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REVIEW OPEN ACCESS

The Implications of DNMT Mutations and the Prognostic and Therapeutic Relevance of DNMTis in AML: A Literature Review

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Abstract

Introduction: Acute myeloid leukemia (AML) is a highly heterogeneous and aggressive form of blood cancer characterized by the halted differentiation and proliferation of hematopoietic stem cells (HSCs). Normal hematopoietic functioning is regulated by DNA methyltransferase (DNMT) enzymes which modify the DNA epigenetic landscape. DNMT malfunction is associated with AML, therefore, DNMT inhibitors (DNMTis), such as azacytidine, are being investigated as a potential treatment option for AML patients. This literature review aims to identify the implications of DNMT mutations in AML and the therapeutic value of DNMTis.

Methods: A literature search was conducted using databases including the York University library and PubMed using keywords such as "AML", "DNMT", "DMNTi". Studies were restricted to publication dates between 2010 to 2024.

Results: DNMT3A mutations, specifically at Arginine 882, are common amongst AML patients. Additionally, ten-eleven translocation methylcytosine dioxygenase 2 (TET2) mutations correlate with AML incidence. Reduced catalytic activity of DNMTs caused by mutations can cause hypomethylation and increased gene transcription or hypermethylation and decreased gene transcription. Depending on the patient genome and responsiveness, DNMTis promote normal cell functioning in malignant cells. Aberrant HSC clonal expansion and proliferation within the bone marrow leads to dysregulated hematopoiesis. This characteristic of AML is correlated with DNMT mutations.

Discussion: DNMTis have high therapeutic potential because of their ability to reverse aberrant DNMT methylation patterns while having synergistic effects alongside other treatments. Also, DNA methylation pattern sequencing, such as chromatin accessibility studies, can be useful as predictive biomarkers for AML. The research limitations include navigating the complexity of AML and the variability of responses to DNMTi therapies. Future research should investigate patient biomarkers which could tailor treatment options.

Conclusion: The mortality and complexity of AML warrant further investigation into its underlying causes and potential treatments. As a combinatorial and generally well-tolerated treatment, DNMTis are highly promising. Genomic testing that includes methylation level assessment is vital in appropriately detecting biomarkers that can direct patient treatment plans.

Keywords: acute myeloid leukemia; DNA methyltransferase; DNMT inhibitor, hematopoietic stem cell; epigenetic therapy; azacytidine; halted differentiation; hematopoiesis; CpG islands; decitabine

Introduction

Acute myeloid leukemia (AML) occurs when white blood cell development is disrupted, resulting in cell hyperproliferation and halted differentiation of hematopoietic stem cells (HSCs) [1]. Of the types of blood cancers, AML is one of the most common. AML is highly malignant, aggressive, and complex, with a 5-year overall survival rate of 32% [2]. Treatment methods traditionally involve chemotherapy and/or bone marrow transplants [3].

Hematopoiesis is the process describing the production of blood cells and is mediated by the differentiation of HSCs within the bone marrow. HSCs give rise to myeloid cells, which further divide into specific blood cells [4]. Distinctively, HSCs are one of a few types of stem cells present in adults. HSCs are multipotent stem cells which can differentiate into different types of blood cells [5]. HSC fate can include cell proliferation, cell death, self-renewal, and differentiation and is determined by highly controlled extrinsic, intrinsic, and epigenetic regulation factors. When these processes become dysregulated, AML may develop [5].

Epigenetic modifications, such as DNA methylation, regulate hematopoietic functioning; and includes HSC differentiation, self-renewal, lineage determination, and homeostasis [6,7]. DNA methylation is controlled by the enzyme family DNA methyltransferases (DNMTs) which catalyze the addition of a methyl group to position 5 on cytosine residues on DNA [8]. DNMT methylation inhibits

gene expression by condensing chromatin structure and blocking transcription factor binding [8]. DNMTs catalyze the methylation of CpG islands, regions of DNA with high cytosine-guanine dinucleotide content [9]. The hypermethylation of these regions is associated with AML by contributing to HSC self-renewal and to the differentiation blockade [9].

The main types of DNMTs include DNMT1 and DNMT3 [8]. DNMT1 is primarily involved in the maintenance of DNA methylation patterns, specifically in hemimethylated DNA. DNMT1 also prevents mutagenic events by coordinating functions with DNA repair mechanisms [8]. DNMT3A/DNMT3Bs are involved in *de novo* methylation, adding new methyl groups to cytosine residues in CpG islands and creating new methylation patterns [8]. Although approximately 25% of AML patients have mutations in DNMT3A, commonly missense mutations, the specific pathways in which DNMT regulates human hematopoiesis remain elusive [9,10]. Complementary to DNMTs are ten-eleven-translocation (TET) enzymes which counter the function of DNMTs by demethylating cystine residues on DNA. Mutations affecting TET are also associated with AML [6].

Because of the influential role of epigenetics on hematopoiesis, recent research has focused on the application of epigenetic therapies in clinical use as cancer treatments [11]. DNMT inhibitors (DNMTis) can prevent the methylation mediated by DNMT and help reverse the hypermethylation of tumor-suppressing genes [12]. By inducing epigenetic, long-term, and reversible changes, DNMTis are promising as a cancer treatment option. Additionally, DNMTis can be used synergistically with other therapies, cumulating their positive effects on treatment outcomes [12].

For example, azacytidine, a type of DNMTi, is a cytosine nucleotide analog that is incorporated into DNA and noncompetitively inhibits DNMT1, therefore hypomethylating DNA by blocking cytosine methylation [13]. Azacytidine is a generally well-tolerated drug that is especially beneficial for patients who are not suited for traditional chemotherapy, such as elderly patients. It is also useful for patients who are at high risk of developing AML, such as myelodysplastic syndrome patients [14]. Furthermore, azacytidine can be used in combination with other treatments, such as chemotherapy [14]. A major limitation of azacytidine is that only some patients are responsive to its therapeutic benefits. Additionally, it can take months to determine if it is effective [14]. However, current research has been directed toward discovering biomarkers to determine patient responsiveness to azacytidine [10,14]. Using this information, this literature review will expand upon the knowledge of the effects of DNMT mutations on aberrant hematopoietic differentiation and how DNMTis can be manipulated therapeutically to treat AML.

Methods

A literature search was conducted using the York University Library database, Google Scholar, and Pub Med using keywords such as "Acute myeloid leukemia", "AML", "DNMT", "DNA methyltransferase", "hematopoietic differentiation", "hematopoietic stem cell", "HSC", "epigenetic therapy", "DNMT inhibitor", "DNMTi", "Azacytidine". The literature search was focused on publications from January 2010 to May 2024. This date range was used to examine the most recent literature on AML and epigenetics.

Results

Genetic Landscape of AML Patients

Despite the molecular heterogeneity of the genetic profile of AML patients, some key molecular modifications are common [15]. This literature review will focus on the genetic mutations that specifically result in epigenetic changes. Approximately 20-30% of AML patients have DNMT3A mutations. Of those patients, two-thirds have missense mutations at Arginine 882 (R882) [15]. The arginine amino acid can be incorrectly substituted with a histidine (R882H), cysteine (R882C), proline (R882P), or serine (R882S) [15]. Compared to patients with DNMT3A frameshift mutations, patients with missense mutations exhibit higher levels of peripheral blood cells and higher peripheral blood blast percentages, therefore implying altered hematopoietic functioning caused by the mutations [16].

R882 aids in stabilizing the interaction between DNMT3A and DNA [17]. R882 mutations result in the loss of DNMT3A functioning, leading to aberrant methylation patterns and focal and/or global hypomethylation, therefore disrupting normal gene regulation [10]. R882 mutations in AML patients are generally associated with poorer prognosis with a worse survival outcome, increased chemotherapy resistance, and increased rates of remission [18]. Although R882 mutations are common in AML, they are infrequent in other hematological disorders. Thus, these mutations can act as specific prognostic indicators of AML [15]. For example, in R882H mutations, where arginine is replaced with histidine, the Asp-Glu-Ala-Asp (DEAD) box polypeptide 43 (DDX43) gene is hypomethylated which has been associated with a more favourable prognosis [19]. With increased prognostic indicators, treatment planning efficiency can increase and the direction of clinical trial research can be focused [15]. Additionally, the presence or absence of R882 mutations is a useful biomarker in determining treatment efficacy with a loss of mutation serving as a positive indicator [20].

Another common group of mutations found in AML patients are the TET methylcytosine dioxygenase 2 (TET2) associated mutations which are present in approximately 27% of AML patients [21]. There are 42 variations of TET2 missense mutations in evolutionarily conserved DNA regions [21]. These missense mutations often result in the loss-of-function of the TET2 protein, while nonsense and

frameshift mutations often result in a truncated protein, leading to altered DNA methylation [21]. TET2 mutation rates increase with age, higher red blood cell counts, and lower platelet counts [21]. Similarly to DNMT mutations, TET2 mutations are associated with poorer patient outcomes and synergistic effects with co-mutations like FMS-like tyrosine kinase 3 (FLT3) [22].

Normal DNMT Structure and Functioning

DNA methylation mediated by DNMT3 enzymes consists of the recognition and binding to the target DNA sequence, the transfer of a methyl group from S-adenosylmethionine (SAM) to the 5C position of cytosine, and the formation of 5-methylcytosine. This process is what regulates epigenetic mechanisms and therefore alters gene expression [23]. The new methylation patterns created by the *de novo* methylation activity of DNMTs include gene silencing, imprinting, X chromosome inactivation, and differentiation [23].

Despite differing functionalities, all DNMTs possess a similarly structured C-terminus that controls the enzyme's methylation activity [10]. DNMT3L, although catalytically inactive, aids in DNA methylation by flanking two DNMT3A subunits with DNA strands in the middle, thus stabilizing the positioning of the DNA and serving as a regulatory factor in the process of DNA methylation [10]. In one binding event, each DNMT3A monomer can methylate two CpG dinucleotides [24]. In order to function enzymatically, four DNMT3A subunits join to form a tetramer [25]. DNMT3A forms a continuous surface with DNA by recognizing and binding the target recognition domain (TRD), which penetrates the DNA major groove, and the catalytic loop, which interacts with the DNA minor groove [24]. This stabilizes and facilitates the methylation process. Once bound, the DNA strand structure undergoes conformational changes to accommodate the enzyme [24].

The DNMT complex preferentially methylates CpG sites by targeting cytosine bases. The reaction begins with the DNMT complex attacking a cysteine residue on position C6 of the aromatic ring. Next is the rate-limiting step, where SAM donates a methyl group to be transferred to position C5 [17]. During lineage commitment in normally functioning HSCs, some changes to CpG islands are observed, including the hypermethylation and downregulation at promotor regions and at cell cycle genes [26].

Malignant DNA Methylation Patterns

Since DNMT3A mutations in AML are mostly loss-of-function and have reduced catalytic activity, the resulting DNA is hypomethylated and triggers gene expression [27]. In malignant cells when DNA is hypomethylated, there is an inherent linkage to increased chromosome instability, spontaneous mutation, and transposable element re-expression [27]. When DNA methylation is abnormal, carcinogenesis may follow [28]. In previous studies involving knockout (KO) models, DNMT3A KO HSCs displayed significantly increased self-renewal, although differentiation is only slightly impaired [29]. DNMT3A KO germline mice appear normal at birth, but ultimately die after around 4 weeks because of severely stunted growth [29]. Although DNMT3B KO HSCs only result in an overall slight increase in methylation [5], the deletion of DNMT3B in germline mice results in termination at E9.5 because of growth impairment and neural tube defects [29]. DNMT1 KO HSCs are also associated with DNA hypomethylation, causing significant disruptions to the cell's homeostatic and self-renewal abilities [6]. In mice models where gene deletion occurs at the germline, DNMT1 loss results in termination at gastrulation [29].

In mouse models, although the deletion of DNMT3B only minorly alters DNA methylation patterns, the deletion of both DNMT3A and DNMT3B results in higher dysfunction than would have otherwise been with DNMT3A deletion alone [6]. DNMT3 KO methylation patterns include increased HSC self-renewal proliferation and blocked differentiation [6]. Both DNMT3A and DNMT3B KO mice die soon after gastrulation [29] (Table 1). These results suggest a synergistic effect between DNMT3A and DNMT3B on maintaining DNA methylation patterns [30]. Since DNMT mutations are common in AML, DNMT KO studies provide insight into how these mutations correlate to cell dysfunction and AML.

Table 1. Summary of the Effects of Experimental Gene Knockout on HSCs and Germline Mice and Gene Mutational Prevalence in AML

Gene	Paper(s)	HSC KO Phenotype	Germline KO Phenotype	KO Methylation Pattern	Mutation Prevalence in AML
DNMT1	Celik et al. (1), An et al. (2)	Disruption to cell homeostasis and decreased self-renewal	Termination at gastrulation	↓↓ Methylation (severe hypomethylation)	Rare
DNMT3A	Celik et al. (1)	Increased self-renewal, slightly impaired differentiation	Normal at birth, severely stunted growth, termination at 4 weeks	↓ Methylation (Mild hypomethylation)	20-30%
DNMT3B	Celik et al. (1)	Impaired differentiation, abnormal self-renewal	Growth impaired, neural tube defects, termination at E9.5	↓ Methylation (Mild hypomethylation)	Rare
DNMT3A + DNMT3B	Celik et al. (1), An et al. (2)	Increased self-renewal, blocked differentiation	Termination shortly after gastrulation	↓↓ Methylation (severe hypomethylation)	Unknown

Additionally, evidence suggests that R882 mutations in DNMT3A hinder the ability to form a tetramer with wildtype DNMT3As, decreasing enzyme activity [25]. Also, suppressor of cytokine signalling 3 (SOCS3) genes act as tumour suppressor genes that can inhibit tumour growth, induce apoptosis, and reduce proliferation. In AML, DMNTs hypermethylate the SOCS3 gene, inhibiting its function [3].

Although about 70-80% of mammalian cells exhibit genome methylation, certain regions of those cells called canyons feature hypomethylation [26]. Canyons are rich in H3K4me3 and/or H3K27me3. Chromatin canyons marked by H3K4me3 tend to harbor HSCs and its dysfunction is linked to AML [26]. AML is not only associated with hypomethylation, but also with hypermethylation in certain regions [27]. For example, CpG islands are silenced which can cause malignancies when the regions are tumor supressing regions [26].

DNMTi Therapeutic Use and Efficacy

In normal cells, DNMTis non-competitively inhibit DNMTs which reactivate the expression of silenced genes, such as tumour-suppressing genes, thereby inhibiting abnormal cell proliferation [12]. DNMTis include both cytosine analogue inhibitors and non-nucleotide analogue inhibitors. The two main nucleotide DNMTis which have been FDA approved include 5-aza-cytidine (azacytidine) and 5-aza-2'-deoxycytidine (decitabine) [11]. Each drug has relatively high toxicity levels at high doses, so low doses are used in practice. Azacytidine incorporates as a cytosine analog into RNA which then disrupts tRNA-rRNA interactions, blocking transcription [11]. Azacytidine can also inhibit AML cell growth and induce AML cell apoptosis by reactivating the SOCS3 gene [3]. This gene encodes for a protein that negatively regulates cytokine signalling, therefore the hypomethylation of SOCS3 helps to control cell proliferation [3].

The efficacy of azacytidine in clinical trials displays mixed results depending on a few key variables. Firstly, because of the molecular heterogeneity of AML, the patient response rate to azacytidine treatment varies. For example, clinical trials with TET2 complete loss-of-function mutations exhibit increased sensitivity to the growth-inhibitory effects of azacytidine [31,32]. Low blast count and more favourable cytogenetic risk also predict positive responses to azacytidine [32]. Additionally, the patient's overall health status influences azacytidine usefulness. As a less harsh treatment compared to chemotherapy, elderly patients and patients with comorbidities benefit from azacytidine as an AML treatment [14].

Other potential AML therapeutic agents, NSC-311068 and 370284, inhibit the oncogenic protein, TET1, in malignant cells with high TET1 expression. These therapies inhibit TET1 by targeting its upstream regulator, signal transducer and activator of transcription (STAT)3/5, binding to its DNA-binding domains, and preventing its interaction with TET1 promotors [33]. By specifically targeting STAT/TET1 axis, the oncogenic catalytic activity of the protein decreases. This method does not lead to drug resistance like other inhibitors that target catalytic activity [33]. This novel approach is useful for TET1-high AML subtypes and like azacytidine and decitabine, can be used in combination with other chemotherapies [33].

Combinatory Applications of DNMTis

In AML, the proliferation of HSCs are observed because of their halted differentiation. HSC proliferation implies reduced production of erythrocytes and lymphocytes. The main curative treatment for AML is an allogenic hematopoietic stem cell transplantation which

consists of replacing the patient's bone marrow with healthy donor stem cells [34]. However, this option leads to high relapse rates since the underlying disease cause has not been targeted, the chance of patient rejection is high, and graft-versus-host disease (GvHD) is a threat therefore pointing to the importance of other treatment options [34]. Bone marrow transplant also takes time a significant amount of time to find a match [34]. To maximize the effectiveness of hematopoietic stem cell transplantation, donor lymphocyte infusion (DLI) is often used to induce a graft-versus-leukemia (GvL) effect and eradicate residual malignant leukemic cells [35]. DLI can also be used in combination with hypomethylating agents (HMAs) but should be used after a sufficient amount of time because of the cytotoxic nature of HMAs [34].

Additional therapy commonly used to treat AML includes cytotoxic chemotherapy which works by inhibiting DNA and RNA synthesis [36]. The reversible, yet stable, nature of methylation by DNMTs makes them prime targets as treatment options for cancers such as AML [34]. Patients with a FMS-like tyrosine kinase 3 (FLT3) mutation, the most common mutation in AML, effective therapy is seen with a combination of HMAs and Ventoclax as a salvage therapy [37]. DNMTis may be used in combination with histone deacetylase inhibitors (HDACis) [38]. A small number of study results suggest synergistic antitumoral effects when HDACi are used with HMAs [34]. Another promising study demonstrates that a combination treatment regimen of all-*trans* retinoic acid (ATRA), low dose azacytidine, and pioglitazone (PGZ) aids in targeting malignant AML HSCs by inducing myeloid differentiation [39].

Discussion

Predictive Usefulness

To predict patient response to a certain treatment, karyotypic analysis proves useful. About 30% of AML patients possess unfavourable, complex, monosomal karyotypes where chemotherapy is less effective and epigenetic therapies are more useful [38]. In such unfavorable AML karyotypes, the most frequent cytogenetic changes include the deletion of either all or parts of chromosomes 5 or 7 [38]. Azacytidine and decitabine are both HMAs which are more active in leukemic patients with complex karyotypes [38].

Testing for the presence of abnormal DNA methylation can be done using non-invasive blood tests, making it a promising diagnostic tool to detect cancer. The stable and genetic nature of abnormal DNA methylation also increase its usefulness. Some research has focused on finding genes with prognostic relevance relating to AML diagnosis. Some genes include ZNRF2 (Zinc and Ring Finger 2), which has high expression in AML, and ATP11A (ATPase phospholipid transporting 11A) and ITGAM (integrin alpha M) which both have low expression in AML [28].

Because of the influential nature of epigenetics on disease, new treatment strategies use DNA methylation sequencing as biomarkers. This studies the methylation levels of primarily CpG sites on DNA strands [41]. This sequencing can be done at the single-cell level, aiding in the tracking of heterogeneous diseases like AML by identifying sub-clonal groups through their epigenetic signatures [26]. Similarly, chromatin accessibility studies use techniques like ATAC-seq to provide knowledge on the methylation levels of DNA by assessing their accessibility to transcription factors. This technique examines the physical structure of chromatin and displays the cancer-specific signatures implicated in hematopoietic diseases such as AML [40]. Methylation status of specific genes also gives insight on the future survival of AML patients [26].

Limitations

Some key limitations exist regarding the DNMT mutations, epigenetic regulation, and DNMTi applications. Firstly, the epigenetic processes contributing to cellular differentiation are extremely complex, involving multiple pathways that may malfunction independently of DNMT mutations. Additionally, AML itself is complex and highly heterogenous, making it difficult to attribute the disease to a single cause. This complexity likely contributes to a related limitation of the variable responsivity to DNMTi therapies. Additionally, while combination therapies have promising potential, the research on its efficacy and responsivity is in its early stages.

Regarding the limitations of this paper, the narrow focus on DMNT mutations neglects the other significant epigenetic modification factors, such as chromatin remodelling and histone modification, that also contribute towards normal cellular functioning and differentiation. As a review, this paper lacks novel data, instead offering a synthesis and commentary on existing research. Furthermore, the novelty of DNMTi-based treatments leaves gaps in current understandings about long-term efficacy and safety.

Future Directions

Despite the added understanding towards DNMT mutations and the use of DNMTis in AML, several areas warrant further investigation. Future research should address the variability in patient responsiveness to DNMTis. This may involve the identification of biomarkers or genetic profiles which would aid in increasing the efficacy of tailored of therapies. Additionally, further research is needed to determine the effectiveness of different therapeutic combinations, as well as the underlying mechanisms explaining those results.

Conclusions

DNMTs play an integral role in accurately methylating DNA. When DNA that codes for DNMT enzymes accumulate mutations, their functionality is impaired, leading to either the hypermethylation or hypomethylation of DNA, affecting gene transcription. The mutations to DNMT3A, DNMT3B, and DNMT1 correlate with the

halted differentiation and clonal expansion of HSCs, hallmark characteristics of AML.

The complex heterogeneity of AML poses a barrier to treatments. However, DNMTis may overcome this challenge through its potential to combine with other therapies, generating opportunities to create individualized treatment plans. However, the need for research remains to maximize the effectiveness of DNMTis as AML treatments. For example, dosages, time frames, and patient demographics, such as age, can all be manipulated. Additionally, patient responsiveness to DNMTis is variable, so future research can be directed towards elucidating the reasons behind those inconsistencies. Sequencing and biomarker technologies can both aid in that search.

This paper fills in gaps of current knowledge surrounding AML by detailing the role of DNMT mutations towards hematopoietic differentiation despite the molecular heterogeneity of AML. The paper's focus on DNMTis underscores their therapeutic importance and it contributes to the growing field of epigenetics.

List of Abbreviations Used
AML: acute myeloid leukaemia
ATP11A: ATPase phospholipid transporting 11A
ATRA: all-*trans* retinoic acid
Azacytidine: 5-aza-cytidine
DDX43: DEAD box polypeptide 43
Decitabine: 5-aza-2'-deoxycytidine
DLI: donor lymphocyte infusion
DNMT: DNA methyltransferase
DNMTi: DNMT inhibitor
FLT3: FMS-like tyrosine kinase 3
GvHD: graft-versus-host disease
GvL: graft-versus-leukemia
HDACi: histone deacetylase inhibitor
HMA: hypomethylating agent
HSC: hematopoietic stem cell
ITGAM: integrin alpha M
KO: knockout
PGZ: pioglitazone
SAM: S-adenosylmethionine
SOCS3: suppressor of cytokine signalling 3
STAT: signal transducer and activator of transcription
TET2: TET methylcytosine dioxygenase 2
TET: ten-eleven-translocation
TRD: target recognition domain
ZNRF2: Zinc and Ring Finger 2

Conflicts of Interest
The author declares that they have no conflict of interests.

Ethics Approval and/or Participant Consent
As a literature review that only examined pre-existing studies, there is no requirement for ethics approval nor participant consent.

Authors' Contributions
KD: Made substantial contributions to the work, including all literature searches, study analyses, data interpretations, drafts, revisions of the manuscript, and gave final approval of the version to be published.

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References
[1] Deveau AP, Forrester AM, Coombs AJ, Wagner GS, Grabher C, Chute IC, et al. Epigenetic therapy restores normal hematopoiesis in a zebrafish model of NUP98–HOXA9-induced myeloid disease. Leukemia. 2015 Oct;29(10):2086–97. http://doi.org/10.1038/leu.2015.126
[2] SEER [Internet]. [cited 2024 Jul 14]. Acute Myeloid Leukemia - Cancer Stat Facts. Available from: https://seer.cancer.gov/statfacts/html/amyl.html
[3] Zhang X, Zhang K, Zhang J, Chang W, Zhao Y, Suo X. DNMTs-mediated SOCS3 methylation promotes the occurrence and development of AML. Eur J Haematol. 2024;112(3):439–49. http://doi.org/10.1111/ejh.14134
[4] Jagannathan-Bogdan M, Zon LI. Hematopoiesis. Development. 2013 Jun 15;140(12):2463–7. http://doi.org/10.1242/dev.083147
[5] Lunger I, Fawaz M, Rieger MA. Single-cell analyses to reveal hematopoietic stem cell fate decisions. FEBS Lett. 2017;591(15):2195–212. http://doi.org/10.1002/1873-3468.12712
[6] An J, Ko M. Epigenetic Modification of Cytosines in Hematopoietic Differentiation and Malignant Transformation. Int J Mol Sci. 2023 Jan;24(2):1727. http://doi.org/10.3390/ijms24021727
[7] Wang T, Nandakumar V, Jiang XX, Jones L, Yang AG, Huang XF, et al. The control of hematopoietic stem cell maintenance, self-renewal, and differentiation by Mysm1-mediated epigenetic regulation. Blood. 2013 Oct 17;122(16):2812–22. http://doi.org/10.1182/blood-2013-03-489641
[8] Jin B, Robertson KD. DNA methyltransferases, DNA damage repair, and cancer. Epigenetic Alterations in Oncogenesis. 2013;3–29. http://doi.org/10.1007/978-1-4419-9967-2_1
[9] Spencer DH, Russler-Germain DA, Ketkar S, Helton NM, Lamprecht TL, Fulton RS, et al. CpG Island Hypermethylation Mediated by DNMT3A Is a Consequence of AML Progression. Cell. 2017 Feb 23;168(5):801-816.e13. http://doi.org/10.1016/j.cell.2017.01.021

[10] Khrabrova DA, Yakubovskaya MG, Gromova ES. AML-Associated Mutations in DNA Methyltransferase DNMT3A. Biochem Mosc. 2021 Mar 1;86(3):307–18. http://doi.org/10.1134/S000629792103007X
[11] Lu Y, Chan YT, Tan HY, Li S, Wang N, Feng Y. Epigenetic regulation in human cancer: the potential role of epi-drug in cancer therapy. Mol Cancer. 2020 Apr 27;19(1):79. http://doi.org/10.1186/s12943-020-01197-3
[12] Zhou S, Ou H, Wu Y, Qi D, Pei X, Yu X, et al. Targeting tumor endothelial cells with methyltransferase inhibitors: Mechanisms of action and the potential of combination therapy. Pharmacol Ther. 2023 Jul 1;247:108434. http://doi.org/10.1016/j.pharmthera.2023.108434
[13] Khan C, Pathe N, Fazal S, Lister J, Rossetti JM. Azacitidine in the management of patients with myelodysplastic syndromes. Ther Adv Hematol. 2012 Dec 1;3(6):355–73. http://doi.org/10.1177/2040620712464882
[14] Kagan AB, Garrison DA, Anders NM, Webster JA, Baker SD, Yegnasubramanian S, et al. DNA methyl transferase inhibitor exposure–response: Challenges and opportunities. Clin Transl Sci. 2023 Jun 21;16(8):1309–22. http://doi.org/10.1111/cts.13548
[15] Yuan XQ, Peng L, Zeng WJ, Jiang BY, Li GC, Chen XP. DNMT3A R882 Mutations Predict a Poor Prognosis in AML: A Meta-Analysis From 4474 Patients. Medicine (Baltimore). 2016 May;95(18):e3519. http://doi.org/10.1097/MD.0000000000003519
[16] Yang L, Shen K, Zhang M, Zhang W, Cai H, Lin L, et al. Clinical Features and MicroRNA Expression Patterns Between AML Patients With DNMT3A R882 and Frameshift Mutations. Frontiers in Oncology. 2019 Oct 24;9. https://doi.org/10.3389/fonc.2019.01133
[17] Gowher H, Jeltsch A. Mammalian DNA methyltransferases: new discoveries and open questions. Biochem Soc Trans. 2018 Oct 19;46(5):1191–202. http://doi.org/10.1042/BST20170574
[18] Schmalbrock LK, Bonifacio L, Bill M, Jentzsch M, Schubert K, Grimm J, et al. Prognostic relevance of DNMT3A R882 mutations in AML patients under going non-myeloablative conditioning hematopoietic stem cell transplantation. Bone Marrow Trans plantation. 2018 Jan 15;53(5):640–3. http://doi.org/10.1038/s41409-017-0060-x
[19] Tabatabaei T, Rezvany MR, Ghasemi B, Vafaei F, Zadeh MK, Zaker F, et al. Effect of DNMT3A R882H Hot Spot Mutations on DDX43 Promoter Methylation in Acute Myeloid Leukemia. BioMed Res Int. 2024;2024(1):9625043. http://doi.org/10.1155/2024/9625043
[20] Jeziskova I, Musilova M, Culen M, Foltankova V, Dvorakova D, Mayer J, et al. Distribution of mutations in DNMT3A gene and the suitability of mutations in R882 codon for MRD monitoring in patients with AML. Int J Hematol. 2015 Nov 1;102(5):553–7. http://doi.org/10.1007/s12185-015-1856-3
[21] Weissmann S, Alpermann T, Grossmann V, Kowarsch A, Nadarajah N, Eder C, et al. Landscape of TET2 mutations in acute myeloid leukemia. Leukemia. 2012 May;26(5):934–42. http://doi.org/10.1038/leu.2011.326
[22] Pan X, Chang Y, Ruan G, Zhou S, Jiang H, Jiang Q, et al. TET2 mutations contribute to adverse prognosis in acute myeloid leukemia (AML): results from a comprehensive analysis of 502 AML cases and the Beat AML public database. Clin Exp Med. 2024;24(1):35. http://doi.org/10.1007/s10238-024-01297-0
[23] Moore L, Le T, Fan G. DNA methylation and its basic function. Neuropsychopharmacology. 2013 Jan;38(1):23–38. http://doi.org/10.1038/npp.2012.112
[24] Zhang ZM, Lu R, Wang P, Yu Y, Chen D, Gao L, et al. Structural basis for DNMT3A-mediated de novo DNA methylation. Nature. 2018 Feb;554(7692):387–91. http://doi.org/10.1038/nature25477
[25] Cypris O, Franzen J, Frobel J, Glück P, Kuo CC, Schmitz S, et al. Hematopoietic differentiation persists in human iPSCs defective in de novo DNA methy lation. BMC Biol. 2022 Jun 15;20:141. http://doi.org/10.1186/s12915-022-01343-x
[26] Guillamot M, Cimmino L, Aifantis I. The impact of DNA methylation in hematopoietic malignancies. Trends Cancer. 2016 Feb;2(2):70–83. http://doi.org/10.1016/j.trecan.2015.12.006
[27] Schoofs T, Müller-Tidow C. DNA methylation as a pathogenic event and as a therapeutic target in AML. Cancer Treat Rev. 2011 Jan 1;37:S13–8. http://doi.org/10.1016/j.ctrv.2011.04.013
[28] Hu L, Gao Y, Shi Z, Liu Y, Zhao J, Xiao Z, et al. DNA methylation-based prognostic biomarkers of acute myeloid leukemia patients. Ann Transl Med. 2019 Dec;7(23):737. http://doi.org/10.21037/atm.2019.11.122
[29] Celik H, Kramer A, Challen GA. DNA methylation in normal and malignant hematopoiesis. Int J Hematol. 2016 Jun 1;103(6):617–26. http://doi.org/10.1007/s12185-016-1957-7
[30] Challen GA, Mayle A, Sun D, Jeong M, Luo M, Li W, et al. Dnmt3b Has Few Specific Functions In Adult Hematopoietic Stem Cells But Shows Abnormal Activity In The Absence Of Dnmt3a. Blood. 2013 Nov 15;122(21):734–4. https://doi.org/10.1182/blood.V122.21.734.734

[31] Stölzel F, Fordham SE, Nandana D, Lin WY, Blair H, Elstob C, et al. Biallelic TET2 mutations confer sensitivity to 5′-azacitidine in acute myeloid leukemia. JCI Insight. 2022 Dec 8;8(2). http://doi.org/10.1172/jci.insight.150368

[32] Itzykson R, Kosmider O, Cluzeau T, Mansat-de Mas V, Dreyfus F, Beyne-rauzy O, et al. Impact of TET2 mutations on response rate to azacitidine in myelo dysplastic syndromes and low blast count acute myeloid leukemias. Leukemia. 2011 Jul;25(7):1147–52. http://doi.org/10.1038/leu.2011.71

[33] Jiang X, Hu C, Ferchen K, Nie J, Cui X, Chen CH, et al. Targeted inhibition of STAT/TET1 axis as a therapeutic strategy for acute myeloid leukemia. Nat Commun. 2017 Dec 13;8(1):2099. http://doi.org/10.1182/blood.V130.Suppl_1.857.857

[34] Yang G, Wang X, Huang S, Huang R, Wei J, Wang X, Zhang X. Generalist in allogeneic hematopoietic stem cell transplantation for MDS or AML: Epigenetic therapy. Front Immunol. 2022;13:1034438. http://doi.org/10.3389/fimmu.2022.1034438

[35] Schroeder T, Rautenberg C, Haas R, Germing U, Kobbe G. Hypomethylating agents for treatment and prevention of relapse after allogeneic blood stem cell transplantation. Int J Hematol. 2018 Feb 1;107(2):138–50. http://doi.org/10.1007/s12185-017-2364-4

[36] Vetrie D, Vignir HG, Mhairi C. The leukaemia stem cell: similarities, differences and clinical prospects in CML and AML. Nat Rev Cancer. 2020;20(3):158–73. http://doi.org/10.1038/s41568-019-0230-9

[37] Ghorab A, Litzow M, Gangat N, Al-Kali A, Shah M, Murthy H, et al. AML-497 Salvage Treatment With Venetoclax (Ven) and Hypomethylating Agents (HMA) for Relapsed/Refractory FLT3-mutated Acute Myeloid Leukemia (AML) Patients: Clinical Characteristics and Outcomes. Clin Lymphoma Myeloma Leuk. 2023 Sep 1;23:S306. http://doi.org/10.1016/S2152-2650(23)01070-4

[38] O'Hagan HM, Rassool FV, Nephew KP. How epigenetic therapy beats adverse genetics in monosomy karyotype AML. Cancer Res. 2021 Feb 15;81(4):813–5. http://doi.org/10.1158/0008-5472.CAN-20-4108

[39] Klobuch S, Steinberg T, Bruni E, Mirbeth C, Heilmeier B, Ghibelli L, et al. Biomodulatory treatment with azacitidine, all-trans retinoic acid and pioglitazone induces differentiation of primary AML blasts into neutrophil-like cells capable of ROS production and phagocytosis. Front Pharmacol. 2018 Nov 27;9:1380. http://doi.org/10.3389/fphar.2018.01380

[40] Corces MR, Buenrostro JD, Wu B, Greenside PG, Chan SM, Koenig JL, et al. Lineage-specific and single cell chromatin accessibility charts human hema topoiesis and leukemia evolution. Nat Genet. 2016 Oct;48(10):1193–203. http://doi.org/10.1038/ng.3646

[41] Wee EJH, Rauf S, Shiddiky MJA, Dobrovic A, Trau M. DNA ligase-based strategy for quantifying hetero geneous DNA methylation without sequencing. Clin Chem. 2015 Jan;61(1):163–71. http://doi.org/10.1373/clinchem.2014.227546

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