Med Clin (Barc). 2015;144(5):223–229

MEDICINA CLINICA

www.elsevier.es/medicinaclinica

Review

Acute lymphoblastic leukemia of T progenitors: From biology to clinics☆

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ARTICLE INFO

Article history:
Received 16 October 2013
Accepted 23 January 2014
Available online 16 October 2015

Keywords:
Acute T-cell lymphoblastic leukemia
Molecular markers
Biology
Treatment

ABSTRACT

Acute lymphoblastic leukemia (ALL) is the most common cancer in children and the main cause of morbidity among childhood blood disorders. There are 2 subtypes according to the affected lymphoid progenitor: B-ALL and T-ALL. The T-ALL is the less common and, although historically was associated with poor prognosis in both adults and children, at present, treatment outcomes do not differ significantly between the 2 types of ALL. The T-ALL subtype is the most complex and heterogeneous at the genetic level and currently the one with less new therapeutic alternatives available. This trend is changing thanks to the remarkable progress upon understanding its biology. This review summarises the most recent and important biological findings in T-ALL and their possible therapeutic implications.

Leucemia aguda linfoblástica de precursores T: de la biología a la clínica

Palabras clave:
Leucemia aguda linfoblástica T
Marcadores moleculares
Biología
Tratamiento

RESUMEN

La leucemia aguda linfoblástica (LAL) es la neoplasia más frecuente en niños y la principal causa de morbilidad entre las alteraciones hemáticas infantiles. Existen 2 subtipos, según el progenitor linfoide afectado: LAL-B y LAL-T. La LAL-T es menos frecuente e históricamente se asociaba a mal pronóstico tanto en adultos como en niños, aunque en la actualidad los resultados del tratamiento no difieren significativamente entre ambos tipos de LAL. La LAL-T es el subtipo más complejo y heterogéneo a nivel genético y el que menos alternativas terapéuticas nuevas presenta en el momento actual. Esta tendencia está cambiando merced a los progresos notables que se están efectuando en el conocimiento de su biología. En esta revisión se resumen los hallazgos biológicos más importantes en la LAL-T efectuados en los últimos años y sus posibles implicaciones terapéuticas.

Introduction

Acute lymphoblastic leukemia (ALL) is characterised by being a multistage oncogenic process that leads to the blockage of maturation and the malignant transformation of lymphoid haematopoietic progenitors.[1] The incidence of ALL is not homogeneous throughout life. It presents an early peak at 4 or 5 years of age (incidence rate of 4–5 per 100,000 persons/year) an incidence decrease in young adults, and a slight increase after 50 years of age (incidence rate of up to 2 per 100,000 persons/year). The cure rate is lower in adults than in children, with a long-term disease-free survival of approximately 80% in children and 35–45% in adults (www.seer.cancer.gov/statistics). Specifically, the T-ALL corresponds to 15% of childhood acute leukemias and 25% of the adult ones. The curve of incidence presents only one peak located in the child/adult boundary and the survival does not differ from that of the precursors B-ALL. This T subtype is characterised by presenting a greater heterogeneity and genetic complexity, making it attractive for research, despite being a rare ALL subtype.

The purpose of this study is to summarise the latest scientific advances in T-ALL, at a basic level as well as at a clinical level, and

☆ Please cite this article as: Genescà E, Ribera J, Ribera J-M. Leucemia aguda linfoblástica de precursores T: de la biología a la clínica. Med Clin (Barc). 2015;144:223–229.

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2387-0206/

Table 1
Main recurrent chromosomal lesions in T-cell acute lymphoblastic leukemia that define molecular subgroups.

Affected gene	Chromosomal lesion	Frequency (%)
HOXA-RCTß	Inv(7)(p15;q34); t(7;7)(p15;q34)	3
HOXA(SET-NUP214)	del9q34; inv(14)(q11.2q13)	3
HOXA(MLL-ENL)	t(11;19)(q23;p13)	1
HOXA(CALM-AF10)	t(10;11)(p13;q14)	10
TLX1(HOX11)	t(10;14)(q24;q21); t(7;10)(q34;q24)	4–7 (c)/14 (a)
TLX3(HOX11L2)	t(5;14)(q35;q32)	20 (c)/13 (a)
NKX2.1	Inv(14)(q13;q32.33); t(7;14)(q34;q13)	5
NKX2.2	t(14;20)(q11;p11)	1
TAL1-RCTα/δ	t(1;14)(p32;q11); t(1;7)(p32;q34)	3
SIL-TAL1	del1p32	9–30
TAL2	t(7;9)(q34;q32)	1
LYL1	t(7;19)(q34;p13)	<1
OLIG2(BHLHB1)	t(14;21)(q11.2;q22)	One case described
LMO1	t(11;14)(p15;q11); t(7;11)(q34;p15)	1
LMO2	t(11;14)(p13;q11); t(7;11)(q34;p13); del11p13	6; 3(del)
LMO3	t(7;12)(q34;p12)	<1
c-MYB	t(6;7)(q23;q34)	6 (c)/7

a: adults; c: children.

show where the research is headed in this ALL subtype and which are the key items to resolve at medium–long term with the purpose of improving the treatment and survival of patients with this disease.

Towards a molecular characterisation "a la carte"

Variations in the number of gene copies in precursor T-acute lymphoblastic leukemia

In these last years, the studies based on the use of large-scale and high-resolution genomic techniques have been of vital importance for the comprehension of ALL, and especially revealing in T-ALL. Since in 2005 Irving et al. demonstrated that through *arrays* of *single nucleotide polymorphisms* (SNP) *loss of heterozygosity* (LOH) could be successfully identified in ALL,[2] there have been numerous studies that involved new genes in the development of T-ALL through screening of *copy number variations* (CNV) with SNP arrays or with comparative genomic hybridisation arrays. Thus, focal alterations of copy number that imply a *TAL1*, *LMO2*, *PTEN*, *FBXW7* and *MYB* deregulation, among others, have been identified[3] (Tables 1 and 2).

Arrays of expression

From the comparative studies of the pattern of expression of human T-ALL samples and normal T cells at different stages of differentiation, a consensus has been reached regarding 3 big T-ALL subtypes that group the different subtypes based on the chromosomal abnormalities present in the leukemic cell: (a) *early T-cell precursor* (ETP), characterised by the absence of CD1a, CD4 and CD8 immunomarkers and the presence of myeloid or pluripotent cell markers such as CD117, CD34, HLA-DR, CD13, CD33, CD11b, or CD65[4]; (b) cortical subtype, characterised by the aberrant expression of the transcription factor family with a *homeobox* domain, such as *TLX3*, *NKX2.1* and *NKX2.2*,[5–7] and by the expression of the CD1, CD4 and CD8 immunomarkers[5] and Pre-T1 or Pre-T2/Pre-T3 (E),[6] and (c) mature subtype, characterised by the expression of the *TAL oncogene*,[5–7] CD4, CD8 and CD3 immunomarkers[5] and T cell receptorαβ.[6] In Table 1, there is a summary of the main chromosomal alterations that characterise these 3 molecular subtypes.

Table 2
Other genes recurrently altered in T-cell acute lymphoblastic leukemia.

Affected gene	Genetic lesion	Frequency (%)
NOTCH1	t(7;9)(q34;q13); activating mutation	<1; 60 (activating mutation)
FBXW7	Inhibitory mutation	8–30
CDKN2A/2B	del(9q21); methylation	70 (c)/15 (a)
CCND2	t(7;12)(q34;p12); t(12;14)(p13;q11)	1
RB1	del(13q14)	4
Unknown	del(6q)	18 (c)
CDKN1B	del(12p13)	2
MYC	t(8;14)(q24;q11)	1
WT1	Inhibitory mutation; deletion	13 (c)/12 (a)/8
LEF1	Inhibitory mutation; deletion	7–11 (c)
ETV6	Inhibitory mutation; deletion	17 (c)/12 (a)
BCL11B	Inhibitory mutation; deletion	9 (c)
RUNX1	Inhibitory mutation; deletion	4.4 (c)/18 (a)
GATA3	Inhibitory mutation; deletion	5 (c)
PTEN	Point mutation; del(10q22)	10 (c)
NUP214-ABL1	Episomal amplification 9q34	4
EML1-ABL1	t(9;14)(q34;q32)	<1
ETV6-ABL1	t(9;12)(q34;p13)	<1(c)
BCR-ABL1	t(9;22)(q34;q11)	<2
NRAS	Activating mutation	5–10
NF1	Inhibitory mutation; deletion	3 (c)
JAK1	Activating mutation	4–18 (a)
ETV6-JAK2	t(9;12)(p24;p13)	<1 (a)
JAK3	Activating mutation	5 (c)
FLT3	Activating mutation	2 (c)/4 (a)
IL7R	Activating mutation	10 (c)
EZH2	Inhibitory mutation; deletion	10 (c)/15 (a)
SUZ12	Inhibitory mutation; deletion	10 (c)/4 (a)
EED	Inhibitory mutation; deletion	10 (c)
PHF6	Inhibitory mutation; deletion	16 (c)/38 (a)

a: adults; c: children.

Next-generation sequencing

Another great advance in the knowledge of new genes that participate in the development of T-ALL was produced with the development of the new *next generation sequencing* (NGS) platforms. This technique enables the detection of punctual mutations with very high sensitivity and LOH and CNV with very high resolution. Table 2 shows the main genes with recurring punctual mutations that affect T-ALL. At the beginning of the year 2012, the Mullighan group, at the *St. Jude Children's Research Hospital*, published the first complete sequencing of the ALL genome performed in 12 samples of ETP type childhood T-ALL,[8] and they demonstrated that this ALL subtype presents activating somatic mutations in cytokines and genes that participate in the *RAS pathway*, such as *NRAS*, *KRAS*, *FLT3*, *IL7R*, *JAK3*, *JAK1*, *SH2B3* and *BRAF*, as well as genetic alterations that inactivate genes that participate in the haematopoietic development, such as *GATA3*, *ETV6*, *RUNX1*, *IKZF1* and *EP300*, and histone-modifying genes (*EZH2*, *EED*, *SUZ12*, *SETD2* and *EP300*). It is worth mentioning that the mutational spectrum identified in the ETP leukemia was similar to that of the poor-prognosis acute myeloid leukemias (AML), with affected genes that define the pluripotent character of the myeloid cell.[8] Recently, another complete exome study in ETP leukemia samples in adults has identified mutations in the *DNMT3A* methyltransferase in 16% of the patients (10/68), a similar frequency to the one detected in AML. Moreover, mutations have been found in the *FAT1* (25%) and *FAT2* cadherins (20%), thus involving genes that participate in cell adhesion and in the interaction between stromal and leukemic cell.[9] Using this same technique, De Keersmaecker et al. identified mutations in the *CNOT3* gene in 3.8% (8/211) of the T-ALL samples analysed. The mutations identified cause a lower gene expression, which evidences that *CNOT3* could act as a tumour suppressor gene.[10]