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The Central Role of Hematopoietic Stem Cells in Leukemia such as Acute Lymphoblastic Leukemia or Chronic Myeloid Leukemia

Ahmad Reza Rahnemoon*

Department of Hematology, Iran University of MedicalSciences, Tehran, Iran

***Corresponding author**: Ahmad Reza Rahnemoon, Department of Hematology, Iran University of Medical Sciences, Tehran, Iran. E-mail: ar.rahnemoon@gmail.com

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Abstract

Leukemia is the most common type encountered in pediatric and adult patients. In acute leukemia, Hematopoietic Stem Cells (HSCs) reside in specialized niche in the Bone Marrow (BM). These stem cells are thought to provide signals that support key HSC properties. Normality, cytokines regulate a variety of hematopoietic cell functions through the activation of multiple signal transduction pathways. In this regard, regulation of proliferation and differentiation of HSCs is related by the gene expression pattern in the cell and the composition of external signals from the BM niche. Transcription factors regulate express of gene, meanwhile external signals can be mediated by cell-cell interactions, cell- extracellular matrix interactions and growth factors as well which may promote proliferation, differentiation, migration and apoptosis. Moreover, HSCs are multipotent stem cells defined by their ability to self-renewal, differentiation and maintenance of all blood cell types in hematological system. These properties make HSCs like other tissue stem cells, prime targets for malignant transformation. Also we know, molecular advances of acute leukemia have led to discovery of numerous additional changes including mutation involving key cellular pathways in myeloid and lymphoid development, tumor suppression, and cell cycle regulation as well. Hence, I want to explain concerning genetic basis of acute leukemia particularly in Acute Lymphoblastic Leukemia (ALL), HSCs source as well, also malignant and nonmalignant hematopoietic progenitor cells.

Keywords: Bone marrow; Migration; Blood progenitor; Apoptosis; Self-renewal.

Introduction

Hematopoietic Stem Cells (HSCs) are multipotent stem cells defined by their ability to self-renewal, differentiation and maintenance of all blood cell types in hematological system.In fact, adult Hematopoietic Stem Cells (HSCs) are the cells capable of self-renewal and remain component in the process of hematopoiesis which, together with the cells that makeup the bone marrow stromal environment and other factors. However, when this process of cell production is unbalanced; leading to an exacerbated and uncontrolled proliferation of blood progenitor cells, so leukemia may develop. We can say, normally many of the different types of signals that are exchanged between stem cells and niche cells and some of signaling pathways that control stem cell maintenance, self-renewal and differentiation as well [1].

Moreover, some studied confirmed the central role of osteoblastic lineage cells in HSCs regulation which is emerging as an essential component of HSCs maintenance and hematopoietic recovery from injury. Likewise, Bone Marrow (BM) stroma is a key element of hematopoiesis which is a rare population includes non-hematopoietic skeletal progenitor cells as named Stromal Cells (SC) that closely associated with the vasculature. Furthermore, Mesenchymal Stem Cells (MSCs) play an important role in niche cells particularly in providing the specialized bone marrow microenvironment for HSCs and other hematopoietic progenitor cells. Also, for supporting HSC expansion, the liver can be the main site for hematopoietic [2].

Materials and Methods

As we know, leukemia is the consequence of stepwise genetic alterations that confer both proliferative and survival advantage, as well as self-renewal capacity to the malignant cells. Leukemia Stem Cells (LSCs) possess several key properties of normal cells including self -renewal, unlimited proliferative potential, infrequent or slow replication. LSCs infiltrate the bone marrow and interfere with the normal HSC microenvironment hemostasis. Thus, the major difference between leukemia growth and normal tissue renewal is that whereas normal transit amplifying cells usually differentiate and die at various levels of differentiation, the leukemia transit-amplifying cells can go to differentiate abanormally and instead, accumulate, resulting in leukemia growth.

We know cytogenetic and molecular testing in leukemia is integral to diagnosis and Minimal Residual Disease (MRD) monitoring as well. Regarding, conventional chromosome analysis is a basic way for diagnosis and treatment. In addition in this way evaluation of disease progression is important and so it is the only method that can identify the presence of clonal evolution, particularly in accelerated and relapse phase in the disease. Also conventional cytogenetic can detect chromosomal abnormality associated with its advanced phase [3]. For fusion

genes studies FISH is a more sensitive test in the advantage of routinely interrogating 50 to 200 metaphase or interphase cells. However, one of the most sensitive tests is RT-PCR in molecular fusion gene study and MRD assay as well. Anyhow, the value of translocation rates in interphase and metaphase nuclei in monitoring leukemia is at the time of diagnosis and after treatment additionally. Concerning, results of conventional cytogenetic and other molecular tests which shown and other figures describe some points as follows:

B-ALL with multiple trisomies and between 50 and 66 chromosomes (normal=46) is referred to as hyperdiploid. This usually occurs in children and implies favorable prognosis. Trisomies of chromosome 4, 10, and 17 are considered markers for low- risk disease in pediatric leukemia protocols. I have some points as follows: 1)As we know karyotype can be abnormal in ALL and this abnormality including numerical aberration and structural aberration. In structural aberration, if we had some chromosomal involved or multiple involved, we can say, it is a complex karyotype that generally we see in accelerated phase or in relapse with poor prognosis. My question (**Figure 1)** is what about numerical aberration? What is the meaning of chromosomes between 50 up to 66 and secondly, if we had multiple numerical chromosomal involved, so is it a complex karyotype? And thirdly, what about the prognosis? If good, what is the relationship between complex karyotype and good prognosis? In all, are these questions right?

The question is, why is different in involved chromosomes at ALL? Suppose we have ALL-L1, hence why so different in one of the subtype of ALL? In the and other figure we can say it is a minor clone? If yes, in response all of these chromosomal aberrations or other genetic alterations are minor clones? Also we can say these chromosomal changes or molecular abnormalities may accidental or fortuitously do so. My other question is what do you think about it? Is it right?

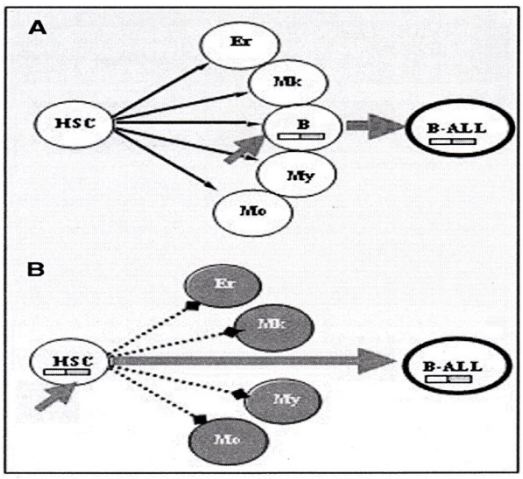

Figure 1: A fusion gene model and chromosomal abnormalities in cell lineage specification, seeing that the abnormalities forced expression of these fusion genes in lineage choice decisions, which imposed in the lineage outcome.

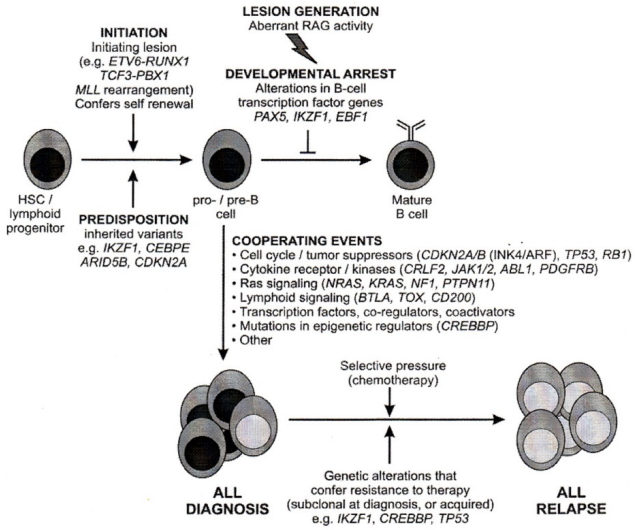

Figure 2: The role of genetic alterations in the B-ALL pathogenesis. These lesions with or without the secondary genetic alterations disrupt lymphoid lineage and go to a maturation arrest, that result in resistance to therapy and promote to disease relapse probably.

On the other hand, genomic profiling transformed our understanding of the genetic basis of leukemia particularly in ALL, (**Figure 2)** which is a malignant clonal proliferation of lymphoid progenitor cells. In this case, I have some problems as follows:

As we know lymphoid malignancies are characterized by recurrent chromosomal aberrations that lead to the formation of fusion genes and the subsequent expression of chimeric proteins with unique properties. The best example concerning the necessity of secondary events is given by leukaemias with fusion gene. Generally, t(12;21) positive patients show frequent deletion of the normal ETV6 gene, suggesting that the fusion gene is an initial event conferring predisposition to leukaemia by the deletion of the gene in 12p as a promoter event [4-5]. So I have some points: 1) Studies with TEL/AML1 knock in mice showed that the expression of the fusion gene is not sufficient for the *in-vivo* induction of ALL. 2) Why the translocation t (12;21) or TEL/AML1 fusion gene can be detected in healthy individuals ? I may say, why can be detected and what about the result? Is it accepted that we say, in this case, likely to be indicative of transient genomic instability? Or is it better, those are complex that we do not understand ? In fact, can these solve? 3) Some researchers believe that leukemia associated fusion genes before birth. They say, in twins with concordant ETV6/RUNX1 positive leukemia, the development of ALL has been found to occur at different times, and postnatal latency can be variable and occasionally protracted; or somebody say, ETV6/RUNX1 translocation occurs in utero, followed by pre-leukemic evolution as a result of further genomic structural variation. My question is, how is it possible and secondly, is this subject, their process and their results detected in the all of children?

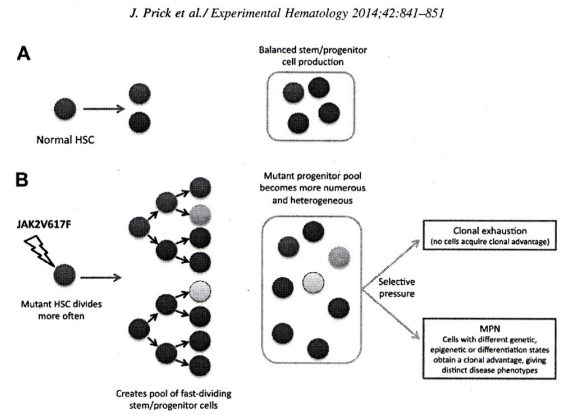

Figure 3: Clonal evolution in myelo-proliferative neoplasms. Please you see carefully, in normal HSC, mutant HSC, balance production, clonal exhaustion in selective pressure and in the end clonal mutant cells. So what's the exact role of "selective pressure" in the position (in HSC, in niche cells , hematopoietic microenvironment or in genetic abnormalities, and/or the whole of these matters)?

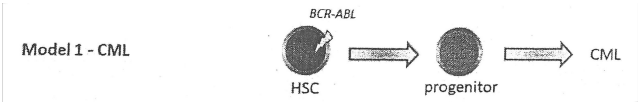

Figure 4: Various models of the disease origin and evolution as well which may be occur in the leukemic process.

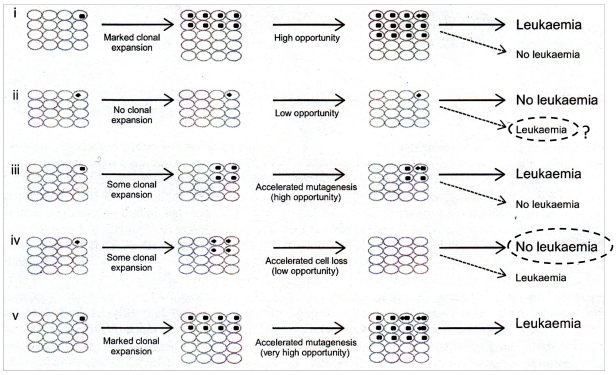

Figure 5: The process of clonal evolution in acquisition of opportunities including early clonal evolution in general and others are acquired late. But is the question or any problem in this figure? Or minimally what's the question mark in the figure and secondly, are the questions marks correct?

In myeloid malignancy, the isolated of stromal cell populations that can harbor genetic abnormalities but these are different from mutations in leukemic clone **(Figure 3)**. Regarding, LSC niche can add to the therapy target for any of hematological malignancy.

BCR-ABL was the first chromosomal abnormality shown with a specific malignancy in humans. In this regard, murine models have demonstrated that disruption of the hematopoietic microenvironment can initiate myeloproliferative disease and even leukemia. Also in murine models, activation of the normal from HSC niche improves recovery from radiation and chemotherapeutic injury and suppresses Chronic Myeloid Leukemia (CML) progression, impairing leukemic stem **(Figure 4)** maintenance in the syngeneic model. In hematologic malignancies, clonal neoplastic cells alter the hematopoietic microenvironment so that it becomes supportive of LSCs and becomes less supportive of normal HSCs, ultimately leading to decreased normal hematopoiesis. In CML, sustained by a range of biological characteristics that enable their long-term survival, and accumulation of myeloid cells that differentiate in normal and abnormal clones, which can change to Acute Lymphoblastic Leukemia (ALL) in accelerated [6]. Furthermore, leukemia induced decrease in CXCL12 expression results in reduced retention of LSCs in CML bone marrow. Moreover, leukemia induced abnormalities in cytokine in CML bone marrow result in selective suppression of normal stem cell growth and enhanced growth of LSC (**Figure 5)**.

My comments are as follows:

1) Firstly, MLL translocations in normal individuals described. This rearrangement and the transcription factor AF4 which results from t(4;11)(q21;q23) were identified from normal children and fetuses as well as fetal liver samples. Then some researchers, the rearrangement detected in healthy individuals. Sequence analysis of individual providing evidence that these rearrangements are not restricted to malignant cells and that they may also be present in a subset of normal hematopoietic cells.

2)Abnormalities of the MLL gene at chromosome region 11q23 are seen in the 5% to7% of cases of ALL , as well as in AML. We can say , translocation t(11;19) (q23;p13.3) is the next most frequent MLL abnormality in ALL but also occurs in AML(monocytic)What does it mean? We have the fusion gene abnormality in two different lineages including myeloid series and the other lymphoid series [7-10]. Is this fusion gene a specificabnormality or non specific abberation? What about the production of the fusion gene in two different lineages? Are these the same? Therefore, we must have a better understanding about the interaction of HSCs with stromal cells and other important agents like genetic abnormalities such as cytogenetic and molecular genetic which can provide therapeutic targets for manipulation to modulate HSCs and their progeny in the diseases.

The Ph' chromosome t(9;22) with a production of a fusion BCR/ABL occurs in about 30%of cases of adult(20% detected at karyotyping) and 6% of cases of childhood ALL .The t(9;22) is the most frequent adult ALL translocation and is associated with poor prognosis. Two types are found: that identical to CML, involving the bcr region of BCR with resultant p210 kD fusion protein, occurring in half of adult cases of Ph' positive ALL; and another p190 kD protein that occurs in most childhood ph' positive cases. Regarding , I have some points: 1) What is the difference between CML and ALL? Are these the same? Because of the proteins of 210 and 190 can be seen in ALL and also in CML? How is it possible? Also, I must say, we have two different lineages completely that producing two different kind of cells So, is this mechanism right? 2) Some researchers stated that BCR/ABL fusion gene detected in normal individuals. What does it mean? And in other words, what is the exact role of this fused gene in the individuals?

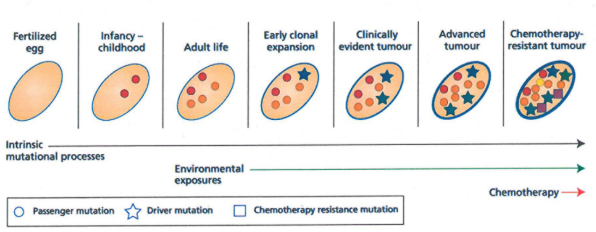

Figure 6: The sequence of somatic mutations in during cell divisions . please look at a single chemo-resistant leukemic cell process , in particular attention to end of mutational process in advanced tumor cell and chemotherapy resistant tumor cell and the role of environmental exposures as well from the fertilized egg.

It is important to know about the diversity of leukemic disease phenotypes which increased proliferation induced by some fusion genes on the mutant clone that results in diverse clonal evolution which can increase a tendency to leukemic transformation but in the follow-up, we understand that the clonal evolution has considerable potential to identify patients at high risk in progression disease ultimately or in other words, clonal evolution means key regulators of the disease in development and progression only. Regarding, if we ask that how are mutations generated? In response, we can say most of them will not state a growth advantage and are deemed to be passengers. So in most cancers particularly in leukemia the minimum mutations are drivers which impart oncogenic properties to the host cells and drive malignancy growth [11-16]. Therefore, instead the driver label, it is better that tell the word of chance in some mutations in any cancer type. In other words, perhaps some of true drivers may not make the cut, while some passengers may do it accidently. In the end of this section, We must have a better understanding about the role of hematopoietic stem cells, their niche and hematopoiesis as well **(Figure 6)**. As per our knowledge HSCs provide homeostatic maintenance of the blood system through their ability to differentiate and generate the hundreds of millions of erythrocytes and leukocytes needed per day. Hence, if we try to make or produce in induced HSCs or HPCs, so there may be more than one way to reprogram cells in the hematopoietic lineage and a next understanding of HSCs biology in leukemia therapy patients. In fact, cell niches play essential roles for self-renewal and differentiation of HSCs *in vivo* and hematopoietic microenvironment show to generate functional hematopoietic stem cells. In this regard, single cell genomics describe to better analyze hematopoiesis in the microenvironment which can provide guidance for promoting HSC expansion and help to prevent hematopoietic malignancy as well. The role of hematopoietic research about single cell studies are important in last decade but we have some complex in the regenerative system. So, it is better to determine the exact role of involved molecules in clonal expansion and implication of invasion for deconstructing the molecular network including the normal situation to abnormal and malignant stem cells as well .

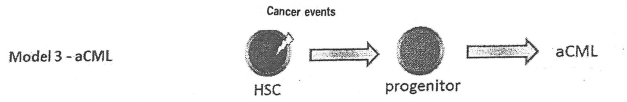

Figure 7: A model of disease origin in the process of leukemia which in my opinion may be occur.

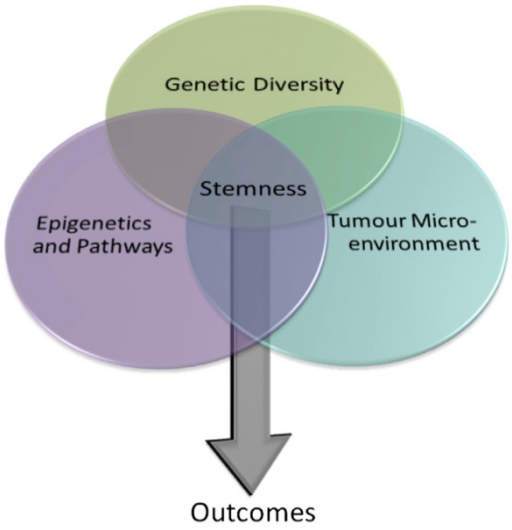

Figure 8: Stem-ness refer to the integrated functioning of molecular programs which control and maintain the stem cell state that have three fields in hamatology including cancer genetics, epigenetics and microenvironment are coming with each other to provide in determine stem-ness and in turn influence clinical outcome.

Discussion

Hence, if we try to understanding of stem-ness properties and most important cells like progenitor and precursor cells as well , so we'll be able to perceive that can drive in sequential rounds of leukemia development. In leukemia, diversity within the cells at the genetic and functional level together with their coexistence with their microenvironment, as well as tumor fitness allowing [17-23] the malignant cells to balance survival pressures imposed by treatment which probably can go to diversity in more effective therapies. On the other hand, some data showed the mutation rate in a group of malignant disease was rather low between early and late patient samples. So, the essential question is what is the result? In response, Please look at the chromosomal and genetic abnormalities respectively, in the which belong three decades ago and (**Figure 7 and 8)** that presented ten years ago, and until now , we have new rearrangement in every malignant disease. So what is our definite position concerning more and more these rearrangements which will be continued? And suppose after some years we will have the most numerical or structural aberration and genetic abnormalities as well which will have very specific role absolutely. So what will happen for our knowledge position? Regarding, in this paper, I try to discuss and perhaps solve the question. So what is the common subject between and is it a common problem in these figures? Could you please look at the and the figures carefully again as well as pay attention and understand them in the similarities and differences as well. Thus, this way may be help us to understand in essential role of HSCs in leukemia. Anyhow and in total, the results and outcomes from understanding of these figures are very important [24-26].

Conclusion

We can say, the crucial role of HSC function can be in mutation in the gene encoding membrane bound stem cell factor that presented to changes in HSC microenvironment which can go to HSC maintenance failure in the bone marrow. In the microenvironment and stem cell niche unit, HSC self-renewal, control in balance between HSCs self- renewal, their differentiation and maturation can be important as well, particularly in CML can emboss, because of in CML , we have three involved lineages includes neutrophilic series and also eosinophilic or basophilic lineages as well which create the morphology and other abnormality in this leukemia; while one aberrant gene (suppose BCR-ABL190) involved initially ina CML patient. I remind that some involved committed stem cells are in CML includes CFU-G (Colony Forming Unit-Granulocyte) CFU-eosinophil, CFU-basophil and may be CFU-megakaryocyte as well. Thus, what about the relationship between BCR-ABL fusion gene and the involved committed stem cells? What is the interpretation ofthis point, in comparison with other leukemia like ALL and in discuss about the exact role of this fusion gene and a committed stem cell which involved (CFU-lymphoid) in ALL? On the other hand, in ALL, the involved fusion gene may be BCR-ABL190 but we have involved lymphoid lineage initially. In these patients (ALL and CML), fusion genes are the same, but we have different involved lineages and two kind of the different diseases. Why? In other words, we want to explain an another problem as follows: we have two different stem cells of two separated branches completely includes CFU-lymphoid and CFU-GEMM (Granulocytic, Erythrocytic, Monocytic, Megakaryocytic). So, the BCR-ABL190 fusion gene can produce two different kind of diseases initially, with two different stem cells and the separated lineages completely, and if this fused gene is the agent of the diseases at diagnosis, so how is it possible? Hence we can say, these changes and the genetic abnormalities can help together in diagnosis and also in the following of patients in ALL and CML diseases which can the best way to solve the problems and answer the questions as well. The other question is, what is the role of single HSC in these diseases? We know concerning the central role of pluripotent stem cell in CML and lymphoid stem cell in ALL; Suppose, look at ALL prognosis. What is the difference between children and adult ALL in prognosis? We know many of ALL children can cure. Why? In response, if we look to childhood BM niche, especially in children from 2 till 10 years old, we can find the ability and power of childhood BM in re-creativity and rebuild soon in disrupted BM particularly in progenitors, precursors , blasts and the maturation cells and also the other cells in BM niche and so we can understand the important role of HSCs in childhood disease . Told all, I accept that there is a complexity of BM hematopoietic stem cell niche; in spite of all that if we see to central role of malignant stem cell with self-renewing toward capable initiating and maintaining of leukemia, so we'll go to understand the role of single HSC which HSC acquires the clonal advantage that can drive toward the aberrant HSC and also a better understanding that how can restore the balance in hematopoietic cells for restore the infrastructural of hematopoietic system including hematopoietic microenvironment, HSCs, progenitor and precursor cells and the other cells of niche. Notability of single cell analysis will permit us to know how can highly, precisely demonstrate to the role of hematopoietic cells in therapy in different hematopoietic malignancy.

References

1. Bydlowski SP (2012) Hematopoietic stem cell in acute myeloid leukemia development. In Pelayo R. Advances in hematopoietic stem cell research. In Tech Europe 261-276.
2. Martinez- Agosto JA (2007) The hematopoietic stem cell and its niche: A comparative view. Genes and Development 21: 3044-3060.
3. Delforge M, Boogaerts MA (1999) BCR/ABL- CD34+ HLA DR- progenitor cells in early chronic phase, but not in more advanced phases, of chronic myelogenous leukemia are polyclonal. Blood 93: 284-292.
4. Swaminathan S (2015) Mechanisms of clonal evolution in childhood acute lymphoblastic leukemia. Nat Immunol 16: 766-774.
5. Raynaud S, Cave H (1996) The t(12;21) translocation involving TEL and deletion of the other TEL allele: Two frequently associated alterations found in childhood ALL.
6. McLean TW, Ring old S (1996) TEL/AML1dimerizes and is associated with a favorable outcome in childhood ALL. Blood 88: 4252.
7. Lugo TG, Pendergast AM (1990) Tyrosine kinase activity and transformation potency of bcr-abl oncogene product. Science 247: 1079-1083.
8. Ferrando AA and Look AT (2000) Clinical implications of recurring chromosomal and associated molecular abnormalities in acute lymphoblastic leukemia. Seminars in Hematology 37: 381-395.
9. Mastrangelo R, Poplack D, Bleyer A (1986) Report and recommendation of the Rome workshop concerning poor-prognosis acute lymphoblastic leukemia in children: Biologic bases for staging, stratification, and treatment. Medical and Pediatric Oncology 14: 191-194.
10. Hammond D, Sather H, Nesbit M (1986) Analysis of prognostic factors in acute lymphoblastic leukemia. Medical and Pediatric Oncology 14: 124-134.
11. Lilleyman JS, Gibson BE, Stevens RF (1992) Cytomorphology of childhood lymphoblastic leukemia: A prospective study of 2000 patients. UK Medical Research Council's Working Party on Childhood Leukemia. Br J Heamatol 81: 52-57.
12. Khalidi HS, Chang KL (1999) Acute lymphoblastic leukemia. Survey of immunophenotype, FAB classification. Frequency of myeloid antigen expression, and karyotypic abnormalities in 210 pediatric and adult cases. American Journal of Clinical Pathology 111: 467-476.
13. Nucifora G, Rowley JD (1995) AML1 and the t (8;21) and t (3:21) translocations in acute and chronic myeloid leukemia. Blood 86: 1-14
14. Mullighan CG, Goorha S (2007) Genome wide analysis of genetic alterations in ALL. Nature 446: 758-764.
15. Parker H, AnQ (2008) The complex genomic profile of ETV6/ RUNX1 Positive ALL highlights a recurrent deletion of TBL1XR1. Genes Chromosomes Cancer 47: 1118-1125.
16. Mullighan CG, Miller CB (2008) BCR/ABL1 Lymphoblastic leukemia is characterized by the deletion of Ikaros. Nature 453:110-114.

17. Tsuzuki S, Karnan S (2007) Genetic abnormalities involved in t(12;21) TEL/AML1 ALL: Analysis by means of array-based comparative genomic hybridization. Cancer Sci 98: 698-706.

18. Kingston RE, Bunker CA, Imbalzano AN (1996) Repression and activation by multi protein Complexes that alter chromatin structure. Genes Dev 10: 905-920.

19. Uchida H, Zhang J, Niemer SD (1997) AML1 A and AML1 B can trans activate the human IL-3 promoter. J Immunol. 2251-2258.

20. Kitabashi I, Yokoyama A (1998) Interaction and functional cooperation of the leukemia- associated factors AML1 and P 300 in myeloid cell differentiation. EMBO J, 17: 2994-3004.

21. Takahashi A, Satake M (1995) Positive and negative regulation of granulocyte macrophage colony- Stimulating factor promoter activity by AML1 related transcription factor, PEBP2. Blood 15: 607-616.

22. Tarle SA (1993) Fusion between transcription factor CBF beta/ PEBP2 beta and a myosin heavy chain in AML. Science 261: 1041-1044.

23. Mavrothalassitis G, Ghysdael J (2000) Proteins of the ETS family with transcriptional repressor activity. Oncogene 19: 6524-6532.

24. Hutchison RE, Schexneider KI (2011) Leukocyte disorders. In Henry's Clinical Diagnosis and Management by Laboratory Methods: 22 nd edition 601-655.

25. Chilton L, Hills RK , Harrison CJ (2013) Hyperdiploidy with 49–65 chromosomes represents a heterogeneous cytogenetic subgroup of acute myeloid leukemia with differential outcome. Leukemia.

26. Matutes E, Morilla R, Morilla AM (2011) Immunophenotyping: In Dacie and Lewis Practical Hematology; Eleventh edition 353-371.