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The impact of epigenetic modifications on allogeneic hematopoietic stem cell transplantation

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The field of epigenetics studies the complex processes that regulate gene expression without altering the DNA sequence itself. It is well established that epigenetic modifications are crucial to cellular homeostasis and differentiation and play a vital role in hematopoiesis and immunity. Epigenetic marks can be mitotically and/or meiotically heritable upon cell division, forming the basis of cellular memory, and have the potential to be reversed between cellular fate transitions. Hence, over the past decade, there has been increasing interest in the role that epigenetic modifications may have on the outcomes of allogeneic hematopoietic transplantation and growing enthusiasm in the therapeutic potential these pathways may hold. In this brief review, we provide a basic overview of the types of epigenetic modifications and their biological functions, summarizing the current literature with a focus on hematopoiesis and immunity specifically in the context of allogeneic hematopoietic stem cell transplantation.

KEYWORDS

bone marrow transplant (BMT), allogenetic hematopoietic stem cell transplantation, DNA methylation, epigenetics, GvHD, histone modifications, non-coding RNA

Introduction

Every cell in the human body carries the same genetic code, yet only a subset of genes is actively expressed at any given time-point in any given cell, in an intricate process that is orchestrated by epigenetics. In the Greek language, "epi" signifies on, upon, or over. Accordingly, the field of epigenetics studies the processes that affect gene expression without altering the DNA sequence itself, the sum of which is described as the epigenome (1, 2).

Epigenetic modifications include DNA methylation, histone modification, Chromatin remodeling, and non-coding RNA regulation (1–3). In brief, a nucleosome, chromatin's basic structural unit, is comprised of negatively charged DNA packed around a positively charged histone octamer. Chemical alterations to this complex can allow or prevent access of the transcriptional machinery to the DNA sequence. Broadly, epigenetic regulators may be classified as "writers", "readers", and "erasers". Writers include a wide variety of enzymes that introduce modifications on DNA and histones, including DNA methyltransferases, histone methyltransferases, histone acetyltransferases. Readers encompass proteins with

domains that recognize and bind specific epigenetic modifications, such as methyl-CpG-binding proteins, histone methylation binding proteins, and histone acetylation binding proteins. Finally, erasers represent proteins which actively remove epigenetic marks and reverse the effects on transcription, such as TET (ten-eleven translocation) proteins which catalyze cytosine demethylation, histone demethylases, and histone deacetylases (4).

Many of these changes can be mitotically and/or meiotically heritable on nascent daughter chromatin strands upon cell division. This results in a type of cellular memory termed epigenetic memory. At the same time, epigenetic modifications are characterized by plasticity in response to factors intrinsic and extrinsic to the cell, such as environmental stimuli (5–7). Therefore, not only can these modifications somatically be inherited after cell division and repress target gene transcription, but they can also be reversed during transitions between cellular fates, making them the focus of significant scientific investigation.

Mechanisms of epigenetic modification

DNA methylation is the most widely studied form of epigenetic modification and generally results in gene silencing. It primarily involves methylation of cytosine residues almost exclusively in the context of CpG dinucleotides. CpG dinucleotides cluster in regions termed CpG islands, where approximately 60% of human gene promoters are located. However, tissue-specific DNA methylation and differential methylation associated with reprogramming are mostly located in regions adjacent to each side of a CpG island, termed shores (1–3). Of the five known human DNA methyltransferases, DNMT1 is thought to be primarily responsible for maintenance methylation, while DNMT3A and DNMT3B are the primary *de novo* methyltransferases. DNMT3L lacks enzymatic activity but interacts with other enzymes and plays a role in maternal imprinting (8, 9).

Histone modifications, at various sites, include methylation (which most commonly represses transcription), acetylation (usually activating in nature), phosphorylation (which contributes to chromatin remodeling and assists in DNA repair), ubiquitylation, and others (1–3, 7). These modifications, along with histone variants within nucleosomes (histones characterized by minor differences in their amino acid sequence from their canonical counterpart) can also result in nucleosome repositioning and chromatic remodeling, such that transcription sites are more or less accessible to interact with transcriptional machinery (1, 3). These chromatin markers and the associated epigenetic signatures have shown to be reversible (1).

Lastly, non-coding RNAs (ncRNAs), particularly regulatory ncRNAs, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), small interfering RNAs (siRNAs) and piwi-interacting RNAs (piRNAs), are transcribed (but non-translated) RNA molecules believed to fine-tune gene expression by contributing to gene silencing. Moreover, non-coding RNAs are known to interact with and guide chromatin-modifying complexes to the appropriate genomic targets (1–3, 5, 7). Notably, the aforementioned epigenetic mechanisms are functionally linked and interdependent, with continuous cross-talk involving both positive and negative feedback.

Epigenetics in human development, health, and disease

Epigenetic processes appear to have an instrumental role in human development, health, and disease (7, 10). In the earliest stages of embryogenesis, the epigenome is "reset". As the zygote, in its one cell glory, transitions from totipotency to pluripotency in the blastocyst stage, complex epigenetically controlled mechanisms guide each cell towards a differentiated state and limit plasticity to maintain a fixed cell type (11, 12). Highlighting the importance of epigenetics in embryogenesis is the fact that *Dnmt3a*- and/or *Dnmt3b*-null mice die during gestation or shortly after birth (13).

As suggested, epigenetic dysregulation can disrupt cellular homeostasis and has been implicated in various diseases (6, 7, 14, 15). Disorders affecting genomic imprinting can result in distinct clinical syndromes, such as Beckwith-Wiedemann, Russell-Silver, and Prader-Willi/Angelman syndromes (16), while germline *DNMT3A* mutations can result in Tatton-Brown-Rahman syndrome (17, 18). In the early eighties, global DNA hypomethylation was first described in cancer. Subsequent work revealed that focal DNA hypermethylation of tumor suppressor genes facilitates stem-like cell behavior in the pathophysiology of carcinogenesis (19–22). Mutations in *DNMT3A* (the product of which catalyzes *de novo* DNA methylation), *TET2* (responsible for regulated demethylation), and *ASXL1* (involved in chromatin regulation), are the most frequently described mutations in clonal hematopoiesis, including clonal hematopoiesis of indeterminate potential (CHIP) and myeloid malignancies such as myeloproliferative neoplasms (MPN), myelodysplastic syndrome (MDS), and acute myeloid leukemia (AML) (23–25). CHIP has been recently identified as a new precursor state for myeloid malignancies (26, 27). Specific types of histone modifications and microRNAs have also been linked to a multitude of malignancies (28–31). In this context, an ever-increasing number of epigenetically targeted therapies have been developed and applied in the care of cancer patients, whether alone or in combination with traditional chemotherapy, targeted agents, or immunotherapy (32, 33). Epigenetic mechanisms with therapeutic potential have also been implicated in neurodegenerative disorders (3, 34).

Epigenetic regulation of hematopoietic stem cells, before and after transplantation

Hematopoietic stem cells (HSCs) are characterized by self-renewal and pluripotency, features that are of paramount importance to the biological functions of hematopoiesis and immunity. As multipotent progenitors arise from HSCs and further commit to the myeloid or lymphoid lineage, epigenetic

regulators define the major differentiation and maintenance events (14). In particular, DNA methylation plays a crucial role in these processes. Epigenetic factors are also associated with cellular senescence, the inevitable cessation in proliferation that characterizes biological aging. In HSCs, cellular aging is associated with a relative increase in the myeloid component, enhanced autoimmunity, accrual of DNA damage, and an increased risk of hematologic neoplasms (35). Genome-wide studies of HSCs show distinct differences in the epigenomic landscape of aging cells with several regions of differential DNA methylation having potential relevance for age-related disease (36). *Dnmt1* deletion in murine HSCs results in rapid death from profound pancytopenia due to absence of all HSCs and progenitors, while low-level *Dnmt1* expression results in a marked decrease of lymphoid progenitors and decreased self-renewal capacity in serial transplantation experiments (37). *Dnmt3a/Dnmt3b*-deficiency in murine HSCs leads to a decline in their differentiation potential with accumulation of hematopoietic progenitors in the marrow. Furthermore, *Dnmt3a*-null and *Tet2*-null cells have a competitive expansion and survival advantage in serial transplantation experiments (38–43). ASXL1 proteins are epigenetic regulators that recruit chromatin modification complexes and transcription factors; in mice, *Asxl1* deficiency in HSCs results in myelodysplasia with accumulation of hematopoietic progenitors but decreased self-renewal, and serial transplantation of *Asxl1*-null HSCs results in acceleration of a lethal myelodysplastic disorder as compared to primary *Asxl1* KO mice (44). *Tet2*-deficient mice demonstrate increase hematopoietic self-renewal and compound *Asxl1* and *Tet2* loss restores the *Asxl1*-loss related self-renewal defect and results in more severe MDS-like features. These findings are in accordance with the fact that *DNMT3A*, *TET2*, and *ASXL1* mutations are some of the most common genetic abnormalities in clonal hematopoiesis and are frequently detected, alone or in combination, in patients with hematological malignancies (23, 45–48).

In the post-transplant setting, allogeneic hematopoietic stem cell transplantation (HSCT) recipients have been found to stably maintain the donor's global methylation status, and differences in global methylation correlate with the evolution of mixed chimerism (49). Moreover, donor methylation levels in the promoters of critical genes such as *IFNG* and *FASL* correlate with the severity of acute graft-versus-host disease (GVHD), suggesting they could be used alongside HLA typing to optimize donor selection (49). Apart from specific DNA methylation signatures, the "epigenetic age" of donor HSCs appears to be cell-intrinsic, and thus remains largely stable after transplantation in concordance with the chronological age of the donor. As such, epigenetic age is not influenced by the recipient's chronological age, even decades after transplantation (50–52). In two separate studies, patients whose donor stem cells exhibited accelerated aging, as determined by the "epigenetic clock", were at higher risk of developing chronic GVHD (53, 54). In xenogeneic murine models of HSCT, this phenomenon is again thought to be cell-intrinsic, rather than host-dependent (55).

Importantly, several studies have now linked donor CHIP to HSCT outcomes. A European study identified 92 clonal mutations in 500 healthy donors over the age of 55; donor CHIP, especially *DNMT3A*-driven CHIP, was associated with increased incidence of chronic GVHD and decreased incidence of relapse or progression. Subsequently, a large US-based study of over 1,700 donors over the age of 40 further confirmed these findings. Additional data suggest that donor *DNMT3A* mutations are independently associated with improved overall survival due to reduced risk of relapse (56–58). Of note, this phenomenon appears to be eliminated by the administration of post-transplantation cyclophosphamide for the prevention of GVHD, suggesting that it is at least partially mediated by *DNMT3A*-mutated donor T-cells, the function of which is altered by cyclophosphamide (58, 59). In these studies, there was a very low risk of donor CHIP evolution to donor cell leukemia (DCL): 2 recipients of 82 mutated grafts in the first study and 6 recipients of 388 mutated grafts in the second (56, 58, 60). No recipients with sole mutations in *DNMT3A* or *TET2* developed DCL. Two smaller studies also examined the CHIP-alloreactivity link: A single-center study found increased risk of acute GVHD but not chronic GVHD and no differences in incidence of relapse; notably, this study included a large number of high-risk patients, with over half of the cohort having active disease at the time of transplantation (61). A more recent study also failed to replicate the results from the larger studies, likely due to the significantly limited sample size (only 25 mutated donor products were identified, with an unusual distribution of CHIP mutations, potentially due to thefact that donors as young as 17 were included) (62). GVHD following liver transplantation (LT-GVHD) is a rare complication, associated with bone marrow failure and a hyperinflammatory state; in a case series of 9 patients where 7 bone marrow samples were available for next generation sequencing, *DNMT3A* mutations were found in 5 out of 7 samples, as compared to 1 of 6 in a LT-non-GVHD cohort (63).

In accord with these clinical observations, laboratory data showed an increase in both acute and chronic GVHD when T-cell lineage-specific *Dnmt3a*-null mice were used as donors in multiple murine allogeneic HSCT models (58, 64). These observations were associated with early proliferation of donor-derived *Dnmt3a*-null T-cells as compared to wild-type T-cells. Furthermore, *Dnmt3a*-null T-cells demonstrated a migration advantage to the gastrointestinal tract and secondary lymphoid organs, enhanced pro-inflammatory cytokine production, and decreased expression of exhaustion and apoptosis markers (64). A comprehensive review of the epigenome and transcriptome of *Dnmt3a*-null donor T-cell subsets post-HSCT, via whole genome bisulfite sequencing and in parallel, bulk RNA sequencing, showed similar global DNA methylation levels to wild-type T-cells but distinct hypomethylation peaks in gene pathways involved with T-cell activation and differentiation. More importantly, donor T-cells lacking DNMT3A provided superior tumor control in graft-versus-leukemia models, corroborating the clinical data cited above (64). In gene-set enrichment analyses of the genes differentially expressed between *Dnmt3a*-null and WT donor T-cells, CD8+ T-cells lacking DNMT3A were highly enriched for effector-like signatures and negatively enriched for exhaustion-like signatures, while CD4+ T-cells were enriched for genes expressed in activated and progenitor cell populations.

These observations are consistent with a growing body of data showing that DNA methylation critically contributes to the functional properties that define T-cell identity. For example, DNMT3A is selectively upregulated 38-fold following T-cell receptor stimulation and subsequently regulates T-helper cell polarization and effector T-cell differentiation, depending on the context of cellular activation (65–67). Following differentiation and activation, the patterns of gene expression that define T-cell subsets are stabilized through DNA methylation. T-cell deletion of DNMT3A enhances the plasticity of T-helper cells by allowing for reprogramming of cytokine expression, and allows CD8+ T-cells to overcome epigenetically-defined exhaustion programs in order to more effectively clear chronic infections (65–71). DNMT3A deletion also appears to enhance the anti-tumor effects of T-cells whether in the context of immune-checkpoint inhibition, chimeric-antigen receptor (CAR) T-cells, or allogeneic HSCT (64, 71, 72). Akin to what was observed in murine models of allo-HSCT, deletion of DNMT3A in CAR T-cells resulted in exhaustion-resistant cells with preservation of the cells' proliferative capacity and ongoing anti-tumor response despite prolonged tumor exposure (72, 73).

Since epigenetic dysregulation is common in neoplasia, and given the reversible nature of epigenetic alterations, pharmacologic agents targeting epigenetic regulators are now regularly used in the treatment of cancer patients (32). Azacitidine and decitabine, the two most widely used hypomethylating agents, are nucleoside analogs that bind and inhibit DNA methyltransferases after being incorporated into newly formed DNA. Both drugs have received FDA approval for the treatment of MDS, AML, and chronic myelomonocytic leukemia. However, both agents are non-specific and despite not being categorized as traditional chemotherapy do have cytotoxic potential, giving rise to adverse events secondary to myelosuppression (32). In addition to their anti-tumor effects, the immune-modulatory potential of azacitidine and decitabine is appealing both in the pre- and post-transplantation setting. Prior to HSCT, these agents are used alone or in combination to decrease disease burden and serve as a bridge to transplant, especially in older patients with MDS and AML (74–77). In the post-transplantation period, there is growing interest in strategies that will help prevent relapse, which is a major driver of mortality (77–79). Preclinical and clinical data suggested that azacitidine may mitigate GVHD without compromising graft-versus-leukemia (GVL) activity (80–82). However, a phase III randomized clinical trial of azacitidine maintenance versus observation post-HSCT for high-risk AML/MDS patients failed to improve relapse-free survival (79, 83). Low-dose decitabine may be more promising, whether alone or in combination with other agents (84, 85). Next-generation DNMT inhibitors, such as guadecitabine, appear to have an improved toxicity profile, and non-nucleoside inhibitors, which have the potential to be more potent and selective, are in development (32, 86).

Histone modifications have been widely targeted in the context of neoplasia and allogeneic HSCT, with several agents inhibiting histone deacetylases now commercially available including but not limited to vorinostat, panobinostat, belinostat, and romidepsin (28, 87, 88). Histone modifications contribute to the regulation of proliferation and cytotoxicity in activated T-cells and histone acetylation was one of the first epigenetic modifications to be studied in preclinical models of acute GVHD (87). Histone deacetylase (HDAC) inhibitors were found to decrease the allo-stimulatory function of dendritic cells, a group of potent antigen-presenting cells known to be instrumental in the induction of acute GVHD, as well as enhance natural regulatory T-cell function, and hence reduce GVHD while preserving GVL effects (89–92). As a result, one of these agents, suberoylanilide hydroxamic acid (SAHA, now known as vorinostat) was tested in two phase I/II trials (NCT00810602, NCT01790568; a third, NCT03842696, underway) for the prevention of GVHD in combination with standard therapy and was found to be safe and potentially effective (93, 94). Panobinostat also showed promising results in two phase I/II studies (NCT01111526, NCT02588339) (95, 96). Results from a phase III trial of panobinostat as post-HSCT maintenance therapy are pending (NCT04326764) (79). Enhancer of zeste homolog 2 (EZH2) is a histone methyltransferase that catalyzes histone 3 lysine 27 trimethylation, a modification that represses gene transcription and is thought to be involved in T-cell immune responses (87). Pharmacologic inhibition of histone methylation via DZNep, an inhibitor that depletes EZH2, was found in one study to arrest ongoing GVHD in mice by inducing apoptosis of alloreactive T-cells without inhibiting donor-derived hematopoiesis or GVL activity (97, 98). However, these findings were not replicated with other agents or in a xenogeneic model using DZNep (99).

Bromodomain and extraterminal (BET) proteins regulate chromatin dynamics by binding acetylated lysine residues in histones and nonhistone proteins, including transcription factors; given the therapeutic potential, BET inhibitors targeting the acetyl-binding domains of these proteins have been developed (100). In murine models of GVHD, BET inhibition suppressed GVHD by altering the cytokine expression profiles of dendritic cells and T-cells, with retention of anti-tumor effects, while certain inhibitors also allow for infused Treg expansion as a combinatorial strategy (101, 102). More recently, Snyder et al. reported on two potent and selective BET inhibitors which improve survival and reduce GVHD severity in mice without sacrificing the beneficial GVL effect; PLX51107 is currently being tested in a phase I/II trial for steroid-refractory acute GVHD (NCT04910152) (103). Both EZH2 inhibition and BET-bromodomain inhibition demonstrated activity in preclinical models of chronic GVHD with lung involvement, with evidence of altered transcriptomes in the germinal centers of treated animals (104).

The role of non-coding RNAs, mainly microRNAs, in T-cell immunobiology is well established and is increasingly being explored in the context of hematopoiesis and allogeneic HSCT (105, 106). Several microRNAs are emerging as important regulators of allogeneic T-cells and may prove to be highly sensitive and specific biomarkers for GVHD and useful targets for anti-GVHD oligonucleotide-based therapeutics (105–108). Ranganathan et al., showed increased expression of microRNA-155 (miR-155) in both CD4- and CD8-positive cells following murine allo-HSCT, as well as ameliorated GVHD in multiple KO and antagonist-treated models and worse phenotype in over-

expression models (109). MicroRNA-155 also influences GVHD via its function in recipient dendritic cells. In study by Chen et al., miR-155–deficient dendritic cells cause less severe GVHD through reduced migration and defective inflammasome activation, supported by the fact that *Nlrp3/miR-155* double-knockout allo-HSCT recipient mice had no increased protection from GVHD compared with *Nlrp3−/−* recipients (110). The role of the microRNA-17-92 cluster in allo-HSCT was explored in a similar study that utilized a T cell-specific KO model, and showed reduced GVHD by demonstrating defects in proliferation, cytokine production and α4β7 integrin expression in KO T cells (111). MicroRNA-146a has a protective role in GVHD, and its anti-GVHD effects were demonstrated in several studies, via its function in both allogeneic T-cells and recipient dendritic cells (112–114). MicroRNA-31 promotes murine chronic GVHD via T-cell metabolic pathway regulation (108). Differential microRNA expression has been detected in skin biopsies of patients at the time of onset of cutaneous acute GVHD, and circulating microRNAs encapsulated within extracellular vesicles were found differentially expressed in patients with chronic GVHD (115, 116). Several long non-coding RNAs (lncRNAs) have been found to influence the function of T-cells, but their role in allo-immune responses is still unknown. *Linc00402* was recently identified as a long non-coding RNA that regulates T-cell function in humans and experimental murine models. RNA sequencing was performed on human T-cells after HSCT and solid organ (cardiac) transplant and compared to T-cells from healthy subjects. *Linc00402*, a T-cell specific molecule, was found to be differentially expressed in recipients of allogeneic mismatched unrelated as compared to autologous HSCT patients, and in donor T-cells from patients who underwent cardiac transplantation. In contrast, *in vitro* and murine *in vivo* data showed that T-cell activation and proliferation are inversely related to *Linc00402* expression, and that depletion of *Linc00402* impairs the allogeneic stimulation of T-cells *ex vivo*. The authors hypothesized that higher levels of tacrolimus exposure were the culprit for the preservation of *Linc00402* abundance in allogeneic HLA-mismatched HSCT. Importantly, the tissue-specific and allogeneic context-specific expression of this molecule, along with its immune regulatory properties, make for an appealing therapeutic candidate (117, 118). In a study by Wang et.al, numerous lncRNAs were found to be dysregulated in B cells from patients with chronic graft-versus-host disease (cGVHD) as compared to normal counterparts. Specifically, lncRNAs NONHSAT040475, NONHSAT142151 and FR118417 were found to be strongly associated with the BCR signaling pathway in cGVHD pathogenesis (119). Another class of non-coding RNAs, termed circular RNAs, has been associated with increased relapse risk in AML patients (120).

In sum, the maintenance and differentiation of hematopoietic stem cells require epigenetic regulatory networks that are 1) simultaneously heritable and reversible, 2) responsive to both intrinsic and extrinsic stimuli, and 3) characterized by interdependence between the DNA sequence, transcriptional processes, and the various forms of epigenetic changes. Despite the evident importance of epigenetic modifications in hematopoiesis and alloreactivity, the exact mechanistic underpinnings of how epigenetics operate in each context continue to elude the scientific community. Future challenges exist not merely in uncovering the full spectrum of epigenetic circuits, but equally importantly, in defining exactly how these complex, interactive, and frequently conflicting pathways ultimately affect donor stem cells, immune cell reactivity, and HSCT outcomes. As the field of epigenetics continues to steadily evolve, HSCT patients will undoubtedly benefit from the knowledge that is yet to be fully appreciated.

Author contributions

Conception: YK and KC. Literature review: YK, MD, LG, and KC. Manuscript writing: YK, MD, LG, and KC. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Allis CD, Jenuwein T. The molecular hallmarks of epigenetic control. *Nat Rev Genet* (2016) 17(8):487–500. doi: 10.1038/nrg.2016.59

2. Al Aboud NM, Tupper C, Jialal I. Genetics, epigenetic mechanism. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing LLC (2022).

3. Portela A, Esteller M. Epigenetic modifications and human disease. *Nat Biotechnol* (2010) 28(10):1057–68. doi: 10.1038/nbt.1685

4. Nicholson TB, Veland N, Chen T. Writers, readers, and erasers of epigenetic marks. In: *Epigenetic cancer therapy*. Elsevier Inc (2015). p. 31–66. Available at: https://www.elsevier.com/books/epigenetic-cancer-therapy/gray/978-0-323-91367-6.

5. D'Urso A, Brickner JH. Mechanisms of epigenetic memory. *Trends Genet* (2014) 30(6):230–6. doi: 10.1016/j.tig.2014.04.004

6. Feinberg AP. The key role of epigenetics in human disease prevention and mitigation. *N Engl J Med* (2018) 378(14):1323–34. doi: 10.1056/NEJMra1402513

7. Zhang L, Lu Q, Chang C. Epigenetics in health and disease. *Adv Exp Med Biol* (2020) 1253:3-55. doi: 10.1007/978-981-15-3449-2_1

8. Hata K, Okano M, Lei H, Li E. Dnmt3L cooperates with the Dnmt3 family of de novo DNA methyltransferases to establish maternal imprints in mice. *Development* (2002) 129(8):1983–93. doi: 10.1242/dev.129.8.1983

9. Lyko F. The DNA methyltransferase family: a versatile toolkit for epigenetic regulation. *Nat Rev Genet* (2018) 19(2):81–92. doi: 10.1038/nrg.2017.80

10. Kanherkar RR, Bhatia-Dey N, Csoka AB. Epigenetics across the human lifespan. *Front Cell Dev Biol* (2014) 2:49. doi: 10.3389/fcell.2014.00049

11. Condic ML. Totipotency: what it is and what it is not. *Stem Cells Dev* (2014) 23 (8):796–812. doi: 10.1089/scd.2013.0364

12. Sun L, Fu X, Ma G, Hutchins AP. Chromatin and epigenetic rearrangements in embryonic stem cell fate transitions. *Front Cell Dev Biol* (2021) 9:637309. doi: 10.3389/fcell.2021.637309

13. Okano M, Bell DW, Haber DA, Li E. DNA Methyltransferases Dnmt3a and Dnmt3b are essential for de novo methylation and mammalian development. *Cell* (1999) 99(3):247–57. doi: 10.1016/S0092-8674(00)81656-6

14. Avgustinova A, Benitah SA. Epigenetic control of adult stem cell function. *Nat Rev Mol Cell Biol* (2016) 17(10):643–58. doi: 10.1038/nrm.2016.76

15. Zoghbi HY, Beaudet AL. Epigenetics and human disease. *Cold Spring Harb Perspect Biol* (2016) 8(2):a019497. doi: 10.1101/cshperspect.a019497

16. Soejima H, Higashimoto K. Epigenetic and genetic alterations of the imprinting disorder beckwith-wiedemann syndrome and related disorders. *J Hum Genet* (2013) 58 (7):402–9. doi: 10.1038/jhg.2013.51

17. Ostrowski PJ, Tatton-Brown K. Tatton-Brown-Rahman syndrome. In: Adam MP, et al. editors. Seattle (WA): GeneReviews® [Internet] (1993).

18. Shen W, Heeley JM, Carlston CM, Acuna-Hidalgo R, Nillesen WM, Dent KM, et al. The spectrum of DNMT3A variants in tatton-Brown-Rahman syndrome overlaps with that in hematologic malignancies. *Am J Med Genet A* (2017) 173(11):3022–8. doi: 10.1002/ajmg.a.38485

19. Feinberg AP, Vogelstein B. Hypomethylation distinguishes genes of some human cancers from their normal counterparts. *Nature* (1983) 301(5895):89–92. doi: 10.1038/301089a0

20. Feinberg AP, Tycko B. The history of cancer epigenetics. *Nat Rev Cancer* (2004) 4(2):143–53. doi: 10.1038/nrc1279

21. Feinberg AP, Koldobskiy MA, Gondor A. Epigenetic modulators, modifiers and mediators in cancer aetiology and progression. *Nat Rev Genet* (2016) 17(5):284–99. doi: 10.1038/nrg.2016.13

22. Baylin SB, Jones PA. Epigenetic determinants of cancer. *Cold Spring Harb Perspect Biol* (2016) 8(9). doi: 10.1101/cshperspect.a019505

23. Xie M, Lu C, Wang J, McLellan MD, Johnson KJ, Wendl MC, et al. Age-related mutations associated with clonal hematopoietic expansion and malignancies. *Nat Med* (2014) 20(12):1472–8. doi: 10.1038/nm.3733

24. Challen GA, Goodell MA. Clonal hematopoiesis: mechanisms driving dominance of stem cell clones. *Blood* (2020) 136(14):1590–8. doi: 10.1182/blood.2020006510

25. Warren JT, Link DC. Clonal hematopoiesis and risk for hematologic malignancy. *Blood* (2020) 136(14):1599–605. doi: 10.1182/blood.2019000991

26. Jaiswal S, Ebert BL. Clonal hematopoiesis in human aging and disease. *Science* (2019) 366(6465):eaan4673. doi: 10.1126/science.aan4673

27. Gondek LP, DeZern AE. Assessing clonal haematopoiesis: clinical burdens and benefits of diagnosing myelodysplastic syndrome precursor states. *Lancet Haematol* (2020) 7(1):e73–81. doi: 10.1016/S2352-3026(19)30211-X

28. Audia JE, Campbell RM. Histone modifications and cancer. *Cold Spring Harb Perspect Biol* (2016) 8(4):a019521. doi: 10.1101/cshperspect.a019521

29. Peng Y, Croce CM. The role of MicroRNAs in human cancer. *Signal Transduct Target Ther* (2016) 1:15004. doi: 10.1038/sigtrans.2015.4

30. Sahraei M, Chaube B, Liu Y, Sun J, Kaplan A, Price NL, et al. Suppressing miR-21 activity in tumor-associated macrophages promotes an antitumor immune response. *J Clin Invest* (2019) 129(12):5518–36. doi: 10.1172/JCI127125

31. Feng YH, Tsao CJ. Emerging role of microRNA-21 in cancer. *BioMed Rep* (2016) 5(4):395–402. doi: 10.3892/br.2016.747

32. Feng S, De Carvalho DD. Clinical advances in targeting epigenetics for cancer therapy. *FEBS J* (2022) 289(5):1214–39. doi: 10.1111/febs.15750

33. Liu Z, Ren Y, Weng S, Xu H, Li L, Han X. A new trend in cancer treatment: the combination of epigenetics and immunotherapy. *Front Immunol* (2022) 13:809761. doi: 10.3389/fimmu.2022.809761

34. Srinageshwar B, Maiti P, Dunbar GL, Rossignol J. Role of epigenetics in stem cell proliferation and differentiation: implications for treating neurodegenerative diseases. *Int J Mol Sci* (2016) 17(2)17(2):199.. doi: 10.3390/ijms17020199

35. Cakouros D, Gronthos S. Epigenetic regulation of bone marrow stem cell aging: revealing epigenetic signatures associated with hematopoietic and mesenchymal stem cell aging. *Aging Dis* (2019) 10(1):174–89. doi: 10.14336/AD.2017.1213

36. McClay JL, Aberg KA, Clark SL, Nerella S, Kumar G, Xie LY, et al. A methylome-wide study of aging using massively parallel sequencing of the methyl-CpG-enriched genomic fraction from blood in over 700 subjects. *Hum Mol Genet* (2014) 23(5):1175–85. doi: 10.1093/hmg/ddt511

37. Broske AM, Vockentanz L, Kharazi S, Huska MR, Mancini E, Scheller M, et al. DNA Methylation protects hematopoietic stem cell multipotency from myeloerythroid restriction. *Nat Genet* (2009) 41(11):1207–15. doi: 10.1038/ng.463

38. Challen GA, Sun D, Jeong M, Luo M, Jelinek J, Vasanthakumar A, et al. Dnmt3a is essential for hematopoietic stem cell differentiation. *Nat Genet* (2011) 44(1):23–31. doi: 10.1182/blood.V118.21.386.386

39. Ko M, Bandukwala HS, An J, Lamperti ED, Thompson EC, Hastie R, et al. Ten-Eleven-Translocation 2 (TET2) negatively regulates homeostasis and differentiation of hematopoietic stem cells in mice. *Proc Natl Acad Sci U.S.A.* (2011) 108(35):14566–71. doi: 10.1073/pnas.1112317108

40. Moran-Crusio K, Reavie L, Shih A, Abdel-Wahab O, Ndiaye-Lobry D, Lobry C, et al. Tet2 loss leads to increased hematopoietic stem cell self-renewal and myeloid transformation. *Cancer Cell* (2011) 20(1):11–24. doi: 10.1016/j.ccr.2011.06.001

41. Challen GA, Sun D, Mayle A, Jeong M, Luo M, Rodriguez B, et al. Dnmt3a and Dnmt3b have overlapping and distinct functions in hematopoietic stem cells. *Cell Stem Cell* (2014) 15(3):350–64. doi: 10.1016/j.stem.2014.06.018

42. Jeong M, Park HJ, Celik H, Ostrander EL, Reyes JM, Guzman A, et al. Loss of Dnmt3a immortalizes hematopoietic stem cells *in vivo*. *Cell Rep* (2018) 23(1):1–10. doi: 10.1016/j.celrep.2018.03.025

43. Zhang CR, Ostrander EL, Kukhar O, Mallaney C, Sun J, Haussler E, et al. Txnip enhances fitness of Dnmt3a-mutant hematopoietic stem cells *via* p21. *Blood Cancer Discov* (2022) 3(3):220–39. doi: 10.1158/2643-3230.BCD-21-0132

44. Abdel-Wahab O, Gao J, Adli M, Dey A, Trimarchi T, Chung YR, et al. Deletion of Asxl1 results in myelodysplasia and severe developmental defects *in vivo*. *J Exp Med* (2013) 210(12):2641–59. doi: 10.1084/jem.20131141

45. Delhommeau F, Dupont S, Valle VD, James C, Trannoy S, Massé A, et al. Mutation in TET2 in myeloid cancers. *N Engl J Med* (2009) 360(22):2289–301. doi: 10.1056/NEJMoa0810069

46. Genovese G, Kähler AK, Handsaker RE, Lindberg J, Rose SA, Bakhoum SF, et al. Clonal hematopoiesis and blood-cancer risk. *N Engl J Med* (2015) 372(11):1071–2. doi: 10.1056/NEJMoa1409405

47. Jaiswal S. Clonal hematopoiesis and nonhematologic disorders. *Blood* (2020) 136(14):1606–14. doi: 10.1182/blood.2019000989

48. Medina EA, Delma CR, Yang FC. ASXL1/2 mutations and myeloid malignancies. *J Hematol Oncol* (2022) 15(1):127. doi: 10.1186/s13045-022-01336-x

49. Rodriguez RM, Suarez-Alvarez B, Salvanés R, Muro M, Martínez-Camblor P, Colado E, et al. DNA Methylation dynamics in blood after hematopoietic cell transplant. *PloS One* (2013) 8(2):e56931. doi: 10.1371/journal.pone.0056931

50. Wahlestedt M, Norddahl GL, Sten G, Ugale A, Frisk M-AM, Mattsson R, et al. An epigenetic component of hematopoietic stem cell aging amenable to reprogramming into a young state. *Blood* (2013) 121(21):4257–64. doi: 10.1182/blood-2012-11-469080

51. Weidner CI, Ziegler P, Hahn M, Brümmendorf TH, Ho AD, Dreger P, et al. Epigenetic aging upon allogeneic transplantation: the hematopoietic niche does not affect age-associated DNA methylation. *Leukemia* (2015) 29(4):985–8. doi: 10.1038/leu.2014.323

52. Søraas A, Matsuyama M, de Lima M, Wald D, Buechner J, Gedde-Dahl T, et al. Epigenetic age is a cell-intrinsic property in transplanted human hematopoietic cells. *Aging Cell* (2019) 18(2):e12897. doi: 10.1111/acel.12897

53. Stölzel F, Brosch M, Horvath S, Kramer M, Thiede C, von Bonin M, et al. Dynamics of epigenetic age following hematopoietic stem cell transplantation. *Haematologica* (2017) 102(8):e321–3. doi: 10.3324/haematol.2016.160481

54. Alsaggaf R, Katta S, Wang T, Hicks BD, Zhu B, Spellman SR, et al. Epigenetic aging and hematopoietic cell transplantation in patients with severe aplastic anemia. *Transplant Cell Ther* (2021) 27(4):313.e1–8. doi: 10.1016/j.jtct.2021.01.013

55. Frobel J, Rahmig S, Franzen J, Waskow C, Wagner W. Epigenetic aging of human hematopoietic cells is not accelerated upon transplantation into mice. *Clin Epigenet* (2018) 10:67. doi: 10.1186/s13148-018-0499-7

56. Frick M, Chan W, Arends CM, Hablesreiter R, Halik A, Heuser M, et al. Role of donor clonal hematopoiesis in allogeneic hematopoietic stem-cell transplantation. *J Clin Oncol* (2019) 37(5):375–85. doi: 10.1200/JCO.2018.79.2184

57. Christopher J, Gibson M. (2020). DNMT3A clonal hematopoiesis in older donors is associated with improved survival in recipients after allogeneic hematopoietic cell transplant, in: *ASH: 62nd ASH Annual Meeting.*

58. Gibson CJ, Kim HT, Zhao L, Murdock HM, Hambley B, Ogata A, et al. Donor clonal hematopoiesis and recipient outcomes after transplantation. *J Clin Oncol* (2022) 40(2):189–201. doi: 10.1200/JCO.21.02286

59. Wachsmuth LP, Patterson MT, Eckhaus MA, Venzon DJ, Gress RE, Kanakry CG. Post-transplantation cyclophosphamide prevents graft-versus-host disease by inducing alloreactive T cell dysfunction and suppression. *J Clin Invest* (2019) 129 (6):2357–73. doi: 10.1172/JCI124218

60. Burns SS, Kapur R. Clonal hematopoiesis of indeterminate potential as a novel risk factor for donor-derived leukemia. *Stem Cell Rep* (2020) 15(2):279–91. doi: 10.1016/j.stemcr.2020.07.008

61. Oran B, Champlin RE, Wang F, Tanaka T, Saliba RM, Al-Atrash G, et al. Donor clonal hematopoiesis increases risk of acute graft versus host disease after matched sibling transplantation. *Leukemia* (2021) 36:298. doi: 10.1038/s41375-021-01430-y

62. Kim KH, Kim T, Novitzky-Basso I, Lee H, Yoo Y, Ahn J-S, et al. Clonal hematopoiesis in the donor does not adversely affect long-term outcomes following allogeneic hematopoietic stem cell transplantation: result from 13-year followup. *Haematologica* (2023). doi: 10.3324/haematol.2022.281806

63. Newell LF, Dunlap J, Gatter K, Bagby GC, Press RD, Cook RJ, et al. Graft-versus-host disease after liver transplantation is associated with bone marrow failure, hemophagocytosis, and DNMT3A mutations. *Am J Transplant* (2021) 21(12):3894–906. doi: 10.1111/ajt.16635

64. Ktena YP, Koldobskiy MA, Barbato MI, Fu H-H, Luznik L, Llosa NJ, et al. Donor T cell DNMT3a regulates alloreactivity in mouse models of hematopoietic stem cell transplantation. *J Clin Invest* (2022) 132(13):e158047. doi: 10.1172/JCI158047

65. West EE, Youngblood B, Tan WG, Jin H-T, Araki K, Alexe G, et al. Tight regulation of memory CD8(+) T cells limits their effectiveness during sustained high viral load. *Immunity* (2011) 35(2):285–98. doi: 10.1016/j.immuni.2011.05.017

66. Thomas RM, Gamper CJ, Ladle BH, Powell JD, Wells AD. De novo DNA methylation is required to restrict T helper lineage plasticity. *J Biol Chem* (2012) 287 (27):22900–9. doi: 10.1074/jbc.M111.312785

67. Ladle BH, Li K-P, Phillips MJ, Pucsek AB, Haile A, Powell JD, et al. De novo DNA methylation by DNA methyltransferase 3a controls early effector CD8+ T-cell fate decisions following activation. *Proc Natl Acad Sci USA* (2016) 113(38):10631–6. doi: 10.1073/pnas.1524490113

68. Bird JJ, Brown DR, Mullen AC, Moskowitz NH, Mahowald MA, Sider JR, et al. Helper T cell differentiation is controlled by the cell cycle. *Immunity* (1998) 9(2):229–37. doi: 10.1016/S1074-7613(00)80605-6

69. Gamper CJ, Agoston AT, Nelson WG, Powell JD. Identification of DNA methyltransferase 3a as a T cell receptor-induced regulator of Th1 and Th2 differentiation. *J Immunol* (2009) 183(4):2267–76. doi: 10.4049/jimmunol.0802960

70. Lee GR, Kim ST, Spilianakis CG, Fields PE, Flavell RA. T Helper cell differentiation: regulation by cis elements and epigenetics. *Immunity* (2006) 24 (4):369–79. doi: 10.1016/j.immuni.2006.03.007

71. Ghoneim HE, Fan Y, Moustaki A, Abdelsamed HA, Dash P, Dogra P, et al. De Novo epigenetic programs inhibit PD-1 blockade-mediated T cell rejuvenation. *Cell* (2017) 170(1):142–157.e19. doi: 10.1016/j.cell.2017.06.007

72. Prinzing B, Zebley CC, Petersen CT, Fan Y, Anido AA, Yi Z, et al. Deleting DNMT3A in CAR T cells prevents exhaustion and enhances antitumor activity. *Sci Transl Med* (2021) 13(620):eabh0272. doi: 10.1126/scitranslmed.abh0272

73. Zebley CC, Brown C, Mi T, Fan Y, Alli S, Boi S, et al. CD19-CAR T cells undergo exhaustion DNA methylation programming in patients with acute lymphoblastic leukemia. *Cell Rep* (2021) 37(9):110079. doi: 10.1016/j.celrep.2021.110079

74. Lubbert M, Bertz H, Rüter B, Marks R, Claus R, Wäsch R, et al. Non-intensive treatment with low-dose 5-aza-2'-deoxycytidine (DAC) prior to allogeneic blood SCT of older MDS/AML patients. *Bone Marrow Transplant* (2009) 44(9):585–8. doi: 10.1038/bmt.2009.64

75. Cogle CR, Imanirad I, Wiggins LE, Hsu J, Brown R, Scornik JC, et al. Hypomethylating agent induction therapy followed by hematopoietic cell transplantation is feasible in patients with myelodysplastic syndromes. *Clin Adv Hematol Oncol* (2010) 8(1):40–6.

76. Gerds AT, Gooley TA, Estey EH, Appelbaum FR, Deeg HJ, Scott BL. Pretransplantation therapy with azacitidine vs induction chemotherapy and posttransplantation outcome in patients with MDS. *Biol Blood Marrow Transplant* (2012) 18(8):1211–8. doi: 10.1016/j.bbmt.2012.01.009

77. Mohty R, El Hamed R, Brissot E, Bazarbachi A, Mohty M. New drugs before, during, and after hematopoietic stem cell transplantation for patients with acute myeloid leukemia. *Haematologica* (2023) 108(2):321–41. doi: 10.3324/haematol.2022.280798

78. Nayak RK, Chen YB. Maintenance therapy for AML after allogeneic HCT. *Front Oncol* (2022) 12:895771. doi: 10.3389/fonc.2022.895771

79. Yan Y, Upadhyaya R, Zhang VW, Berg T. Epigenetic maintenance strategies after allogeneic stem cell transplantation in acute myeloid leukemia. *Exp Hematol* (2022) 109:1–10 e1. doi: 10.1016/j.exphem.2022.03.003

80. Choi J, Ritchey J, Prior JL, Holt M, Shannon WD, Deych E, et al. *In vivo* administration of hypomethylating agents mitigate graft-versus-host disease without sacrificing graft-versus-leukemia. *Blood* (2010) 116(1):129–39. doi: 10.1182/blood-2009-12-257253

81. Goodyear OC, Dennis M, Jilani NY, Loke J, Siddique S, Ryan G, et al. Azacitidine augments expansion of regulatory T cells after allogeneic stem cell transplantation in patients with acute myeloid leukemia (AML). *Blood* (2012) 119 (14):3361–9. doi: 10.1182/blood-2011-09-377044

82. Cooper ML, Choi J, Karpova D, Vij K, Ritchey J, Schroeder MA, et al. Azacitidine mitigates graft-versus-Host disease *via* differential effects on the proliferation of T effectors and natural regulatory T cells *in vivo*. *J Immunol* (2017) 198(9):3746–54. doi: 10.4049/jimmunol.1502399

83. Oran B, de Lima M, Garcia-Manero G, Thall PF, Lin R, Popat U, et al. A phase 3 randomized study of 5-azacitidine maintenance vs observation after transplant in high-risk AML and MDS patients. *Blood Adv* (2020) 4(21):5580–8. doi: 10.1182/bloodadvances.2020002544

84. Gao L, Zhang Y, Wang S, Kong P, Su Y, Hu J, et al. Effect of rhG-CSF combined with decitabine prophylaxis on relapse of patients with high-risk MRD-negative AML after HSCT: an open-label, multicenter, randomized controlled trial. *J Clin Oncol* (2020) 38(36):4249–59. doi: 10.1200/JCO.19.03277

85. Wei Y, Xiong X, Li X, Lu W, He X, Jin X, et al. Low-dose decitabine plus venetoclax is safe and effective as post-transplant maintenance therapy for high-risk acute myeloid leukemia and myelodysplastic syndrome. *Cancer Sci* (2021) 112 (9):3636–44. doi: 10.1111/cas.15048

86. Mehdipour P, Chen R, De Carvalho DD. The next generation of DNMT inhibitors. *Nat Cancer* (2021) 2(10):1000–1. doi: 10.1038/s43018-021-00271-z

87. Li A, Abraham C, Wang Y, Zhang Y. New insights into the basic biology of acute graft-versus-host-disease. *Haematologica* (2020) 105(11):2540–9. doi: 10.3324/haematol.2019.240291

88. Kim S, Santhanam S, Lim S, Choi J. Targeting histone deacetylases to modulate graft-Versus-Host disease and graft-Versus-Leukemia. *Int J Mol Sci* (2020) 21(12):4281. doi: 10.3390/ijms21124281

89. Reddy P, Maeda Y, Hotary K, Liu C, Reznikov LL, Dinarello CA, et al. Histone deacetylase inhibitor suberoylanilide hydroxamic acid reduces acute graft-versus-host disease and preserves graft-versus-leukemia effect. *Proc Natl Acad Sci U.S.A.* (2004) 101 (11):3921–6. doi: 10.1073/pnas.0400380101

90. Reddy P, Sun Y, Toubai T, Duran-Struuck R, Clouthier SG, Weisiger E, et al. Histone deacetylase inhibition modulates indoleamine 2,3-dioxygenase-dependent DC functions and regulates experimental graft-versus-host disease in mice. *J Clin Invest* (2008) 118(7):2562–73. doi: 10.1172/JCI34712

91. Choi SW, Gatza E, Hou G, Sun Y, Whitfield J, Song Y, et al. Histone deacetylase inhibition regulates inflammation and enhances tregs after allogeneic hematopoietic cell transplantation in humans. *Blood* (2015) 125(5):815–9. doi: 10.1182/blood-2014-10-605238

92. Wang L, Beier UH, Akimova T, Dahiya S, Han R, Samanta A, et al. Histone/protein deacetylase inhibitor therapy for enhancement of Foxp3+ T-regulatory cell function posttransplantation. *Am J Transplant* (2018) 18(7):1596–603. doi: 10.1111/ajt.14749

93. Choi SW, Braun T, Chang L, Ferrara JLM, Pawarode A, Magenau JM, et al. Vorinostat plus tacrolimus and mycophenolate to prevent graft-versus-host disease after related-donor reduced-intensity conditioning allogeneic haemopoietic stem-cell transplantation: a phase 1/2 trial. *Lancet Oncol* (2014) 15(1):87–95. doi: 10.1016/S1470-2045(13)70512-6

94. Choi SW, Braun T, Henig I, Gatza E, Magenau J, Parkin B, et al. Vorinostat plus tacrolimus/methotrexate to prevent GVHD after myeloablative conditioning, unrelated donor HCT. *Blood* (2017) 130(15):1760–7. doi: 10.1182/blood-2017-06-790469

95. Perez L, Fernandez H, Horna P, Riches M, Locke F, Field T, et al. Phase I trial of histone deacetylase inhibitor panobinostat in addition to glucocorticoids for primary therapy of acute graft-versus-host disease. *Bone Marrow Transplant* (2018) 53 (11):1434–44. doi: 10.1038/s41409-018-0163-z

96. Perez L, Fernandez H, Kharfan-Dabaja M, Khimani F, Betts B, Mishra A, et al. A phase 2 trial of the histone deacetylase inhibitor panobinostat for graft-versus-host disease prevention. *Blood Adv* (2021) 5(13):2740–50. doi: 10.1182/bloodadvances.2021004225

97. He S, Wang J, Kato K, Xie F, Varambally S, Mineishi S, et al. Inhibition of histone methylation arrests ongoing graft-versus-host disease in mice by selectively inducing apoptosis of alloreactive effector T cells. *Blood* (2012) 119(5):1274–82. doi: 10.1182/blood-2011-06-364422

98. He S, Xie F, Liu Y, Tong Q, Mochizuki K, Lapinski PE, et al. The histone methyltransferase Ezh2 is a crucial epigenetic regulator of allogeneic T-cell responses mediating graft-versus-host disease. *Blood* (2013) 122(25):4119–28. doi: 10.1182/blood-2013-05-505180

99. Alahmari B, Cooper M, Ziga E, Ritchey J, DiPersio JF, Choi J, et al. Selective targeting of histone modification fails to prevent graft versus host disease after hematopoietic cell transplantation. *PloS One* (2018) 13(11):e0207609. doi: 10.1371/journal.pone.0207609

100. Doroshow DB, Eder JP, LoRusso PM. BET inhibitors: a novel epigenetic approach. *Ann Oncol* (2017) 28(8):1776–87. doi: 10.1093/annonc/mdx157

101. Sun Y, Wang Y, Toubai T, Oravecz-Wilson K, Liu C, Mathewson N, et al. BET bromodomain inhibition suppresses graft-versus-host disease after allogeneic bone marrow transplantation in mice. *Blood* (2015) 125(17):2724–8. doi: 10.1182/blood-2014-08-598037

102. Copsel SN, Lightbourn CO, Barreras H, Lohse I, Wolf D, Bader CS, et al. BET bromodomain inhibitors which permit treg function enable a combinatorial strategy to suppress GVHD in pre-clinical allogeneic HSCT. *Front Immunol* (2018) 9:3104. doi: 10.3389/fimmu.2018.03104

103. Snyder KJ, Choe HK, Gao Y, Sell NE, Braunreiter KM, Zitzer NC, et al. Inhibition of bromodomain and extra terminal (BET) domain activity modulates the IL-23R/IL-17 axis and suppresses acute graft-Versus-Host disease. *Front Oncol* (2021) 11:760789. doi: 10.3389/fonc.2021.760789

104. Zaiken MC, Flynn R, Paz KG, Rhee SY, Jin S, Mohamed FA, et al. BET-bromodomain and EZH2 inhibitor-treated chronic GVHD mice have blunted germinal centers with distinct transcriptomes. *Blood* (2022) 139(19):2983–97. doi: 10.1182/blood.2021014557

105. Peltier D, Reddy P. Non-coding RNA mediated regulation of allogeneic T cell responses after hematopoietic transplantation. *Front Immunol* (2018) 9:1110. doi: 10.3389/fimmu.2018.01110

106. Vajari MK, Moradinasab S, Yousefi A-M, Bashash D. Noncoding RNAs in diagnosis and prognosis of graft-versus-host disease (GVHD). *J Cell Physiol* (2022) 237 (9):3480–95. doi: 10.1002/jcp.30830

107. Koenecke C, Krueger A. MicroRNA in T-cell development and T-cell mediated acute graft-Versus-Host disease. *Front Immunol* (2018) 9:992. doi: 10.3389/fimmu.2018.00992

108. Wu Y, Mealer C, Schutt S, Wilson CL, Bastian D, Sofi MH, et al. MicroRNA-31 regulates T-cell metabolism *via* HIF1alpha and promotes chronic GVHD pathogenesis in mice. *Blood Adv* (2022) 6(10):3036–52. doi: 10.1182/bloodadvances.2021005103

109. Ranganathan P, Heaphy CEA, Costinean S, Stauffer N, Na C, Hamadani M, et al. Regulation of acute graft-versus-host disease by microRNA-155. *Blood* (2012) 119 (20):4786–97. doi: 10.1182/blood-2011-10-387522

110. Chen S, Smith BAH, Iype J, Prestipino A, Pfeifer D, Grundmann S, et al. MicroRNA-155-deficient dendritic cells cause less severe GVHD through reduced migration and defective inflammasome activation. *Blood* (2015) 126(1):103–12. doi: 10.1182/blood-2014-12-617258

111. Wu Y, Heinrichs J, Bastian D, Fu J, Nguyen H, Schutt S, et al. MicroRNA-17-92 controls T-cell responses in graft-versus-host disease and leukemia relapse in mice. *Blood* (2015) 126(11):1314–23. doi: 10.1182/blood-2015-02-627356

112. Stickel N, Prinz G, Pfeifer D, Hasselblatt P, Schmitt-Graeff A, Follo M, et al. MiR-146a regulates the TRAF6/TNF-axis in donor T cells during GVHD. *Blood* (2014) 124(16):2586–95. doi: 10.1182/blood-2014-04-569046

113. Gartner JG, Durston MM, Booth SA, Ellison CA. Systemic treatment with a miR-146a mimic suppresses endotoxin sensitivity and partially protects mice from the progression of acute graft-versus-Host disease. *Scand J Immunol* (2017) 86(5):368–76. doi: 10.1111/sji.12597

114. Stickel N, Hanke K, Marschner D, Prinz G, Köhler M, Melchinger W, et al. MicroRNA-146a reduces MHC-II expression *via* targeting JAK/STAT signaling in dendritic cells after stem cell transplantation. *Leukemia* (2017) 31(12):2732–41. doi: 10.1038/leu.2017.137

115. Atarod S, Norden J, Bibby LA, Janin A, Ratajczak P, Lendrem C, et al. Differential MicroRNA expression levels in cutaneous acute graft-Versus-Host disease. *Front Immunol* (2018) 9:1485. doi: 10.3389/fimmu.2018.01485

116. Lacina P, Crossland RE, Wielińska J, Czyż A, Szeremet A, Ussowicz M, et al. Differential expression of miRNAs from extracellular vesicles in chronic graft-versus-host disease: a preliminary study. *Adv Clin Exp Med* (2022). doi: 10.17219/acem/155373

117. Peltier D, Radosevich M, Ravikumar V, Pitchiaya S, Decoville T, Wood SC, et al. RNA-Seq of human T cells after hematopoietic stem cell transplantation identifies Linc00402 as a regulator of T cell alloimmunity. *Sci Transl Med* (2021) 13(585): eaaz0316. doi: 10.1126/scitranslmed.aaz0316

118. Peltier DC, Roberts A, Reddy P. LNCing RNA to immunity. *Trends Immunol* (2022) 43(6):478–95. doi: 10.1016/j.it.2022.04.002

119. Wang F, Luo L, Gu Z, Yang N, Wang L, Gao C. Integrative analysis of long noncoding RNAs in patients with graft-versus-Host disease. *Acta Haematol* (2020) 143 (6):533–51. doi: 10.1159/000505255

120. Zhao F, Zhang X, Pei X, Yang D, Han M. Deregulated expression of circular RNAs is associated with immune evasion and leukemia relapse after allogeneic hematopoietic stem cell transplantation. *Genes (Basel)* (2022) 13(11):1986. doi: 10.3390/genes13111986