Global Journal of Life Sciences
2021; 2(1): 10-19.
ISSN Online: 2766-9130; ISSN Print: 2766-9149
Website: http://naturescholars.com
Email: Glo_J_Ls@126.com
Publisher: Scholars Publishing, LLC

Review

Epigenetics in Acute Promyelocytic Leukemia Pathogenesis and Treatment Response

Saruna[1,*], Kexin Li[2,*,✉], and Xiantao Meng[1,✉]

[1]Ordos Institute of Technology, Ordos, 017000, China. [2]School of Life Sciences, Inner Mongolia University, Hohhot, 010010, China.

*** These authors contributed equally.**
✉ Correspondence
Kexin Li and Xiantao Meng, School of Life Sciences, Inner Mongolia University, 24 Zhaojun Road, Saihan District, Hohhot, Inner Mongolia, 010010, China. Phone: +86-13644846120. Email: lkexin8966@163.com.
Received: March 21, 2020. Accepted: December 25, 2020. Published online: January 18, 2021.
Cite this paper: Saruna, Kexin Li, Xiantao Meng. (2020) Epigenetics in Acute Promyelocytic Leukemia Pathogenesis and Treatment Response. *Global Journal of Life Sciences.* 2021, 2(1):10-19. http://naturescholars.com/gjls.020102. https://doi.org/10.46633/gjls.020102.

Abstract

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia (AML), which is characterized by arrest of leukocyte differentiation at the promyelocyte stage due to a specific chromosomal translocation t(15;17) in myeloid cells and generates the oncogenic PML-RARα fusion protein. All-trans retinoic acid (ATRA) is essential for acute promyelocytic leukemia (APL) treatment. It has been reported that ATRA induces degradation of the PML-RARα in APL cells and restores normal RAR transcriptional programs. The PML-RARA fusion protein has been proposed to recruit epigenetic modifiers. The epigenetic regulation has a critical role in normal physiologic hematopoietic stem cell lineage committed progenitors; its dysregulation is an important mechanism of pathogenesis of AML. The primary aim of this review was to evaluate the involvement of different epigenetic mechanisms in PML-RARa-induced acute promyelocytic leukemia (APL) pathogenesis and treatment response.

Key words: Acute Promyelocytic Leukemia, PML-RARA Fusion Protein, All-Trans Retinoic Acid (ATRA), Epigenetics.

Introduction

Acute myeloid leukemia (APL) is a subtype of acute myeloid leukemia (AML) characterized by the arrest of myeloid cells differentiation at the promyelocytic stage (1). Chromosomal translocation produces fusion protein PML-RARA, which is an important genetic feature of acute promyelocytic leukemia (2). Studies have indicated that more than 95% of APL patients carry the t(15;17) (q22-23; q12-21) chromosomal translocation and express the APL-specific fusion protein PML-RARA (3).

Furthermore, in a few APL cases, rare fusion

genes including PLzF-RARd, NPM-RARA, STAT5b-RARa and NuMA-RARa are found(4,5). In recent years, all-trans retinoic acid (ATRA) has been confirmed as an effective clinical drug for the treatment of APL, mainly by inducing the degradation of the fusion protein PML-RARA to promote the apoptosis of cancer cells to achieve therapeutic effects. Furthermore, a few studies have also demonstrated that epigenetic regulation plays an important role in the pathogenesis, development and treatment of APL. Epigenetics refers to the regulation of gene expression without affecting the base sequence of genes (6). Therefore, this review focuses on the current advances in epigenetics in basic research and treatment of acute promyelocytic leukemia.

1 Development of Myeloid Cells

Hematopoietic stem cells (HSCs) Hematopoietic stem cells (HSCs) have the crucial function of long-term maintenance and production of all mature blood cell lineages in the adult. HSCs are adult stem cells with the potential for self-renewal and multi-directional differentiation (7). The differentiation of HSCs into various lineages of hematopoietic cells in the body is a multi-step continuous biological process under the control of an extremely complex and fine-tuned molecular signal network. The underlying cause of the disease is abnormality of key regulators. In the differentiation of HSCs, first three types of cell division: symmetrical self-replicating division (two new stem cells), symmetrical differentiation (two differentiated cells), and asymmetric division (one stem cell and one differentiated cell), etc (8). After the following steps within a normal bone marrow, HSCs differentiate into multipotent progenitors (MPPs), and MPPs differentiates into directional progenitor cells and a series of specific progenitor cells, such as common myeloid precursor (CMP) and lymphoid progenitor cells (CLP) (9). And then CMP differentiates to produce mature erythroid cells and platelet cells potential megakaryocyte Erythroid Precursor (MEP), and simultaneously differentiates into granulocyte monocyte precursor (GMP) (9). At present, the differentiation mechanism of HSCs to blood cells of different lineages has not been fully understand. In recent years, many studies have indicated that transcription factors play a pivotal role in regulating cell differentiation. These transcription factors spontaneously act on targets genes to activate the cells to differentiate into specific type of cells in normal hematopoietic cells (10).

2 Acute myeloid leukemia (APL)

Leukemia is a type of malignant clonal proliferative disease of hematopoietic stem cells. Malignant clonal evolution is the formation of malignant tumor cells from the normal bone marrow blood cells, due to uncontrolled proliferation, impaired differentiation, and blocked apoptosis. Acute promyelocytic leukemia (APL) is M3 subtype acute myeloid leukemia whose main character is retardation of Promyelocytic differentiation and multi-granular promyelocytic proliferation in the bone marrow. (11) More than 95% of APL patients have chromosomal translocations at t (15; 17) (q24.1; q21.2), and the expression of fusion protein PML-RARA (12).

Transgenic mouse experiments have indicated that the fusion protein PML-RARA is the main cause of APL leukemia (13). The PML-RARA fusion protein is extremely important in the pathogenesis of APL. It blocks the normal hematopoietic differentiation process, causes the differentiation of myeloid cells to block indefinite proliferation in the promyelocytic stage, and leading to APL (14,15). In addition, a few APL cases have found rare fusion genes such as PLzF-RARd, NPM-RARA, STAT5b-RARa, and NuMA-RARa (4,5).

Notch1/Sox2, PI3K, MEK/ERK, Notch and other signaling pathways play an important regulatory role in the pathogenesis and development of APL (16). Notch1/Sox2 and

MEK/ERK signaling pathways are mainly involved in the differentiation of APL cells (17,18); Notch signaling pathways are mainly related to the self-renewal of hematopoietic stem cells (19); inhibition of the PI3K signaling pathway enhances the chemical sensitivity of APL cells to arsenic trioxide (ATO) (20). In addition, some transcription factors, such as Pu.1, c-Myc, PMI1, PTEN, C / EBPα, HMGB1, ACTL6A,are involved in the pathogenesis and development of APL (17,21-26).

The ETS family member PU.1, encoded by SPI1, is a main regulator of PML-RARA inhibition of bone marrow differentiation at the transcription level. This inhibition leads to the suppression of targeted genes of PU.1, which directly participates in bone marrow differentiation (15). Wang et al.'s studies showed that PU.1 binds to PML-RARα near the RARE site and form PML-RARα/PU.1 complex (27,28). After ATRA intervention, APL cells restored the expression of PU.1 and differentiated into neutrophils. Moreover PU.1 showed ATAR-like biological effects in PML-RARA leukemia cells (22). Experimental results in transgenic mouse models indicated the incidence of APL increased significantly after PML-RARα mice were crossed with PU.1 +/- mice (23). Therefore, according to the above mentioned reports, the pathogenesis of APL has a significant relationship with some inhibitors related to the inhibition of bone marrow cell differentiation during myeloid cell differentiation.

3 Epigenetics

Epigenetics is the study of changes in the expression of genes that do not result from alterations in the sequence of the genetic code (6). Epigenetics were first discovered in tomatoes (29), and subsequent studies proved that this phenomenon is also common in animals and humans. Epigenetic regulation mechanism is a universal gene expression regulation method in life phenomenon, including DNA methylation, genomic imprinting, histone modification, chromatin remodeling, long non-coding RNAs (lncRNAs), and microRNA-associated post-transcriptional gene silencing (30). Histone modifications is a covalent post-translational modification (PTM) to histone proteins which includes methylation, acetylation, phosphorylation, ubiquitination , sumoylation (31) and lactylation (32). Histone modifications are usually towards the C-terminal end of the specific amino acids within the histone proteins. These modifications can both positive and negative regulation of gene expression by changing the way in which histones bind to DNA. In the recent years, methylation is the most studied and in-depth histone modification (33). Several studies showed that Three methylation modifications occur on lysine residues of histones H3 and H4, including mono-, di-, and tri-methylation. Methylation of H3K4 and H3K36 is associated with transcriptional activation of genes, while methylation of H3K9, H3K27, and H4K20 is associated with transcriptional repression (34). Histone arginine undergoes only one or two methylation modifications (35), involved in the regulation of gene expression, DNA repair and other important life processes, and related to many diseases such as tumors, cardiovascular diseases, viral infections and autoimmune diseases (36-39).

Various histone modifications are dynamically regulated by methyltransferase and demethylase. Histone methylation is the main way to regulate the structure of chromatin and gene transcription. Diseases are often caused by a dynamic imbalance between methylation and demethylation. Thus exploring the process and mechanism from gene deduction to phenotype in diseases, providing theoretical basis and scientific basis for explaining genetic phenomena and elucidating pathogenesis (40).

4 Epigenetic regulation of the development of APL

Recent studies have found that the PML-RARA fusion protein abnormally recruits multiple inhibitory epigenetic modification factors in APL

patients, such as HDAC (41), DNA methyltransferases (DNMTs) (42), lysine methyltransferase SUV39H1 (43) and multi-comb inhibitor complexes 1 and 2 (PRC1/2) (44,45). In addition, PML-RARA down regulates the target genes (such as RARB) and induces arrest of bone marrow cell differentiation.

4.1 Histone modifications

Histones are the major components of chromosomes and are crucial in regulating gene expression and controlling chromatin structure. Recent research has shown that detuning of histone modification levels and disturbance of recognition may be an important cause of diseases (such as cancer), which has made histone modification-related proteins became one of the popular targets for epigenetic drug discovery in recent years. (46-48).

RARa is a retinoic acid receptor which can transmit oncogenic signals in cells (39,44,50). In normal cells, heterodimers of the retinoic acid receptor (RAR) and rexinoid receptors (RXRs) bind to RARE binding sites in the promoter region of target genes (51). In the absence of ligand RA, an auxiliary repressive complex including N-CoR, retinoids, thyroid hormone receptor silencers and histone deacetylases (HDACs) is formed, which collectively leads to chromatin condensation and inactivates gene transcription (52). After binding to ligand RA, the auxiliary repressor complex is dissociated and recruits transcriptional coactivators, such as histone methyltransferase, histone acetyltransferase (HAT) and SRB-containing complexes, causing chromatin decondense and activating the transcription of target genes(53,54,55). The conformational changes by ATRA binding trigger the dissociation of co-repressors and promote the recruitment of coactivators (56). RA enables RAR-RXR to release nuclear cosuppressor complexes and recruits coactivators with histone acetyltransferase (HAT) activity. This leads to high acetylation of histones at the retinoic acid response element (RARE) site, chromatin remodeling, and transcriptional activation of the RAR-target genes.

Other studies have found that the demethylase KDM3B mediates the proliferation of NB4 cells by histone H3K9 lysine methylation (57). in sum, the regulatory mechanism of histone modification during the pathogenesis and development of APL still needs to be clarified.

4.2 DNA Methylation

Blood cells are derived from bone marrow hematopoietic stem cells(HSCs). Based on the regulation of specific growth factors and cytokines, HSC can develop into promyelocytic cells, and then into mature granulocytes. DNA methylation is critical in the typing and differentiation of hematopoietic lineages and abnormal DNA methylation is a potential factor in the pathogenesis of APL. Genomic DNA methylation was increased in APL patients, which has higher plasticity than healthy CD34 + promyelocytic cells (30). Recent studies have found that there is a close cross regulatory mechanism between PML-RARA and DNMT3A. The activity of methyltransferase DNMT3A is required for PML-RARA to drive self-renewal in vitro. Overexpression of DNMT3a and PML-RARα promote together the pathogenesis of APL in vivo (58). Simultaneously， competitive migration advantage by PML-RARA and APL evolution require the participation of the DNMT3A (58). In summary, the PML-RARA fusion gene requires DNMT3A to initiate the development of APL (58). Moreover, other studies have shown that although DNA hypermethylation in APL cells is often formed in genomic regions regulated by polycomb repressive complex 2 (PRC2), but no significant difference was found in DNA methylation in the PML-RARα binding site or near. Therefore, changes in DNA methylation patterns may occur in later stage in APL pathogenesis, during APL maintenance instead of pathogenesis (59). However, decitabine, a DNA demethylation

drug, induce apoptosis of APL cells by activating the TRAIL pathway in vitro, so it may mainly target the cooperative process in later stage (55).

Studies have found that methylation in promoters of p15INK4B and p16INK4a gene occurs in a high frequency in APL (60,61). The mechanism of p15INK4B gene hypermethylation in APL patients is unknown and may have prognostic significance (62). Several other research results have shown that the DNA binding site of PML-RARA is significantly different from wild-type RARA (63-65). The study showed that most PML-RARA binding sites are atypical RARE sites, which are very close to the common binding sites of PU.1, ETS and AP-1, indicating that PML-RARA have synergistic effects with these transcription factors (65). Another study has shown that PML-RARA directly interacts with PU.1 (26). PML-RARA affects RAR signal transduction by regulating the expression of RARA and RARB and binding to classical RAR-RXR target genes. PML-RARA binds to genes for normal hematopoietic differentiation, such as PU.1, GFI1, and RUNX1. Study based on ChIP-seq shows that only a few PML-RARA binding sites have significant changes in DNA methylation after expression of the PML/RARA (63).

5 Epigenetic Regulation of ATRA in APL

All-trans retinoic acid (ATRA) is one of the three isomers of retinoic acid (RA), a metabolic intermediate of vitamin A in animals. and is a therapeutic drug of APL (66). ATRA reduces the stability of the fusion protein PML-RARA, solubilizes the protein, and promotes the differentiation of promyelocytic leukemia cells to have a therapeutic effect (66). Studies have shown that ATRA is a ligand of RARα (retinoic acid receptor α) and a specific antagonist of RARα, which can offset the effects of RARα (56). ATRA exerts a biological effect by transporting retinoic acid binding protein 2 (Crabp2) into the nucleus and regulating transcription of the target genes (67).

All-trans retinoic acid (ATRA) interfered with PML-RARA-positive leukemia cells, and the results showed the DNA methylation have no significant change at most PML-RARA binding sites (65), suggesting that DNA methylation is not the main reason of the suppression of transcription by PML-RARA. Recent studies have shown that DNMT3A is necessary for PML-RARA to induce self-renewal and activation of bone marrow progenitor cells (65).

After all-trans retinoic acid (ATRA) treatment in APL cells, H3K9/K14 acetylation of DNA binding sites increased in PML-RARA, while H3K9me3 levels remained unchanged (65). However, some studies showed increased histone H3 acetylation only in APL cells sensitive to ATRA (68). Histone H3 acetylation binds to RNA polymerase II at or near the PML-RARA fusion protein binding site. In summary, these results indicate that histone acetylation of PML-RARA and recruitment of HDAC are key determinants of ATRA reactivity. Contemporaneously, histone acetylase (HDAC) inhibitors, such as Sodium butyrate (NaF), valproic acid (VPA) and trichostatin A (TSA), combined with ATRA can activate the PML-RARα and inhibit its binding to the conjugate factor complex containing HDACs (69,70). The above findings suggested that combination of targeted histone deacetylase drugs and ATRA may be a suitable strategy to enhance the sensitivity of APL cells to ATRA.

In addition, recruiting histone demethylase PHF8 (KDM7B) recruit to RARA fusions proteins enhances the effect of ATRA in APL cells (71). The demethylase PHF8 with JmjC domain mediates histone H3K9me1/me2 and activates target gene transcription, thereby promoting the sensitivity of ATRA to induce cell differentiation (72). In ATRA-treated cells, PHF8 was significantly enriched in promoter of multiple PML-RARA targets (including RARB, TGM2, and IDH1 (63)), while binding of other PHF8-related promoters was reduced (71). In ATRA-insensitive APL cells, PHF8 is significantly down-regulated, but

overexpression of PHF8 reactivates ATRA-induced differentiation (71).

Reports confirm that ATRA regulates miRNAs, miR-15b, miR-223 and miR-342, which were inhibited in APL, but were up-regulated after ATRA treatment. In contrast, miR-181a and miR-181b were up-regulated in APL but down-regulated after ATRA treatment (73,74). Most of them has been identified as target involving hematopoietic cell growth, differentiation and apoptosis, including HOX genes (75). On one hand, RARA fusion proteins can inhibit the transcription of several miRNAs; on the other hand, ATRA and arsenic trioxide (As2O3) restore RARA expression (73,74). Therefore, the above reports suggest that miRNA can provide a new therapeutic strategy for APL.

In summary, with the constantly improvement of molecular biology, technical means and the rapid development of epigenetic research, many etiology and pathogenesis that cannot be explained by the original theoretical system of acute promyelocytic leukemia (APL) is revealed. Moreover, the mechanism of ATRA-induced differentiation of acute promyelocytic leukemia was also well documented. However, how to reduce the mortality and recurrence rate of high-risk APL is still a major clinical challenge. In addition, the combination of multiple drugs to increase the efficacy or reduce the side effects can improve the patient's remission rate and long-term survival rate. However, the issues of refractory recurrence, high early mortality and adverse drug reactions have not been improved. Therefore, based on better understanding of the cellular and molecular mechanisms of APL pathogenesis and development, it is of great theoretical and clinical value to explore safer and more effective treatments and drugs and to clarify the molecular mechanisms of epigenetic regulation in APL.

Declarations

1) ***Consent to publication***

We declare that all authors agreed to publish the manuscript at this journal based on the signed Copyright Transfer Agreement and followed publication ethics.

2) Ethical approval and consent to participants

Not applicable.

3) ***Disclosure of conflict of interests***

We declare that no conflict of interest exists.

4) Funding

This work is supported in part by grants from the Scientific Research Foundation of Inner Mongolia Autonomous Region Higher Education Institutions (NJZY16384), the National Natural Science Foundation of China (NSFC) (81660024).

5) ***Availability of data and material***

We declare that the data supporting the results reported in the article are available in the published article.

6) Authors' Contributions

Authors contributed to this paper with the design (LKX, Saruna), literature search (LKX), drafting (LKX), revision (LKX, Saruna, MXT), editing (LKX, Saruna, MXT) and final approval (LKX, MXT).

7) ***Acknowledgement***

None

8) Authors' biography

None

References

1. De The H, Lavau C, Marchio A, et al. The PML-RAR alpha fusion mRNA generated by the t(15;17) translocation in acute promyelocytic leukemia encodes a functionally altered RAR . Cell, 1991, 66(4): 675-84.
2. Greenfield G, Michail O, Merron B, et al. Acute promyelocytic leukaemia (APML) with cryptic PML-RARA fusion has a clinical course comparable to classical APML with t(15；17)(q24.1；q21.2) translocation. British Journal of Haematology, 2018, 186(1):155-157.

3. Childs R, Chernoff A, Contentin N, et al. Regression of metastatic renal-cell carcinoma after nonmyeloablative allogeneic peripheral-blood stem-cell transplantation . The New England Journal of Medicine, 2000, 343(11): 750-8.
4. Grimwade D . The significance of minimal residual disease in patients with t(15;17). Best Pract Res Clin Haematol, 2002, 15(1):137-158.
5. Mistry A R, Pedersen E W, Solomon E, et al. The molecular pathogenesis of acute promyelocytic leukaemia: Implications for the clinical management of the disease. Blood Reviews, 2003, 17(2):71-97.
6. Heidi Ledford. Language: Disputed definitions. Nature, 2008, 455(7216):1023-1028.
7. Orkin, S. H . Transcription Factors and Hematopoietic Development. Journal of Biological Chemistry, 1995, 270(10):4955-4958.
8. Morrison S J , Kimble J . Asymmetric and symmetric stem-cell divisions in development and cancer. Nature, 2006, 441(7097):1068-1074.
9. Bhandoola A , Boehmer H V , Petrie H T , et al. Commitment and Developmental Potential of Extrathymic and Intrathymic T Cell Precursors: Plenty to Choose from. Immunity, 2007, 26(6):0-689.
10. Lo-Coco F , Hasan S K . Understanding the molecular pathogenesis of acute promyelocytic leukemia. Best Practice & Research Clinical Haematology, 2014, 27(1):3-9.
11. Sucić M , Zadro R , Burazer B , et al. Acute Promyelocytic Leukemia M3: Cytomorphologic, Immunophenotypic, Cytogenetic, and Molecular Variants. Journal of Hematotherapy & Stem Cell Research, 2002, 11(6):941-950.
12. Doucas V, Brockes JP, Yaniv M, Thé H, Dejean A. The PML-retinoic acid receptor alpha translocation converts the receptor from an inhibitor to a retinoic acid-dependent activator of transcription factor AP-1. Proc Natl Acad Sci USA, 1993;90(20):9345–9.
13. Look A T. Oncogenic Transcription Factors in the Human Acute Leukemias. Science, 1997,278(5340):1059–1064.
14. Hugues de Thé, Chomienne C , Lanotte M , et al. The t(15;17) translocation of acute promyelocytic leukaemia fuses the retinoic acid receptor alpha gene to a novel transcribed locus. Nature, 1990, 347(6293):558-561.
15. Kakizuka A , Jr W H M , Umesono K , et al. Chromosomal translocation t(15;17) in human acute promyelocytic leukemia fuses RARα with a novel putative transcription factor, PML. Cell, 1991, 66(4):663-674.
16. Billottet C , Banerjee L , Vanhaesebroeck B, et al. Inhibition of Class I Phosphoinositide 3-Kinase Activity Impairs Proliferation and Triggers Apoptosis in Acute Promyelocytic Leukemia without Affecting Atra-Induced Differentiation. Cancer Research, 2009, 69(3):1027-1036.
17. Zhong PQ, Zhong L Yao JJ, et al. ACTL6A interacts with p53 in acute promyelocytic leukemia cell lines to affect differentiation via the Sox2/Notch1 signaling pathway. Cellular Signaling, 2019,53:390-399.
18. Zassadowski F, Pokorna K, Ferre N, et al. Lithium chloride antileukemic activity in acute promyelocytic leukemia is GSK-3 and MEK/ERK dependent. Leukemia, 2015,29(12):2277-84.
19. Grieselhuber N R , Klco J M , Verdoni A M , et al. Notch signaling in acute promyelocytic leukemia. Leukemia, 2013, 27(7):1548-1557.
20. Bashash D , Delshad M , Riyahi N , et al. Inhibition of PI3K signaling pathway enhances the chemosensitivity of APL cells to ATO: Proposing novel therapeutic potential for BKM120. European Journal of Pharmacology, 2018, 841:10-18.
21. Federzoni E A , Valk P J M , Torbett B E , et al. PU.1 is linking the glycolytic enzyme HK3 in neutrophil differentiation and survival of APL cells. Blood, 2012, 119(21):4963-4970.

22. Mueller B U , Pabst T , José Fos, et al. ATRA resolves the differentiation block in t(15;17) acute myeloid leukemia by restoring PU.1 expression. Blood, 2006, 107(8):3330-3338.
23. Walter M J , Park J S , Ries R E , et al. Reduced PU.1 expression causes myeloid progenitor expansion and increased leukemia penetrance in mice expressing PML-RAR?. Proceedings of the National Academy of Sciences, 2005, 102(35):12513-12518.
24. Rice K L , Hormaeche I , Doulatov S , et al. Comprehensive genomic screens identify a role for PLZF-RARα as a positive regulator of cell proliferation via direct regulation of c-MYC. Blood, 2009, 114(27):5499-5511.
25. Anna D , Fuad B , Inger K , et al. Retinoic acid-induced cell cycle arrest of human myeloid cell lines is associated with sequential down-regulation of c-Myc and cyclin E and posttranscriptional up-regulation of p27(Kip1). Blood, 2002, 99(6):2199-206.
26. miR-382-5p modulates the ATRA-induced differentiation of acute promyelocytic leukemia by targeting tumor suppressor PTEN. Girard N , Tremblay M , Humbert M , et al. RAR?-PLZF oncogene inhibits C/EBP? function in myeloid cells. Proceedings of the National Academy of Sciences, 2013, 110(33):13522-13527.
27. LIN R J, EVANS R M. Acquisition of oncogenic potential by RAR chimeras in acute promyelocytic leukemia through formation of homodimers . Mol Cell, 2000, 5(5): 821-30.
28. PEREZ A, KASTNER P, SETHI S, et al. PMLRAR homodimers: distinct DNA binding properties and heteromeric interactions with RXR . The EMBO journal, 1993, 12(8): 3171-82.
29. Genomic analyses provide insights into the history of tomato breeding. Nature Genetics, 2014, 46(11):1220-1226.
30. Costa FF. Epigenomics in cancer management. Cancer management and research. 2010;2:255-265.
31. Zhao Y , Garcia B A . Comprehensive Catalog of Currently Documented Histone Modifications. Cold Spring Harbor perspectives in biology, 2015, 7(9):a025064.
32. Sabari BR, Zhang D, Allis CD et al. Metabolic regulation of gene expression by histone lactylation. Nat Rev Mol Cell Biol. 2017, 18(2):90-101.
33. Elphège P Nora, Dekker J , Heard E . Segmental folding of chromosomes: A basis for structural and regulatory chromosomal neighborhoods?. BioEssays, 2013, 35(9):818-828.
34. Martin C , Zhang Y . The diverse functions of histone lysine methylation. Nat. Rev. Mol. Cell. Biol. 2005, 6(11):838-849.
35. Mcdevitt M A . Clinical Applications of Epigenetic Markers and Epigenetic Profiling in Myeloid Malignancies. Seminars in Oncology, 2012, 39(1):109-122.
36. Bedford MT, Richard S. Arginine methylation an emerging regulator of protein function. Mol Cell. 2005;18:263–272.
37. Cheung N , Chan L C , Thompson A , et al. Protein arginine-methyltransferase-dependent oncogenesis. Nature Cell Biology, 2007, 9(10):1208-1215.
38. Wang Z , Tang W H W , Cho L , et al. Targeted Metabolomic Evaluation of Arginine Methylation and Cardiovascular Risks: Potential Mechanisms Beyond Nitric Oxide Synthase Inhibition. Arteriosclerosis, Thrombosis, and Vascular Biology, 2009, 29(9):1383-1391.
39. Auclair Y , Richard, Stéphane. The role of arginine methylation in the DNA damage response. DNA Repair, 2013, 12(7):459-465.
40. Javierre B , Burren O , Wilder S , et al. Lineage-Specific Genome Architecture Links Enhancers and Non-coding Disease Variants to Target Gene Promoters. Cell, 2016, 167(5):1369-1384.e19.

41. Grignani,F. Fusion proteins of the retinoic acid receptor-alpha recruit histone deacetylase in promyelocytic leukaemia. Nature, 1998, 391.
42. Di Croce, L. Methyltransferase Recruitment and DNA Hypermethylation of Target Promoters by an Oncogenic Transcription Factor. Science, 295(5557):1079-1082.
43. Carbone, R, Botrugno, O. A, Ronzoni, S, et al. Recruitment of the Histone Methyltransferase SUV39H1 and Its Role in the Oncogenic Properties of the Leukemia-Associated PML-Retinoic Acid Receptor Fusion Protein. Molecular & Cellular Biology, 26(4):1288-1296.
44. Villa R1, Pasini D, Gutierrez A, et al. Role of the polycomb repressive complex 2 in acute promyelocytic leukemia. Cancer Cell. 2007,11(6):513-25.
45. Boukarabila H , Saurin A J , Batsche E , et al. The PRC1 Polycomb group complex interacts with PLZF/RARA to mediate leukemic transformation. Genes & Development, 2009, 23(10):1195-1206.
46. Nora, Elphège P, Lajoie B R , Schulz E G , et al. Spatial partitioning of the regulatory landscape of the X-inactivation centre. Nature, 2012, 485(7398):381-385.
47. Thomas Vaissière, Carla Sawan, Zdenko Herceg. Epigenetic interplay between histone modifications and DNA methylation in gene silencing. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis, 2008, 659(1-2):40-48.
48. Klose R J , Zhang Y . Regulation of histone methylation by demethylimination and demethylation. Nature Reviews Molecular Cell Biology, 2007, 8(4):307-318.
49. Mangelsdorf D J , Evans R M . The RXR heterodimers and orphan receptors. Cell, 1995, 83(6):0-850.
50. Chambon P . A decade of molecular biology of retinoic acid receptors. Faseb J. 1996, 10(9):940.
51. Jansa P , JiriForejt, . A Novel Type of Retinoic Acid Response Element in the Second Intron of the Mouse H2Kb Gene is Activated by the RAR/RXR Heterodimer. Nucleic Acids Research, 1996, 24(4):694-701.
52. Wu X , Li H , Park E J , et al. SMRTe Inhibits MEF2C Transcriptional Activation by Targeting HDAC4 and 5 to Nuclear Domains. Journal of Biological Chemistry, 2001, 276(26):24177-24185.
53. Minucci S , Maccarana M , Cioce M , et al. Oligomerization of RAR and AML1 Transcription Factors as a Novel Mechanism of Oncogenic Activation. Molecular Cell, 2000, 5(5):811-820.
54. Christopher B, Cole, Angela M, Verdoni, Shamika, Ketkar, et al. PML-RARA requires DNA methyltransferase 3A to initiate acute promyelocytic leukemia. 2016, 126(1):85-98.
55. Arteaga M F , Mikesch J H , Fung T K , et al. Epigenetics in acute promyelocytic leukaemia pathogenesis and treatment response: A TRAnsition to targeted therapies. British Journal of Cancer, 2015, 112(3):413-418.
56. Apfel C , Bauer F , Crettaz M , et al. A retinoic acid receptor alpha antagonist selectively counteracts retinoic acid effects. Proceedings of the National Academy of Sciences, 1992, 89(15):7129-7133.
57. Wang X, Fan H, Xu C, et al. KDM3B suppresses APL progression by restricting chromatin accessibility and facilitating the ATRA-mediated degradation of PML/RARα. Cancer Cell Int. 2019,19:256.
58. Cole C B , Verdoni A M , Ketkar S , et al. PML-RARA requires DNA methytransferase 3A to initiate acute promyelocytic leukemia. Journal of Clinical Investigation, 2015, 126(1):85-98.
59. Schoofs T , Rohde C , Hebestreit K , et al. DNA methylation changes are a late event in acute promyelocytic leukemia and coincide with loss of transcription factor binding. Blood, 2013, 121(1):178-187.

60. Teofili L , Martini M , Luongo M , et al. Hypermethylation of GpG islands in the promoter region of p15INK4b in acute promyelocytic leukemia represses p15INK4b expression and correlates with poor prognosis. Leukemia (Basingstoke), 2003, 17(5):919-924.
61. Chim C S , Liang R , Tam C Y Y , et al. Methylation of p15 and p16 Genes in Acute Promyelocytic Leukemia: Potential Diagnostic and Prognostic Significance. Journal of Clinical Oncology, 2001, 19(7):2033-2040.
62. Baba S M , Azad N A , Shah Z A , et al. p15(Ink4b) Loss of Expression by Promoter Hypermethylation Adds to Leukemogenesis and Confers a Poor Prognosis in Acute Promyelocytic Leukemia Patients. Cancer Research & Treatment Official Journal of Korean Cancer Association, 2017, 49(3):790-797.
63. Joost H.A. Martens, Arie B. Brinkman, Femke Simmer, et al. PML-RARa/RXR Alters the Epigenetic Landscape in Acute Promyelocytic Leukemia. Cancer cell, 2010, 17(2):173-185.
64. Claudia Hoemme, Abdul Peerzada, Gerhard Behre, et al. Chromatin modifications induced by PML-RAR repress critical targets in leukemogenesis as analyzed by ChIP-Chip. Blood, 2008, 111(5):2887-2895.
65. Wang K, Wang P, Shi J, et al. PML/RARalpha targets promoter regions containing PU.1 consensus and RARE half sites in acute promyelocytic leukemia.. 2010, 17(2):186.
66. Shen, Z.-X, Shi, Z.-Z, Fang, J, et al.All-trans retinoic acid/As2O3 combination yields a high quality remission and survival in newly diagnosed acute promyelocytic leukemia. Proc Natl Acad Sci U S A, 101(15):5328-5335.
67. Gimeno A , Zaragozá R , Viña, J R，and Miralles, V. J. Vitamin E activates CRABP-II gene expression in cultured human fibroblasts, role of protein kinase C. FEBS Lett 2004,569(1-3): 240-244.
68. Yoshitaka Sunami, Marito Araki, Shin Kan, et al. Histone Acetyltransferase p300/CREB-binding Protein-associated Factor (PCAF) Is Required for All- trans -retinoic Acid-induced Granulocytic Differentiation in Leukemia Cells *. Journal of Biological Chemistry, 2017, 292(7):2815.
69. Jing Y, Xia L, Waxman S. Targeted removal of PML-RARalpha protein is required prior to inhibition of histone deacetylase for overcoming all-trans retinoic acid differentiation resistance in acute promyelocytic leukemia. Blood. 2002;100:1008–13.
70. Kosugi H, Towatari M, Hatano S, et al. Histone deacetylase inhibitors are the potent inducer/enhancer of differentiation in acute myeloid leukemia: a new approach to anti-leukemia therapy. Leukemia. 1999;13:1316–24.
71. Arteaga M F , Mikesch J H , Qiu J , et al. The Histone Demethylase PHF8 Governs Retinoic Acid Response in Acute Promyelocytic Leukemia. Cancer Cell, 2013, 23(3):376-389.
72. Klaus Fortschegger, Petra de Graaf, Nikolay S Outchkourov, et al. PHF8 Targets Histone Methylation and RNA Polymerase II To Activate Transcription. Molecular and Cellular Biology, 2010, 30(13):3286-3298.
73. Saumet, A, Vetter, G, Bouttier, M, et al.Transcriptional repression of microRNA genes by PML-RARA increases expression of key cancer proteins in acute promyelocytic leukemia. Blood, 113(2):412-421.
74. Garzon, R, Pichiorri, F, Palumbo, T, et al. MicroRNA gene expression during retinoic acid-induced differentiation of human acute promyelocytic leukemia. Oncogene, 26(28):4148-4157.
75. Etienne De Braekeleer, Nathalie Douet-Guilbert, Audrey Basinko, et al. Hox gene dysregulation in acute myeloid leukemia. Future Oncology, 2014, 10(3):475-495.