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RELATION OF THE TLX1 GENE IN THE PATHOGENESIS OF T-LINEAGE ACUTE LYMPHOBLASTIC LEUKEMIA (T-ALL)

RELAÇÃO DO GENE TLX1 NA PATOGÊNESE DA LEUCEMIA LINFOBLÁSTICA AGUDA DE LINHAGEM T (LLA-T)

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ABSTRACT: T-lineage acute lymphoblastic leukemia (T-ALL) is an aggressive form of leukemia that mainly affects children and adolescents, with challenges in treatment and clinical management. This work investigates the impact of the *TLX1/HOX11* gene in the pathogenesis of T-ALL, focusing on molecular alterations, diagnosis and therapeutic implications. Through a literature review (2017-2023), using descriptors such as "T-lineage", "gene expression", "leukemia" and "*HOX11*", it was observed that *TLX1/HOX11* overexpression is associated with a better response to standard chemotherapy regimens, although it presents challenges in disease control. Understanding the role of this gene is crucial to develop targeted therapeutic strategies, aiming at better clinical outcomes and quality of life for patients with T-ALL.

KEYWORDS: T lineage. gene expression. Leukemia. *HOX1*.

RESUMO: A Leucemia Linfoblástica Aguda de Linhagem T (LLA-T) é uma forma agressiva de leucemia que afeta principalmente crianças e adolescentes, com desafios no tratamento e manejo clínico. Este trabalho investiga o impacto do gene *TLX1/HOX11* na patogênese da LLA-T, com foco em alterações moleculares, diagnóstico e implicações terapêuticas. Por meio de uma revisão bibliográfica (2017-2023), utilizando descritores como "linhagem T", "expressão gênica", "leucemia" e "*HOX11*", observou-se que a hiperexpressão do *TLX1/HOX11* está associada a melhor resposta a regimes de quimioterapia padrão, embora apresente desafios no controle da doença. Compreender o papel desse gene é crucial para desenvolver estratégias terapêuticas direcionadas, visando melhores resultados clínicos e qualidade de vida para pacientes com LLA-T.

PALAVRAS-CHAVE: linhagem T.expressão genica. Leucemia. *HOX11*.

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INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is a pathology of lymphoid precursors with distinct biological variations, according to B or T cell lineages (Instituto Nacional do Câncer/ National Cancer Institute - INCA, 2024). It is a disease of abrupt onset and rapid evolution, but it has great potential for cure and has a wide diversity of clinical and biological aspects. In addition, ALL is characterized by immature lymphoid cells that multiply uncontrollably, occupying the bone marrow and interfering with the normal production of blood cells[1].

In a healthy bone marrow, stem cells mature through differentiation[2]. In ALL, a damaged immature lymphocyte appears in the bone marrow due to an error in its material. Consequently, genetic errors can give rise to a leukemic blast cell that has its development inactivated in the early stages of cell development. Thus, the immature blast cell does not mature and has no functionality[3].

In each lymphoblast that emerges after the appearance of leukemia cells, there is a mutant DNA multiplying in an uncontrolled way. Leukemia blasts rapidly accumulate in the bone marrow, suppressing the development of healthy and normal blood cells. As a result, lymphoblasts accumulation lacks functionality and few mature blood cells[4].

According to INCA (2022), T-lineage Acute Lymphoblastic Leukemia (T-ALL) is classified as an aggressive neoplasm that mainly affects children and adolescents. T-ALL affects more men than women, with a prevalence of 10 to 15% in children.

There are different subtypes of lymphocytes (B or T), therefore different types of leukemias are classified according to the cell involved, the duration, and the characteristics of the disease. Within this disease, B cells are responsible for approximately 85% of cases, while T cells represent 15% of this pathology[5]. Therefore, it can be stated that the tumor process is related to changes in the cell cycle, with dynamic processes occurring due to multiple stages where the mutated cell divides and produces a clone of cells that present the mutation. Hence, new mutations can occur at each stage of clonal proliferation. Hematopoietic tissue has a high number of cells in division and differentiation, from the stem cell to the differentiated cells. As cells differentiate, they lose their ability to divide, corroborating that leukemogenesis may be related to alterations in oncogenes and tumor suppressor genes[6].

The symptoms present in ALL are not very specific and can be confused with several common childhood pathologies, such as infectious mononucleosis, pertussis, viral diseases, inflammatory processes, juvenile rheumatoid arthritis, and weakness due to anemia, lymphadenomegaly, splenomegaly, and hepatomegaly[7].

T-ALL is subdivided into three groups that differentiate according to normal intrathymic differentiation antigens: pre-T, intermediate-T, and mature ALL3[3]. The most common mutations in this type of ALL occur in the TLX1 (HOX11), TLX3 (HOX11L2), LYL1, TAL1, and MLL (KMT2A) genes, while the least recurrent ones occur in the fusion of TEL-AML1 (ETV6-RUNX1) and E2A-PBX1 (TCF3-PBX1). Thus, a chromosomal evaluation of this hematological disease becomes extremely important, not only for its diagnosis but also for understanding the mechanisms and genes of biological importance.

As stated by INCA, ALL's diagnosis is made through cytological examination of peripheral blood, bone marrow, and cerebrospinal fluid. The diagnosis is established when 25% or more lymphoblasts are found in the bone marrow (INCA, 2019). Several tests are performed to confirm ALL's diagnosis, such as cytochemistry, cytomorphology, immunophenotyping, and conventional cytogenetics of peripheral blood or bone marrow[8].

The TLX1/HOX11's presence gene is strongly associated with cell cycle dysregulation and cell differentiation, contributing to the malignant transformation of T lymphocytes. This gene acts as a

transcription factor, modulating the expression of several genes essential for the development and function of T lymphocytes.

Complementary exams such as radiographs, ultrasound, physical examination, and fundus examination are also used[9]. Treatment is commonly carried out with chemotherapy. Thus, patients need treatment as soon as the diagnosis is confirmed, and the initial goal is remission with restoration of normal production of red and white blood cells and platelets in the patient's body[5]. The presence of unfavorable prognostic factors or recurrence of the disease should direct the patient's approach to more aggressive treatments, considering bone marrow transplantation in its various modalities[10].

It is highly relevant to establish the genetic alterations present in patients diagnosed with ALL, to define more accurate prognoses, and to establish personalized therapeutic approaches. The evolution of target-molecular therapies directed to specific genetic profiles reinforces the importance of this type of analysis[11]. In this context, the genetic characterization of patients with T-subtype ALL (T-ALL) becomes crucial, allowing the evaluation of individualized treatments and exploring the development of new therapeutic interventions based on the specific genetic mutations and translocations that characterize this leukemia subtype.

Thus, the objectives of this article are to investigate the TLX1 (HOX11) T-ALL gene, characterize the TLX1/HOX11 gene in T-ALL, analyze its regulation and mechanisms of action, analyze the main influences of the genetic alterations of the TLX1/HOX11 gene associated with T-ALL, and addressing its etiology, impact on the pathogenesis of the disease, and clinical implications for diagnosis.

METHODOLOGY

This work is a bibliographical research, which aims to analyze and interpret the theme addressed without using statistical methods. The literature review may include experimental and non-experimental research, combining empirical and theoretical data to direct the definition of concepts, identify gaps in areas of study, review theories, and methodologically analyze studies on a given topic. The guiding question of this review is: "What is the influence of genetic alterations of the TLX1 gene related to the pathogenesis of T-cell Acute Lymphoblastic Leukemia, and how can these mutations be exploited to improve the diagnosis and treatment of the disease?".

The first stage involved the establishment of criteria for inclusion and exclusion of studies/sampling or search in the literature. The following databases were used to search for articles: Google Scholar, Scientific Electronic Library Online (SciELO), and the National Library of Medicine (PubMed). The search strategies used descriptors such as T lineage, gene expression, leukemia, and HOX11. Potentially relevant articles were obtained, read in full, and evaluated according to eligibility criteria.

Studies were included in the systematic review if they fit the following criteria:

a) Articles published between 2017 and 2023;
b) Articles published in English, Portuguese and Spanish;
c) Articles that addressed T-Lineage Acute Lymphoid Leukemia, focusing on early diagnosis, treatment, and prognosis;
d) Studies on molecular alterations associated with T-ALL, including genetic mutations of the TLX1 gene, chromosomal rearrangements, and gene expression profiles in the context of the TLX1 gene in T-ALL.

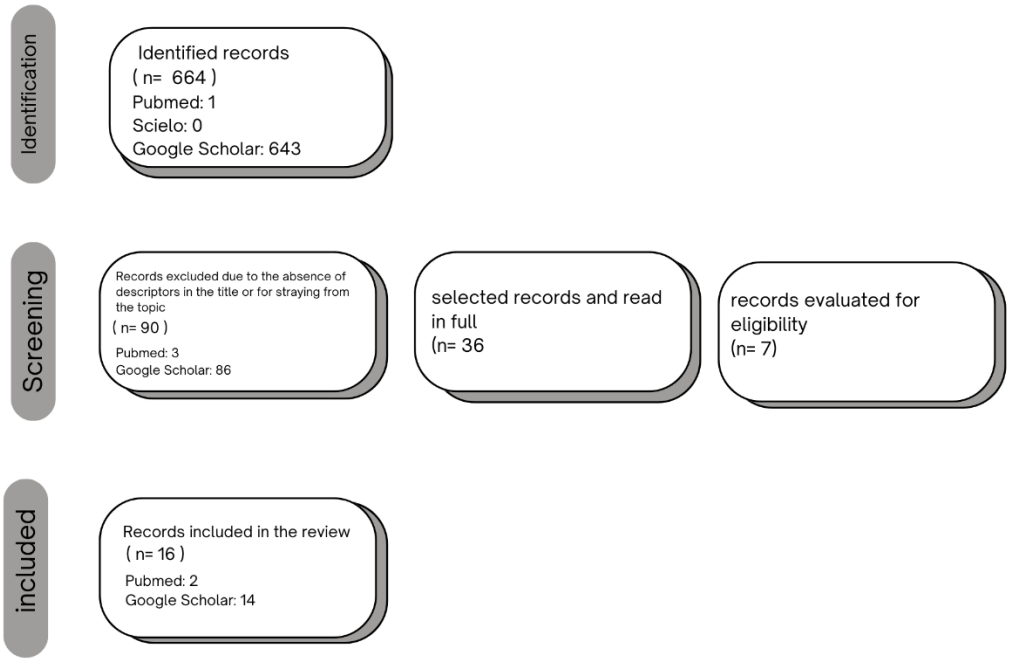
Studies were excluded from the systematic review if they fit at least one of the following criteria:

a) Duplicate article;
b) Absence of descriptors in the title or abstract;
c) Articles that did not fit the theme of the study.

The search strategy identified 644 publications. Of these, 609 were excluded after analysis of the title and abstracts because they did not comply with the combination of descriptors, duplicity, or did not fit the theme of the study. In the end, 36 studies were read in full, of which 7 were used in the present review.

The general steps of the data search, the exclusion and inclusion criteria, and other relevant information are presented in Figure 1.

Figure 1 - Flowchart with the eligibility criteria



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RESULTS

The article's reading results included in this study are presented in Chart 1, they inform the authors and year of publication of their work, as well as the theme of the research, objectives, and conclusions obtained and exposed by the researchers.

Chart 1 - Summary of articles on genetic alterations in T-ALL

AUTHOR, YEAR	THEME	OBJECTIVE	CONCLUSION
Maciel, 2019	CRLF2 expression associated with NOTCH1/IKZF1 status in T-cell acute lymphoblastic leukemia.	To identify and track the presence of molecular alterations in T-ALL.	It confirmed that the TLX1 gene is based on chromosomal translocations involving one of the T-cell receptor (TCR) genes.
Riz, 2019	*TLX1* and NOTCH co-regulate transcription in acute lymphoblastic leukemia T cells.	To identify how the *TLX1* gene regulates T cell transcription and potential critical therapeutic targets for the malignant phenotype in T-ALL.	It has been found that *TLX1* synergistically regulates transcription in T-ALL and that the *TLX1*/NOTCH/MYC network is a central determinant that promotes *TLX1* cell growth.
Mei, 2020	Association of TLX1 gene polymorphisms with the risk of acute lymphoblastic leukemia and B-lineage acute lymphoblastic leukemia in Han Chinese children.	To determine whether *TLX1* is associated with Acute Lymphoblastic Leukemia and which SNP plays a significant role in ALL.	*TLX1* gene polymorphisms are associated with ALL and play a significant role in T-ALL.
Alexandrino, 2021	NF-κB in T-cell Acute Lymphoblastic Leukemia: Oncogenic Functions in Leukemia and Microenvironmental Cells.	To define oncogenic changes in T-cell acute lymphoblastic leukemia in the *TLX1* gene.	*TLX1*+ cases have a gene expression profile corresponding to that of lymphocytes in the cortical stage that become positive simple mature T cells, CD4+ CD8+ or CD4+CD8- .
Marramaque, 2023	Acute Lymphoblastic Leukemia: Characterization, diagnosis and therapeutic approaches.	To provide a current view on the main themes related to lymphoblastic leukemia. To highlight genetic aspects (including cytogenetics and epigenetics), diagnosis, risk factors and therapies.	The translocation of the *TLX1* gene is the main genetic target, responsive to genes that determine maturation inhibition, as cell cycle inhibitors or as transcription factors.
Matias, 2019	Acute Lymphoblastic Leukemia: Pathophysiology, Diagnosis and Therapeutic Approaches.	The characterization of the entire theme underlying acute lymphoblastic leukemia, with the pathophysiological mechanisms of the disease being evidenced.	The treatment of ALL is moving towards the development of individualized treatment plans suited to each case. The agents' investigation with specificity for the therapeutic target and low toxicity to the body is essential, as well as the achievement of high remission rates with a reduced probability of relapse.
Coelho, et al, 2020	Acute Lymphoblastic Leukemia (ALL) in the pediatric population: molecular markers and therapeutic implications.	To provide a comprehensive overview of the key molecular markers and therapeutic implications associated with ALL in the pediatric population.	Markers not only impact prognosis but also underlie therapeutic approaches. Targeted therapies, notably those focused on specific mutations, such as BCR-ABL1, and immunotherapy innovations, such as CAR-T therapy, emerge as promising strategies, promoting significant advances in ALL's pediatric treatment.

Source: created by authors.

DISCUSSION

All the authors pointed out similar ideas. They concluded that the expression of the *TLX1* gene in patients with T-ALL leads to an alteration of the cell cycle, which contributes to the mismatch of T lymphocytes's differentiation. However, this variation is not only related to the *TLX1* gene due to ectopic gene expression, but rather to Acute Lymphoblastic Leukemia[12].

Integrating the results of authors Riz (2019) and Maciel (2019), it is possible to infer that the *TLX1* gene participates in the spleen's formation and the destination of neuronal cells. They also comment that the oncogenic role of this gene in T Acute Lymphoblastic Leukemia occurs due to its abnormal activation, which is caused by the t(7,10) or t(10,14) translocation, superimposing this gene on T cell receptors (TCR)[13,14].

Riz (2019) highlights in his studies that the *TLX1* gene, formerly known as HOX11, encodes a nuclear transcription factor necessary for normal spleen development during embryogenesis. This protein is also involved in specifying the fates of neuronal cells, with the abnormal expression associated with T-ALL[13].

Although *TLX1* is not expressed in the hematopoietic system, its inadequate expression occurs due to the chromosomal alterations of translocations involving T-cell receptor genes. From the analysis of two independent cohorts of T-ALL patients, Maciel (2019) also revealed that patients with the hyper-expressed *TLX1* gene share a similar expression profile, characterized by the arrest of lymphopoiesis in the early cortical stage of T cells[8].

The bibliographical review carried out by Matias (2019) showed that the translocation of the *TLX1* gene in ALL dysregulates the expression of transcription factors, making it oncogenic, which results in critical cell cycle alterations, mismatching the differentiation of T lymphocytes. In agreement, Mei (2020), through a study with 214 ALL cases, observed that the *TLX1* gene was identified in ALL based on its abnormal expression in T8-ALL[8,18].

Confirming this information, the research made by Marramaque (2023) concluded that the translocation of the *TLX1* gene culminates in the dysregulation of the expression of genes that, under normal conditions, act as cell cycle inhibitors or transcription factors, proving that genetic variations of the *TLX1* gene are associated with ALL[12].

As pointed out by Alexandrino (2021), derived from the observation of the gene expression profile of a *TLX1* cell line in the patients' T-ALL, it was possible to conclude that *TLX1* is a central determinant that promotes the growth and survival of T cells in ALL. The investigation of TLX1 in the pathogenesis of ALL concluded that this gene may influence the initial cortical development of T cells, which may have significant implications for understanding and treating immune system disorders in patients with T-ALL[17].

Escorted by the analysis of the expression of the *TLX1* gene, it is noted that the series of molecular alterations favor uncontrolled cell proliferation and resistance to apoptosis, typical characteristics of T-ALL. Early identification of genetic alterations that may influence the T-ALL 's development is essential to predict the favorable prognosis of patients with this pathology. Early identification of these abnormalities allows for the personalization of treatment and the introduction of targeted therapies, such as tyrosine kinase inhibitors, contributing to a significant improvement and increased survival prospects for patients with important genetic alterations related to T-ALL[18].

Another convenient tool for the early diagnosis of T-ALL is Next-Generation Sequencing (NGS), which plays an important role in the prognosis and treatment of T-ALL. It allows the detection of specific genetic alterations characteristic of T-ALL, helping to confirm the diagnosis and better understand the

characteristics of the pathology. The identification of genetic alterations in T-ALL through NGS contributes to the personalization of the patient's treatment, individualizing the treatment and contributing to the regression of the disease[12].

Despite the results obtained, the present literature review was carried out with limitations of information considered pertinent to the theme. Few studies relate the *TLX1* gene to T-ALL. However, even so, it was possible to achieve results that fit the focus of the investigation on the influence of the *TLX1* gene on T-ALL, the subject of this review.

The relationship between the *TLX1* gene and the pathogenesis of T-lineage acute lymphoblastic leukemia (T-ALL) has aroused increasing interest, given its critical role in modulating cellular pathways essential for oncogenesis. Studies have shown that aberrant *TLX1* expression in immature T cells is associated with cell cycle dysregulation and inhibition of apoptotic processes, contributing significantly to the malignant transformation of these cells. Understanding the function of *TLX1* in T-ALL allows not only a clearer view of the mechanisms underlying pathogenesis but also offers new perspectives for the development of molecular-targeted therapies.

From a clinical point of view, the identification of *TLX1* gene expression can be used as a prognostic marker. Patients with T-ALL who have overpressure of *TLX1* have shown a differentiated response to conventional treatments, which may imply the need for more specific therapeutic approaches. The adoption of targeted therapies that block the oncogenic function of *TLX1* could result in a significant impact on the treatment response rate and overall survival of these patients[10].

In addition, in-depth knowledge about the interaction of *TLX1* with other molecular pathways involved in leukemogenesis may pave the way for further investigations into more effective therapeutic combinations. Future studies exploring selective inhibition of *TLX1* may open new horizons in T-ALL's management, enabling personalized treatments with less toxicity, increasing the chances of complete remission, and improving patients' quality of life.

These implications reinforce the importance of incorporating genetic analysis of markers such as *TLX1* into clinical protocols, making early detection of such alterations an essential component for risk stratification and choosing more appropriate therapies in T-ALL.

CONCLUSION

The study on the interference of the TLX1/HOX11 gene in the pathogenesis of T-ALL revealed crucial aspects for understanding and treatment of this disease.

TLX1 expression in T-ALL is generally associated with a more favorable prognosis compared with other T-ALL subtypes. Studies show that T-ALL patients who express the TLX1 gene tend to have higher survival rates and better responses to conventional treatment. However, it is important to consider other genetic and molecular factors that may influence individual prognosis.

Therefore, one of the pillars of health promotion is prevention through early diagnosis. The detection of genetic alterations, such as mutations in the TLX1 gene, may allow risk stratification in predisposed individuals, facilitating faster and more targeted clinical interventions. Genetic screening programs and access to information on hereditary predispositions can help in the secondary prevention of T-ALL, by identifying risk groups before the appearance of symptoms, promoting greater survival and better quality of life.

In sum, it was possible to conclude that understanding the genetic panel of T-ALL is crucial in the research and treatment of the disease. Genetic changes play a key role in the development and

progression of T-ALL. Therefore, the characterization of the impact of the TLX1/HOX11 gene on T-lineage ALL not only advances scientific knowledge about the pathogenesis of this disease but also opens the way for the development of new therapeutic strategies, aiming to increase the efficacy of treatment and the survival rate of patients.

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Anexo 1

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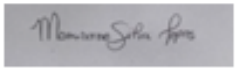

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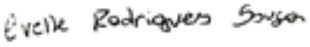

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