Advances in Bioresearch
Adv. Biores., Vol 12 (6b) November 2021: 257-262
©2021 Society of Education, India
Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.12.6b.257262

Advances in Bioresearch

REVIEW ARTICLE

Gene Deregulations as Key Players in Acute Myeloid leukemia

E.S Deepak Shyl[1], Beutline Malgija M[2], Samuel Gnana Prakash Vincent[3*]
[1]Research Scholar (Reg. No. 12436) 1Affiliated to ManonmaniamSundaranar University, Abishekapatti, Tirunelveli – 627 012, Tamil Nadu, India.
[1,3]International Centre for Nanobiotechnology (ICN), Manonmaniam Sundaranar University, Rajakkamangalam-629502, Kanyakumari District, Tamil Nadu, India.
[2]Madras Christian College, Chennai 600 059, Tamil Nadu, India.

ABSTRACT
Acute Myeloid Leukemia is a phenotypic and genetically heterogeneous disease, categorized by numerous genetic abnormalities, gene mutations and epigenetic changes in hematopoietic cells which affect normal processes like cell growth, proliferation and differentiation. Insights from several gene expression studies enriched our understanding of the genes and mechanisms that regulate these processes in normal and leukemic cells. This review highlights the gene expression changes associated with AML with a special focus on their revelation from next-generation sequencing technologies. Some important protein families contributing to such changes are also discussed.
Keywords: *Acute myeloid leukemia; gene expression profiling; RNA-sequencing; gene deregulation; Bcl2; protein kinase C.*

Received 09.08.2021 Revised 21.10.2021 Accepted 13.11.2021

How to cite this article:
E.S Deepak Shyl, Beutline Malgija M, Samuel Gnana Prakash Vincent. Gene Deregulations as Key Players in Acute Myeloid leukemia. Adv. Biores. Vol 12[6] November 2021: 257-262

INTRODUCTION

Acute Myeloid Leukemia (AML) is a cancer of the myeloid lineage hematopoietic cells and is clonally heterogeneous since all myeloid precursors and progenitors can undertake malignant transformation [1,2]. It is characterized by clonal expansion of myeloid precursors with reduced capacity for differentiation [2]. It is the most common type of leukemia among haematological malignancies in adults, affecting ~21k people annually and around 11k deaths in United States [3]. Though there is a decrease in mortality rates from acute and chronic leukemias by around 1% per year between 2005 and 2014, the death rates kept on stable for AML [4]. It accounts for 15 to 20% of acute leukemia cases in children and 80% in adults. AML is the most dominant form of leukemia in neonatal and adult ages but signifies a small fraction of cases during infancy and adolescence [5]. AML usually starts in the bone marrow, but most often it quickly moves into the blood, as well. It can sometimes spread to other parts of the body including the lymph nodes, spleen, liver, central nervous system (brain and spinal cord), and testicles.

GENE EXPRESSION PROFILING (GEP)

All biological events in the cell are mainly controlled by the changes in expression of key genes. Transcription of a gene is important in normal events such as cell division, proliferation, differentiation and cell death. On the other hand, it assists the pathogenic process that renders the development and progression of the disease, as well as governing response to therapy. By comparing gene expression profiles under different conditions, individual or group of genes that plays a vital role in particular disease etiology can be identified. Therefore research focusing on the delineation of gene expression profiles for the identification of key genes and gene clusters which are altered in disease states comparable with normal is found to be important [6]. GEP is the determination of gene expression patterns at transcription level, in a specific cell or under specific conditions to give a global picture of cellular function. It has become an important tool in the field of hematology, providing key insights in understanding the biology of hematologic malignancies and aid in clinical inferences. Techniques to

measure gene expression patterns include DNA microarrays which measure the relative activity of previously recognised target genes, or sequencing technologies like RNA sequencing (RNA-Seq), which allow profiling of all active genes.

GEP analysis successfully distinguish AML and ALL (Acute Lymphoid Leukemia) samples and established a gene expression-based predictor which assigned new leukemia cases based on the predicted model of each of the two leukemia types with high accuracy [7]. Advances in massive sequencing technologies have reported several mutations associated with AML and some of such reported genes include KIT, FLT3, NPM1, CEBPα, BAALC, WT1, RAS, ERG, MN1, DNMT, TET2, IDH, ASXL1, CBL and PTPN11 [8,9]. Among these the genes FLT3, NPM1 and CEBPα are focussed by the World Health Organization (WHO) due to their importance in treatment response and disease progression [10]. FLT3, a member of receptor tyrosine kinase family is usually expressed in hematopoietic progenitor cells and is highly expressed in most of the AML cases [11]. NPM1, a chaperone protein plays an important role in maintaining homeostasis and any disruption of these can cause malignancy and is commonly up-regulated in various cancers [12,13]. CEBPα is a transcriptional factor possessing key roles in tissue-specific gene expression [14] and proliferation arrest and is over expressed during granulocyte differentiation [15]. Mutation of these genes is common in AML and is discussed below under genetic mutations section.

RNA-SEQUENCING IN LEUKEMIA RESEARCH

After the complete tumor genome sequencing of AML in 2009 [16], numerous studies are being reported various novel somatic mutations in AML and cancer in common, rather it's inadequate to elucidate the leukemogenic process completely [17]. Luckily, massively parallel sequencing has been implemented to sequence cDNA libraries obtained from reverse transcription of different RNA sources, a technique generally denoted as RNA sequencing (RNA-Seq) [18,19]. It has become an essential tool to find disease-associated transcriptional profiles and determine the molecular keystones of diseases. It is an important technology behind the wide-ranging analysis of disease transcriptomes and offers great promise for clinical applications including disease diagnosis, therapeutic selection and precision medicine approaches [20-23]. This has been predominantly helpful in understanding the pathogenesis and classification of leukemia [24,25]. For example, it has been utilized for the identification of a broad range of diagnostic biomarkers [26], fusion-genes and persistent mutations [27,28], expressed variants [29], differential gene expression among different biological conditions and alternative splicing events [30] in various leukemia types.

With the development of sequencing techniques, targeted therapy facilitated by molecular biology and genetics is a promising area for therapy of AML [31]. High throughput technologies such as RNA sequencing have enabled the revelation of global transcriptomic changes in AML, especially key molecules in the pathogenesis. Currently, studies indicated that during the pathogenesis of AML regulation of a variety of signaling pathways were overexpressed which was caused by mutations contributing to hematopoietic transformation in terms of transcriptional targets during pathogenesis, such as TET2, DNMT3A, ASXL1, IDH1 and IDH2 [32].

Potential targets in AML based on whole-genome RNA-seq by analysing the transcriptomic profile during diagnosis. They marked a change in transcriptomic profile of patients and found the novel genes namely Rh associated glycoprotein (RHAG), succinate receptor 1 (SUCNR1), transmembrane-4 L-six family member-1 (TM4SF1) and Adhesion G Protein-Coupled Receptor A3 (ADGRA3) which may act as potential targets in AML [33]. AML cellular subpopulations augmented for leukemia stem cells (LSCs) possess different gene expression pattern, which shares essential stemness landscapes with profiles of hematopoietic stem cells (HSCs) [34]. LSC-like gene expression signature was related to cytogenetically normal AML patients [35]. Moreover, this LSC signature was also linked with a specific microRNA expression pattern. These findings help the LSC theory for AML pathogenesis and agree with the factual biological features at cellular and transcriptomic stages, with precise significance to clinical outcome. An approach for the diagnosis and genomic classification of paediatric ALL from RNA-seq data. They have identified the IKZF1 deletions, which are usually detected by standard-off-care diagnostics, but failed to detect by RNA-seq, due to low expression. They showed that RNA-seq can be implemented in clinical investigation of individuals which can improve the existing risk classification in molecular diagnostics of ALL [36].

Genetic Mutations and AML

Multiple gene mutations that affect AML process have been identified and several pieces of evidence suggest the role of splicing events in cancer. RNA-seq profiling disclosed aberrant splicing in AML patients during treatment, which would be an additional source for biomarkers and even therapeutic target discovery. Moreover, this may assist the better understanding of leukemogenesis [37]. An

approach for finding the mutations in AML cells using single-cell RNA-sequencing. They identified many cells with tumor-specific mutations and differentiated the AML cells from normal cells to detect the expression signatures related to subclonal mutations, cell surface markers [38]. Their approach can connect genotype to phenotype, which can be widely used to detect any genotypically and phenotypically heterogeneous sample. FLT3 is the most prominent genetic alteration correlated with poor prognosis in AML patients[39]. This occurs in ~30% of all AML cases and is reported in around one-third of newly diagnosed adults [40], with the internal tandem duplication (ITD) being the most frequent type (FLT3-ITD) [41] and is also prevalent in pediatric AML [42]. NPM1 is another commonly mutated gene in AML with ~20-30% of AML cases [43]. CCAAT/enhancer-binding protein α (CEBPA) mutation occurs in 5–10% of AML cases [44]. Moreover, Schmidt et al. [45] identified MLL1 complex as a potential target in AML with CEBPA mutations. The role of these mutations in AML is reviewed [43-46], and depicted in Fig. 1.

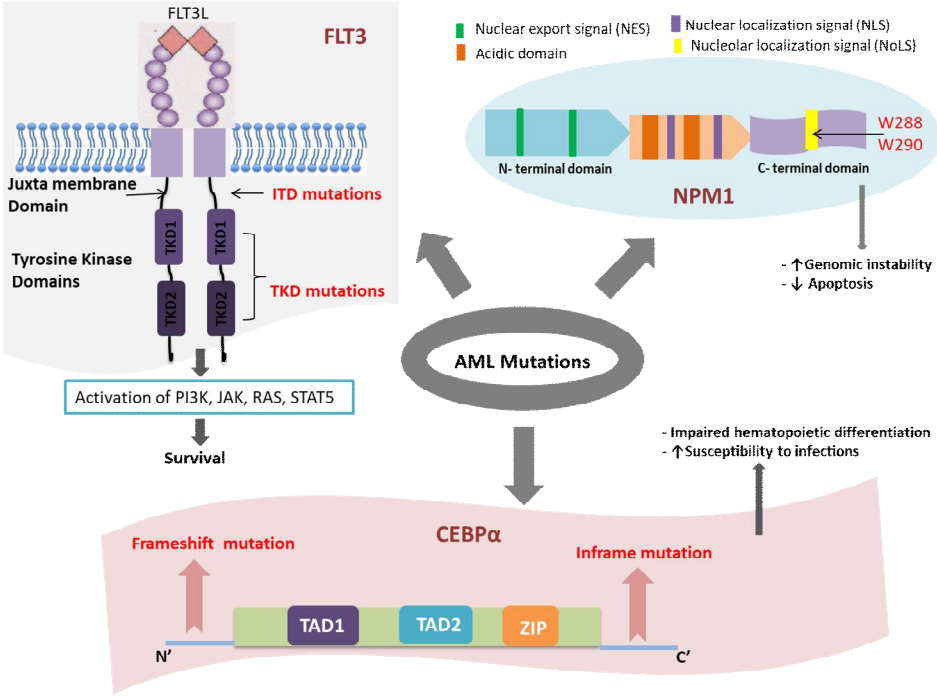

Fig. 1. Mechanisms of Leukemogenesis in AML due to FLT3, NPM1 and CEBPα mutations

FLT3 mutation involves two broad categories namely Internal tandem duplications (ITD) and point mutations in the tyrosine kinase domain (TKD). This activates other signaling pathways like PI3K, JAK/STAT, RAS leading to cell survival. NPM1 mutations at the C-terminal domain lead to genome instability and decrease in apoptosis, favouring cell survival (with the involvement of other genes). CEBPα possesses N-terminal frameshift mutation and C-terminal in-frame insertions or deletions causing impaired hematopoietic differentiation.

Genetic Aberrations in AML

Around 50-55% of AML shows specific balanced chromosomal abnormalities in fusion genes encoding fusion proteins, possessing vital role in formation of leukemia through their impact on cell proliferation, survival and apoptosis [47]. AML is caused by genetic aberrations which are structurally diverse and can be detected by various diagnostic tests. Increased expression of EVI1, correlated with very poor prognosis even without structural aberrations involving 3q26 [48].

MAJOR PROTEIN FAMILIES CONTRIBUTING AML

Bcl2 Family Members

B-cell lymphoma-2 (BCL-2) family proteins have either anti-apoptotic or pro-apoptotic roles, studied broadly for their significance in regulating apoptosis, tumorigenesis and cellular response to anti-cancer therapy. The proteins in BCL-2 family shares sequence homology via the presence of Bcl-2 homology (BH) domains. Four BH domains exist in this family and each member has at least one. The family includes two groups: one with pro-apoptotic and the other with anti-apoptotic effects. The pro-apoptotic group, which

promotes cell death, has two subgroups: one group contains proteins such as Bax and Bak and the other includes Noxa, PUMA, Bim and Bid. The latter group is often denoted as the BH3 only proteins, as they share sequence similarity to the other members of the family only through their BH3 domain. The anti-apoptotic group includes the proteins BCL-2, BCL-XL, MCL1, BCL-w and BCL-b. The Bcl-2 family plays a prominent role in intrinsic apoptotic pathway and is essential for cell survival. Overexpression of Bcl-2 family proteins are found in many tumors including AML and causes chemotherapy resistance, which is correlated with poor prognosis [49-51]. The expression of MCL-1, which possesses a short half-life compared to other members of the family showed great heterogeneity in AML patients.

Expression levels of Bcl-2 family members are also found to influence by other proteins like Protein kinase C (PKC). PKC phosphorylates Bcl-2 and Bax modulates Bcl-2 dimerization [52]. Bax and PKCα expression levels which affect Bcl-2 function impact the prognosis of Bcl-2 [53]. Kurinna and group correlated Bcl-2 phosphorylation and PKCα with poor prognosis in AML [54].

Protein Kinase C (PKCs)

PKC kinases are involved in multiple cellular functions such as differentiation, proliferation, survival and motility [41]. Different types of PKCs are reported namely a) conventional or classical PKCs which include PKCα, PKCβ variants (PKCβI and PKCβII) and PKCγ, b) Novel PKCs (nPKCs) holding PKCδ, PKCε, PKCη and PKCθ and c) Atypical PKCs (aPKCs) namely PKCζ and PKCι(λ). PKC α and β family members are over-expressed in numerous AML studies and targeting them is cytotoxic [55,56]. PKC isoforms have also been associated with resistance to DNA damaging agents in AML cells by affecting Bcl-2 phosphorylation [57]. Studies suggested the poor prognostic potential of PKC facilitated activation of pro-proliferative signaling cascades in AML patients [55] and their role in promoting chemoresistance and hematopoietic stem cell quiescence [58, 59].

CONCLUSION

The development and progression of AML usually encompass the deregulation of several genes and their regulatory mechanisms. Several studies reported such abnormalities which enhanced our current understanding of their role in pathogenesis and progression of disease and thereby had led to the improvements in targeted therapies. Moreover, these studies provide insights into the divergent mechanisms and leukemic pathways that can be exploited for enhanced diagnostic and therapeutic strategies.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Short NJ, Rytting ME, CortesJE. (2018). Acute myeloid leukaemia. The Lancet. 392(10147):593-606.
2. Estey E, Dohner H. (2006). Acute myeloid leukaemia. The Lancet. ;368(9550):1894-1907.
3. Kadia TM, Kantarjian HM, Konopleva M. (2019). Myeloid cell leukemia-1 dependence in acute myeloid leukemia: a novel approach to patient therapy. Oncotarget. 10(12):1250.
4. Siegel R, Jemal A. (2015). Cancer facts & figures. American Cancer Society Cancer Facts & Figures; 2015.
5. Lagunas FA, Chavez VV, Gomez MA, Cortes CP. (2017). Acute myeloid leukemia—genetic alterations and their clinical prognosis. International Journal of Hematology-Oncology and Stem Cell Research. 11(4):328.
6. Murray D, Doran P, MacMathuna P, Moss AC. (2007). *In silico* gene expression analysis–an overview. Molecular cancer. 2007;6(1):1-10.
7. Golub TR, Slonim DK, Tamayo P, Huard C, Gaasenbeek M, Mesirov JP, Lander ES. (1999). Molecular classification of cancer: class discovery and class prediction by gene expression monitoring. Science. 286(5439):531-537.
8. Martelli MP, Sportoletti P, Tiacci E, Martelli MF, Falini B. (2013). Mutational landscape of AML with normal cytogenetics: biological and clinical implications. Blood Reviews. 27(1):13-22.
9. Takahashi S. (2011). Current findings for recurring mutations in acute myeloid leukemia. Journal of Hematology& Oncology. 4(1):1-11.
10. Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW. (2008). WHO classification of tumours of haematopoietic and lymphoid tissues. SH. Swerdlow (Ed.). Lyon, France: International Agency for Research on Cancer. ;2:439.
11. Carow CE, Levenstein M, Kaufmann SH, Chen J, Amin S, Rockwell P, Witte L, Borowitz MJ, Civin CI, Small D. (1996). Expression of the hematopoietic growth factor receptor FLT3 (STK-1/Flk2) in human leukemias. ;1089-1096
12. Tsui KH, Cheng AJ, Pan TL, Yung BY. (2004). Association of nucleophosmin/B23 mRNA expression with clinical outcome in patients with bladder carcinoma.Urology. 64(4):839-44.
13. Grisendi S, Mecucci C, Falini B, Pandolfi PP. (2006). Nucleophosmin and cancer. Nature Reviews Cancer. ; 6(7):493-505.

14. Fasan A, Haferlach C, Alpermann T, Jeromin S, Grossmann V, Eder C, Weissmann S, Dicker F, Kohlmann A, (2014). Schindela S, Kern W. The role of different genetic subtypes of CEBPA mutated AML. Leukemia. ;28(4):794-803.
15. Koschmieder S, Halmos B, Levantini E, Tenen DG. (2009). Dysregulation of the C/EBPα differentiation pathway in human cancer.Journal of Clinical Oncology. 27(4):619.
16. Mardis ER, Ding L, Dooling DJ, Larson DE, McLellan MD, Chen K, Ley TJ. (2009). Recurring mutations found by sequencing an acute myeloid leukemia genome. New England Journal of Medicine. ;361(11):1058-1066.
1. 17. Chen J, Odenike O, Rowley JD. (2010). Leukaemogenesis: more than mutant genes. Nature Reviews Cancer. 10(1): 23-36.
17. Wang Z, Gerstein M, Snyder M. (2009). RNA-Seq: a revolutionary tool for transcriptomics. Nature reviews genetics. 10(1):57-63.
18. Ozsolak F, Milos PM. (2011). RNA sequencing: advances, challenges and opportunities. Nature Reviews Genetics. 12(2):87-98.
19. Kontro M, Kumar A, Majumder MM, Eldfors S, Parsons A, Pemovska T, Porkka K. (2017). HOX gene expression predicts response to BCL-2 inhibition in acute myeloid leukemia. Leukemia. ;31(2):301-309.
20. Xu J, Gong B, Wu L, Thakkar S, Hong H, Tong W. (2016). Comprehensive assessments of RNA-seq by the SEQC consortium: FDA-led efforts advance precision medicine. Pharmaceutics.;8(1):8-13
21. Byron SA, Van Keuren-Jensen KR, Engelthaler DM, Carpten JD, Craig DW. (2016). Translating RNA sequencing into clinical diagnostics: opportunities and challenges. Nature Reviews Genetics. ;17(5):257-271.
22. Keuren-Jensen KV, Keats JJ, Craig DW. (2014). Bringing RNA-seq closer to the clinic. Nature biotechnology. ;32(9):884-885.
23. Cancer Genome Atlas Research Network. (2013). Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia.New England Journal of Medicine.368(22):2059-2074.
24. Andersson AK, Ma J, Wang J, Chen X, Gedman AL, Dang J, Downing JR. (2015). The landscape of somatic mutations in infant MLL-rearranged acute lymphoblastic leukemias.Nature Genetics. ;47(4):330-337.
25. Lavallee VP, Krosl J, Lemieux S, Boucher G, Gendron P, Pabst C, Sauvageau G. (2016). Chemo-genomic interrogation of CEBPA mutated AML reveals recurrent CSF3R mutations and subgroup sensitivity to JAK inhibitors. Blood, The Journal of the American Society of Hematology. ;127(24):3054-3061.
26. Lilljebjorn H, Ågerstam H, Orsmark-Pietras C, Rissler M, Ehrencrona H, Nilsson L, Fioretos T. (2014). RNA-seq identifies clinically relevant fusion genes in leukemia including a novel MEF2D/CSF1R fusion responsive to imatinib. Leukemia. 28(4):977-979.
27. Gianfelici V, Chiaretti S, Demeyer S, Di Giacomo F, Messina M, La Starza R, Foà R. (2016). RNA sequencing unravels the genetics of refractory/relapsed T-cell acute lymphoblastic leukemia. Prognostic and therapeutic implications.Haematologica. 101(8):941-950.
28. Trino S, Lamorte D, Caivano A, Laurenzana I, Tagliaferri D, Falco G, De Luca L. (2018). MicroRNAs as new biomarkers for diagnosis and prognosis, and as potential therapeutic targets in acute myeloid leukemia. International journal of molecular sciences. ;19(2):460.
29. Shih AH, Abdel-Wahab O, Patel JP, Levine RL. (2012). The role of mutations in epigenetic regulators in myeloid malignancies.Nature Reviews Cancer. 12(9):599-612.
30. El Masry OS, Al Amri AM, Alqatari A, Alsamman K. (2020). RNA psequencing based identification of potential targets in acute myeloid leukemia: A case report. Biomedical reports. 2020;13(5):1-1.
31. Eppert K, Takenaka K, Lechman ER, Waldron L, Nilsson B, Van Galen P, Dick JE. (2011). Stem cell gene expression programs influence clinical outcome in human leukemia. Nature medicine. 17(9):1086-1093.
32. Metzeler KH, Maharry K, Kohlschmidt J, Volinia S, Mrozek K, Becker H, Bloomfield CD. (2013). A stem cell-like gene expression signature associates with inferior outcomes and a distinct microRNA expression profile in adults with primary cytogenetically normal acute myeloid leukemia. Leukemia. ;27(10):2023-2031.
33. Brown LM, Lonsdale A, Zhu A, Davidson NM, Schmidt B, Hawkins A, EkertPG. (2020). The application of RNA sequencing for the diagnosis and genomic classification of pediatric acute lymphoblastic leukemia. Blood advances. ;4(5):930-942.
34. Li XY, Yao X, Li SN, Suo AL, Ruan ZP, Liang X, Yao Y. (2014). RNA-Seq profiling reveals aberrant RNA splicing in patient with adult acute myeloid leukemia during treatment. Eur Rev Med Pharmacol Sci. 18(9):1426-1433.
35. Petti AA, Williams SR, Miller CA, Fiddes IT, Srivatsan SN, Chen DY, Ley TJ. (2019). A general approach for detecting expressed mutations in AML cells using single cell RNA-sequencing. Nature Communications. ;10(1):1-16.
36. Papaemmanuil E, Gerstung M, Bullinger L, Gaidzik VI, Paschka P, Roberts ND, Potter NE, Heuser M, Thol F, Bolli N, Gundem G. (2016). Genomic classification and prognosis in acute myeloid leukemia. New England Journal of Medicine. 374(23):2209-21.
37. Kiyoi H, Kawashima N, Ishikawa Y. (2020). FLT3 mutations in acute myeloid leukemia: Therapeutic paradigm beyond inhibitor development. Cancer Science. 111(2): 312-22.
38. Bolouri H, Farrar JE, Triche T, Ries RE, Lim EL, Alonzo TA, Ma Y, Moore R, Mungall AJ, Marra MA, Zhang J. (2018). The molecular landscape of pediatric acute myeloid leukemia reveals recurrent structural alterations and age-specific mutational interactions. Nature Medicine. 24(1):103-12.
39. Daver N, Schlenk RF, Russell NH, Levis MJ.(2019). Targeting FLT3 mutations in AML: review of current knowledge and evidence.Leukemia. ;33(2):299-312.

40. Falini B, Mecucci C, Tiacci E, Alcalay M, Rosati R, Pasqualucci L, La Starza R, Diverio D, Colombo E, Santucci A, Bigerna B. (2005). Cytoplasmic nucleophosmin in acute myelogenousleukemia with a normal karyotype. New England Journal of Medicine. 352(3):254-66.
41. Mannelli F, Ponziani V, Bencini S, Bonetti MI, Benelli M, Cutini I, Gianfaldoni G, Scappini B, Pancani F, Piccini M, Rondelli T. (2017). CEBPA–double-mutated acute myeloid leukemia displays a unique phenotypic profile: a reliable screening method and insight into biological features. haematologica. 102(3):529.
42. Zarka J, Short NJ, Kanagal-Shamanna R, Issa GC. (2020). Nucleophosmin 1 mutations in acute myeloid leukemia. Genes. 11(6):649.
43. Pabst T, Mueller BU. (2009). Complexity of CEBPA dysregulation in human acute myeloid leukemia. Clinical Cancer Research. 15(17):5303-7.
44. Schmidt L, Heyes E, Scheiblecker L, Eder T, Volpe G, Frampton J, Nerlov C, Valent P, Grembecka J, Grebien F. (2019). CEBPA-mutated leukemia is sensitive to genetic and pharmacological targeting of the MLL1 complex. Leukemia. 33(7):1608-19.
45. Annesley CE, Brown P.(2014). The biology and targeting of FLT3 in pediatricleukemia. Frontiers in oncology. ;4:263.
46. Fröhling S, Scholl C, Gilliland DG, Levine RL. (2005). Genetics of myeloid malignancies: pathogenetic and clinical implications. Journal of Clinical Oncology. ;23(26):6285-6295.
47. Arindrarto W, Borràs DM, de Groen RA, van den Berg RR, LocherIJ, van Diessen SA, Veelken H. (2021). Comprehensive diagnostics of acute myeloid leukemia by whole transcriptome RNA sequencing. Leukemia. ;35(1):47-61.
48. Venditti A, Del Poeta G, Maurillo L, Buccisano F, Del Principe MI, Mazzone C, Amadori S. (2004). Combined analysis of bcl-2 and MDR1 proteins in 256 cases of acute myeloid leukemia. Haematologica. 89(8):934-939.
49. Del Poeta G, Venditti A, Del Principe MI, Maurillo L, Buccisano F, Tamburini A, Amadori S. Amount of spontaneous apoptosis detected by Bax/Bcl-2 ratio predicts outcome in acute myeloid leukemia (AML) Presented in part at the 42nd annual meeting of the American Society of Hematology, San Francisco, CA, December 1-5, 2000.46. Blood, The Journal of the American Society of Hematology. 2003;101(6):2125-2131.
50. Tothova E, Fricova M, Stecova N, Kafkova A, Elbertova A. High expression of Bcl-2 protein in acute myeloid leukemia cells is associated with poor response to chemotherapy. Neoplasma. 2002;49(3):141-144.
51. Tzifi F, Economopoulou C, Gourgiotis D, Ardavanis A, Papageorgiou S, Scorilas A. (2012). The role of BCL2 family of apoptosis regulator proteins in acute and chronic leukemias. Advances in Hematology; 20-25.
52. Kornblau SM, Vu HT, Ruvolo P, Estrov Z, O'Brien S, Cortes J, May WS. (2000). BAX and PKCα modulate the prognostic impact of BCL2 expression in acute myelogenousleukemia. Clinical Cancer Research. 6(4):1401-1409.
53. Kurinna S, Konopleva M, Palla SL, Chen W, Kornblau S, Contractor R, Ruvolo PP. (2006). Bcl2 phosphorylation and active PKC α are associated with poor survival in AML. Leukemia. 20(7):1316-1319.
54. Griner EM, KazanietzMG. (2007). Protein kinase C and other diacylglycerol effectors in cancer. Nature Reviews Cancer. 7(4): 281-294.
55. Guzman ML, Li X, Corbett CA, Rossi RM, Bushnell T, Liesveld JL, Hébert J, Young F, Jordan CT. (2007). Rapid and selective death of leukemia stem and progenitor cells induced by the compound 4-benzyl, 2-methyl, 1, 2, 4-thiadiazolidine, 3, 5 dione (TDZD-8). Blood, The Journal of the American Society of Hematology. ;110(13):4436-44.
56. Ruvolo PP, Zhou L, Watt JC, Ruvolo VR, Burks JK, Jiffar T, Kornblau S, Konopleva M, Andreeff M. (2011). Targeting PKC-mediated signal transduction pathways using enzastaurin to promote apoptosis in acute myeloid leukemia-derived cell lines and blast cells. Journal of Cellular Biochemistry. 112(6): 1696-707.
57. Jiffar T, Kurinna S, Suck G, Carlson-Bremer D, Ricciardi MR, Konopleva M, Andreeff M, Ruvolo PP. (2004). PKC α mediates chemoresistance in acute lymphoblastic leukemia through effects on Bcl2 phosphorylation. Leukemia. ;18(3):505-12.
58. Nicholson RL, Knapper S, Tonks A, (2019). Darley RL. PKC-Epsilon Overexpression Is Associated with Poor Outcomes in AML and Promotes Chemoresistance and Hematopoietic Stem Cell Quiescence. Blood. 134(1): 2704.

ABBREVIATIONS

KIT: KIT Proto-Oncogene, Receptor Tyrosine Kinase, FLT3: Fms-like tyrosine kinase 3, NPM1 : Nucleophosmin, CEBPα : CCAAT Enhancer Binding Protein Alpha, BAALC : BAALC Binder Of MAP3K1 And KLF4, WT1 : Wilms' tumor suppressor gene1, ERG: ETS Transcription Factor ERG, MN1: Meningioma 1, DNMT : DNA (cytosine-5)-methyltransferase 1, TET2: Ten-Eleven Translocation 2, IDH: Isocitrate dehydrogenase, ASXL1 : ASXL transcriptional regulator 1, PTPN11 : Tyrosine-protein phosphatase non-receptor type 11, IKZF1: Ikaros family zinc finger protein 1