Chapter 3

Pathophysiology of Acute Lymphoblastic Leukemia

M. P. Gallegos-Arreola, C. Borjas-Gutiérrez,
G. M. Zúñiga-González, L. E. Figuera,
A. M. Puebla-Pérez and J. R. García-González

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1. Introduction

The Acute lymphoblastic leukemia (ALL), it produced as a result of a process of malignant transformation of a progenitor lymphocytic cell in the B and T lineages. In ALL, the majority of the cases, the transformation affects the B lineage cells. Leukemia and other cancers share biological characteristics, as clonality. The molecular alterations that are required for the development of a malignant disease is a rare phenomenon when one considers the large number of target cells susceptible to this condition, in other words, a single genetic change rarely be sufficient for developing a malignant tumor. This means that a small percentage of people (1%) who develop malignant hematological disease, probably only 1 cell mutated in a critical gene for the proliferation, differentiation and survival of progenitor cells. There is evidence supporting a sequential multistep process, of alterations in several oncogenes in tumor suppressor genes or microRNA genes in cancerigen cells.

Genes involved in leukemia

Most of what is known of the influence of some mutant genes of the origin of leukemia, derived from studies in molecular virology, in the gene transfection, and in the generation of leukemia in-vivo in transgenic mice. These studies are based on bacterial DNA recombinant methods. Most of the mutations in leukemia are acquired and occur in the lymphoid cell progenitor, less frequently (1% to 5% of leukemia) the mutated genes are inherited, this involved a numerical chromosome abnormality, for example: constitutive trisomy 21.

Genetic factors of acute leukemia have been extensively studied. The results of studies of gene expression analysis of high resolution whole genome, copy number alterations of DNA, loss of heterozygosity epigenetic changes and whole genome sequencing, have allowed the rec-

ognition of new genetic alterations, so that virtually all patients with ALL can be classified according to the specific genetic abnormality. This information has increased our knowledge of leukemogenesis, the prognosis and has served as the basis for the development of the target therapy. However, the understanding of how genetic alterations collaborate to induce leukemic transformation remains unclear.

The altered genes in the leukemia can be result in loss or gain of the function through several mechanisms, for example: abnormal recombination (chromosomal, translocation, inversion, insertion) loss of genetic material (deletion) gain of genetic material (duplication) point mutation and the presence additional copies of certain chromosomes as in the case of hyperdiploidy; previous alterations favoring the activation of oncogenes, this encode proteins that control cells proliferation, apoptosis or both.

The advances in the conventional cytogenetic techniques, as the fluorescence *in situ* hybridization, have shown the chromosomal rearrangements. In this sense, recently has been reported that the incidence of chromosomal change is related with the age, so the translocation t(9;22) (q34;q11) increases in each successive decade, up to 24% between the 40-to 49 years old, the t(4;11) (q21;q23) and t(1;19) (q23;q13) are rare in patients older than 60 years old, but t (8;14) (q24;q32) and t(14;18)(q32;q21) increased with age. The hiperdipoidia occurs in 13% of patients under 20 years old and only 5% of elderly patients. The hypodiploidy and complex karyotype (presence of more than 2 chromosomal abnormalities) also increase with age of 4% in the range of 15 to 19 years old to 16% older than 60 years old.

When an oncogen is activated by mutation, encoded protein is structurally modified so that enhances its transforming activity, thus remains on active status, continuously transmitting signals through the binding of tyrosine and treonina cinasa. These signals induce cell growth continued incessant. This mechanism of activation of ocogenes is more evident in others forms of leukemia, for example: severe myeloblastic leukemia and other myelodysplastic syndromes where the genes NRAS are mutated. There are mutations that suppress the function and are observe in tumor suppressor genes such as TP53, however, less than 3% of patients with ALL are TP53 mutations, although all cells have a resistance abnormal apoptosis induced by lack of significant proportion of p53, which is explained in large part by epigenetic medications.

By other hand, some authors have found alterations in the number of copies (ANCs) to 50 recurrent regions in ALL, some are really small and they have less than 1 Mb, however occur in genes encoding regulatory proteins of normal lymphoid development in 40% of cases of ALL progenitors B. The target most common are lymphoid transcription factor PAX5 that have deletions or amplifications until 30% of cases with ALL-B, also found in genes ANCs of transcription factor IKZF1 the IKZF3, EBF1, LEF1 and TCF3, RAG1 and RAG2.

Another important point, is the dihydrofolate reductase (DHFR) gene amplification has been considered as the most relevant in the ALL, this amplification produce cytogenetic abnormalities evident as the amplified of high DNA segment that included some hundreds of kilobases.

The ALL of T-cell type represents about 10% to 15% of the ALL in adults and the 25% in children and their clinical behavior is the most aggressive, the patients have a higher percentage of failure of remission induction, relapse rate is also higher, and had infiltration at central nervous

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system compared with B-cell ALL. In this sense, is known that the oncogenes and tumor suppressor genes are implicated in ALL-T are: c-MYC, NOTCH, LMO1 / 2, LYL1, TAL1 / 2, Hox11 and HOX11L2. It is clear that NOTCH activated is able to induce leukemogenesis of T cell and this is critical for the progression to ALL-T. Family members of NOTCH are transmembrane receptors that are involved in controlling the differentiation, proliferation and apoptosis in several cell types including T cells. The binding of its ligand to the extracellular domain, resulting in cleavage of the intracellular domain of NOTCH, this reaction is catalyzed by γ-secretase complex, and the intracellular domain free of translocase to the nucleus, that regulates transcription of genes regulated by NOTCH.

The NOTCH target genes are mainly cyclina D1 and c-Myc. Both NOTCH as c-MYC regulate cell cycle progression by inducing expression of cyclins and reduced expression of p27. An important aspect is that NOTCH is able to inhibit apoptosis induced by p53 allowing the tumor regression. In the development of ALL-T there is strong evidence of pro-oncogenic function of signals transduced by NOTCH, and that modulates the activity of downstream signaling pathways, through transcriptional regulation of their target genes. Is possible regulators of signaling downstream of NOTCH especially in murine models are some intermediate signaling routes as: phosphatidylinositol 3-kinase (PI3K), Akt / protein kinase B, extracellular signal-regulated kinase-1/2, and nuclear factor kB. In general, the products of oncogenes can be classified into six categories: transcription factors, chromatin remodeling, growth factors, growth factor receptors, signal transducers, and finally regulators of apoptosis. Transcription factors generally require interacting with other proteins to act, for example: Fos transcription protein dimerizes with the transcription factor Jun to form the AP1 transcription factor is really a complex, and this increases the expression of several genes control cell division, all they have been involved in the development of leukemia.

Aberrant methylation of CpG sites in promoter regions of genes has been identified in ALL cell lines, to respect it is important to note that methylation of CpG dinucleotides in position near the site of transcription initiation can silence gene expression, hypermethylation of tumor suppressor genes and hypomethylation of oncogenes can lead to various forms of cancer.

Other mechanism important in the development of the ALL is the angiogenesis and signal transducers on the binding of tyrosine kinase receptors, finally the molecules regulators of the apoptosis, where the BCL2 gene encodes for a cytoplasmic protein that is localized in the mitochondria and increases the survival of the cell by inhibiting apoptosis.

Secondary leukemias

Secondary hematological malignancies are a serious complication of cancer treatment. They usually manifest as acute leukemias and myelodysplastic syndromes. This also touch the item on secondary leukemias and its frequency is high and has increased possibly due to increasingly frequent use of genotoxic agents and by increased survival to other types of cancer. So, learn more about these could eventually help reduce its appearance. It is known that this type of leukemia may arise as a result to exposure to cytotoxic treatments (side effects of genotoxicity) and / or radiation therapy and as a result of other blood disorders; probably as a result

of environmental or genetic causes. In particular in this we will focus more on the former. In most cases it is suggested that the mechanism of leukemogenesis is associated with DNA damage of hematopoietic cells from bone marrow by agents such as those used in chemotherapy. Although the majority of secondary leukemias are acute myeloid leukemia (AML) has been reported cases of lymphoid leukemia and chronic myeloid leukemia (CML) associated with chemotherapy treatments. Finally, we intend to touch points as the classification of secondary leukemias, its relationship to chemotherapeutic agents and ionizing radiation, etiology, individual susceptibility, pathogenesis, and treatment as well as their behavior in infants and adults.

In this way one can conclude that the pathophysiology of ALL involved mechanisms genetic and environmental complex at different levels, and also have a close and complex relationship. The key features in the pathophysiology of the ALL is its monoclonal origin, uncontrolled cell proliferation by sustained self-stimulation of their receptors for growth, no response to inhibitory signals, and cellular longevity conditioned by decreased apoptosis.

Acute lymphoblastic leukemia (ALL) is the result of a process of malignant transformation of progenitor cell lineage of the B and T lymphocytes. (Pui et al, 2011) In most cases of ALL, this transformation affects B lineage cells. (Heltemes et al, 2011)

In the last 3 decades, there has been a significantly improvement in treatment outcome of ALL in children, 70% to 80% of children can get cured of their disease, a situation that is different in adults with ALL, since only 30% -35% of them may heal. (Sotk et al, 2000; Mullighan and Downing, 2009)

The required molecular alterations, for the development of malignant disease, are a rare phenomenon, when it is considered the large number of target susceptible cells to such alteration (Greaves, 2002) ie, a single genetic change is unlikely to be sufficient for the development of a malignant tumor (Croce, 2008), this means that in a very low percentage of people (1%) is developed a hematologic malignancy, only 1 cell will likely experience a mutation in a critical gene for proliferation, differentiation and survival of progenitor cells (Greaves, 2002), that`s what we mean when we mention the monoclonal origin of cancer.

It is important to mention that when we refer to the origin of cancer, in this cases ALL, reference is made to the terms: Cell Origin and Stem Cell Cancer. Actually, the concept implies that normal cells of distinct origin acquire the first mutation(s) to promote cancer, ie, that is the cell that will initiate the cancer, while the cancer stem cell will disseminate it (figure 1). (Visvader, 2011)

Malignant diseases, including acute leukemias, show a marked heterogeneity in cellular morphology, rate of proliferation, genetic lesions and, as a result, the response to treatment. The molecular mechanisms, underlying the heterogeneity of malignant neoplasia, are important points in the study of the cancer's biology. (Visvader, 2011) Above mentioned alterations may be due to somatic mutations, although alterations in the germline may predispose to familial (or hereditary) cancers. (Croce, 2008)

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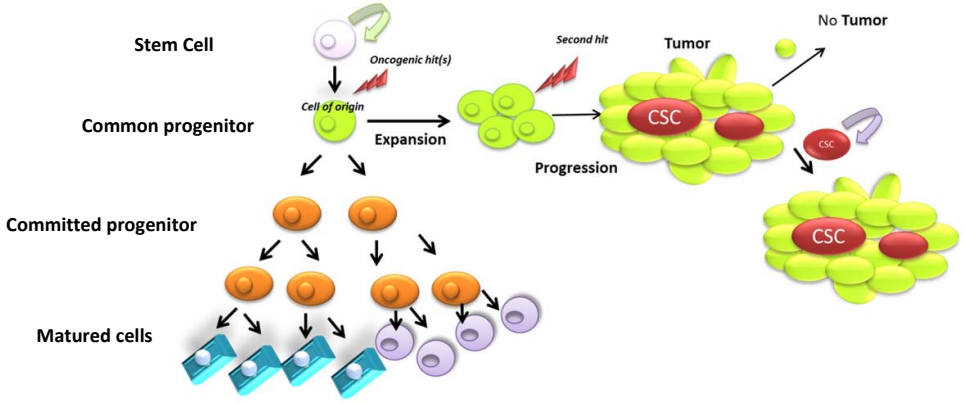

Figure 1. Cell origin and evolution of a cancer stem cell (modified of Visvader, 2011)

There is growing evidence that supports a multi-step process in leukemogenesis, ie, sequential steps and serial number of alterations in oncogenes, tumor suppressor genes, or microRNA genes in cancer cells. (Greaves, 2002; Croce, 2008) Oncogenes are dominant genes that once mutated, from a normal cellular gene (proto), encode abnormal proteins that cannot control cell proliferation, apoptosis, or both, thereby contributing to cancer development. (Pierce, 2009)

A suppressor gene normally inhibits cell division, and favors the growth of cancer when both alleles are mutated, i.e., they are recessive mutations, where the lack of function of both alleles is promoting the development of malignancy. (Pierce, 2009)

Unlike the genes involved in cancer development, microRNA genes do not encode proteins, their products are small RNA molecules (single strands of 21 to 23 nucleotides) that recognize and bind a nucleotide sequence of messenger RNA (mRNA), to the complementary microRNA sequence, and thus blocking the translation of protein from mRNA; then, their function is to regulate gene expression. (Calin et al., 2002; Croce, 2008)

2. Genes involved in the leukemias

Much of what we know about the great influence of certain mutant genes, in the origin of leukemia, is derived from mouse transgenesis studies in molecular virology, with gene transfection and the generation of leukemia *in vivo*. These studies are based on bacterial recombinant DNA methods. (Pui et al, 2011)

This knowledge has increased our understanding of leukemogenesis and prognosis, and additionally has served as foundation for the development of targeted therapy. However, the comprehension of how genetic alterations that collaborate to induce leukemic transformation is not clear yet.(Pui et al, 2011)

Most mutations in leukemia are acquired, and occur *de novo* in the lymphoid progenitor cells, less frequently (1% to 5% of leukemias) the mutated genes are inherited (vgr, p53, DNA ligase), or a numeric chromosomal abnormality is involved, for example constitutive trisomy 21. (Greaves, 2002)

Acute leukemias are the most studied malignant disorders from a genetic standpoint, the results of whole-genome studies, e.g.: gene expression analysis of high-resolution, genome-wide alterations in DNA copy number variation (CNA), loss of heterozygosity, epigenetic changes, and complete genome sequencing have favored the recognition of new genetic alterations, then virtually all patients with LLA can be classified according to the specific genetic abnormality, as shown in Figure 2, which is evident in children with ALL the high frequency of genetic abnormalities. (Mullighan et al, 2007; Pui et al, 2011)

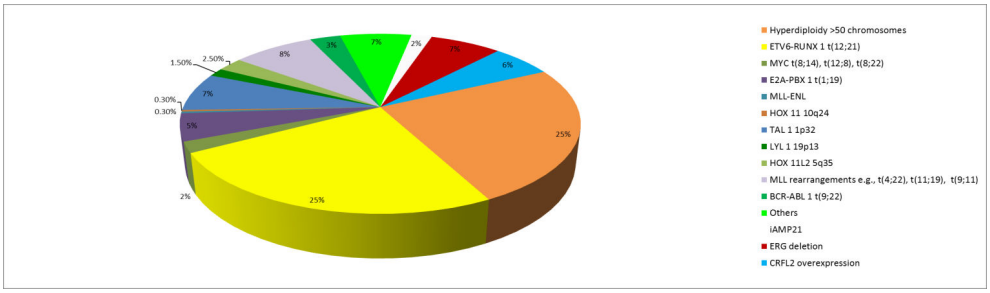

Figure 2. Frequency of genetic abnormalities in childrenwith ALL. (modified of Puiet al, 2011.)

As discussed previously, the altered genes in leukemia can result in loss or gain of function, and this is achieved through various mechanisms, for example, abnormal recombination (chromosomal translocation, inversion, or insertion), loss of genetic material (deletion), gain of genetic material (duplication), or mutation. Also can be present additional copies of certain chromosomes, as in the case of hyperdiploidy. With these chromosomal alterations, the activation of oncogenes is favored. Oncogenes can be activated by: chromosomal rearrangements, gene mutation and gene amplification. (Croce, 2008)

i. The demonstration of chromosomal rearrangements have been evidenced by improved conventional of cytogenetic study. The standard analysis can detect primary chromosomal abnormalities in more than 75% of all cases. (Liang et al, 2010)

Recently, it was reported that the incidence of chromosomal alterations is associated with age. (Moorman et al, 2010) In fact, age is a determining factor in the prognosis and treatment outcome for patients with ALL. In long term survival, the rates are close to 80% in children under 5 years of age, but will decrease to 50% or 60% in adolescents and young adults, and approximately 30% in adults of 45 to 54 years, but rarely exceed 15% in older adults. The Philadelphia chromosome (Ph) is the most common cytogenetic abnormality associated with ALL in adults. (Zuo et al, 2010; Lee et al, 2011)

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The Philadelphia chromosome positive (Ph+) ALL is a product of reciprocal translocation between the long arm of chromosome 9(q34), where the oncogene *ABL1* is located, and the long arm of chromosome 22(q11), where the *BCR* gene lies, leading to the formation of the BCR-ABL1 chimeric protein (Figure 3), and as a result of this fusion the Bcr-Abl tyrosine kinase, constitutively active, is produced, which is responsible for the acute and chronic leukemia forms. (Martinelli et al, 2009)

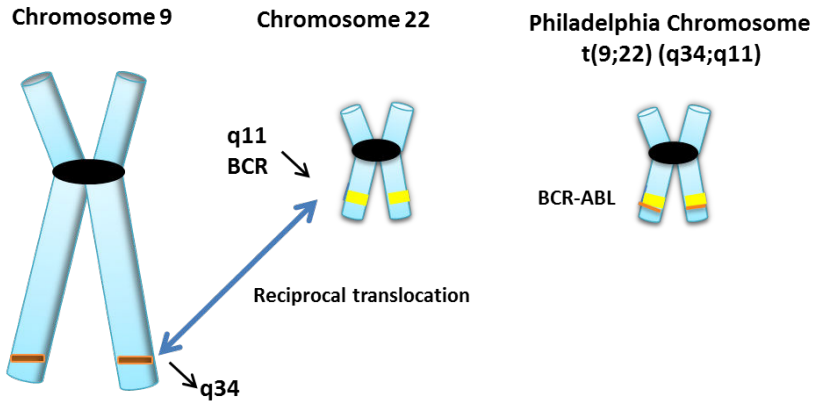

Figure 3. Philadelphia chromosome translocation (translocation between 9 and 22 chromosomes). (modified of Satter- and James, 2003)

This alteration is relatively rare (approximately 5%) in infants with ALL, but not in adults where its frequency range between 20% and 30%, it was the first known cytogenetic abnormality associated with chronic myeloid leukemia (CML) and Ph+ALL.

Despite the Ph+ ALL occurs in only about 5% of patients under 20 years of age, the incidence increases to 33% in patients over 40 years and it reaches 49% in patients over 40 years, to decrease the incidence to 35% in patients over 60 years. (Lee et al, 2011)

A significant proportion of patients with ALL Ph+ (approximately 85%), and high-risk ALL without BCR-ABL1 fusion (~28%), have *IKZF1* gene deletion, and both situations are associated with adverse prognosis. (Martinelli et al, 2009; Cazzaniga et al, 2011)

The gene *IKZF1* is located on 7p12, and encodes the transcription factor Ikaros, which is a member of the family of transcription factors containing zinc fingers (Martinelli et al, 2009). Deletion of *IKZF1* is not observed in the chronic phase of CML, but is detected in two out of three samples analyzed during the lymphoid blast crisis. (Mullighan et al, 2009) *IKZF1* genomic alterations, causing loss expression or expression of dominant negative isoforms, are critical in the pathogenesis of BCR-ABL1 ALL Ph+. (Mullighan et al, 2009)

Almost half of patients with BCR-ABL1 ALL and lymphoid blast crisis CML also harbor deletion of *CDKN2A/B and PAX5* genes; approximately 20% of these cases have deletion of the

three genes. These data support the concept that it is required the alteration of several cellular pathways to induce the development of **ALL**. It has been correlated the *ALL IKZF1* focal deletion with clinical response to treatment, overall response rate of relapse and disease-free survival; and it has also been shown that deletion of Ikaros gene represents the most important prognostic factor so far described, in ALL Ph+.(Mullighanh et al, 2009; Martinelli et al, 2009)

Other chromosomal abnormalities associated with age are the t(4;11)(q21;q23) and t(1;19)(q23;p13), that are rare in patients older than 60 years of age, but on the other way t(8;14)(q24;q32) and t(14;18)(q32;q21) increases with age. (Moorman et al, 2010)

The translocation t(4;11)(q21;q23) leads to the formation of the *MLL-AF4* fusion gene, and is responsible for more than 50% of ALL cases in children younger than 6 months in 10-20% of older infants, in approximately 2% of children and only 10% of adults with *de novo* ALL. Chromosomal abnormality in adults with ALL is considered to be of high risk. (Marchesi et al, 2011)

The gene Mixed Lineage Leukemia (*MLL*) is frequently involved in hematological malignancies, particularly acute leukemia, both lymphoblastic and myeloblastic, it is located at 11q23, and plays an important role in the positive regulation of gene expression during early embryonic development (ie it is a HOX gene) and also in hematopoiesis. (Marchesi et al, 2011)

MLL gene encodes a 500 kD protein containing several conserved functional domains, a target of proteolytic activity of Caspasa 1, a cleaving protein specialized in N-terminal fragments of 320 kD and C-terminal of 180 kD. This latter is responsible for methyltransferase activity in lysine 4 of histone H3 (H3K4), which mediates changes in chromatin associated with epigenetic transcriptional activation. (Milne et al, 2002; Hsieh et al, 2003)

The main chromosomal alterations that may occur with the *MLL* gene are mainly reciprocal translocations, causing fusion with other different genes, and partial tandem duplication of genes. (Schnittger et al, 2000)

Translocations in which *MLL* gene is involved can result in a chimeric protein, that fuses the MLL N-terminal with the C-terminal portion of the associated genes; the methyltransferase domain (SET domain) is invariably lost in the MLL fusion protein. This fusion of genes can alter normal cellular proliferation and differentiation processes, which favors leukemogenesis. (Ayton et al, 2001)

MLL gene is a target of about 104 different rearrangements, of which 64 are translocations with other genes. The proteic products of the fusions are nuclear localization signals, and play an important function as potent transcription factors. (Meyer et al, 2009)

Genes that most commonly fuses with *MLL* gene are, in order of frequency: *AF4*, *AF9*, *ENL*, *AF10*, *AF6*, *ELL*, and *AF1P*. The leukemias that express the fusion gene *MLL-AF4* are diagnosed primarily as pro-B, in pediatric and adult patients, while the fusion with genes *AF9*, *AF6*, or *AF10* are common in AML subtypes myelomonocytic or monoblastic variety. (Kohlmann et al, 2005; Moriya et al, 2012)

The t(1;19)(q23;p13) is recurrent in children and adults, and results from the fusion of gene TCF3 transcription factor 3 (E2A immunoglobulin enhancer binding factors E12/E47) locat-

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ed at 19p13.3, with gene pre-B-cell leukemia homeobox 1 (*PBX1*), located at 1q23.3, the fusion gene *TCF3 (E2A)-PBX1* encodes a chimeric protein with transforming properties. (Garg et al, 2009)

The gene encoding E2A transcription factors E12 and E47 binds enhancer elements of the gene of κ light chains of immunoglobulins, as well as some other gene regulatory elements. (Garg et al, 2009)

The transcriptional activator domain of the chimeric protein encoded by the fusion gene *E2A-PBX1* is provided by *E12/E47*, and the DNA binding domain is provided by the (HOX) Homebox *PBX1*, this protein promotes leukemogenesis by activation of several genes that are not normally expressed in lymphoid tissues. (Garg et al, 2009)

The t(12; 21)(p13, q22) is a consequence of gene fusion *ETV6/RUNX1* (also known as *TEL/AML1*) and is the hallmark of one of the most common genetic subtypes of ALL of precursor of B cells in children, in whom is the most common molecular genetic alteration occurring in 20% to 25% of pediatric cases; while in adults this translocation is rare. (Pui et al, 2011)

The current model involves several steps, the fusion of these genes can occur already during fetal development and is the initial event, but is not sufficient for the neoplastic transformation (Fuka et al, 2011). Indeed, the development of ALL of infancy B cell lineage involves (at least) 2 genetic events (hits), the first of which often arises in prenatal stage. (Thomsen et al, 2011)

The fusion gene that encodes a chimeric transcription factor, involves the N-terminus of the protein ETV6 and the most of the RUNX1 protein, it is believed that normally RUNX1 acts as a modulator of transcription; transcriptional repressor becomes the target genes *RUNX1*. (Fuka et al, 2011)

Hyperdiploidy is detected in approximately 25-30% of children with ALL precursor B cells. In these patients the clinical phenotype is usually associated with low risk and good prognosis. (Grumayer et al, 2002; Pui et al, 2011) It is interesting to mention that a hyperdiploid karyotype refers to a higher number of chromosomes than the normal diploid number (e.i., greater than 46 chromosomes), but having a *chromosome* number that is not a *multiple of the haploid number* (23 chromosomes), the modal number can be located between 47-57 chromosomes (Shaffer et al, 2009). This karyotype arises through a simultaneous gain of multiple chromosomes, from a diploid karyotype, during a single abnormal cell division. (Grumayer et al, 2002)

The hyperdiploidy occurs in 13% of young adults, and only 5% of elderly patients. The hypodiploidy and complex karyotype (presence of more than 2 chromosomal abnormalities) also increase with age, from 4% in the range of 15 to 29 years of age and 16% older than 60 years. (Moorman et al, 2010)

ii. When an oncogene is activated by mutation, the encoded protein is structurally modified in such a way that increases their transforming activity, ie, remains in the active state, continuously transmitting signals by binding of tyrosine and threonine kinase. These signals induce cell growth continued incessant. This mechanism of activation of oncogenes is more evident in other forms of leukemia, for example, AML and myelodysplastic syndromes (MDS) where the *NRAS* gene is mutated. There are

mutations that suppress the function, and it is observed in tumor suppressor genes such as *TP53*, however, less than 3% of patients with ALL have *TP53* mutations, although all the cells have abnormal resistance to apoptosis induced by lack of a significant proportion of p53, which is explained in large part by epigenetic. (Zornoza et al, 2011)

On the other hand, some authors have found change in the number of copies (CNVs) to 50 regions in ALL recurring, some are very small and have less than 1 Mb, however, occur in genes encoding regulatory proteins of normal lymphoid development up to 40% of cases of ALL stem B. The most common targets are lymphoid transcription factor PAX5, that can hold deletions or amplifications in up to 30% of cases of ALL-B, also found CNVs in transcription factor genes IKZF1, the IKZF3, EBF1 (factor Cell B early), LEF1 and TCF3, and RAG1 and RAG2 genes. (Mullighan et al, 2009)

iii. The most relevant gene amplification in LLA is the dihydrofolatereductase (*DHFR*). The amplification of this gene causes evident cytogenetic alterations because the amplified DNA segment may involve several hundred kilobases. (Croce, 2008)

A variety of acute leukemia to consider is the T-cell ALL (ALL-T), it represents about 10% to 15% of ALL in adults and 25% of children. The clinical behavior is more aggressive, patients have a higher percentage of failure of remission, relapse rate is also higher as well, and the central nervous system infiltration compared with B-cell ALL type. (Demarest et al, 2011)

Oncogenes and tumor suppressor genes that have been implicated in T-ALL are: *c-MYC, NOTCH, LMO1 / 2, LYL1, TAL1 / 2, Hox11* and *HOX11L2*. It is clear that activated Notch is able to induce T cell leukemogenesis and is critical for the progression to T-ALL. (Demarest et al, 2008)

Members of the NOTCH family are transmembrane receptors that are critically involved in controlling the differentiation, proliferation and apoptosis in several cell types including T cells. The Notch receptor binding to its ligand exhibits a cleavage site for extracellular ADAM metalloproteinase, and a cleavage site in the transmembrane region for the γ-secretase, thus releasing the intracellular domain of Notch, which transmits this signaling to the cell nucleus, where it is associated with a DNA-binding complex. (Palomero et al, 2006; Chan et al, 2007; Sanda et al, 2010; Gomez et al, 2012)

Notch signaling cooperates with the signaling of T cell receptors (TCR) to expand the number of thymocytes undergoing β-selection. Over 50% of T-cell ALL have activating mutations in Notch1. (Gomez et al, 2012)

NOTCH target genes are mainly cyclin D1 and c-Myc. Both Notch and c-Myc regulates cell cycle progression by inducing expression of cyclins and reduced expression of *p27*. An important aspect to point out is that Notch is able to inhibit apoptosis induced by p53. When Notch expression is suppressed, the p53 pathway is activated and leads to tumor regression. (Demarest et al, 2008; Sanda et al, 2010)

An important aspect of Notch, is that depending on the type of cells, the extracellular environment, and the intensity of the signal, Notch can transmit signals as pro-oncogenic or

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tumor suppressor (Leong and Karsan, 2006). In the development of T-ALL there is strong evidence of pro-oncogenic function of signals transduced by Notch, and that modulates the activity of downstream signaling pathways, through transcriptional regulation of its target genes. (Chan et al, 2007)

Possible regulators of signaling downstream of Notch, especially in murine models, are some intermediate signaling pathways, such as phosphatidylinositol 3-kinase (PI3K), Akt /protein kinase B, extracellular signal-regulated kinase-1/2, and nuclear factor kB. (Chan et al, 2007)

In general, the products of oncogenes can be classified as described below:

1. **Transcription factors:** They generally require interacting with other proteins to act, for example: Fos transcription protein dimerizes with the transcription factor Jun to form the AP1 transcription factor which is a complex, and this increases the expression of several genes control cell division.

2. **Chromatin remodeling:** It plays an important role in the degree of compaction of chromatin and therefore in the control of gene expression, replication and chromosome segregation, by the action of two types of enzymes: the ATP-dependent enzymes, which have important role in changing the position of histones, and enzymes that modify N-terminal tails of histones. (Peterson and Workman, 2000)

   Indeed, the epigenetic code is made by the pattern of histone modification, and determines in this way the interaction between nucleosomes and chromatin-associated proteins, thereby determining its transcriptional capacity. (Croce, 2008)

   On this basis it is important to note that methylation of CpG-dinucleotides in position near the site of transcription initiation can silence gene expression, hypermethylation of tumor suppressor genes and hypomethylation of oncogenes can lead to various forms of cancer. Aberrant methylation of CpG sites in promoter regions of genes has been identified in ALL cell lines. (Milani et al, 2009)

   In this way it has been found some improperly methylated genes that are involved in the p53 pathway suggesting that despite not having an activating mutation of this gene in ALL, there is an abnormal function of p53 mediated by epigenetic mechanisms. In fact, hypermethylation of genes involved in the TP53 pathway is an independent poor prognostic factor in patients with ALL. (Zornoza et al, 2011)

3. **Growth factor receptors:** They are altered in many cancers. A deletion of the ligand binding domain causes constitutive receptor activation in the absence of ligand binding sites of interaction by providing cytoplasmic proteins containing the SRC homology domain binding and other domains, this way deregulates multiple signaling pathways. Vascular endothelial growth factor (VEGF) regulates hypoxia-dependent control of gene transcription. VEGF activity is mediated by three tyrosine kinase receptors: VEGFR1 (FLT1), VEGFR2 (Flk1-KDR) and VEGFR3 (FLT4).

   The importance of angiogenesis and signaling pathways related to angiogenesis in the growth and expansion of cells in acute leukemia has been well established. *In vitro* in the

leukemic cell, activation of VEGFR1 (FLT1) promotes cell migration and proliferation, whereas in vivo cells overexpressing FLT-1It accumulate in the bone marrow.

At the same time, the FLT-1 neutralization affects leukemia cell location (now in the bone marrow of the diaphysis), increased apoptosis, and prevents their departure to other tissues, which prolongs survival of mice inoculated. (Fragoso et al, 2006)

4. **Signal transducers:** They on the binding of receptor tyrosine kinases, to appropriate ligand receptor, lead to reorganization and autophosphorylation of tyrosine in the intracellular portion of the molecules, this increases the activity of the receptor or receptor interaction promotes intracytoplasmic domain with other proteins such as with the SRC homology domains. (Croce, 2008)
5. **Regulators of apoptosis:**Regulators that finally lead to apoptosis, where the *BCL2* gene encodes for a cytoplasmic protein that is localized in the mitochondria and increases the survival of the cell by inhibiting apoptosis.

Cytogenetics in acute lymphoblastic leukemia

The cytogenetic studies of human neoplasia began in 1960 with the discovery by Nowell and Hungerford of the Philadelphia chromosome in individuals with chronic myelogenous leukemia. Thirteen years after, Rowley performed chromosomal banding techniques and defined the origin of the Philadelphia chromosome as the result of the chromosomal translocation t(9;22)(q34;q11). (Mitelman et al, 2007; Croce, 2008; Pui et al, 2011; Dowing et al, 2012) These findings established the beginning for the cytogenetic studies of many solid and hematologic tumors. Currently, it has been consolidated a public database (Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer) containing 61,846 reported cases of cytogenetic studies and 975 different gene fusions in diverse human tumors. (Mitelman et al, 2012)

The ALL is the most common malignancy in pediatric population with a frequency of 19.7%. It is markedly different from the frequency observed in adults (1.2%). In both groups, the commitment of B-cell lineage is most frequent than the T-cell lineage. The variety of chromosomal abnormalities observed during the malignant development is also different between pediatric and adult ALL. The chromosomal abnormalities most frequent in pediatric ALL are the t(12;21)(p13;q22) with the *ETV6-RUNX1* gene fusion (21%) and hiperdiploidy of >50 chromosomes (19%). In adult ALL the most recurrent chromosomal abnormalities are the t(9;22)(q34;q11) with the *BCR-ABL1* gene fusion (25%) and *MLL* (11q23) gene fusions (10%). (Dowing et al, 2012)

The chromosomal translocation t(9;22) fuses the tyrosine kinase *ABL1* (*v-abl Abelson murine leukemia viral oncogene homolog 1*) gene located on 9q34 band with the *BCR* (*Breakpoint Cluster Region*) gene situated on 22q11 band raising the *5′-BCR/ABL1*-3′ gene fusion. Various forms of this hybrid gene are generated depending on the breakpoint at BCR gene occurred. The e13a2 and e14a2 BCR/ABL1 transcripts code for a 210 KD protein and the e19a2 produces a 230 KD protein. These isoforms are related mainly to CML. The e1a2 transcript codes for a 190 KD protein which is mostly related to ALL and a trend towards poor-

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er therapy outcome. Currently, BCR/ABL1 expressing cells can be selectively killed with the Imatinib (or STI571, imatinib mesylate, Gleevec or Glivec; Novartis) which inhibits the excessive tyrosine kinase activity of the hybrid protein. Most of the patients achieve complete remission with this approach; however, sometimes relapse occurs mainly by mutations in the *ABL1* segment that render resistance to the Imatinib. (Mitelman et al, 2007; Croce, 2008; Pui et al, 2011; Dowing et al, 2012)

During the progression of the disease multiple genetic alterations accumulate over time being selected by their potential to give fitness advantage to the new clones. Irrespective which is the primary change, the most frequent secondary numerical chromosomal changes in ALL are +X, +6, -7, +8, and +21; whereas, the most recurrent secondary structural aberrations are dup(1q), i(7q)(q10), and der(22)t(9;22). (Johansson et al, 1994)

Leukemia and immunity

Although little is known about the etiology of leukemia, this has a multifactorial behavior with risk factors that may contribute to its development such as ionizing radiation, chemotherapy and chromosomal abnormalities. (Han et al, 2010) By other hand, there are three hypotheses one called delayed infection, the second population mixing and the third hygiene hypothesis, (Strachan, 1989; Kinlen, 1995; Greaves, 2006) the first two suggest that the immune system deficiency in an early stage of development can cause an abnormal immune response to infections which may arise in the development of human beings. Both hypotheses are similar to third called hygiene hypothesis, which explains an increase in allergies in Western populations. (Chang et al, 2010) Although most studies support to infections and immune system factors in the etiology of ALL, little is known about the role of genes in this etiology. The relation of immune system in the ALL is a complex process that involves the interaction of many cells that including leukocytes, epithelial barriers, complement proteins, colexinas, pentraxins, cytokines (TNF, IL-1, chemokines, IL-2, IFN type I, IFN etc.), Th1, Th2, Treg and Th17 cells, CD28, FCGR2, GATA3, STAT4, STAT6 and may other. (Chang et al, 2010) Variations in the genes of these cells can affect their development and function in the immune response and therefore it may increase susceptibility to developing ALL. (Han et al, 2010; Chang et al, 2010) Moreover it was found that the CD47 molecule protects the macrophage leukemic clones to bind to a molecule on the surface of these cells. The interaction between macrophages and leukemic cells inhibits macrophage specific action which allows the cancer cell to proliferate. So that although the macrophage plays an important role in the destruction of cancer cells, leukemic cells with greater metabolic potential, and the potential escapes annihilating the macrophage. (Tesniere et al, 2008; Jaiswal et al, 2009) In the innate immune system, macrophages and other immune cells involved in immune surveillance protect the body permanently cell rate unexpectedly mutates. In contrast, the adaptive immune system through T and B cells upon activation attempt to destroy leukemic cells; however these also evade cellular immunity. It has been shown that the human genome sequencing is useful to identify oncogenic mutations useful in predicting the diagnosis, prognosis and therapeutic choice. What has provided important insights into the pathogenesis of leukemias. (Kalender et al, 2012)

Polymorphisms environmental in leukemia

Although the clinical and biological aspects of the ALL are well documented, little is known about individual susceptibility. Polymorphic variants of several genes, diet, environmental exposure to carcinogens and individualities of immune system are potential factors that could be increase predisposition to leukemia. (Buffleret al., 2005) However some speculation exist about the mechanism of the potential agents carcinogenic that could cause such alterations to ALL origin.(Smith, 1996; Kamdar et al., 2011)

Polymorphisms in the via of folate metabolism

The genetic regulation of folate metabolism have been the focus of many investigations that may influence in the preleukemic clone origin, by the via DNA hypomethylation of key regulatory genes, as well as uracil misincorporation into DNA leading to double-strand breaks and chromosomal aberrations.(Kamdar et al., 2011) The presence of some polymorphisms in genes involved in folate metabolism (*MTHFR, MTR, CBS, SHMT1* and *TYMS*) may cause deficiency in the enzyme activity and lead to inadequate folate metabolism and hypomethylation of DNA, which may lead to a neoplastic process. (Sharp and Little, 2004; Kamdar et al., 2011) The insufficient input of folate produces elevated plasma concentration of Homocysteine (Hcy) and adenosylmethionine (SAM) elevation, so that SAM is inhibitor methyltransferase enzyme. (Sharp et al., 2004) This inhibition may alter both, the DNA methylation process, and the regulation of gene expression. (Sharpand Little, 2004; Lightfoot et al., 2010) The hypomethylation is associated with activation of oncogenes and neoplastic processes, whereas the hypermethylation of CpG islands in promoter regions, of some tumor suppressor genes, prevents the transcription and promotes the development of tumors. (Das and Singal, 2004) (figure 4) Associations studies have been developed to identify genetic variants associated with ALL susceptibility, among them are: methylenetetrahydrofolatereductase (MTHFR), an enzyme that participates in Hcy and folate metabolism, plays an important role in DNA methylation and provision of nucleotides for DNA synthesis. (Robien and Ulrich, 2003)

Variations in the MTHFR gene sequence may result in enzymatic deficiency, low plasma folate levels and hyperhomocysteinemia, a risk factor for many diseases as: coronary diseases, neural tube defects, cancer, and leukemia, among others. (Lordelo et al, 2011) Association studies have been described between C677T and A1298C MTHFR polymorphisms and risk of leukemia (Skibola et al, 1999; Franco et al., 2001; Robien and Ulrich, 2003; Gallegos et al, 2008), which produces an decreased catalytic activity of MTHFR and subsequent availability of 5,10-MeTHF and SAM, have been extensively studied in relation to childhood leukemia, these findings have been inconsistent and their frequency vary among ethnic groups.(Robien and Ulrich, 2003)

Methionine synthase (MTR): Other studied polymorphisms, in association with ALL, are the missense polymorphism MTR c.2756A>G (D919G), that has been reported that alter the susceptibility to various cancers, (Linnebank et al, 2004; Yu et al, 2010) however the results have been contradictories. MTR is a vitamin B12-dependent enzyme, which catalyzes the remethylation of Hcy to methionine and the demethylation of 5-meTHF to THF, and has influence on DNA methylation, as well as on nucleic acid synthesis (Greene, 2010) (figure 4). A meta-analysis including 24896 cancer patients and 33862 controls, from 52 published papers, for MTR

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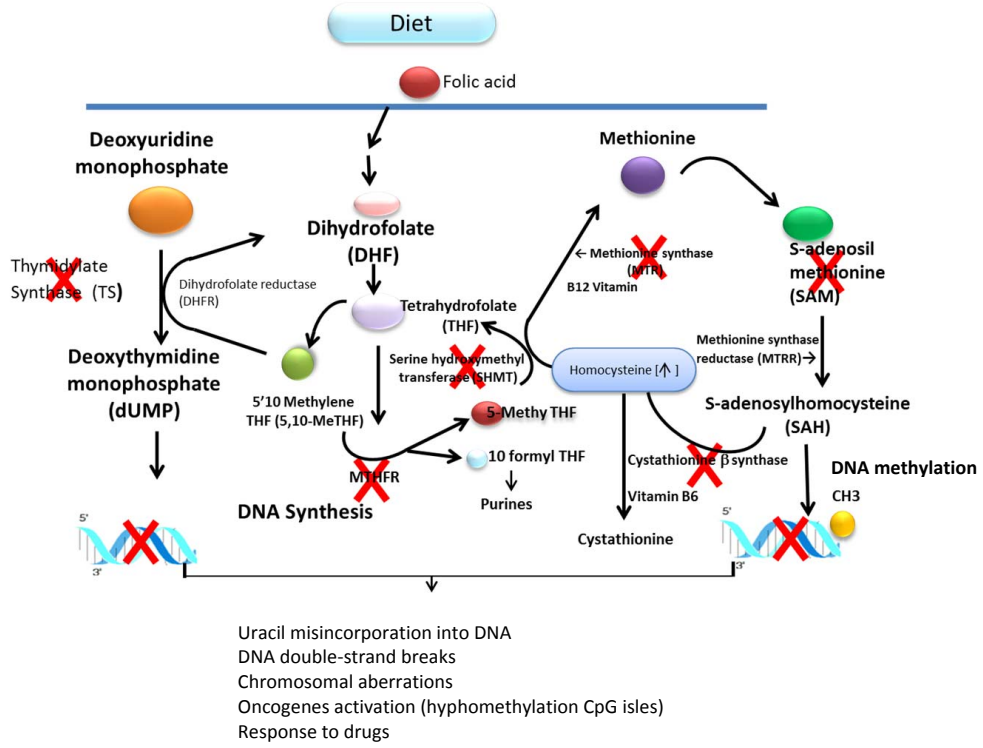

Figure 4. Polymorphisms (MTHFR, CBS and TS) of the via of folate in the development of ALL

A2756G was reviewed. Overall, individuals carrying MTR 2756GG genotype had a reduced cancer risk, under a recessive genetic model, in European populations. However, in Asian populations, it has a significantly high association. In stratified studies by tumor site, there was a *statistically significant* reduced risk with ALL. (Yu et al, 2010)

Cystathionine-β-synthase (*CBS*; gene localized to 21q22.3), the polymorphism most studied with leukemia are T833C, that co-segregates with 844ins68, and the G919A. (Ge et al, 2011) The frequencies of these polymorphisms are variable depending of the studied populations. The CBS participate in the trans-sulfuration pathway, catalyzes the condensation of serine and Hcy to form cystathionine, an intermediate step in the synthesis of cysteine. (figure 4) The 844ins68 polymorphism was associated in Down Syndrome (DS) with leukemia myeloblasts, detecting a 4.6-fold higher rate ($P < 0.001$) when compared to non-DS individuals. (Ge et al, 2011) The biological function of this polymorphism is even contradictory, it has been demonstrated that carriers of 844ins68 have significantly lower total plasma Hcy levels, after a methionine load, and concluded that this polymorphism was associated with higher CBS enzyme activities. (Ge et al, 2011)

Serine Hydroxymethyltransferase 1 (SHMT1)

Cytosolic SHMT1 regulates 5,10-MeTHF,that acts as substrate for MTHFR. The 1420C>T polymorphism of this gene reduces circulating folate levels, and may mimic folate deficiency, consequently shunting 5,10-MeTHF towards DNA synthesis, and have been shown that moderate the risk of hematological malignancies. (Lightfoot et al, 2005) Folate is a component important in the development of the embryogenesis and early fetal development, via its effects on DNA methylation and synthesis. Then, the well-documented in utero origin of ALL has led to hypothesize that deficient folate intake may be important in its etiology. (Lightfoot et al, 2005; de Jonge et al, 2009)

Thymidylate Synthase (TYMS)

Thymidylate synthase (TS) has been shown to moderate the risk of hematological malignancies. (Valiket al, 2004; Lightfoot et al, 2005) Although, it has been proposed that arise by genetics and environmental factors. (Krajinovic et al, 2004) Consistent with this paradigm, variants of genes involved in xenobiotic metabolism, DNA repair pathway and cell cycle checkpoint functions, have been shown to influence the susceptibility to ALL. (Pui, 2009) Many enzymes are involved in the folate metabolism, among which, thymidylate synthase (TS) is a crucial enzyme and hence a good candidate for studying the effect of polymorphisms in the folate metabolism gene, on the development of malignancies. TS, encoded by the *TS,* gene located on chromosome 18p11.32, plays a vital role in maintaining a balanced supply of deoxynucleotides, required for DNA synthesis and repair, by catalyzing the conversion of dUMP to dTMP. (Nazki et al, 2012)

The polymorphisms in *TYMS* gene include a 6-bp deletion (1494del6), in the 3′-untranslated region of *TS* that influences RNA levels; and a polymorphic tandem 28-bp repeat sequence within the promoter enhancer region of *TS*, where the triple repeat increases gene expression levels and reduces DNA damage. In fact, it is thought that the input of deoxynucleotides for DNA synthesis is controlled by TYMS, which has a polymorphic tandem repeat sequence within the promoter enhancer region containing a double (2R)or triple (3R) 28–bp repeat. The presence of the triple repeat leads to increased levels of gene expression and a reduction in DNA damage. (Skibola et al, 2004; Lightfoot et al, 2010) Methotrexate, an antifolic acid agent, has demonstrated to be an effective chemotherapeutic drug for the treatment of lymphoid malignancies, indicating an association between the folate metabolism and the development of such malignancies. (Hishidaet al, 2003) This increased expression may, in turn, increase the conversion of dUMP to dTMP, thereby; decreasing uracil levels and the consequent erroneous incorporation of uracil into DNA of rapidly dividing hematopoietic stem cells, and could work protectively against the development of ALL. (Skibola et al, 2004) The TS 28-bp repeat polymorphism has been shown to modulate the risk of ALL in various populations, but the obtained results are controversial and require further investigation to be confirmed and clarified. (Skibola et al, 2004; deJonge et al, 2009)

Polymorphisms in the xenobiotics metabolism

An ability that man has acquired in the course of evolution is the way to metabolize foreign compounds for the body to facilitate disposal. These compounds are called xenobiotics, in food

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and the environment are mostly lipophilic, so it tends to accumulate in lipophilic environments the body and are difficult to remove so they tend to trigger toxicity phenomena. (Gonzalez and Gelboin, 1994) The liver removes lipophilic xenobiotics, through a set of known reactions of biotransformation. The end result is the formation of metabolites less lipophilic and more soluble, which are easily eliminated in the urine or bile compounds. That is why these reactions are known as detoxification or deactivation. (DeAnn, 1998) In this sense, drugs are a class of compounds that are absorbed xenobiotics on the body and distributed in body fluids, tissue and organ. Where exert their pharmacological action and pharmacodynamics specified; only a small part reaches the tissue-receptor-target enzyme, while most are metabolized and eliminated. (Sheweita, 2000) Moreover, the processes of biotransformation of xenobiotics are subdivided into two phases: phase I metabolism, carried out by two families of enzymes oxygenases: those dependent on cytochrome P450 (CYP450) monooxygenases and the flavin (FMO). Their metabolism is characterized by the action of chemical processes of different nature mainly oxidation, oxygenation, reduction and hydrolysis, so as dealquilations and dehalogenations. These chemical reactions produce metabolites capable of binding covalently to endogenous molecules such as glucuronic acids, glutathione, sulfate and amino acids that generate conjugates, which are metabolized by Phase II which is characterized by solubility in generating molecules and decreased toxicity, generated by the modification of new functional groups, which transform the more polar metabolite, which facilitates their removal. In this regard, when a drug enters the body usually is modified by conjugation reactions to be easily removed. However, when there modifications in the concentrations concentration (high or low) of enzymes that perform the conjugation process and if the xenobiotic is lipophilic nature, tends to accumulate in the cell, which will lead to different processes: 1) accumulation of reactive metabolites adduct forming with DNA, 2) formation of a toxic compound 3) a nontoxic compound becomes a toxic derivative. This generates secondary metabolic pathways may have a carcinogenic action, toxicological, genotoxic or mutagenic in the body. (Marmiroli and Maestri, 2008) Different studies in the literature have suggested the association of polymorphisms in genes involved in xenobiotic metabolism phase I and II in patients with leukemia. (Aydin et al, 2006; Gallegos et al,2008, Lordelo et al, 2011)

Secondary leukemias

Secondary hematological malignancies represent a serious complication of cancer treatment. Usually manifiest as acute leukemia and MDS, and known more about these could eventually help reduce its appearance (Levine and Blomifield, 1992). It is known that this type of leukemias may arise as a result of exposure to cytotoxic treatments (with genotoxicity secondary effects) and/or radiotherapy (RT) and as a result of other hematological disorders (Harris et al, 1999; Brunning et al, 2001), and possibly also, product of environment or genetic causes. (Levine and Blomifield, 1992) In most cases it is proposed that the mechanism of leukemogenesis is associated with DNA damage in hematopoietic cells of the bone marrow by agents such as those used in chemotherapy (CT). (Levine and Blomifield, 1992) Although most secondary leukemias are acute AML, there have been reports of lymphoid leukemia and CML is associated with CT. (Andersen et al, 2000; Krishnan et al, 2000; Pedersen-Bjergaard et al, 2002)

The AML are hematologic malignancies characterized by the uncontrolled myeloid blast proliferation in the bone marrow and in peripheral tissues. (Sevilla et al, 2002) Differ according to the cytological, immunophenotypic and cytogenetic characteristics. (Paietta, 1995; Head, 1996) On the other hand the MDS are dis-hematopoietics processes of bone marrow, characterized by alteration in the maturation and differentiation of hematopoietic cell lines (with involvement of one, two or all three blood cell lineages) and in some cases, by the presence of bone marrow blasts, without showing acute leukemia criteria. (Bennet et al, 1982; Cheson, 1997)

The term secondary leukemia has referred to the development of AML as result of CT treatment, particularly alkylating agents (Levine and Blomifield, 1992) or topoisomerase II inhibitors, RT, or by exposure to environmental carcinogens (Harris et al, 1999; Brunning et al, 2001). Within the term of secondary acute leukemias (SAL) different entities are grouped by etiopathogenesis, prognosis and response to therapy. In general can be distinguished two groups: those that are a result of exposure to cytotoxic treatments such as CT and/or RT and those that are a result of the final evolution of other hematological disorders, such as, myeloproliferative syndromes, MDS, paroxysmal nocturnal hemoglobinuria. (Harris et al, 1999; Brunning et al, 2001)

In close relationship with these two groups of SAL also found leukemias result from environmental or occupational exposure to carcinogens, (Levine and Blomifield, 1992) or those that develop in patients with genetic disorders as chromosomal fragility syndromes such as Fanconi anemia and Bloom syndrome (Popp and Bohlander, 2010)

The increase is due to the increased number of survivors of other forms of cancer, (Ng et al, 2000) is important to know more about SAL, especially AML or MDS relating to previous therapies (AML-PT, MDS-PT). The cumulative risk of developing AML-PT/MDS-PT after ten years of receiving CT for breast cancer, non-Hodgkin´s lymphoma, ovarian cancer or Hodgkin ´s disease, has been estimated at 1.5, 7.9, 8.5, and 3.8% respectively. (Bolufer et al, 2006) Moreover, generally the cases of AML-PT/MDS-PT, the primary disease may be a solid tumor, other haematological malignancy or non-malignant disorder.

Today it is clear that AML-PT/MDS-PT can develop after exposure to cytotoxic CT with alkylating agents, topoisomerase II inhibitors, and/or RT, for the treatment of other neoplasias or in treating non-malignant disorders. In this sense, has been described after the use of immunosuppressants such as azathioprine (Harris et al, 1999; Brunning et al, 2001). While the study of these entities has been important, the maximum latency between exposure to leukemogenic agent and the development of AML-PT/MDS-PT has not been established with certainty.

Due to history of exposure to certain agents and the association with some cytogenetic abnormalities characteristic, two groups are recognized in AML-PT/MDS-PT: (Harris et al, 1999; Brunning et al, 2001)

Which appears as a result of the mutagenic effect of alkylating agents treatment, ionizing radiation or both, that occur after a long latency period between 5 to 7 years of exposure to cytotoxic agents and often show a phase of myelodysplasia prior to the evolution to AL, and often show a phase of myelodysplasia prior to the evolution to AL, which often produce al-

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terations of chromosomes 5 and 7, (-5/5q- and -7/7q-) frequently refractory to treatment. (Andersen and Pedersen, 2000)

Those in patients treated with drugs that inhibit DNA-topoisomerase II as epipodophyllotoxins and anthracyclines, with a short latency period of between 2 to 3 years, without prior myelodysplasia phase and in which observed balanced translocations as 11q23 (MLL) and 21q22 (AML1/RUNX1), although there are some discrepancies. The treatment response is not significantly different from those of patients with *de novo* AML. (Penderse, 2002)

Leukemias have been associated with exposure to various agents as benzene and its metabolites (phenol, hydroquinone), environmental carcinogens demonstrated relationship to increased risk of developing leukemia. (Lan et al, 2004) Other compounds studied with controversial relationship, are some agricultural pesticides, heavy metals, smoke snuff, alcohol intake and exposure to cosmic rays of airlines pilots. (Larson, 2007) Ionizing radiation is a known leukemogenic agent and the main action mechanism includes the breakage of the DNA strands which can cause the aforementioned chromosomal deletions and translocations. Breaks may result from a direct effect of high doses of radiation or indirectly by free radicals generation. Furthermore, ionizing radiation can induce changes of bases in the DNA sequences, crosslinking strands, multiple damages or epigenetic alterations (Finch, 2007). In the case of RT, induced leukemia seems to start in the first 5 years after exposure, peaks at 10 years and decreases significantly after 15 years. The relative incidence of leukemias by RT is dose dependent, duration of exposure, and area of exposed bone marrow. (Finch, 2007) Fractionated doses of radiation are less leukemogenic than higher single doses, because it allows greater efficiency of DNA repair mechanisms. The leukemogenic risk appears to be greater when low-dose exposure affects large areas of bone marrow, whereas high doses of radiation over limited areas appear to have less effect. This is attributed to increased apoptosis induced by high doses of radiation on cells exposed. (Inskip, 1999; Smith et al, 2002) Estimates show, that patients undergoing RT for the treatment of malignancies or other non-malignant diseases has a risk of two to three times more to develop AML-PT/MDS-PT. (Smith et al, 2002) On the other hand, a younger ages at the time of exposure, greater the leukemogenic risk. The increased risk for developing AML-PT/MDS-PT, after treatment of non Hodkin lymphomas, breast cancer, cervical cancer and uterine body and Ewing's sarcoma, is attributed to the use of RT, while associated with Hodgkin's disease, ovarian cancer and testicular cancer, has been associated with the use of CT. (Levine and Blomifield, 1992; van Leeuwen et al, 1994; Inskip, 1999; Smith et al, 2002)

Many drugs used as CT in the treatment of a primary cancer, have been linked to the subsequent development of AML-PT/MDS-PT, thus, alkylating agents were the first to be evidenced leukemogenic potential, (Pedersen, 2002) effect related to the cumulative dose of the drug, the effect being greater with increasing patient age (Pedersen, 2002). All alkylating agents have effect leukemogenic, such is the case of drugs such as mechlorethamine, procarbazine, chlorambucil, cyclophosphamide, melphalan, semustine, lomustine, carmustine, prednimustine, busulfan. However, although the relative risk leukemogenic of these drugs has not been definitively established, drugs such melphalan and busulfan seem to condition an increased riesk than others as cyclophosphamide for reason which are unknown. (Stott et al, 1977; Greene et

al, 1986; Krishnan et al, 2000) Although, this seems to suggest that more genotoxic and cytotoxic drugs are chosen that have less leukemogenic potential. Alkylating agents besides the aforementioned chromosomal damage can cause point mutations in some oncogenes like RAS. (Pedersen et al, 1988) However, these effects are no restricted to certain genes or chromosomal regions and possibly the selection of cells with abnormalities of chromosomes 5 and 7 come conditioned by a proliferative advantage to cells carrying these alterations. (Johansson et al, 1991; de Greef and Hagemeiger, 1996; Andersen et al, 2000)

Meanwhile, drugs that act by inhibiting topoisomerase II, as the epipodophyllotoxins (etoposide and teniposide) (et al, 1999) and intercalating agents such as anthracyclines (doxorubicin, daunorubicin, idarubicin) o las anthracenediones (mitoxantrone), have been associated with balanced translocations that originates function genes. The most common affect 11q23, 21q22, inv(16) and t(15;17) (Andersen et al, 1998; Rowley and Olney, 2002). Recently high-dose CT followed by autologous hematopoietic transplantation, have been associated with the development of AML-PT/MDS-PT, with time of onset of 47-50 months after transplantation. (Nademanee et al, 1995; Traweek et al, 1996; Krishnan et al, 2000; Pedersen et al, 2000; Gilliland and Gribben, 2002)

An important point to consider is individual susceptibility, since only a minority of patients develop secondary leukemia after exposure to CT, therefore it is suggested that differences in drug metabolism may predispose to the development of AML-PT/MDS-PT of some patients. (Bolufer et al, 2006) In this way, polymorphisms of genes encoding enzymes involved in drug metabolism could contribute to the risk of developing these pathologies. These genes could explain differences in metabolizing of these agents and condition a lower detoxification capacity or repair of genetic damage induced by the drug. (Bolufer et al, 2006) Genes have been studied encoding cytochrome P450 (CYPs) related to phase I metabolism, glutathione S-methyltransferase (GSTT1, GSTM1, GSTP1) involved in phase II metabolism (conjugation/detoxification), the NAD(P)H: qinone oxo-reductase 1 (NQO1) which acts on the metabolism of free radicals and oxidative stress, genes related to folate metabolism (MTHFR, TYMS, SHMT1, MTRR), also involved in DNA synthesis and genes related to DNA repair (hMLH1, hMSH2, hMSH3, RAD51, XRCC1, XRCC3, XPD, XPG, CHEK2, and ATM) that can cause genomic instability. (Bolufer et al, 2006)

The AML-PT/MDS-PT pathogenesis includes clonal alterations in the some genes function due to single mutations, chromosomal abnormalities or epigenetic phenomena. Many of the altered genes are tumor suppressor that have a recessive character and therefore, requires the loss of both alleles. The loss of a single copy of the gene can result in reduction of gene products and predispose to malignancy. Current evidence indicates that AML results from at least two mutations classes. The class I, confers proliferative advantage and/or cell survival without affecting their differentiation capacity, while the class II, prevent the normal hematopoietic cell differentiation. (Deguchi and Gilliland, 2002)

The AML-PT represent 10 to 15% of total AML and its incidence is increasing substantially in recent years, (Ng et al, 2000) the AML-PT are often associated with clonal cytogenetic abnormalities similar to those found in newly diagnosed AML, but with higher incidence of poor prognosis karyotypes and have particular clinical and biological features that include a poor

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response to CT commonly used in the treatment of AML and therefore have a significantly adverse prognosis.

Different authors have been relationship to drugs and radiation with specific emphasis on the balanced rearrangements chromosomes. (Andersen et al, 1998) Increased frequency of dicentric chromosomes in therapy-related MDS and AML compared to de novo disease is significantly related to previous treatment with alkylating agents and suggests a specific susceptibility to chromosome breakage at the centromere. (Andersen and Pedersen, 2000)

3. Conclusion

In this way one can conclude that the pathophysiology of acute lymphoblastic leukemia is very complex and involves various factors (genetic, immunes, environmental, and drugs) at different levels, and also has a close and complex relationship. The key features in the pathophysiology of the ALL is its monoclonal origin, uncontrolled cell proliferation by sustained self-stimulation of their receptors for growth, no response to inhibitory signals, and cellular longevity conditioned by decreased apoptosis.

Author details

M. P. Gallegos-Arreola[1], C. Borjas-Gutiérrez[3], G. M. Zúñiga-González[2], L. E. Figuera[4], A. M. Puebla-Pérez[5] and J. R. García-González[4]

1 Laboratorio de Genética Molecular, División de Medicina Molecular, CIBO-IMSS, Guadalajara, Jal., México

2 Laboratorio de Mutagénesis, División de Medicina Molecular, CIBO-IMSS, Guadalajara, Jal., México

3 División de Genética, CIBO-IMSS, &UMAE-Hospital de Especialidades, Servicio de Hematología, CIBO-IMSS, Guadalajara, Jal., México

4 División de Genética, CIBO-IMSS, Guadalajara, Jal., México

5 Laboratorio de Inmunofarmacologia, CUCEI, UdeG, Guadalajara, Jal., México

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