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Targeted Treatment of Acute Myeloid Leukemia Based on Epigenetic Regulation Mechanism

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Abstract:

Acute myeloid leukemia (AML) is a kind of malignant clone system disease of hematopoietic ancestor cells. Objects genetic modification plays an important role in the occurrence and development of AML. The current research shows that apparently, genetic modifications, such as DNA methylation, group protein modification, non-encoding RNA-mediated regulation, etc., play a key role in AML and become potential treatment targets. However, there are still research gaps in the targeted therapy for AML epigenetics, and further exploration and research need to be done. This article summarizes the epigenetic pathogenesis and types of AML and analyzes targeted therapeutic strategies for AML epigenetic modification, including DNA methyl metastase inhibitors, histone deaminase inhibitors, and non-encoding RNA. The results showed that these strategies showed potential treatment effects in preclinical and clinical studies and provided new ideas for AML treatment. The significance of this summary is to provide a reference for future AML therapy research, which indicates the importance of apparent genetic modification in AML treatment. However, there are still many problems that need to be solved, including the durability, drug resistance, and side effects of treatment. Future research can focus on these issues so as to bring more effective treatment plans to patients with AML.

Keywords: Cancer; leukemia; epigenetics.

1. Introduction

Cancer remains a significant health challenge in the world, and traditional cancer treatments typically target specific genetic mutations. However, many studies show that the dysregulation of epigenetic mechanisms is crucial in tumor development. Acute myeloid leukemia (AML)can be caused by abnormal epigenetic mechanisms, which is a heterogeneous hematological malignancy. Although some treatments of chemotherapy and hematopoietic stem cell transplantation have been applied to patients, the prognosis of many AML patients remains poor. Therefore, there is a need for new treatment methods for various types of patients. In recent years, an increasing number of studies have shown that epigenetic disorder is a factor in AML, which provides new opportunities for targeted therapy.

Understanding the epigenetic mechanisms underlying AML development is crucial for making precision medical strategies to improve patient prognosis. Epigenetic modifications, including DNA methylation, histone modifications, and noncoding RNA, can alter gene expression patterns without altering DNA sequences and change the level of abnormal gene expression patterns in AML cells. DNA methylation, which adds a methyl group to the 5 ,carbon of cytosine, is the most widely epigenetic marker at the moment. The different DNA methylation patterns among AML patients have been used to classify. Histone modifications involving histone acetylation and methylation can change chromatin structure, gene expression, and the self-renewal ability of leukemia stem cells. The expression imbalance of noncoding RNAs, especially microRNAs and long noncoding RNAs, further leads to changes in the gene regulatory network in AML. Studies show that abnormal genetic regulation can affect the expression of AML-related genes and may cause abnormal activation of carcinogenic genes and silence of cancer suppression genes. Furthermore, it provides potential treatment targets, aiming at treatment strategies with abnormalities in epigenetic regulation, such as DNA methyl metastase inhibitors and histone deaminase inhibitors, which have been widely studied and applied to AML treatment. Genetic regulation abnormalities are also related to the prognosis of patients with AML. Some studies have shown that the existence of abnormalities of apparent genetic regulation may be related to the prognosis of AML patients [1].

In this review, an overview of the current state of epigenetics and epigenetic therapy in AML will be given. Besides, this review aims to investigate the epigenetic function in AML and detect the potential of targeted therapy based on epigenetic mechanisms, focusing on the impact of epigenetic modifications on tumor and treatment response. In addition, the efficacy of epigenetic targeted drugs in various models of cancer will be evaluated, and the ultimate goal is identifying new therapeutic targets and improving treatment outcomes for cancer patients. The exploration of epigenetic mechanisms in AML provides an opportunity to develop targeted therapies that selectively remove leukemic cells while reserving normal hematopoietic cells. The finding approach can improve treatment outcomes, minimize drug resistance, and reduce the toxicity related to conventional chemotherapy regimens in future therapy. Organization of the Text

2. Epigenetic Regulations in AML

2.1 The Principle of DNA Methylation

Generally, DNA methylation refers to the methylation process that occurs in the fifth carbon atom in CPG dilate. DNA methylation is mediated by DNA Methyltransferase (DNMT), and DNMT maintains the internal DNA methylation of the cells. It is the only found form of mammalian DNA methylation. DNA methylation, as a relatively stable modification state, can inherit the newborn sub-DNA with the DNA‘s replication process under the action of DNA methyl metastases, which is an important epigenetic mechanism. When receiving the paper, we assume that the corresponding authors grant us the copyright to use the paper for the book or journal in question.

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2.2 The Pathogenic Mechanism of DNA Methylation In AML

In recent years, DNA methylation studies have found that the abnormal methylation of DNA is closely related to the occurrence of tumors. The main carcinogenic mechanism is that the promoter of the cancer-suppressive gene is inhibited by abnormal methylation of cancer, and the silence leads to tumors. To exemplify, SOX7 directly interacts with β-Catenin and regulates the WNT pathway of acute myeloblast leukemia, leading to AML cells [2]. A great number of studies about AML found that abnormal DNA methylation levels are AML‘s significant pathological characteristics. Some experts hold a viewpoint that the abnormality of DNA methylation affects the differentiation of bone marrow, which is another mechanism that causes AML. Bone marrow MSC can support the proliferation and survival of the cells of leukemia ancestors and produce resistance to cytotoxic therapy [3].

2.3 Common Types Of DNA Methylation Genes In AML Patients

2.3.1 DNMT3A

DNMT3A mutations occur in about 25% of AML patients. DNMT3A is mainly responsible for introducing new methyl group groups on the DNA‘s new chain to achieve DNA methylation. This DNA methylation process is completed by metastatic S-A notable methylsulfate (SAM) to the cytokine base of DNA. DNMT3A is added to the cytosine residues on the DNA chain through its methyl metastases activity, forming a 5-methylcytosine (m5C). Studies have also found that the CPG island with high expression for DNMT3A is a universal feature in wild-type DNMT3A in the AML cells, which doesn‘t relate to gene silence [4].

2.3.2 TET2

The protein encoded by the TET2 gene is a DNA hydroxymethyl transferase that works in the process of DNA hydroxymethylation. TET2 protein plays an important role in DNA methylation processes. It introduces a hydroxyl group on methyl groups of m5C to form 5-hydroxymethylytosine (5hmC). TET2-mediated mRNA demethylation regulates leukemia stem cell homing and self-renewal.

2.4.3 IDH1/2

IDH1/2 encodes in different citric acid dehydrogenases 1 and 2, catalyzing the oxidation of alcohol-oxidized decarboxyls into α-kg. IDH1/2 has the highest variable frequency of metabolic genes in human cancer and interferes with cell metabolism and apparent genetic regulation, thereby promoting tumors. The mutations of IDH1/2 lead to excessive accumulation of 2-HG, which in turn affects the methylation state of DNA and group protein, affects the regulation of gene expression, and promotes the occurrence of AML tumors [5].

2.4 Histone Acetylation

2.4.1 The Pathogenic mechanism of histone acetylation in all cells

In addition to DNA methylation, many epigenetic modifications on histones, including acetylation, methylation, and ubiquitination, have been found. Histone methylation is methylated on H3 and H4 in groups of protein N -end

lysine (K) or arginine (s) residues. Its functions are designed to form and maintain the structure, genome marks, DNA repair, and X chromatin regulation and control.

2.4.2 Common types of histone acetylation genes in aml patients

1) Histone methyl transferases (HMTs):
HMTs are a type of enzyme that is responsible for catalytic methylation reactions on the histone and transferring the methyl group to a specific lysine residue. This methylation modification can affect chromatin structure and gene expression, thereby causing the abnormality of AML cells.
2) Histone acetyltransferases (HAT) and deacetylases (HDAC):
HATs catalyze acetylation reactions on histones, transferring acetyl groups to specific lysine residues. This acetylation modification can affect the degree of chromatin relaxation, promote chromatin relaxation, and enhance gene transcriptional activity.
It alters the N-terminal charge state of histones by adding acetyl groups to specific lysine residues, thereby affecting the affinity between histones and DNA. This acetylation modification is often considered an activating modification that can make chromatin more relaxed and promote gene transcription.
HDACs catalyze the removal of the acetyl group on the protein, thereby regulating the acetylated state of the protein. The acetylated modification of the histone is usually related to the activation of genes because acetylation can cause the relaxation of the chromatin structure and the enhancement of the transcriptional activity of the gene. The role of HDACS is to remove acetylation modification, which prompts the tightening of the chromatin structure and the silence of genes. HDACs remove the acetyl group on the group to make the chromatin closer and prevent the combination of the transcription factors, thereby suppressing the transcription of genes. The process of this acetylation modification reversal can be regarded as a mechanism of gene silence, regulating the balance of gene expression in the cell. The abnormal levels brought by the two can lead to the occurrence and development of AML tumor cells.
HATS and HDACS jointly regulate the acetylated balance of protein in the group to maintain the normal state of chromatin. When the balance between HATS and HDACs is broken, it may cause abnormal levels of protein acetylation, which will affect the expression and cell function of the gene, which will cause AML.
3) Demethylases (KDMs) and Lysine Methyltransferases (KMTs):
KDMs remove the methylation modification on the protein, especially the methylation modification for the lysine residues. By removing the methyl group on the group protein, KDMS can change the tightness of the chromatin and affect the transcription activity of the gene.KDMs are responsible for catalytic methylation reactions on the group protein and transfer the methyl group to a specific lysine residue. KMTs and KDMs jointly regulate the methylation balance of histones and maintain the normal state of chromatin. And their imbalance can lead to histone abnormalities, which in turn can cause AML cells [6].

2.5 NcRNA

2.5.1 MicroRNA

MicroRNA is a non-coded single-chain RNA molecule with an internal gene -encoded in endogenous genes. microRNA binds to the mRNA of the target genetic, resulting in degradation or translation suppression of MRNA in AML cells. The aberrant expression of microRNAs contributes to AML heterogeneity [7].
microRNA expression is correlated with bone marrow (BM) morphology. microRNA can indirectly regulate the expression of genetic decorative enzymes and the expression of indirect regulation genes, such as histone-modifying enzymes. Moreover, different microRNA expressions can be utilized to define myeloid or lymphoid lineage leukemia and distinguish ALL from AML. There are differences in the microRNA expression spectrum of patients with different types of leukemia. The expression level of specific miRNA can be used as biomarkers to distinguish different types of leukemia.

2.5.2 LncRNA

LncRNA is an RNA with a length greater than 200 nucleotides greater than 200 nucleotides. They are involved in various molecular processes, such as chromatin interaction, modulating gene transcription through binding the promoter region, acting as competing endogenous RNAs (ceRNAs) for microRNAs interacting with the ribosome and thus interfering in translation as well as interacting with various proteins and determining cellular localization. For example, miR-155 interacts with transcription factor PU.1 to regulate the differentiation of hematopoietic cell lines. Cellular Localization [8]. Help design more accurate targeted therapy strategies. By intervening in the protein localized in the cell membrane, nucleus, or other cellular device, you can more effectively inhibit the growth and proliferation of AML cells and reduce damage to normal cells [9].

2.5.3 CircRNA

Different from the traditional linear RNA (Linear RNA,

including 5 ,and 3‘), the circRNA molecule is a closed ring structure. It is not affected by RNA exterior enzymes. The expression is more stable and cannot be degraded. circRNA molecules are rich in microRNA binding sites, which play the role of microRNA sponge in the cells and then relieve microRNA‘s inhibitory effect on its target genes [10].

3. Application in AML Targeted Therapy

3.1 DMNTi

DNA methaltransferase (DNMT) is an enzyme responsible for DNA methylation. Its abnormal activity can cause DNA methylation level abnormalities. DNA methylase inhibitors such as 5-azacitidine can be used to interfere with DNA methylation levels and restore the normal expression of genes. Studies have found that the reversal of DNMT and AML may be expected to help potential new therapeutic targets [11].

DNA methylated inhibitors with DNMTS as the target can be divided into nucleoside and non -nucleoside based on their molecular structure. Nucleosides DNMT inhibitors are belonged to nucleoside analogs, which are mixed with dNA, and inhibit DNA cytopine metastase DNMT1, DNMT3A, and DNMT3B through irreversible covalent interactions. Azacitidine and Dacogen belong to this type of drug, which has been used for the treatment of acute myeloid leukemia.DNMT1-selective inhibitor GSK3685032 has been proven to have a significant therapeutic advantage for AML.GSK3685032 is selectively combined with DNMT1 through unique interaction, and crystalline studies show that it and DNMT1‘s active sites are competitive. Target recognition domain (TRD) interaction. This participation leads to the rapid loss of DNA methylation and strong transcriptional activation [12].

3.2 HDAC Inhibitors (HDACis)

3.2.1 Hydroximates

Hydroximates is the first HDACi to be found, so it has been widely researched. It has a simple mechanism for histone deacetylase. The structure of Hydroximates enables it to be combined with HDAC, preventing HDAC from the de -acetylization of histone so that the acetyl base on the group protein can be retained. Because HDAC is suppressed, acetyl -based acetyl -based acetima is retained or accumulated. In this way, the level of acetylation of histone increases, which can promote the apoptosis of AML cells, inhibit proliferation or promote differentiation, and reduce the proliferation and spread of AML cells [13].

3.2.2 Panobinostat

Panobinostat catalyzes the removal of acetyl groups from the lysine residues of histone to induce AML cell apoptosis. By inhibiting the functional activity of all HDACs, the drug promotes the accumulation of acetylchized protein and other non-group proteins, thereby inducing cell cycle blocking and apoptosis [14]. However, in the early clinical trials of AML, Panobinostat‘s curative effect is not obvious, and the overall and part of the relief rate are very low. By contrast, using a combination treatment of Panobinostat and other inhibitors is confirmed to be very efficient. It can work efficiently with other inhibitors, such as MK-1175. The anti-leukemia effects presented in these examples induce apoptosis and inhibitory cell proliferation in AML cells and patients with primary leukemia cells. In most cases, the survival rate of patients with AML is increased.

3.2.3 Belinostat

Belinostat increased the level of acetylization of protein by inhibiting the activity of HDAC. It has been confirmed to have an effective antileukemic effect in AML cells [15]. In addition, some combination treatments have been explored in AML‘s preclinical research. Among them, Belinostat and DZNEP are the most widely used medications. These two compounds are combined with ATRA or ATRA and Idarubicin [16].

3.3 ncRNA

3.3.1 MicroRNA mimics

MicroRNA MIMICS is a synthetic RNA molecule design similar to the target microRNA sequence. They can be transfected into AML cells to simulate the function of microRNA and adjust the expression of downstream genes. microRNA MIMICS inhibits the proliferation of AML cells and promotes apoptosis. For instance, microRNA-193P-3P (MiR-193 B) expressed generally reduced in a series of hereditary children‘s and adult AMLs. The instantaneous recovery of miR-193B has a strong anti-leukemia effect. It can be used in PDX-based clinical-related systems to treat leukemia [17].

3.3.2 MicroRNA

MicroRNA antagonists are used to inhibit tumors that are excessively expressed and promote microRNA. In AML, some microRNAs are found to be overly expressed, such as miR-155, which may promote the development of AML. By using microRNA antagonists, these microRNA functions can be reduced, thereby inhibiting the proliferation of AML cells and promoting apoptosis [18,19].

3.3.3 LncRNA

By intervening in the expression of specific LNCRNA, the biological behavior of AML cells can be adjusted. For instance, MALAT1 adjusts the expression of CXCR4 in AML cells through sponge-like miR-146A to regulate the migration, proliferation, and apoptosis of AML cells [19]. Tap MALAT1 and increase miR-96 to inhibit acute myeloid leukemia cell proliferation.

Moreover, lncRNA NR-104098 can effectively suppress EZH2 transcription by combining directly with E2F1 and recruiting E2F1 to the EZH2 promoter. In addition, ATPR can significantly increase the expression of lncRNA NR-104098, and knockout NR104098 can inhibit AML cell proliferation and induction differentiation, thereby inhibiting AML cells [20].

4. Conclusion

This review summarizes the targeted therapy of AMLs that have apparently been modified, covering the pathogenic mechanism of DNA methylation, group protein, and non-encoding RNA, as well as corresponding targeted treatment solutions. These apparently modified abnormalities play an important role in the occurrence and development of AML. DNA methyl metastase inhibitors, HDAC inhibitors, ncRNA regulators, and other targeted therapeutic strategies have shown positive effects in preclinical and clinical research. DNMT inhibitors are mentioned as a typical one for the treatment targeting DNA methylation. For HDACis, cooperation therapy is essential for increasing the targeted therapy field of AML apparent modification; other inhibitors are waiting to be found that have such a function. Regulating these epigenetic modifications that affect AML cell behavior can reduce symptoms, remove tumor cells, and cure AML patients.

The analysis of these findings emphasizes the importance of the complicated interaction and the epigenetic modification in the AML pathogenic mechanism. Except for the common types and methods in the review, there are still other categories and cure approaches that are not mentioned but are available as targeted therapies. In addition to targeted therapies, immunotherapy is also a new progress and research direction of treatment. However, the new potential treatment targets, prognosis signs, drug resistance mechanisms, and potential side effects related to apparent modification targeted therapy have not been mentioned in this summary, which is of great importance and needs to be explored more in future research.

Further research should focus on the new epigenetic targets that may provide enhanced therapeutic effects and specificity. In addition, the exploration of long-term prognosis, understanding the mechanism of drug tolerance, and the reduction of potential adverse reactions are the key areas of future research. The development of AML-targeted therapy will focus on discovering more targets, improving the specificity and efficacy of treatment, and solving the problem of drug resistance and side effects. Based on the concept of individual chemical medical care, customized treatment schemes will be applied. By applying advanced technologies, such as combining immunotherapy and gene editing technology, more therapy methods can be discovered. The research on epigenetic therapy for AML aims to reduce the incidence rate and improve the recovery rate, ultimately improving people‘s quality of life.

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