[Frontiers in Bioscience, Landmark, 20, 728-742, January 1, 2015]

Epigenetic programming contributes to development of drug resistance in hematological malignancies

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1. ABSTRACT

Epigenetics is the study of long term and stable but not necessarily heritable alterations in transcriptional potential and gene expression profile of a cell that are not due to any alterations in the DNA sequence. Epigenetic modifications include DNA methylation, posttranslational modifications of histone proteins and expression of small regulatory RNAs. In recent years, the role of epigenetic modifications in the development of hematological malignancies and drug resistance has been studied in depth and has shed light on this important issue. Here, we review the major epigenetic mechanisms that contribute to the generation and evolution of hematological malignancies and development of resistance to chemotherapy. We will also discuss the development of epigenetic drugs that can overcome resistance to conventional chemotherapy.

2. INTRODUCTION

The concept of epigenetics was first introduced by Conrad H. Waddington in 1939 to describe “the causal interactions between genes and their products, which bring the phenotype into being” (1). It was later defined as heritable changes in gene expression that are not due to any alterations in the DNA sequence (2). This change usually occurs during somatic cell proliferation and development and can be passed on though mitosis. Since the Human Epigenetic Program was implemented by the American Association of Cancer Research in 2005, the role of epigenetic modifications in carcinogenesis and drug resistance has been increasingly appreciated. The generation and evolution of hematological malignancies have been studied in detail, but the role of epigenetics in their biological behavior is still blurred.

Epigenetic modifications include DNA methylation, posttranslational modifications of histone residues and expression of small regulatory RNAs (3) (Figure 1). In this review, we focus on the major epigenetic mechanisms that contribute to the generation, evolution and development of resistance to chemotherapy inhematological malignancies, as well as the role of epigenetic drugs in overcoming resistance to conventional chemotherapy.

3. DNA METHYLATION

DNA methylation occurs almost exclusively at the C5 position of cytosine–phosphate–guanine rich sequences (CpG islands). CpG islands, which are mainly located in promoter regions, can be demonstrated in approximately 70% of all human genes (4). Hypermethylation of CpG

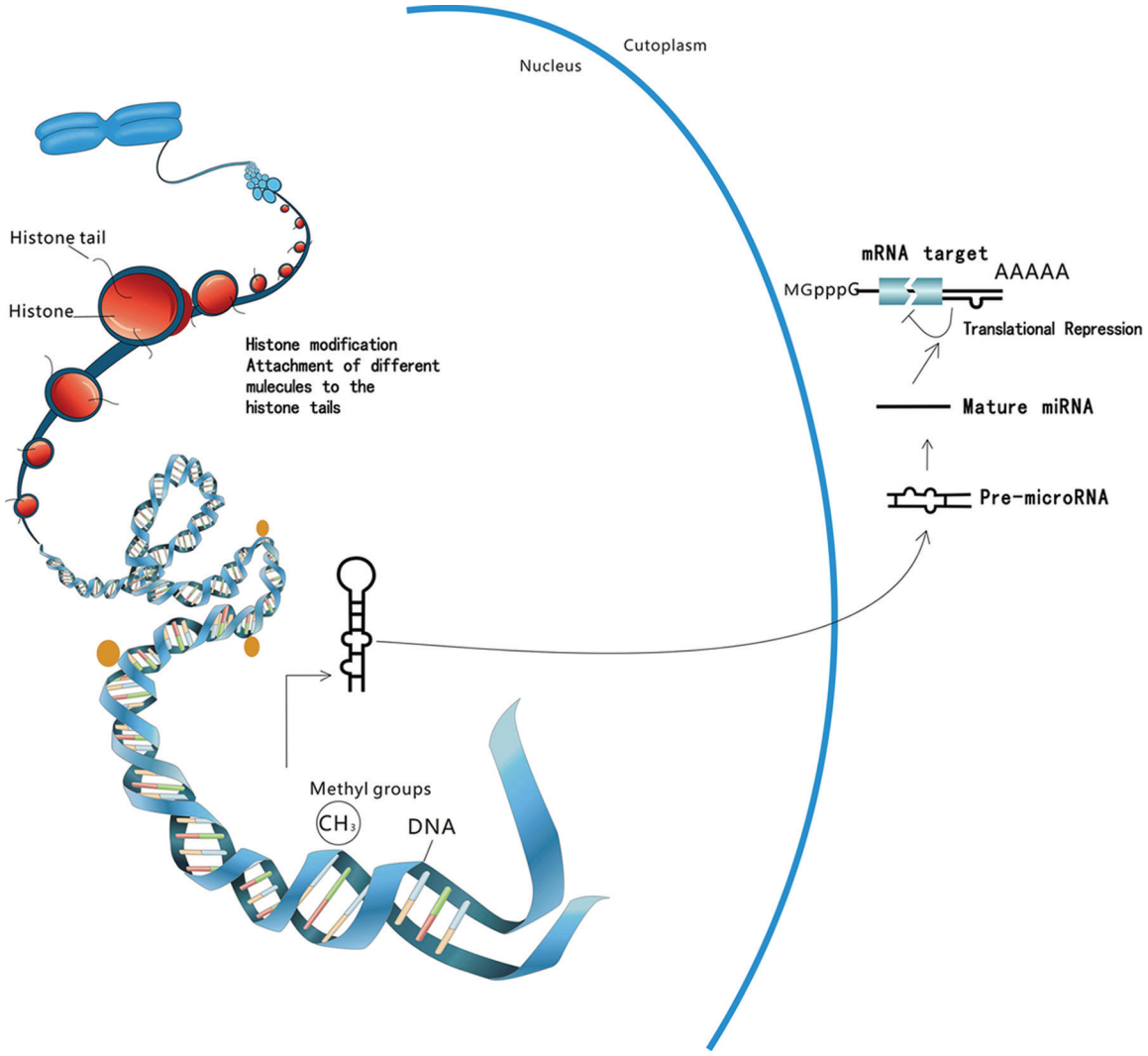

Figure 1. A summary of epigenetic modifications. Epigenetic modifications include DNA methylation, posttranslational modifications of histone residues and expression of small regulatory RNAs.

islands generally represents repression of gene transcription. The corresponding silenced pathways are mechanistically linked to tumor suppressor genes (5). This process is mediated by DNA methyltransferases (DNMTs) which transfer a methyl-group from 5´-adenosylmethionine to the C5 position within the CpG dinucleotide.

Under normal physiological circumstances, DNA methylation plays an important part in the regulation of genome imprinting and X-chromosome inactivation (6). Aberrant DNA methylation has been shown to participate in carcinogenesis, acting by silencing tumor suppressor genes in many tumor types including hematological malignancies (7). DNA hypermethylation can be commonly found in various types of hematological malignancy, including acute myeloid leukemia (AML) (8), acute lymphoblastic leukemia (9) and chronic lymphocytic leukemia (10). It has also been shown to predict the prognosis in some patients with myelodysplastic syndrome (MDS) (11). Moreover, detection of gene promoter hypermethylation can be regarded as a specific phenomenon in hematological malignancies (12).

Loss of methylation by active DNA demethylation processes is initiated by the ten–eleven translocation (TET) family of dioxygenases,

a class of proteins that convert 5-methylcytosine (5mC) by oxidation to 5-hydroxymethylcytosine (5hmC) and subsequently to 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC) (2,3). TET2 (a member of the TET family) was later identified to be deleted or mutated in diverse myeloid malignancies, including AML, MDS, myeloproliferative neoplasm (MPN), chronic myelomonocytic leukemia (CMML), and systemic mastocytosis (6–8). The overall frequency of TET2 mutations is about 10–20% in AML (6) and as high as 50% in patients with CMML (8). The resulting TET2 inactivation was shown to induce clonal expansion of hemopoietic Stem cells (HSCs) in humans and is an early event in AML leukemogenesis (9). Another investigation uncovered frequent loss of the original TET2 mutations at AML relapse (10).

The efficacy of chemotherapy can be adversely influenced by metabolic dysfunction. Methylation of CpG islands in the promoter region of the reduced folate carrier (RFC) gene (a predominant transporter of methotrexate (MTX) in most malignant cell types) can cause defective transportation of MTX, which eventually results in MTX resistance and treatment failure (13). Multidrug resistance (MDR) is the most well-known mechanism of acquired drug resistance. The MDR1 gene product P-gp functions as a transmembrane efflux pump for a variety of chemotherapeutic drugs, including anthracyclines. Overexpression of the MDR1 gene is a negative prognostic factor in acute myelogenous leukemias (AMLs). There is evidence that MDR1 expression is associated with demethylation of the MDR1 promoter; this can be found not only in blood cell lines but also in patients with chronic lymphocytic leukemia (14, 15, 16).

Great success has been achieved since imatinib was introduced into treatment protocols for chronic myeloid leukemia (CML). However, the frequent acquisition of imatinib resistance has been an obstacle to long-term survival. Aberrant DNA methylation was found to be strongly associated with disease progression and resistance to imatinib in CML. Abnormal methylation of a Src suppressor gene PDZ and LIM domain 4 (PDLIM4) was associated with shortened survival, which was an independent negative prognostic impact factor of the resistance to imatinib (17). Protocadherin 10 (PCDH10), a protocadherin subfamily gene represented as a tumor suppressor in a variety of tumors, has also been shown to be a target of epigenetic silencing in CML and ALL. Hypermethylation of the PCDH10 promoter serves as a biomarker of chemotherapy resistance in ALL and attenuated apoptosis in an imatinib-resistant CML cell line K562 (18, 19). Expression of the pro-apoptotic BCL-2-interacting mediator (BIM) was recently shown to be implicated in imatinib-induced apoptosis of BCR-ABL1+ cells. A recent paper revealed that BIM was epigenetically controlled by aberrant methylation in a percentage of patients with CML and had an unfavorable prognostic impact. Combination of imatinib with a demethylating agent may result in improved response in patients with decreased expression of BIM (20). Cancer-testis (CT) antigens, especially PRAME (a family of CT antigens), represent attractive targets for tumor immunotherapy. The expression of PRAME can be increased by the application of demethylation agents such as 5'-aza-2'-deoxycytidine. Sustained expression of PRAME indicates that a concurrent immunotherapeutic approach may be able to eradicate residual CML cells during conventional tyrosine kinase inhibitor (TKI) therapy (21).

Administration of all-trans retinoic acid (ATRA) with chemotherapy is the standard of care for acute promyelocytic leukemia (APL), and results in cure rates exceeding 80%. Recognized as a retinoic acid-regulated tumor suppressor gene, RARβ2 is frequently silenced as a result of aberrant epigenetic interplay. This process is stimulated by AML1/ETO translocation recruiting DNA methyltransferase, histone deacetylase and DNA-methyl-CpG binding activities that promote a repressed chromatin conformation. Based on this evidence, resistance to retinoic acid can be reversed by 5-azacytidine through reactivation of the RA signaling pathway (22).

Bone marrow stromal cells are thought to contribute to the protection of leukemia cells from chemotherapy-induced death (23, 24). However, human bone marrow mesenchymal stem cells (BMMSCs) are usually resistant to chemotherapeutic drugs. A recent study revealed that methylation of the tumor suppressor gene p73 in human BMMSCs leads to lack of response to chemotherapy and inhibits the methylation process by 5-aza-2'-deoxycytidine that could sensitize BMMSCs to cisplatin (25).

4. HISTONE MODIFICATIONS

4.1. Histone methylation

Histone methylation occurs at lysine (K) or arginine (R) residues of the histone tails, in contrast to acetylation which is found exclusively at lysine residues.

It is under mutual control of methyltransferase and demethylase, which organize chromosomal events. Previous studies considered histone methylation to be an irreversible process and a stable epigenetic marker. However, the discovery of enzymes antagonizing histone methylation illuminated its reversibility in later studies (26). The methylation mediated by histone methyltransferase occurs mainly at H3 and H4. It can transfer the methyl group from S-adenosyl-methionine and form the products monomethyl-lysine and S-adenosyl-L-homocysteine (AdoHcy) (27). Histone methylation can mediate both gene transcriptional activation and repression. This seems to depend on proteins that can identify defined methylation marks, thereby eliciting functional effects on the surrounding chromatin. Generally speaking, lysine methylation at H3K9, H3K27 and H4K20 is related to transcriptionally silenced chromatin, whereas methylation at H3K4, H3K36 and H3K79 is associated with transcriptionally active regions (28, 29, 30). In addition to the site of lysine modification, the state of the modified lysine residue (mono-, di- or trimethylation) also plays an important role in determining the functional outcome of this epigenetic modification. It is typically accepted that trimethylation of lysine residues at positions 9 and 27 of histone H3 leads to a much denser packaging of histones and no accessibility of transcription factors to DNA (31). In contrast to acetylation and phosphorylation, histone methylation does not generally change the amino acid charge, but it does increase their hydrophobicity. Recent studies have revealed that arginine methylation plays an important role in mediating hematopoiesis and leukemogenesis. Balint *et al.* have suggested that histone methylation at H4R3 might affect the differentiation of leukemia cells (32). Protein arginine methyltransferase 1 (PRMT1) was identified to be an essential component of the MLL-oncogenic fusion proteins which enhance self-renewal of primary hematopoietic cells (33). Targeted by oncogenic JAK2 kinases, PRMT5 (protein arginine methyltransferase 5) is downregulated in its methyltransferase activity, thus promoting myeloproliferation (34).

Poly-comb group (PcG) proteins are expressed at high levels in a variety of hematological malignancies. PRC2 (a subunit of the poly-comb group) has the ability to catalyze trimethylation of lysine 27 on histone H3 (H3K27Me3), which is involved in mediating gene transcriptional silencing (35). It is associated with the onset of acute promyelocytic leukemia (APL), mix-lineage leukemia (MLL) and chronic myelocytic leukemia (CML) (36, 37, 38).

The PML–RAR fusion protein exhibits much stronger transcriptional repression than natural RAR, owing to its ability to induce chromatin modifications and silencing of PML–RAR target genes. Aside from histone deacetylase and DNA methyltransferase, histone methyltransferase SUV39H1, which catalyzes trimethylation of histone H3 on lysine 9, was shown to exhibit a cancer-promoting function in leukemia by contributing to the transcriptional repressive potential of PML–RAR (39). SUV39H1 was also previously reported to participate in silencing growth-promoting genes in lymphoma cells; the absence of SUV39H1 inhibits activation of a senescence checkpoint which holds a tumor suppressive potential, indicating that H3K9 methylation is a decisive factor in lymphoma development (40). In a recent report, a small molecule that specifically inhibits DOTL1/KMT4 (another histone methyltransferase that catalyzes H3K79 methylation) was shown selectively to eradicate leukemic cells bearing the MLL gene translocation. It acts through elective ablation of cellular H3K79 methylation, thereby reducing transcription of key genes associated with leukemogenesis in MLL (41).

Enforced expression of H3K4me2/3 and reduced expression of H3K27me3 genes may be found to be critical for the development of hematopoietic malignancies (42). MLL5, which serves as a mono- and di-methyl transferase to H3K4, can be activated by nuclear GlcN acylation. Thereby, H3K4 methylation restores the retinoic acid response in the retinoic acid-resistant HL60-R2 cell line and facilitates RA-induced granulopoiesis (43).

4.2. Histone acetylation

Histone acetylation is dictated dynamically by histone acetyltansferase (HAT) and histone deacetylase (HDAC). Apart from histone, other proteins that exist in the cytoplasm, such as TP53, can be reversibly acetylated at the same time (44). HAT is recognized to catalyze histone acetylation. When an acetyl group combines with a lysine residue, it can neutralize the positive charge of lysine, resulting in a loose DNA–nucleosome that enhances DNA accessibility for sequence-specific transcription factors and subsequent transcriptional activation (45). Eighteen kinds of HDAC have been identified in the human genome. They are divided into four categories. The first, second and fourth categories include 11 HDACs which can be inhibited by histone acetyltansferase inhibitors (HDACis). The 11 classic HDACs bear a part in modulating vital biological activities of malignant cells, such as

proliferation, apoptosis, differentiation, angiogenesis, infiltration and drug resistance.

Aberrant modifications of histones are found in a variety of primary hematological malignance and cell lines (46). Researchers of histone acetylation suggest that overexpression of a certain family of HDAC is linked to cancer dedifferentiation, accelerated proliferation, infiltration, evolution and prognosis (47). Reduced expression of HDAC1, HDAC2 and HDAC3 leads to inhibition of cell proliferation, cell cycle arrest and resensitization of cancer cells to chemotherapy (48, 49). For example, vorinostat and other types of HDACi (HDAC inhibitor) can also induce tumor cell cycle arrest and cell differentiation (50). They were also reported to accelerate cell death by activating both endogenous and exogenous apoptosis pathways (51), and to be associated with mitosis failure, autophagy (52) and restoring the expression of tumor suppressor genes which are generally suppressed in malignant T cells, such as p21WAF1 (44, 53). Furthermore, it is intriguing that HDACis can also block tumor cell angiogenesis (54). Several HDACis were demonstrated to sensitize different leukemic T cell lines to apoptosis induction by TRAIL (tumor necrosis factor (TNF)-related apoptosis-inducing ligand). They are regulated by different anti-apoptotic factors and pro-apoptotic proteins which are involved in the mitochondrial apoptotic pathway (55).

Distinct chromosomal translocations can be commonly found in hematological malignancies. The fusion proteins encoded by gene translocation can recruit HDAC, which would lead to aberrant HDAC activity (56). Hematological malignancies such as AML and MLL were also identified with oncogenic translocations involving histone methyltransferases such as KAT3A and KAT3B (32).

Improved cure rate and disease-free survival have been observed in patients with CD20+ B-cell lymphoma since rituximab was introduced in combination with specific conventional chemotherapies. However, resistance to rituximab frequently occurs as a result of low expression of CD20 protein. Intriguingly, evidence has provided new insight into CD20 deregulation that CD20 gene expression is epigenetically repressed. Reexpression of CD20 protein may occur after treatment with the HDAC inhibitor TSA (57).

Glucocorticoid resistance is another common reason for treatment failure in hematological malignancies. It exerts a curative effect by binding to functional GRα (glucocorticoid receptor α) rather than nonfunctional GRβ. 5-AzaC and HDAC inhibitors such as TSA have been proven to upregulate the expression of GRα. This may alter the protein expression profile responsible for GRα and GRβ transcript stabilization and translational regulation, and therefore sensitize cells to glucocorticoid (58).

According to work by Maria *et al.*, the HDACi TSA and SAHA can downregulate the expression of endogenous P-gp in the murine leukemia drug resistant cell line L1210/R, thereby restoring sensitivity to daunorubicin (59). Another HDACi, AN-9, also exhibits a reversing effect on the drug resistant cell line HL-60/ADR (60). Vorinostat (an HDACi) was shown to inhibit HL cell proliferation and to induce changes in the gene expression profile. More intriguingly, it restores cisplatin sensitivity in resistant HL cells by downregulating CD30 and the poxvirus and zinc finger domain (PATZ1) (61). Currently, there are studies suggesting that HDAC1 and HDAC6 are directly involved in autophagy, which may induce CML cell lines to become resistant to vorinostat (62, 63, 64).

Multiple studies have demonstrated that the interaction of leukemia cells with the bone marrow stromal microenvironment represents an important pathway in hematological malignancies and contributes to the survival of leukemia cells. Through cell surface receptor CXCL12/CXCR4-mediated chemotaxis, leukemia cells migrate to microscopic niches within the bone marrow, which induces retention of HSCs within the niches and leads to increased proliferation and survival. This phenomenon is linked to the resistance to traditional chemotherapy. CXCR4 is found to be a target of valproic acid (an HDACi), thus throwing light on the reversal of drug resistance (65). Mahlknecht *et al.* showed that the α4β1 integrin very late activation antigen-4 (VLA-4) plays a key role in the retention of leukemic blast cells in bone marrow in which stromal cells express the vascular cell adhesion molecule-1 (VCAM-1). VLA-4 is associated with bone-marrow minimal residual disease (MRD), which causes relapse and drug resistance after chemotherapy in AML. By targeting VLA-4, HDACis can downregulate its expression, thereby contributing to the reduction of MRD and the rate of relapse (66).

Wang *et al.* found that many genes are differentially expressed at ALL relapse; these are named relapse-specific genes. Aberrant

epigenetic programming occurring in these genes leads to chemoresistance and drives relapse in ALL. Furthermore, by administering the HDACi vorinostat or the DNMT decitabine it is possible to reactivate the aberrantly silenced genes, resulting in leukemic blasts that are once more sensitive to chemotherapy. Administration of these agents (vorinostat in combination with Decitabine) together with prednisolone could achieve the most robust cytotoxicity (67, 68). Consistent with these reports, Kalac *et al.* also reported the highly synergistic effect of a combination of an HDACi (panobinostat) and a DNMT inhibitor (decitabine) in growth inhibition and apoptosis in diffuse large B-cell lymphoma cells (69). Recently, concurrent promoter hypermethylation and deacetylation has been frequently found in Burkitt lymphoma/leukemia, which leads to BIM silencing. This could be reversed by reactivating BIM expression with HDACis (70).

5. MICRORNAS

MicroRNAs (MiRNAs) are non-protein-coding RNAs, 19–25 nucleotides (nt) in length, that regulate the expression of a variety of genes, including translation repression and mRNA degradation in eukaryotic cells, by binding messenger RNA (mRNA) 3' untranslated (3'UTR) regions in a sequence-specific manner (71). MiRNAs are thought to regulate the translation of more than 60% of protein-encoding genes (72). Their targets are usually a number of enzymes involved in epigenetic regulation such as DNA methylthansferases (DNMTs), histone deacetylases (HDACs) and histone methyltransferase (73). Expression of MiRNAs relies on an intricate interplay of DNA methylation and chromatin modifications.

Various miRNAs have recently been reported to be implicated in multiple biological processes, including cell differentiation, metabolism, apoptosis, development and hematopoiesis (71). Recent studies have shown that miRNA plays a decisive role in the regulation of early hematopoiesis. For example, the overexpression of miR-155 or miR-29a in mouse hematopoietic stem cells contributes to pathological granulocyte/monocyte (GM) expansion or AML by converting myeloid progenitors into self-renewing LSC (leukemia stem cells) (74, 75). Furthermore, miR-15a/16-1 deletion causes development of indolent B-cell-autonomous, clonal lymphoproliferative disorders, recapitulating the spectrum of CLL-associated phenotypes by modulating the expression of genes controlling cell-cycle progression (76, 77). MiR-146a expression was found to be negatively correlated with overall survival in patients with AML and ALL (78). Loss of miR-328 was affirmed in the blast crisis of chronic myelogenous leukemia, and restoration of miR-328 expression rescues differentiation and impairs survival of leukemic blasts (79).

The expression of miRNA genes is influenced by DNA or histone modifications. Nalls revealed that both 5-aza-2´-deoxycytidine (DNMTi) and vorinostat (HDACi) are able to restore miR-34a expression, thereby inhibiting the protein expression of BCL2, CDK6 and SIRT1 and inducing apoptosis (80). MiR-34b/c was recognized as a direct transcriptional target of TP53 and a tumor suppressor. The promoter of miR-34b/c was found aberrantly hypermethylated in multiple myeloma. 5-Aza-2'-deoxycytidine (5-azadC) could restore miR-34b expression and enhance apoptosis of myeloma cells (81). Via targeting of TNF receptor-associated factor 6 (TRAF6), microRNA-146a downregulates NFk B activity and functions as a tumor suppressor. It has potent prognostic implication in NK/T cell lymphoma. 5-azadC could again reverse the low level of miRNA-146a by demethylation in the promoter (82). MiR-203 presents as a tumor suppressor in chronic myelogenous leukemia and Ph positive acute lymphoblastic leukemia by targeting the ABL gene. Hypermethylation of the miR-203 promoter could be found in CML cell lines KCL-22 and K562, and 5-Aza-dC in combination with 4-phenylbutyrate (an HDACi) was able to re-induce miR-203 expression and inhibit tumor cell proliferation in an ABL-dependent manner (83).

The roles of miRNAs in the drug resistance of hematological malignancies seem to be involved in regulating the expression of resistance-related genes, tumor suppressor genes and proto-oncogenes. MiR-16 can downregulate overexpressed oncogenic proteins such as cyclin D1, and it enhances drug sensitivity in a New Zealand black mouse model of CLL (76). A wide-ranging evaluation by unsupervised cluster analysis of the roles of 19 miRNAs in patients with CML suggested differential expression between IM resistant and responder samples (84). Liu et al. revealed that a regulatory pathway between myc and miR-144/451 mediates the resistance of CML cell line K562 to imatinib, highlighting that restoration of miR-144/451 can sensitize K562R cells to imatinib therapy (85). In K562 cells, levels of expression of miR-27a and miR-331-5p were inversely correlated with doxorubicin resistance, and direct interference

of both miRNAs with ABCB1 mRNA expression was shown (86). Hao et al. demonstrated that, via suppression of miRNA-15a expression and consequently high vascular endothelial growth factor (VEGF) secretion, bone marrow stromal cells provide survival support and protect myeloma cells from bortezomib-induced apoptosis (87). Bai et al. reported that stable transfection of miR-21 induced daunorubicin resistance in the K562 cell line. This may act though the PI3K/Akt pathway and subsequent downregulation of PTEN protein expression (88). MiR-34a downregulation is associated with chemotherapy resistance in CLL (89).

6. EPIGENETIC THERAPY IN THE CLINIC

Epigenetic therapy is an emerging area, targeting a variety of malignancies particularly in the setting of refractory and therapy-resistant diseases. Resistance to chemotherapy is multifactorial. Several major mechanisms are involved in drug resistance, such as enhancement of DNA damage repair, decline of cell apoptosis, metabolic abnormalities of chemotherapy drugs, enhancement of energy-dependent drug discharge, and changes in glutathione S-transferase as well as topoisomerase II (90, 91). Studies in AML patients revealed ABCB1 expression induced by drug treatment was observed only 4h upon chemotherapy administration (92). In contrast to genetic alterations such as base-pair mutation, changes in epigenetics are commonly mediated by enzymes, which can be reversed by enzyme inhibitors. Moreover, epigenetic alterations tend to develop early in malignant progression. They have also been described in preinvasive lesions and/or high-risk tissues with the potential to serve as targets for chemoprevention (93).

Until now, major targets of epigenetic therapeutic include DNA methyltransferase (DNMT) and histone deacetylase (HDAC). The DNMTis 5-azaC and 5-aza-2'-deoxycytidine (decitabine) are approved for the treatment of myelodysplastic syndromes, which are characterized by global promoter hypermethylation (94). A meta-analysis and systematic review revealed that, compared with conventional care, treatment with hypomethylating agents, and specifically 5-azacitidine, prolongs overall survival and time to AML transformation or death (95).

Several HDACis such as valproic acid and sodium phenylbutyrate have been introduced into the treatment of leukemia. Used alone or in combination with DNA demethylating agents or all-trans retinoic acid, they have achieved clinical remission (96, 97). Vorinostat, which is a potent inhibitor of the activity of HDAC1, HDAC2, HDAC3 and HDAC6, was approved by the US FDA in October 2006 for the treatment of progressive, persistent or recurrent cutaneous T-cell lymphoma. It is the first time that a new class of anticancer agents which has a critical role in the epigenetic regulation of gene expression has been introduced into clinical application (98). In two Phase II studies, patients with cutaneous T-cell lymphoma (CTCL) treated with oral vorinostat demonstrated significant reductions in skin lesions and decreased disease progression (99, 100). In addition, apart from histones, HDACi can regulate gene transcription by modifying nonhistone proteins, including p53 (101), NF-κB (102) and MYC (103). These proteins were previously all confirmed to have key roles in tumorigenesis and drug resistance.

It is interesting that, while cancer cells are sensitive to HDACis, normal cells remain relatively tolerant. This is possibly due to the multiple defects within tumor cells which result in a failure to compensate for the inhibition of pro-survival factors and the activation of death pathways (104).

7. PROSPECTS

In the past few years, multiple studies have been performed to shed light upon the role of epigenetic modifications in the onset, development and drug resistance of hematological malignancies. New drugs aiming to reverse aberrant epigenetic alterations have been applied clinically or are under clinical trial. The application of epigenetic drugs bears the risk of side effects caused by nonspecific alterations, not only in correcting deregulated gene expression but they may also affect normal gene expression. Although several epigenetic drugs have been used clinically, the safety of the therapy still needs to be elucidated. Nonspecific epigenetic inhibitors can lead to nonspecific gene and transposon activation. Until now, most HDACis have ben nonspecific, inhibiting several families of HDAC or failing to demonstrate a certain inhibition spectrum. However, it has been demonstrated that the DNA demethylation induced by 5-azacytidine (azacytidine, AZA) and 2'-deoxy-5-azacytidine (decitabine, DAC) is highly specific and non-random (105).

As revealed in recent studies, exposure of AML cells to HDACi induces a pleiotropic drug resistance phenotype by upregulating MDR1, which

may result in treatment failure (106, 107). Another study suggested that acetylation of histones, particularly H3, facilitates ABC1 expression in addition to ABCG2 (another MDR-related drug transporter). HDACCis, such as FK228, could reduce itself antitumor efficacy through upregulation of ABCB1 in APL (107). Aside from epigenetic modifications, there are still other mechanisms contributing to the role of acquired resistance, such as genetic alterations or stem cell renewal (108). However, these observations throw light on the potential that conventional therapy will be enriched by epigenetic drugs that induce the reversion of non-responsive cells to a drug-responsive state (109). The molecular mechanisms resulting in aberrant epigenetic regulation are still largely unknown. However, striking findings are the frequent and often recurrent mutations in enzymes involved in establishing epigenetic patterns, which suggests a mechanistic link of genetic alterations and aberrant epigenetic reprograming (1). Cancer genome sequencing projects frequently detect recurrent mutations in enzymes. IDH1 and DNMT3A, which encode enzymes involved in establishing and maintaining DNA methylation, were recently found to be mutated in acute myeloid leukemia (4, 5). Generally, the study of epigenetic modification will increase our knowledge of drug resistance in cancer and provide a novel way to treat relapsed and refractory hematological malignancies.

8. ACKNOWLEDGMENTS

This work was supported by grants from: Shanghai Health Bureau fund (ZYSNXD-CC-ZDYJ001) and National Natural Science Foundation of China (81270626)

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Abbreviations: CpG island: cytosine–phosphate–guanine rich sequences; DNMTs: DNAmethyltransferases; CMML: chronic myelomonocytic leukemia; MDR: Multidrug resistance; AMLs: acute myelogenous leukemias; CML: chronic myeloid leukemia; BIM: BCL-2-interacting mediator; BMMSCs: bone marrow mesenchymal stem cells; PRMT1: Protein arginine methyltransferase 1; PcG: Poly-comb group; MLL: mix-lineage leukemia; APL: acute promyelocytic leukemia; CML: chronic myelocytic leukemia; HAT: histone acetyltansferase; HDAC: histone deacetylase; TRAIL: tumor necrosis factor (TNF)-related apoptosis-inducing ligand; VCAM-1: vascular cell adhesion molecule-1;

Key Words: Epigenetic Programming, Drug Resistance, Hematological Malignancies, Review

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