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Epigenetics and Targeted Therapy in Acute Leukemia

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1. Introduction

Chromatin is a highly ordered structure consisting of repeats of nucleosomes connected by linker DNA. It consists of DNA, histone, and nonhistone proteins condensed into nucleoprotein complexes and it functions as the physiological template of all eukaryotic genetic information. Histones are small basic proteins containing a globular domain and a flexible charged NH_2 terminus known as the histone tail, which protrudes from the nucleosome. Epigenetic codes are set up by modifications on the DNA (methylation) or on the histones (acetylation, methylation, phosphorylation, ubiquitination, and ADP ribosylation, etc.), by different classes of enzymes in a precise and targeted manner. Posttranslational modification to histones affects chromatin structure and function resulting in altered gene expression and changes in cell behavior. These modifications do not alter the primary sequence of DNA but have an impact on gene expression regulation, most frequently gene suppression. They lead to pathological states in hematopoietic system resulting in acute leukemia.

DNA methylation is catalyzed by DNA methyltransferases (DNMTs), of which three active enzymes have been identified in mammals, namely DNMT1, DNMT3A and DNMT3B. DNMT1 is responsible for maintaining pre-existing methylation patterns during DNA replication, while DNMT3A and DNMT3B are required for initiation of de novo methylation. Acetylation is a reversible process. The balance between acetylation (transcriptional activation) and deacetylation (transcriptional repression) is regulated by histone acetyltransferase (HATs) and histone deacetylases (HDACs) in specific lysine residues in the N-termini of histone tails and/or in transcription factors (eg, p53, E2F1, GATA1, RelA, YY1, and Mad/Max) without directly binding to the DNA (Minucci et al., 2006, Gallinare et al., 2007), and is critical in regulating gene expression. Mammalian HDACs are classified into three classes based on their homology to yeast HDACs. Class I HDACs (HDAC1, 2, 3, 8, and 11) are homologues of *Sacharomyces cerevisiae* histone deacetylase Rpd 3 (reduced potassium dependency 3) and those with greater similarity to yeast Hda1, are class II HDACs (Gray & Ekstrom, 2001; Gao et al., 2002; Kao et al., 2002). Class III HDACs are called Sirtuins, which are homologoues of yeast sir2 (silence information regulator). Histones can be mono-, di-, or tri-methylated at lysine and arginine residues by HMTs, and the recent identification of histone lysine demethylases such as KDM1/LSD1 and the Jumonji-domain (JMJD)-containing protein family shows that histone

methylation is an enzymatically dynamic process (Lan et al., 2008). In general, methylation at H3K4, H3K36, and H3K79 is associated with transcriptional activation, whereas H3K9, H3K27, and H3K20 methylation is associated with transcriptional repression (Kouzarides et al., 2007). The involvement of HMTases, more so of DNMTs (DNA methyltransferase) is observed in cancer (Zhang et al., 2005). Several chromosomal translocations in acute myeloid leukemia (AML) that produce chimerical fusion oncoproteins have been shown to repress genes involved in cell-cycle growth inhibition, differentiation, and apoptosis (Bhalla et al., 2005; Hormaeche, 2007) . The reversal of aberrant epigenetic changes has therefore emerged as a potential strategy for the treatment of cancer. DNA methylation and histone deacetylation inhibitors and a number of compounds targeting enzymes that regulate DNA methylation, histone acetylation and histone methylation have been developed as epigenetic therapies, with some demonstrating efficacy in hematological malignancies and solid tumors. The aberrance of DNA methylation, histone acetylation and methylation has been found in acute leukemia. We found that PHI (Phenylhexyl isothiocyanate), synthetic phenylhexyl isothiocyanates, could correct the aberrance (Ma et al., 2006; Xiao et al., 2010 ; Jiang et al., 2010) .

2. Epigenetic event in acute leukemia

Epigenetic mechanisms controlling transcription of genes involved in cell differentiation, proliferation, and survival are often targets for deregulation in malignant development. Misregulation of epigenetic modification may be as significant as genetic mutation in driving cancer development and growth. There are some acute leukemias with cytogenetic translocations in WHO classification, which involved in epigenetic modification change. DNA methylation is established during early embryogenesis and continues through different generations of cell cycle and development. Abnormal patterns in DNA methylation are one of epigenetic deregulation to be characterized in human cancers, either as a result of DNMT over expression or aberrant recruitment. Acetylation and methylation are the two histone modification that has been clinically associated with pathological epigenetic disruption in cancer cells. Specific recurring chromosomal abnormalities are commonly associated with acute myeloid leukemia. These chromosomal anomalies influence the molecular and cellular phenotype of the leukemia blasts and may be responsible for their malignant potential (Caligiuri et al., 1997; Thandla et al., 1997). The aberrations often lead to the formation of one or more fusion genes resulting in the over expression or untimely expression of a normal gene, eg, the MYC/Ig gene enhancer fusion produced by the t (8;14) in Burkitt's lymphoma (Crosce et al., 1986; Thandla et al., 1997) , or the creation of a new gene product by fusing genes as in the PML-RAR fusion produced by the t(15;17) characteristic of acute promyelocytic leukemia (Zelent et al., 2001). Some regions are common partners in fusion events, and 11q23 is involved in at least 40 different translocations in acute leukemia.

2.1 DNA methylation and acute leukemia

The maintenance of appropriate DNA methylation within CpG nucleotide islands plays a significant role in regulation of a wide variety of molecular processes including stability of chromosomal structure and control of gene expression (Das, 2004). DNA methylation can

also result in the recruitment of proteins that bind methylated CpG sequences (methyl-CpG-binding domain [MBD] proteins) complexes with histone deacetylases (HDACs) and histone methyltransferase (HMTase) prompting coordinated epigenetic modifications of the surrounding chromatin (Esteller, 2005). Tumor cell-specific promoter hypermethylation in genes that play important roles in regulating cell cycle, apoptosis, DNA repair, differentiation, and cell adhesion is often a hallmark of disease (Esteller, 2008). In addition, hypomethylation of repetitive sequences may result in chromosomal and genetic instability, leading to further oncogenic events. Transcriptional silencing via DNA hypermethylation can often be associated with poor clinical outcome in several malignancies (Bhalla et al., 2005; Das, 2004; Herranz, 2007). Abnormal gain in DNA methylation with aberrant silencing of transcription may occur at specific gene promoter regions and represents a mechanism for inactivation of tumor-suppressor genes. In a clinical experiment, the methylation profiles of 344 patients with acute myeloid leukemia (AML) were examined. A common aberrant DNA methylation signature consisting of 45 genes in most of them hypermethylated was identified, that was consistently detected in at least 10 of the 16 clusters' methylation signatures and affecting at least 70% of the cases studied. Genes in this signature are likely to be part of a common epigenetic pathway involved in leukemic transformation of hematopoietic cells. They are the tumor suppressor PDZD2, transcriptional regulators (ZNF667, ZNF582, PIAS2, CDK8), nuclear import receptors (TNPO3, IPO8), and CSDA, a repressor of GM-CSF. They could predict the clinical outcome (Maria et al., 2010). Silencing of CDKN2A and CDKN1A has been associated with poor clinical outcome in acute leukemias (Herman, 2003; Bernstein et al., 2007). Aberrant p15CDKN2B has been widely reported in leukemias and other myeloid neoplasms (Cameron et al., 1999; Christiansen et al., 2003; Shimamoto et al., 2005; Toyota et al., 2001). Roman-Gomez et al. reported an incidence of *p21CIP1* methylation of 41% in 124 patients with acute lymphocytic leukemia (ALL). Most importantly, they observed that *p21CIP1* methylation was an independent predictor of poor prognosis both in adults and children with this disease (Roman-Gomez et al., 2002). Zheng et al. reported that there are 35.29%, 48.65% hypermethylation of the p15 INK4, p16 INK4 gene exon 1 in acute leukemia respectively, 25%, 37.5% hypermethylation of the p15 INK4, p16 INK4 gene exon 1 in acute myeloid leukemia respectively, 60%, 69.23% hypermethylation of the p15 INK4, p16 INK4 gene exon 1 in acute lymphoid leukemia respectively (Zheng et al., 2004a, 2004b).

2.2 Histone acetylation and acute leukemia

Histone acetylation is associated with transcriptionally active chromatin, which has been established over 40 years ago (Littau et al., 1964). The acetylation of the histone tails was surmised to result in a decreased affinity of the histone for the DNA, on account of the decreasing positive charge, establishing an 'open' chromatin state. The transcriptionally active state may be mediated via the transient formation of $(H3\text{-}H4)_2$ tetrameric particle that could adopt an open structure only when H3 and H4 tails are acetylated (Morales et al., 2000). Mistargeting and mutations in HATs and HDACs are major factors leading to diseases and disorders. A classic example of one such disorder is the Rubinstein-Taybi syndrome (RSTS), which is a consequence of a single mutation in the gene encoding the HAT CREB binding protein (CBP) located on chromosome 16p13.3. In addition to functioning as a bridge between transcription factors and the basal transcription machinery, CBP has histone acetyltransferase activity (Bannister et al., 1996; Ogryzko et al., 1996). CBP

causes an acetylation of core histone proteins, such as H2A, H2B, H3 and H4, and interacts with histone acetyltransferases, such as PCAF (P300/CBP associated factor), SRC-1 (steroid receptor coactivator-1) and ACTR (coactivator for nuclear hormone receptors). It is generally accepted that CBP is involved in the remodeling of nucleosomes via these factors. Altered HAT (histone acetylase) activity has been reported in both hematological and solid cancers, by inactivation of HAT activity through gene mutation or through deregulation of HAT activity by viral oncoproteins. Chromosomal translocations involving HATs and their consequent fusion proteins have been implicated in the onset and progression of acute leukemia. Such translocations have been identified in acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) cases in which the translocation t (11;16) (q23;p13) results in a fusion protein (MLL-CBP) consisting of the CBP and the mixed lineage leukemia (MLL) protein. The underlying mechanisms of effects of this fusion protein in the formation of AML may involve deregulation of MLL target genes by CBP-mediated chromatin remodeling and increased chromatin accessibility (Ayton et al., 2001). The fusion protein has A/T hooks and cysteine-rich DNA recognition domain of MLL fused to intact CBP and fails to recruit SWI/SNF to its target as it lacks the SET domain, which is important for interacting with hSNF5 (Taki et al., 1997). MLL can also be aberrantly fused to p300 in AML via the t (11;22)(q23;p13) translocation (Ida et al., 1997). In addition to p300 and CBP fusion proteins involving the HATs, TIF2, MOZ (monocytic zinc finger protein) and MORF that arise as a result of chromosomal translocations have also been identified in hematological malignancies (Cairns, 2001; Cairns et al., 2001; Panagopoulos et al., 2001; Liang J et al., 1998). The MOZ-CBP fusion proteins is expressed due to a translocation t (8;16)(p11;p13), associated with a subtype of acute monocytic leukemia (AML M5). The resulting fusion protein has been recently shown to increase expression of genes regulated by NF-κB (Chan et al., 2007). MORF gene fusions are expressed in t (10;16) (q22;p13) in childhood AML and myelodysplastic syndrome, in which the MORF gene is fused with the CBP gene (Champagne et al., 1999). The MOZ-TIF2 fusion is one of a new family of chromosomal rearrangements that associate HAT activity, transcriptional coactivation, and acute leukemia (Jian et al., 1998). The CBP gene has been shown to fuse with MOZ in AML patients with t (8;16)(p11;p13) (Borrow et al., 1996; Giles et al., 1997), and in MLL patients with therapy-related acute leukemia with t(11;16)(q23;p13) (Rowley et al., 1997; Satake et al., 1997; Sobulo et al., 1997; Taki et al., 1997).

Deregulation of HDAC activity by chromosomal translocations has been strongly implicated in aberrant gene silencing and the promotion of tumorigenesis, especially in leukemia. A well-understood link between tumorigenesis and aberrant HDAC activity occurs in acute promyelocytic leukemia (APL). In APL, the chromosomal translocations t (15;17) and t (11;17) results in fusion proteins RARα-PML (promyelocytic leukemia protein) and RARα-PLZF (promyelocytic zinc finger), respectively. These aberrant proteins retain the ability to bind RAREs and HDACs with high affinity and are no responsive to retinoids, resulting in the deregulated transcriptional silencing of RAR-targeted genes and prevention of cell differentiation (Zelent et al., 2001). The retinoic acid receptor (RAR) is important for myeloid differentiation and acts as a transcriptional regulator by binding its heterodimerization partner RXR, which in turn bind to retinoic acid response elements (RAREs) within the promoters of target genes (Bolden et al., 2006). Both PML-RARalpha and PLZF-RARalpha fusion proteins recruit the nuclear co-repressor (N-CoR)-histone deacetylase complex through the RARalpha CoR box (Iris & Luciano, 2011). AML1-ETO is a

fusion protein that results from t (8;21) and CBFβ-MYH11 caused by the chromatin inversion 16(p13;q22) in cases of AML. It is of translocations in leukemogenesis that is capable of altering protein acetylation. Fusion proteins from these translocations result in the recruitment of HDACs to target gene promoters and consequent gene silencing (Wang et al., 2007; Bhalla et al., 2005).

We have studied on the state of histone acetylation in acute leukemia. The levels of acetylated H3 and H4 were examined in patients with or without complete remission response. The deficient histone acetylation existed in all 15 cases of acute leukemias, including both myeloid and lymphoid lineages. The results showed that both levels of histone H3 and H4 acetylation in 15 AL patients were significantly lower, as compared with 4 individuals without leukemia(H3 0.128±0.013 *vs* 0.386±0.104, H4 0.096± 0.008 *vs* 0.341±0.096 respectively, both $p<0.01$). This deficiency was revealed in all the acute leukemia cases investigated in all age groups from 2.5 to 69 years, including both myeloid and lymphoid lineages (Xiao et al., 2010).

2.3 Histone methylation and acute leukemia

Histone methylation is brought about by histone methyltransferases (HMTases), which catalyze the transfer of methyl group from the donor SAM (S-adenosyl methionine) predominantly to the lysine or arginine residues on the N-terminal histone tails. Based on the basis of amino acids that get modified, they are classified into the lysine methyltransferases (Martin & Zhang, 2005) and arginine methyltransferases (Bedford et al., 2005). The residues can be mono-, di- or tri-methylated, which further increase the scope and range of methylation-mediated regulation. Arginine methyltransferase have an additional level of regulation in catalyzing the formation of asymmetricdimethylarginine (aDMA) or symmetricdimethylarginine (sDMA). HMTases are versatile enzymes with their modifications being involved in both activation and repression. The exact residue on the histone tails that gets modification determines transcriptional activation or repression. The lysineme methyltransferases are involved in transcriptional activation (methylation on H3K4, H3K36 and H3K79) as well as transcription repression (methylation of H3K9, H3K27 and H4K20), while the arginine methyltransferases so far have been shown to be involved in transcriptional activation (Kourzarides et al., 2007). There are a form of chromosomal translocations involving HMTs (e.g., MLL1, NSD1, NSD3), gene over expression or amplification (e.g., EZH2, MLL2, NSD3, BMI1, GASC1), gene silencing (e.g., RIZ1), and gene deletion (e.g., MLL3).

Chromosomal rearrangements, affecting chromosome 11q23 and involving the human MLL gene, is a histone methyltransferase. It recurrently associated with the disease phenotype of acute leukemias (Pui et al., 2002, 2003). There are a total of 87 different MLL rearrangements of which 51 TPGs are now characterized at the molecular level. The four most frequently found TPGs (AF4, AF9, ENL and AF10) encode nuclear proteins that are part of a protein network involved in histone H3K79 methylation (Meyer et al., 2006). Because H3K79 methylation is important for transcriptional elongation (Krogan et al., 2003), global hypomethylation could also lead to a reduced expression of a great number of genes (Dik et al., 2005).

The key transcriptional pathways that are subordinate to both wild-type and oncogenic MLL proteins include Hox genes, which are master regulators of cell fate, proliferation, and morphogenesis (Owens & Hawley, 2002). Hematopoietic cells transformed by MLL

oncoproteins consistently hyperexpress several Hoxa cluster genes, some of which have been shown to be direct targets of MLL and key contributors to the pathologic features of MLL associated leukemia (Ayton & Cleary, 2003; Kumar et al., 2004; Wang et al., 2005). This subtype of acute leukemia has a particularly aggressive with a very dismal prognosis. Thus, an interesting scenario about the contribution of CALM-AF10 in leukemogenesis can be envisioned whereby the CALM-AF10 fusion, in addition to up-regulating specific oncogenes (eg, HOXA5 genes) via local hypermethylation, might promote leukemogenesis by interfering with multiple cellular pathways through global hypomethylation of H3K79.

Lin et al. suggested that the increased chromosomal instability associated with H3K79 hypomethylation caused by the CALM-AF10 fusion might accelerate the acquisition of additional genetic abnormalities required for leukemogenesis. AF10 fusion proteins seem to use at least 2 mechanisms that promote leukemogenesis: (1) deregulation of target genes resulting from local epigenetic changes, and (2) increasing genomic instability due to global epigenetic changes (Lin et al., 2009).

ALL-1 is a member of the human trithorax/Polycomb gene family and is also involved in acute leukemia. ALL-1 is associated in a stable complex with at least 27 proteins (Tatsuya et al., 2002), most ALL-1-associated proteins can be classified into well-known complexes involved in transcription. The ALL-1 protein was found to be posttranslationally processed into two polypeptides, p300 and p180. The two ALL-1 polypeptides are present within a single supercomplex, which is physical association between segments spanning residues 1979–2130 and 3613–3876. p180 contains the SET domain which methylates H3-K4, as well as a domain (TAD) with transcriptional activation capacity. p300 comprises the HAT hooks which bind DNA, a bromodomain which binds acetylated lysines within histone H4 (Dhalluin et al., 1999; Jacobson et al., 2000), the PHD zinc fingers domain, and a region with homology to DNA methyltransferase. The cleavage might enable the formation of a spatial configuration accommodating the many interactions of ALL-1 with proteins and DNA. ALL-1-associated leukemias show some unusual and intriguing features (DiMartino et al., 1999). A study showed 16/22 (68%) infant's acute leukemia with ALL-1 gene rearrangements. It demonstrated that ALL-1, a highly intricate chromatin modifier, in acute leukemia is abnormal in its function (Cimino et al., 1997).

The t (8;21) is found in 10–15% of myeloid leukemia and gives rise to a fusion protein that contains the N-terminal portion of RUNX1 fused to nearly all of myeloid translocation gene on chromosome 8 (MTG8, also known as eight-twenty-one (ETO)) (Miyoshi et al., 1991, 1993; Erickson et al., 1994). The fusion protein appears to function as a transcriptional repressor of RUNX1-regulated genes (Peterson et al., 2004). The t (12;21) is found in up to 25% of pediatric B-cell acute leukemia and creates a chimerical gene encoding the TEL–RUNX1 fusion protein (Golub et al., 1995; Nucifora et al., 1995). RUNX1 function is also impaired by the inv (16), which fuses the RUNX1 associating factor, core binding factor b (CBFb or polyoma enhancer binding protein 2 betas) to the smooth muscle myosin heavy-chain gene MYH11, in approximately 8% of acute myeloid leukemia (Liu et al., 1993). Two SUV39H1 contact points within repression domain 2 of RUNX1, with one of these RUNX1 domains also contacting HDAC1 and HDAC3, begins to provide a mechanistic basis for gene silencing mediated by RUNX1. Both Runt and RUNX1 are required for gene silencing during development and a central domain of RUNX1, termed repression domain 2 (RD2). RD2 contacts SUV39H1, a histone methyltransferase, via two motifs and that endogenous SUV39H1 associates with a Runx1-regulated repression element in murine erythroleukemia

cells. In addition, one of these SUV39H1-binding motifs is also sufficient forbidding to histone deacetylases 1 and 3, and both of these domains are required for full RUNX1-mediated transcriptional repression. The association between RUNX1, histone deacetylases and SUV39H1 provides a molecular mechanism for repressor (E et al., 2006).

The state of histone methylation in acute leukemia has been studied. Aberrant histone methylations showed downregulation of H3K4 methylation and upregulation of H3K9 methylation in all acute leukemia. The methylation status of histone H3 at lysines 4 and 9 of mononuclear cells from 19 patients with acute leukemia, aged from 6 to 78, including AML and ALL and that from 9 individuals without leukemia were compared. The results showed that the level of H3K4 methylation was significantly lower in 19 AL patients than that in non leukemia (0.220±0.096 *vs* 0.447±0.186, P<0. 01), while the level of H3K9 methylation was significantly higher (0.409 4±0.106 *vs* 0.168±0.015, P<0.01). These results clearly demonstrated that the patients with acute leukemias are hypomethylated at H3K4, and hypermethylated at H3K9. (Ma et al., 2010).

3. Epigenetic therapy in acute leukemia

The cause of most epigenetic diseases can be traced to the enzymes that establish them. A great deal of research has gone into the discovery of the modulators of these enzymes, which not only leads to a better understanding of the mechanism, but also to therapeutic possibilities. Fusion protein, such as MLL-MOZ, PML-RARA results mutations in HATs, HDACs and HMTas, and misregulating gene expression. Inactivation of tumor suppressor genes is central to the development of cancer. Silencing of these genes occurs by epigenetic means and inhibition of these factors lead to reversal of tumor suppressor gene silencing and inhibition of tumorigenesis (Gibbons et al., 2005).

Chemical compound acting on epigenetic control of gene expression mainly fall into two broad categories: inhibitors of DNA methyltransferases and inhibitors of histone deacetylase (HDACi). Recently, compounds regulating histone methylations have been studied. These drugs have been used in phase I and II trials in patients with hematological and solid tumor. Some of them have been approved by FDA (U.S. Food and Drug Administration) to treat hematological disorders and solid tumor.

Pharmacologic inhibition of DNA methylation causes the trapping of DNMTs and their targeted degradation results in re-expression of genes that have been aberrantly silenced by hypermethylation, concomitant with inhibition of clonal expansion and tumor cell growth, induction of cell differentiation, and cancer cell death (Issa, 2007). A number of DNA methylation inhibitors are currently under investigation, including the pyrimidine nucleoside analogs Decitabine (Dacogen, SuperGen, Inc., Dublin, CA) and Azacitidine (Vidaza, Celgene, Summit, NJ), and the nonucleoside inhibitor Hydralazine. Azacitidine and Decitabine are both approved by FDA for the treatment of a number of myelodysplastic syndrome subtypes, including refractory anemia and chronic myelogenous leukemia (CML) (Gal-Yam et al., 2008; Issa. 2007; Wong et al., 2007).

Most current DNA-demethylating agents block the action of DNA methyltransferases (DNMTs), whose expression levels are usually moderately elevated in human tumors. The genetic inactivation of two DNMTs, DNMT1 and DNMT3B, induces demethylation of all known hypermethylated tumor-suppressor genes and remarkably slow growth. DNMTs have two binding sites: one for the cytosine residue and another for S-adenosyl- methionine.

It is expected that chemicals tightly binding any of these pockets will reduce the methylation rate because of competitive inhibition. The cytidine and 2-deoxycytidine analogs are the most extensively studied members of this class. The first analog tested to determine whether it was an inhibitor of DNA methylation was 5-azacytidine (5-aza-CR), which was first synthesized almost 50 years ago. 5-azacytidine could incorporate into DNA forming covalent adducts with cellular DNMT1, thereby depleting cells from enzyme activity and causing demethylation of genomic DNA as a secondary consequence. Schneider-Stock reported that 5-aza-CR caused a marked down-regulation of DNMT1 and DNMT3A mRNA levels, in contrast to a null effect on DNMT3B (Schneider-Stock, et al., 2005). In various in vitro experiments, 5-aza-CR treatment leads to re-expression of former silenced genes. The resulting DNA hypomethylation has been linked to the induction of cellular differentiation and altered expression of genes involved in tumor suppression. It was demonstrated to have a wide range of anti-metabolic activities when tested against cultured cancer cells and to be an effective chemotherapeutic agent for acute myelogenous leukemia. Their clinical efficacy in hematological malignancies has been demonstrated in vitro and in a series of phase I and II trials. Azacitidine was first approved by FDA in 2004 for the treatment of myelodyspalstic syndrome (MDS). The phase II trials recorded complete remission (CR), partial remission (PR) and hematological improvement (HI) rates of 15%, 2% and 27%, and of 17%, 0% and 23% in the CALGB 8421 and CALGB 8921, respectively. A subsequent phase III randomized trial in 191 MDS patients reported an overall response rate of 60% on the Azacitidine arm (CR, 7%) compared with 5% of patients receiving supportive care (Silverman et al., 1993). A recent re-analysis of three CALGB trials by applying WHO classification and International Working Group (IWG) responds criteria confirmed those response figures, with 90% of patients achieving a response by six cycles; however, whereas quality of life significantly ameliorated, there was no improvement in overall survival in the whole patient population or in the separate classes of risk (Silverman et al,. 2006). Because of 5-azacytidine's general toxicity, other nucleoside analogs were favored as therapeutics. There is now a revived interest in the use of Decitabine (5-aza-2 -deoxycytidine) as a therapeutic agent for cancers in which epigenetic silencing of critical regulatory genes has occurred (Christman, 2006).

Decitabine was approved by FDA in 2006 for the treatment of MDS. It is an analog of deoxycytidine that incorporates into DNA and forms irreversible covalent bonding with DNA-methyltransferases (Mtase) at cytosine sites targeted for methylation. That leads to DNA synthesis stalling and eventual degradation of DNA-Mtase. Resumption of DNA replication in the absence of Mtase results in gene hypomethylation and reactivation of gene expression, as has been demonstrated for multiple epigenetically inactivated loci (Karpf et al., 2002; Li et al., 1999; Toyota et al., 2002). At high doses, treated cells die via apoptosis triggered by the DNA adducts and DNA synthesis arrest. By contrast, at low doses, cells survive but change their gene expression profile to favor differentiation, reduced proliferation, and/or increased apoptosis. Thus, Decitabine has potentially dual effects on treated cells. Clinical development of Decitabine was initiated more than 2 decades ago, with classical phase I studies that defined 1500 to 2250 mg/m^2 per course as the maximum tolerated dose (MTD), and demonstrated a short half-life for the drug (Santini et al., 2001). In a multicenter, phase II study, patients older than 60 years who had AML (i.e., $>$20% bone marrow blasts) and no prior therapy for AML were treated with Decitabine 20 mg/m^2 intravenously for 5 consecutive days of a 4-week cycle. Response was assessed by weekly CBC and bone marrow biopsy after cycle 2nd and after each subsequent cycle. Patients

continued to receive Decitabine until disease progression or an unacceptable adverse event occurred. Fifty-five patients (mean age, 74 years) were enrolled and were treated with a median of three cycles (range, 1 to 25 cycles) of Decitabine. The expert-reviewed overall response rate was 25% (complete response rate, 24%). The response rate was consistent across subgroups, including in patients with poor-risk cytogenetics and in those with a history of myelodysplastic syndrome. The overall median survival was 7.7 months, and the 30-day mortality rate was 7%. The most common toxicities were myelosuppression, febrile neutropenia, and fatigue (Amanda et al., 2010). Decitabine has been used also in Imatinib-resistant CML (Issa, et al., 2005) or in combination with Imatinib in patients with accelerated or leukaemic-phase CML (Oki et al., 2007).

Several classes of HDACIs have been identified, including: (a) short-chain fatty acids (e.g., butyrates); (b) organic hydroxamic acids (e.g., TSA and hybrid polar compounds [HPCs]); (c) cyclic tetrapeptides containing a 2-amino-8-oxo 9,10-epoxy-decanoyl (AOE) moiety (e.g., trapoxin); and (d) cyclic peptides not containing the AOE moiety (e.g., FR901228, apicidin).

HDAC inhibitors (HDACIs) also impact epigenetic expression. They display ability to affect several cellular processes which are dysregulated in neoplastic cells. One of the mechanism is that HDACIs could upregulate acetylation of histones, activate tumor suppressor genes and repress oncogenes. They are potent inducers of differentiation with arrest of cells in the G1 but sometimes also in the G2 phase. They activate transcription of the cyclin-dependent kinase (CDK) inhibitor WAF1 which are responsible for cell cycle arrest and subsequent cell differentiation (Rocchi et al., 2005). Another mechanism is that they can induce apoptosis in vitro and in vivo by activating both the death-receptor and intrinsic apoptotic pathway (Nebbioso et al., 2005; Peart et al., 2005) and increase p53 acetylation diminishes Mdm2-mediated ubiquitination and the subsequent proteasome-facilitated degradation (Luo et al., 2000). In addition, HDAC inhibitors might lead to activation of the host immune response and inhibition of tumor angiogenesis by multifactorial processes.

Drugs belonging to several classes of HDACIs are in clinical trials. TSA is a fermentation product of Streptomycin with anti-fungal properties and was found to be a reversible inhibitor of HDACs in vitro, as well as in vivo. It is a highly potent HDAC inhibitor. Because of its known pharmacology, it has come to be a "reference" substance in research aimed at changing the acetylation-deacetylation state of proteins for clinical as well as research applications. Januchowski R et al. found that TSA down-regulate DNMT1 mRNA and protein expression in Jurkat T leukemia cells clone E6-1. They also observed that TSA decreased DNMT1 mRNA stability and reduced this transcript half-life from approximately 7 to 2 h. The finding suggests that TSA not only alters histone acetylation, but also may affect DNA methylation (Januchowski et al, 2007).

Vorinostat, suberoylanilide hydroxamic acid (SAHA), is an inhibitor of class I and II HDAC enzymes, promoting cell-cycle arrest and apoptosis of cancer cells (Marks et al., 2007). Relevant target genes have been characterized through gene expression analysis (Peart et al., 2005). SAHA has been shown to have clinical activity in a transgenic animal model of therapy resistant acute promyelocytic leukemia, restoring sensitivity to retinoic acid, and to induce differentiation of human breast cancer cells (He et al., 2001). It has been approved by FDA for the treatment of CTCL in 2006. In phase I clinical trials, it was demonstrated that the maximum tolerated dose was 400 mg qd and 200 mg bid for continuous daily dosing and 300 mg bid for 3 consecutive days per week dosing. Histones isolated from peripheral-blood mononuclear cells showed consistent accumulation of acetylated histones post-therapy, and enzyme-linked immunosorbent assay demonstrated a trend towards a dose-

dependent accumulation of acetylated histones from 200 to 600 mg of oral SAHA. There was one complete response, three partial responses, two unconfirmed partial responses, and 22 (30%) patients remained on study for 4 to 37+ months (William et al., 2005). Phase I studies with vorinostat (SAHA) have also resulted in complete and partial responses (CRs and PRs, respectively) in both refractory solid and hematological malignancies. The major adverse events (AEs) observed with vorinostat differ by route of administration, i.v. or oral, possibly due to differences in pharmacokinetics. Oral vorinostat produced fatigue, diarrhea, anorexia and dehydration as major AEs, whereas i.v. vorinostat produced myelosuppression and thrombocytopenia as major AEs (O'Connor et al., 2006). In another phase I/II study, vorinostat was used to treat 41 patients with leukaemia or MDS who were relapsed or refractory to previous therapy or who were not candidate to chemotherapy. Hematological improvement was observed in 17% of cases including two complete responses in AML. Evidence of histone H3 acetylation was found in peripheral blood and bone marrow cells, and down-regulation of proliferation-associated genes was associated with hematological improvement (Garcia-Manero et al., 2008).

Phenylbutyrate is a fatty acid with HDACi activity that has been studied extensively in patients with solid tumors, leukemia, and myelodysplastic syndromes (MDS). Depsipetide (FK-228) is a cyclic tetrapeptide with potent HDACi activity especially of Class I HDACs. Depsipeptide also has been studied in several clinical trials.

Valproic Acid is a short chain fatty acid that is clinically used as an anticonvulsant. It has excellent bioavailability and can be given orally. Its elimination half-life is 6–17 hours. And overall, it has a good toxicity profile (Garcia-Manero G &Issa, 2005). Clinical activity has been demonstrated in studies in MDS patients who received VPA orally on a continuous schedule to maintain a serum concentration of 50–100 mg/ml. The first pilot study reported a 44% overall response rate in MDS with a median response duration of 4 months (Kuendgen et al., 2004). In a follow-up study on 122 patients with MSD and AML, an overall response rate of 20% was reported, including one CR. A higher percentage of response was observed in low-risk MDS, according to morphological subtype (Kuendgen et al., 2007). VPA has been used in combination with all-trans retinoic acid in patients with acute leukaemia, eventually in association with cytotoxic therapy, without appreciable or with only minor improvements (Raffoux et al.,2005; Pilatrino et al., 2005; Bug et al., 2005).

The field of HMTase is relatively unexplored with just a few examples of which majority are substrate analogues. The only specific inhibitor is Chaetocin, a SU(VAR)3–9 inhibitor (Greiner et al., 2005) and the documented analogue inhibitors are AMI-1, analogue inhibitor of PRMT (Cheng et al., 2004). Chaetocin killed human tumor cell lines and primary myeloma cells in vitro whereas normal human B cells were insensitive to the compound (Isham et al., 2007). We have designed siRNA segments targeting JARID1B and SU (VAR) 3–9 gene and transfected them into tumor cells. The result showed that JARID1B siRNA upregulated histone methylated H3K4 remarkbly and histone acetylation of H3 slightly. SU (VAR) 3–9 siRNA downregulated H3K9, upregulated histone acetyaltion H3. JARID1B and SU (VAR) 3–9 siRNA upregulated P27 and suppressed the proliferation in tumor cells. The expression of BCL-2, procaspase-9, procaspase-3, and C-myc decreased and cells apoptosis induced. (Cai, et al., unpublished; Ma et al., unpublished).

Sinefungin is another analogue inhibitor of Arginine methyltransferase (Amur et al., 1986). Since the role of HMTases in cancer manifestations is well established, these inhibitors will be of great use for cancer treatment. The small molecule inhibitor BIX-01294 inhibited

methylation at H3K9 at several G9a-targeting genes. 3-Deazaneplanocin (DZNep) is a compound capable of depleting levels of the polycomb-recessive complex 2 (PRC2) components EZH2, SUZ12, and EED. Treatment of tumor cell lines with DZNep inhibited methylation at H3K27 but not H3K9 reactivated a series of genes that are transcriptionally repressed by PRC2 and induced potent tumor cell-selective apoptosis (Tan et al., 2007). An alternative way to reactivate epigenetically silencing genes is to inhibit the activity of histone demethylases. Recently, polyamine-based inhibitors of LSD1 have been developed that induce mono- and di-methylation at H3K4 and concomitant reactivation of previously silenced genes in treated tumor cell lines (Huang et al., 2007). The biological effects of these agents have not yet been evaluated but they represent an important step forward in the development of new agents to target the epigenetics.

Both HDAC inhibitors and DNA demethylating agents have shown clinical efficacy as single agents; yet combination of the two therapies has been shown to have strong synergistic effects on the reactivation of silenced genes and antiproliferative and cytotoxic effects on cancer cells (Bhalla et al., 2005; Glaser et al., 2007).

Combination therapies employing DNMT inhibitors and HDACIs together or with other agents are being pursued clinically. The combination of azacitidine with histone deacetylase inhibitors, such as sodium phenylbutyrate (Maslak et al., 2006), valproic acid and all-trans retinoic acid (Soriano et al., 2007), has been explored with little evidence of improvement in patients with leukaemia or high-risk MDS.

A phase I/II trial of vorinostat in combination with azacitidine (NCT00392353) are currently underway; preliminary results from phase I of the combination trial indicated that the therapy is safe and well tolerated and appears superior to azacitidine alone for time to response, overall response and CR rate (Silverman et al., 2008).

Isothiocyanates has been found potential anti-tumor agents. Natural isothiocyanates occur as thioglucoside conjugates, i.e. glucosinolate, in a wide variety of cruciferous vegetables including broccoli, cabbages, watercress, and Brussel's sprouts. The isothiocyanates (ITS) are released when the vegetables are cut or masticated. The research currently demonstrated that natural and synthetic isothiocyanates are potent cancer chemopreventive agents in a number of carcinogen-induced cancer models in rodents. The primary mechanism is the blocking of initiation of carcinogenesis via inhibiting cytochrome P450s, and inducing detoxifying enzymes to remove carcinogens (Chiao et al, 2002). We have demonstrated that Phenylhexyl isothiocyanate (PHI), one of ITC, a man-made isothiocyanate, may induce cell cycle blocking and apoptosis via altering epigenetic modification. PHI inhibited cell cycle CDK activity and up-regulated p21WAF1 (p21) in cancer cells. Exposure of HL-60 and Molt-4 leukemia cells to PHI induced G1 arrest and apoptosis. Additionally, PHI reduced the expression of HDAC and increased the level of acetyl transferase p300, in favor of accumulation of acetylated histones. Within hours, global acetylation of histones was enhanced. PHI further mediated selective alterations of histone methylation, with upregulated H3K4 and downregulated H3K9, a pattern consistent to the marks of transcription competent chromatins. ChIP assay showed that chromatins from cells exposed to PHI contained more p21 DNA in the precipitates of hyperacetylated histones, indicating more accessibility of transcription machinery to the p21 promoter after chromatin unfolding (Ma XD et al., 2006; Xiao et al., 2010). On the other hand, PHI could induce DNA demethylation in Molt-4 cells. Hypermethylation of gene p15 was reversed and activation transcription could be de novo by PHI. Hypermethylation of gene p15 was attenuated and

p15 gene was activated de novo after 5 days exposure to PHI in a concentration-dependent manner(0-40μM). DNMT1 and DNMT3B were inhibited by PHI ($P<0.05$). Alteration of DNMT3A was not significant at those concentrations (Jiang et al., 2010). PHI has multi-target in epigenetic, it might represent a combination target for correcting aberrant histone acetylation, histone methylation and DNA methylation, and a promising potential epigenetic regulators for preventing the progression of leukemia.

4. Conclusion

Epigenetic disorder may be the mechanism in acute leukemia. It is now understood that deregulated epigenetic mechanisms can cause, as well as compound, the effects of oncogenic mutations to promote tumor development and growth. Epigenetic therapy is a promising approach for the prevention and treatment of malignancies. The discovery of modulators of HATs and HMTases which are highly specific may bring a new era of epigenetics based drugs.

5. References

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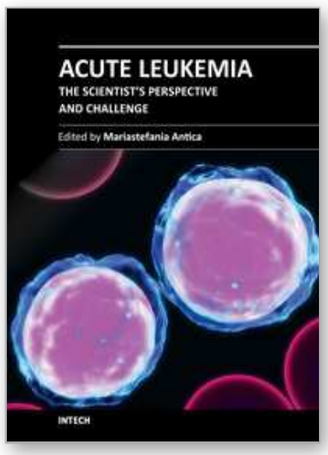

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This book provides a comprehensive overview of he basic mechanisms underlying areas of acute leukemia, current advances, and future directions in management of this disease. The first section discusses the classification of acute leukemia, taking into account diagnoses dependent on techniques that are essential, and thankfully readily available, in the laboratory. The second section concerns recent advances in molecular biology, markers, receptors, and signaling molecules responsible for disease progression, diagnostics based on biochips and other molecular genetic analysis. These advances provide clinicians with important understanding and improved decision making towards the most suitable therapy for acute leukemia. Biochemical, structural, and genetic studies may bring a new era of epigenetic based drugs along with additional molecular targets that will form the basis for novel treatment strategies. Later in the book, pediatric acute leukemia is covered, emphasizing that children are not small adults when it comes to drug development. The last section is a collection of chapters about treatment, as chemotherapy-induced toxicity is still a significant clinical concern. The present challenge lies in reducing the frequency and seriousness of adverse effects while maintaining efficacy and avoiding over-treatment of patients.

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