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Short Communication

Bioinformatics analysis of TAL and LYL1 transcription factor associated oncogenesis

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INTRODUCTION

The present study investigated the common primary tumors-specific alteration of the TALI gene induces almost 25% of patients with T-cell acute lymphoblastic leukemia. The TAL gene product induces a helix-loop-helix transcription factor especially homologous to the LYL1. TAL1, TAL2, and LYL1 constitute discrete subgroup bHLH transcription factor potential contribution to the development of T-cell oncogenesis. The TAL2 translocated chromosome 9 breakpoint of t (7; 9) (q34; 7. q32) especially associated with T-cell. The TAL2 is juxtaposed with sequences from the T-cell receptor beta-chain gene on a chromosome 7. The sequence homologs TAL1, TAL2, and LYL1 are conserved during evolution. The TAL1, TAL2, and LYL1 constitute a unique family of bHLH transcription factor potential mediator of T-cell leukaemogenesis. TAL1, TAL2, and LYL1 encode a helix-loop-helix transcription factor involved in the malignant development of lymphocytes. We accumulate eukaryotes organism i.e. Homo sapiens and Mus musculus for comparative and functional analysis. Our data provide evidence that the total 6, 2, 2 TAL1, TAL2, and LYL1 in Homo sapiens and Mus musculus respectively including domain, motifs, phylogeny, chromosome location, and gene expression. In this study, we performed bioinformatics and computational analysis to validate the current knowledge of the TAL1, TAL2 and LYL1 transcription factor

Deregulation of transcription factor genes is a hallmark of acute leukemia . A number of oncogenes and tumor suppressors have been identified from the breakpoints of chromosomal translocations, many of which are also involved in normal hematopoiesis. TAL1/SCL is one example that was originally cloned from a chromosomal translocation in T-cell acute lymphoblastic leukemia (T-ALL) . This gene was soon recognized as an essential regulator of both primitive and definitive hematopoiesis. Studies with animal models demonstrated that the misexpression of TAL1 leads to the disruption of T-cell development and often to T-ALL Early studies demonstrated that TAL1 exerts its oncogenic properties by blocking T-cell differentiation; however, the detailed transcriptional program controlled by TAL1 in human T-ALL cells has remained unclear until recently. Accumulating evidence has shown that this factor serves as a master transcription factor that induces a unique regulatory circuit and regulates a variety of downstream targets that are orchestrated and affect several different cellular machineries required for the development and/or maintenance of T-ALL.

T-ALL is a kind of blood cancer that develops from immature T-cell progenitors (T-lymphoblasts) . T-ALL is most common in young children, however it can also affect adults. For juvenile T-ALL cases, the adoption of highly aggressive chemotherapy has resulted in a 75–90 percent 5-year event-free survival rate . Short- and long-term negative impacts, on the other hand, remain serious concerns. T-ALL has a multitude of chromosomal and genetic abnormalities, many of which disrupt genes that code for transcription factors. Several genes, including TAL1, TAL2, LYL1, LMO2, TLX1/HOX11, and TLX3/HOX11L2, were discovered to be overexpressed as a result of chromosomal translocations involving the TCR regulatory element in early investigations Subsequent studies have demonstrated that these genes act as oncogenes in T-ALL, and many are also essential regulators of normal hematopoiesis. Importantly, gene expression profiles have revealed that, depending on the expression of oncogenic transcription factors, T-ALL cases can be divided into various subgroups that are mutually exclusive the TAL-positive subgroup (expressing TAL1 or TAL2 alongside LMO2 or LMO1) the TLX-positive subgroup (expressing TLX1 or TLX3) the NKX2-1-positive subgroup; and the HOXA-positive subgroup. Other forms of genetic mutations that are widespread across distinct subgroups of T-ALL have been reported (dubbed "type B abnormalities") in addition to these abnormalitie. In over half of T-ALL cases, activating mutations in NOTCH1 and inactivating variants in FBXW7, both of which result in constitutive activation of NOTCH1 protein, are discovered NOTCH1 primarily activates the MYC oncogene in T-ALL cells, thereby driving cell-proliferation. Similarly, genetic mutations or deletions in the cell cycle regulator CDKN2A/CDKN2B are frequently found in T-ALL. Additionally, recent genomic studies have provided a comprehensive catalog of chromosomal and genetic abnormalities involved in T-ALL, including mutations of epigenetic regulators (e.g., PHF6, EZH2, SUZ12), the PI3K-PTEN-AKT pathway (e.g., PTEN, PIK3R1), the JAK-STAT pathway (e.g., JAK3, IL7R), ribosomal genes (e.g., RPL10), USP7, BCL11B, and NRAS genes, for example [35, 36]. It should be noted that although it is not exclusive, some of these abnormalities are more frequently found in specific subgroup(s) of T-ALL (e.g., PTEN mutations in TAL-positive cases) suggesting a potential collaborating effect between type A and type B abnormalities. Please also refer to several recent review articles for more details regarding genetic abnormalitie.

TAL1 belongs to the class II bHLH family of transcription factors that can form heterodimers with the class I bHLH proteins, called E-proteins (E2A, HEB and E2-2) [39, 40]. The TAL1-E-protein dimer subsequently forms a regulatory complex with other transcription factors, including LMO (LMO1 or LMO2), GATA (GATA1, GATA2 or GATA3) and LDB1 proteins. The RUNX1 and ETS family of transcription factors often co-occupy the same regulatory elements and coordinately regulate gene expression with the TAL1 complex .In normal hematopoiesis, TAL1 is required for the specification of the blood lineage and maturation of

several hematopoietic cells . In the adult bone marrow, TAL1 is expressed in hematopoietic stem cells (HSCs), progenitor cells and erythro-megakaryocyte lineages. Early studies using murine models demonstrated that genetic knockout of Tal1 is embryonic lethal due to a lack of primitive erythropoiesis Subsequent studies revealed that Tal1 is also required for definitive hematopoiesis, in particular for the specification of blood lineages A study using conditional knockout mice indicated that Tal1 is required for the maturation of erythrocytes and megakaryocyte lineages On the other hand, there is some contradictory evidence in terms of the ability of TAL1 to affect HSC maintenance. A study using conditional knockout mice suggested that TAL1 is not essential for the function of long-term HSCs , while others reported that TAL1 is required for the function of short-term HSCs and progenitor cells. The lack of a phenotype in adult HSCs of the knockout mice could be partially explained by functional redundancy with the LYL1 protein, which is another class II bHLH protein expressed in HSCs and progenitor cells. Interestingly, a recent study has shown that the introduction of TAL1 with RUNX1, GATA2, LMO2 and ERG genes is able to reprogram murine fibroblasts into hematopoietic cells that have a multilineage potential ("iHSCs"). This study demonstrated the ability of TAL1 and its regulatory partners to act as hematopoietic reprogramming factors, which can initiate and maintain the regulatory program that determines the cell identity of HSCs.