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Epigenetics and Epi-miRNAs: Potential markers/therapeutics in leukemia

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ABSTRACT

Epigenetic variations can play remarkable roles in different normal and abnormal situations. Such variations have been shown to have a direct role in the pathogenesis of various diseases either through inhibition of tumor suppressor genes or increasing the expression of oncogenes. Enzymes involving in epigenetic machinery are the main actors in tuning the epigenetic-based controls on gene expressions. Aberrant expression of these enzymes can trigger a big chaos in the cellular gene expression networks and finally lead to cancer progression. This situation has been shown in different types of leukemia, where high or low levels of an epigenetic enzyme are partly or highly responsible for involvement or progression of a disease. DNA hypermethylation, different histone modifications, and aberrant miRNA expressions are three main epigenetic variations, which have been shown to play a role in leukemia progression. Epigenetic based treatments now are considered as novel and effective therapies in order to decrease the abnormal epigenetic modifications in patient cells. Different epigenetic-based approaches have been developed and tested to inhibit or reverse the unusual expression of epigenetic agents in leukemia. The reciprocal behavior of miRNAs in the regulation of epigenetic modifiers, while being regulated by them, unlocks a new opportunity in order to design some epigenetic-based miRNAs able to silence or sensitize these effectors in leukemia.

1. Introduction

Epigenetics is known as a field for studying some modifications which occur on chromatin [1,2]. In epigenetics, the modifications are not directly dealing with DNA sequences, but on DNA structure via different ways. This phenomenon is occurred by some changes in histone proteins or DNA molecule in a covalent and/or non-covalent manner, which subsequently leads to alteration of the whole chromatin structure. Some of the famous epigenetic mechanisms are including histone modifications, DNA methylations and the new discovery microRNAs which can play an outstanding regulatory role in controlling the whole epigenetic machinery [3–5]. Cancers as one of the worse disorders showed not to be unassociated with DNA methylation and epigenetic changes [6,7]. Development of acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) which are two well-known blood cancers have shown to be associated with some mutations in the genes of epigenetic elements [8]. Based on some reports, more than 70% of AML patients showed at least one mutation in their epigenetic regulatory genes [8–10]. Similarly, according to the results of a cohort survey, distinct a signature in DNA methylation was observed in almost all the ALL cases, which resulted in a different cellular gene expression pattern [11]. Recognizing these mutations and their effects on the development of AML and ALL will give a hopeful insight for designing novel strategies for preventing these cancers. In this review, we tried to cover present information about the role of epigenetic changes and miRNAs in leukemia, as well as the potential of these mechanisms to be targeted for prevention of these cancers. Furthermore, we mentioned a new miRNA based epigenetic therapy as a novel approach to fight against leukemia.

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1.1. Epigenetic changes in leukemia

1.1.1. DNA hypermethylation

DNA methylation is one of the famous epigenetic occurrences in tumorigenesis which usually occurs in the promoter region of genes [12–14]. Regions full of CpG dinucleotides (CpG islands) and in more details cytosine bases in CpG islands are the targets of methyltransferase enzymes for DNA methylation. The consequence of methyl addition at cytosine bases of a promoter is stopping the expression of downstream genes. In here, an abnormal methylation can cause some problems, especially if it happens in the promoter region of tumor suppressor genes. Hypermethylation at promoter sites of such guardians (tumor suppressors), finally can lead to a huge disturbance in different pathways such as DNA repairing, apoptosis, cell differentiation, even checkpoints of the cell cycle. Nevertheless, DNA hypermethylation of tumor suppressor genes can cause other problems such as drug resistance [15,16] and/or trigger the invasion pathways in cancer cells [17,18]. Presence of a distinct DNA hypermethylation of various genes in both AML and ALL cancers have been shown by many investigations [19–25]. As pointed above, results of a cohort study, which investigated about 30 T-lineage and 137 B-lineage pediatric ALL samples, revealed that the hypermethylation is the main cause of gene deregulation in almost all cases [11]. Similarly, in another experiment, about 325 genes were found to be hypermethylated and down-regulated in pediatric B-ALL cases [26]. Silencing of tumor suppressors by DNA hypermethylation was also shown in AML cases. Famous proteins in cell cycle checkpoints (*p15, p57, p73*) [27] were the first choices for evaluations of epigenetic alterations in patients with leukemia. The hypothesis of such evaluations was to check if there is any protein with prognostic value for early detection of leukemia. For example at first, the occurrence of *p57* methylation was confirmed in leukemia patients [28]. Further investigations also showed the methylated forms of *p15* and/or *p73* in leukemia cases. However, there is no consensus about the occurrence of methylation in genes of such proteins and their valuable role for leukemia prognosis. *P21* is another controversial protein in this family. Based on some investigations, the *p21* methylation can be considered as a valuable prognostic marker for leukemia [29] while others were unsuccessful to catch any connotation [30]. Until now various regulatory genes such as *TET2* from ten-eleven translocation family [31], *DNMT3a* [32], isocitrate dehydrogenase 1 and 2 enzymes (*IDH1/2*) [33], and so many other effectors have been shown to be associated with both DNA hyper and hypomethylation of various genes in AML and ALL cases. As an example, mutations in *TET2* gene sequences were detected in about 7 to 23% of AML cases. *TET* proteins, also known as DNA methylation regulators, are responsible for the conversion of 5-methylcytosine (5-mc) to 5-hydroxymethylcytosine (5hmC) and consequently stopping the activities of transcriptional silencing agents [34–36]. Transcriptional regulatory elements such as *OCT4*, *NANOG*, *REST* and *SOX2* are other targets of hypermethylation in lymphoma and leukemia. Table 1 shows some critical genes, which showed to be methylated/hyper-methylated in ALL and AML.

In addition to the presence of aberrant gene promoter hypermethylation, its quantity might vary among young and old patients with AML. In one cohort experiment, the frequency of aberrant DNA hypermethylation in the promoter of different genes was shown to be different among young and adult subjects with AML [49]. Moreover, mutations in DNMT3 A, which are considerably high among adults with AML, were not detected in any pediatric cases [49]. Such findings revealed the different hypermethylation profile and the mutations in pediatric AML, which should be of utmost attention for possible treatments.

1.1.2. Histone modifications

The structure of chromosomes is maintained by some proteins named histones. These proteins form a core, called nucleosome. These protein cores have protruding amino-terminal tails, which are liable to changes mostly via post-translational modifications. Acetylation, methylation, ubiquitination, phosphorylation, and ADP ribosylation are some well-known modifications, which frequently occurs on histones. Such changes finally will affect different cellular processes such as DNA replication, DNA repair, transcription, etc., by activation or inactivation of gene transcription [50,51]. Acetylation and methylation are two important modifications, which can directly affect gene transcription. Sometimes methylation can have a reciprocal behavior on gene expression. For example, methylation of lysine 9 from histone 3 (H3) will finally lead to inactivate of the gene expression. On the other hand, methylation of the lysine 4 from the same histone (H3), will lead to activation of gene expression. Histone acetyl-transferases (HAT), are known as gene activators via the addition of acetyl groups on histone tails. On the contrary, removal of these acetyl groups by other enzymes called histone deacetylases or HDACs will silence genes [52]. An equilibrium between these enzymes is utmost critical for cells to have a normal gene expression profile [53]. Mutations, which can directly or indirectly affect histones and their behaviors in changing the structure of chromosomes, are characterized in ALL and AML cases [54–57]. The presence of abnormal levels of histone methyltransferases, demethylases and acetyltransferases in cells, as well as mutations in their genes also observed in other hematologic malignancies. In one experiment, due to mutations in *HAT CREB* binding protein (*CBP*), an impaired histone acetylation and consequently abnormal transcriptional regulation were identified in 18% of all studied ALL cases [54]. As another example in this family, TIP60 with functional roles in tumor suppression, apoptosis, and DNA repair mechanisms was showed to be in reduced amounts in AML cases [58]. Some other altered histone modifying enzymes that showed to be involved directly and/or indirectly in leukemia progression are including *NSD1*(methyltransferase) [59], *UTX* (lysine demethylases) [60], *PCAF* (*HAT*) [61] *PRMT4* and *PRMT5* (protein arginine methyltransferases) [62], *CREBBP* (*HAT*) [54,63] and *EZH2* (methyltransferase) [64]. Recognizing such altered forms of histone modifying enzymes, and their exact effects on leukemia progression could be valuable for preventing or inhibition of leukemia cells proliferation.

Table 1
DNA methylation of some prominent genes involved in ALL and AML.

Gene	Function	Methylation status	Disease/s	Reference
OCT4	Transcription factor	Hyper methylated	AML	[37]
SOX2	Transcription factor	Hyper methylated	AML	[37]
TET2	Methylcytosine dioxygenase	Methylated	AML	[38]
PTEN	Phosphatase and tensin homolog	Hypermethylated	ALL	[11]
PTPN6	Protein tyrosine phosphatase	Methylated	ALL	[39]
p57KIP2	Cyclin-dependent kinase inhibitor	Methylated	ALL	[27]
CDKN2A	Cyclin dependent kinase inhibitor	Hypermethylated	AML	[11]
CDKN2B	Cyclin dependent kinase inhibitor	Hypermethylated	ALL	[11,40,41]
CDH1	E-cadherin	Hypermethylated	AML	[42,43]
DLC1	Rho GTPase activating protein	Methylated	ALL,AML	[44,45]
APAF1	Tumor suppressor	Methylated	AML	[46]
TP73	Tumor suppressor	Methylated	ALL	[47]
HIC1	HIC ZBTB transcriptional repressor 1	Hypermethylated	AML,ALL	[43,48]

1.1.3. MiRNA variations

MicroRNAs (miRNAs) are classified as endogenous ribonucleic acids (RNA) molecules with approximately 22 nucleotides [65,66]. These small non-coding RNAs have a key role in the post-translational regulation of various genes. So far, different experiments have revealed the