promoting relapse by altering the degree of differentiation at the same time [62].

Many studies have explored the therapeutic value of targeting *TET2* mutations from two directions: restoring TET2 function and inhibiting *TET2* mutant clones. Restoring the genomic methylation modification status of *TET2* mutant cell populations or eradicating *TET2* mutant cell populations to promote the eradication of tumor clones may be promising leukemia treatment strategies (Fig. 2C).

Restoration of TET2 function

Vitamin C as a reducing agent enhances the activity of a large class of dioxygenases, including TET dioxygenases, by maintaining the reducing state of the Fe^{2+} ion [63]. Experiments with mice carrying the *TET2* inactivated mutation have shown that vitamin C promotes DNA demethylation by enhancing the activity of residual TETs (including TET1/3 and monoallelic mutated *TET2*). It could reverse the epigenetic consequences caused by TET2 deficiency and restore normal 5mC/5hmC spectrum [64]. The restoration of TET2 function could block aberrant HSPCs self-renewal and myeloid disease progression, even in the complete absence of functional TET2 [65]. In addition, one study has shown that vitamin C levels are significantly decreased in patients with AML at the time of initial diagnosis, further decreasing during disease progression and returning to normal upon achievement of CR [66]. Therefore, vitamin C could have therapeutic potential for AML patients with *TET2* mutations. However, in clinical application, the beneficial effect of treating those patients with vitamin C remains controversial, possibly due to the limited uptake of vitamin C by malignant cells [67, 68].

The GLUT3 encoded by the *SLC2A3* gene is the major transporter for vitamin C in AML cells; the knockdown of endogenous GLUT3 expression is sufficient to abolish the effect of ascorbic acid completely. Further study showed that upregulating the expression of GLUT3 could improve vitamin C-induced TET2 restoration [68, 69]. These studies suggested that the antileukemic effect of vitamin C treatments in AML can be improved, potentially acting as a promising adjunctive therapeutic agent for leukemia.

Hypomethylation agent

5-azacytidine (AZA) and 5-aza-2'-deoxycytidine (Decitabine, DAC) could be incorporated into DNA and target DNA methyltransferases (DNMTs) for degradation, inhibit DNA methyltransferases, and decrease the methylation of cytosine residues [70]. In patients with MDS, T-ALL, and AML, the presence of *TET2* mutations could sensitize cells to treatment with AZA and predict a higher response rate [71–74]. Treatment with AZA reverted 5hmC profiles, reduced the competitive advantage of *TET2* KO cells, and slowed the expansion of *TET2*-mutant clones in vivo [75].

Selective inhibition of TET2 protein

Analysis of mutations in patient cohorts of AML and MDS showed that *TET2* mutations and *IDH1/2* mutations were mutually exclusive. Since increased levels of D-2-hydroxyglutarate (D-2HG) produced by mutated *IDH1/2* enzymes could inhibit TET enzymatic activity, cells with *TET2* defects may not survive in the presence of *IDH1/2* mutations due to the inability to maintain minimum residual TET activity [76, 77]. This inspired the design and development of selective inhibitors of TET protein to inhibit malignant cell clonal using this targeted lethal effect. TETi76, a selective small-molecule inhibitor, can reduce cytosine hydroxymethylation and limit the clonal growth of *TET2* mutant, while its effects on normal HSPCs are reversible. This preferential inhibition of *TET2* mutant clones has huge therapeutic implications in leukemia [77]. Inhibitors that specifically target the enzymatic activity of TET proteins have also been reported, but their potential use for anti-leukemia has not been thoroughly studied [78].

Other drugs

Studies of TET2/3-deficient DKO mice have revealed that TET proteins influence the expression of DNA damage repair genes in myeloid cells [79]. TET2-deficient cells relied on PARP1-mediated alternative non-homologous end-joining (Alt-NHEJ) for protection from the toxic effects of spontaneous and drug-induced DNA double-strand breaks, making these cells sensitive to PARP1 inhibitors [80]. Similarly, Tyrosyl-DNA phosphodiesterase 1 (TDP1) is an important enzyme for removing TOP1 cleavage complexes (TOP1cc). The aberrantly low levels of TDP1 in TET2-deficient cells produce sensitivity to TOP1-targeted drugs [81]. Both PARP1 inhibitors and TOP-1 targeted drugs could selectively kill *TET2*-mutant HSPCs, but the significant DNA damage limited their therapeutic value. Drug screening tests conducted in zebrafish models and AML patient samples have also identified several drugs with targeted effects. The exportin 1 (XPO1) inhibitor is found to selectively kill *TET2*-mutant HSPCs in zebrafish models, while this inhibition can be tolerated by non-neoplastic cells. [82]. AML patient samples with *TET2* mutations were found to have a strong response to combination therapy with the STAT5 inhibitor and the MCL1 inhibitor [83].

Further studies of the biological effects of *TET2* mutations have also uncovered some potential targeting therapies. A recent study uncovered the function of TET2 in suppressing mTORC1 signaling and inhibiting cell growth. TET2 negatively regulates the urea cycle and arginine production, which suppresses mTORC1 signaling, thereby inhibiting cell growth and promoting autophagy. TET2 deficiency sensitizes tumor cells to mTORC1 inhibition [84]. Findings on the role of TET2 in the regulation of lipid metabolic processes make statins a potential therapeutic strategy. TET2 directly regulates the expression of HMG-CoA synthase (HMGCS1) expression and the mevalonate pathway. TET2 deficiency leads to a shortage of GGPP, which is essential for post-translational prenylation of many GTP-binding proteins, resulting in cell dysfunction. Treatment with statin exaggerates the crisis of GGPP and leads to increased cell apoptosis, which is encouraging because it makes a potential therapeutic strategy using an already approved safe medicine [85].

In addition, a high-throughput reporter screen identifies a large network of miRNAs that inhibits *TET2* 3' UTR, but their therapeutic effects on TET2-deficient tumor cells have not been studied [86]. These inhibitors of TET2 proteins reduce TET2 proteins to lethal levels by inhibiting the activity of residual TET2 proteins in cells that are already TET2-deficient. This reversible and transient inhibitory effect avoids adverse effects on normal cells. However, the therapeutic value of these currently identified inhibitors is limited by their effects on normal cell function and the lack of more in-depth studies.

The exploitable value of *TET2* mutation in *CAR*-T therapy

Another interesting direction is the *TET2* modification in enhancing the efficacy of CAR-T cells. The impact of TET2 defects on the efficacy of CAR-T cell therapy was first highlighted in a case study by Joseph et.al [35]. In a patient with chronic lymphocytic leukemia (CLL) treated with CAR-T cell therapy, lentiviral vector-mediated insertion of the CAR transgene disrupted the methylcytosine dioxygenase *TET2* gene. Sequencing analysis of the T cell receptor beta repertoire indicated that 94% of the CD8^{+} CAR T cell repertoire derived from a common ancestor clone at the peak of the response. These CAR T cells showed an unexpectedly significant antitumor effect, enabling the patient to achieve complete remission. Followed experimental knockdown of *TET2* recapitulated the enhancing effect in CAR-T cells [35]. These

findings highlighted the potential of *TET2* modification to enhance T cell immunity and CAR T cell therapy.

However, the main concern is that *TET2* is a cancer suppressor gene with extensive and complex regulatory functions. Knockout of the *TET2* gene to enhance CAR T cell function carries a significant risk of secondary tumor development. It has been reported that loss of *TET2* could lead to unexpected BATF3-induced antigen-independent clonal expansions of CAR T cells [87]. Exploiting its proliferative effect without causing excessive amplification is a great challenge. Researchers are trying to figure out how *TET2* loss enhances CAR-T effectiveness by affecting more specific downstream genes. Most of the CAR T cells in the reported CLL patient had a central memory phenotype at the peak of in vivo expansion, supporting that *TET2* loss promotes the development of memory CAR T cells which could lead to robust antitumor activity. Further investigation of this phenomenon has revealed the important role of the transcription factor thymocyte selection-associated high mobility group box protein (TOX) and TOX2 proteins in regulating T cell exhaustion. High levels of TOX2 expression are sufficient to increase central memory CAR T cell differentiation, while it does not improve CAR T function because of the up-regulation of exhaustion precursor pathways [88]. One significant limitation of CAR-T cell therapy is the limited in vivo expansion and persistence of CAR-T cells [89]. Further study of these specific downstream genes will help to understand the mechanism of CAR-T cell effects and promote the development of durable CAR-T therapies.

Since *TET2* mutations are not driving mutations in malignant tumors, restoring the function of TET2 and thereby suppressing tumor cells may not be sufficient to eliminate tumor clones. So, drugs that restore TET2 function may be more suitable as an adjuvant to a conventional treatment regimen. Targeted killing of cells harboring *TET2* mutations may be a more potent approach, but it is limited by the lack of ideal drugs so far. Among these therapeutic applications, the modification of *TET2* in CAR-T cells is a unique modality with the potential for intensive research.

Conclusion

The role of *TET2* mutations in the pathogenesis of AML underscores their importance in the disease's molecular landscape and therapeutic strategies. TET2 serves as a key regulator of DNA demethylation and epigenetic modification. *TET2* mutations lead to abnormal epigenetic patterns, significantly affect the function and differentiation of HPSCs, and are important genes for clonal hematopoiesis formation.

The impact of *TET2* mutations on processes such as cell proliferation and clonal evolution promotes the occurrence of leukemia. These roles highlight their importance in the molecular landscape and therapeutic strategies of AML. Understanding the interactions between *TET2* mutations and other genetic and epigenetic factors and the mechanisms that promote leukemogenesis can help with early treatment of leukemia, overcoming treatment resistance, and preventing disease recurrence.

Furthermore, *TET2* mutations provide promising therapeutic targets. Inhibitors and other drugs that target *TET2* mutations, while still in the early stages of development, have shown potential to aid in the treatment of AML. Additionally, modification of *TET2* may enhance the efficacy of CAR-T cell therapy despite challenges related to off-target effects and long-term safety. These findings open new avenues for immunotherapy in AML.

In summary, *TET2* mutations may play a role as key catalysts in AML pathogenesis and progression, and although challenges remain in fully elucidating the downstream effects of *TET2* variants and translating these findings into clinical practice, ongoing research is expected to pave the way for the development of new treatment strategies provide valuable insights.

Abbreviations

5caC 5-Carboxycytosine
5fC 5-Formylcytosine
5hmC 5-Hydroxymethylcytosine
5mC 5-Methylcytosine
ALPS Autoimmune lymphoproliferative syndrome
Alt-NHEJ Alternative non-homologous end-joining
AML Acute myeloid leukemia
AP site Apyrimidinic site
ATAC-seq Assay for transposase-accessible chromatin with high-throughput sequencing
AZA 5-Azacytidine
BER Base excision repair
CFU-E Colony-forming unit-erythroid
cGAS-STING Cyclic GMP-AMP synthase-stimulator of interferon genes
CH Clonal hematopoiesis
CHIP Clonal hematopoiesis of indeterminate potential
CLL Chronic lymphocytic leukemia
CMML Chronic myelomonocytic leukemia
CSR Class switch recombination
D-2HG D-2-Hygroxyglutarate
DAC Decitabine
DNMTs DNA methyltransferases
DSBH Double-stranded β-helix fold
EFS Event-free survival
GC Germinal center
HMG-CoA β-Hydroxy β-methylglutaryl coenzyme A
HMGCS1 HMG-CoA synthase
HSPC Hematopoietic stem and progenitor cell
HSPCs Hematopoietic stem and progenitor cells
iNKT cells Invariant natural kill T cells
KIR Killer immunoglobulin-like receptor
LSC Leukemia stem cell
LSCs Leukemia stem cells
m5C Methyl-5-cytosine
MDS Myelodysplastic syndrome
MHC Major histocompatibility complex
NETs Neutrophil extracellular traps

OS	Overall survival
SCF	Stem cell factor
STING	Stimulator of interferon genes
TDG	Thymine DNA glycosylase
TDP1	Tyrosyl-DNA phosphodiesterase 1
TET	Ten–eleven translocation
TF	Transcription factor
TFs	Transcription factors
TILs	Tumor-infiltrating lymphocytes
TOX	Thymocyte selection-associated high mobility group box protein
VAF	Variant allele frequency
α-KG	*α*-Ketoglutarate

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Data availability
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Declarations

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Not applicable.

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