



# Oncogenic transcriptional program driven by TAL1 in T-cell acute lymphoblastic leukemia

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## Abstract

*TALI/SCL* is a prime example of an oncogenic transcription factor that is abnormally expressed in acute leukemia due to the replacement of regulator elements. This gene has also been recognized as an essential regulator of hematopoiesis. *TALI* expression is strictly regulated in a lineage- and stage-specific manner. Such precise control is crucial for the switching of the transcriptional program. The misexpression of *TALI* in immature thymocytes leads to a widespread series of orchestrated downstream events that affect several different cellular machineries, resulting in a lethal consequence, namely T-cell acute lymphoblastic leukemia (T-ALL). In this article, we will discuss the transcriptional regulatory network and downstream target genes, including protein-coding genes and non-coding RNAs, controlled by TAL1 in normal hematopoiesis and T-cell leukemogenesis.

**Keywords** TAL1 · T-cell acute lymphoblastic leukemia · Transcription factor

## Introduction

Deregulation of transcription factor genes is a hallmark of acute leukemia [1]. 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. *TALI/SCL* is one example that was originally cloned from a chromosomal translocation in T-cell acute lymphoblastic leukemia (T-ALL) [2]. This gene was soon recognized as an essential regulator of both primitive and definitive hematopoiesis [3–9]. Studies with animal models demonstrated that the misexpression of *TALI* leads to the disruption of T-cell development and often to T-ALL [10, 11]. 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.

## Overview of T-ALL

T-ALL is a hematological malignancy that arises from immature T-cell precursors (T-lymphoblasts) [12, 13]. T-ALL primarily occurs in young children but is also found in adults. The introduction of highly intensive chemotherapy has achieved a 75–90% 5-year event-free survival rate for pediatric T-ALL cases [14]. However, short-term and long-term adverse effects are still major problems associated with T-ALL therapy.

A number of chromosomal and genetic abnormalities have been identified in T-ALL, many of which affect genes encoding transcription factors [15]. In early studies, several genes were found to be overexpressed as a result of chromosomal

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translocations involving the *T-cell receptor (TCR)* regulatory element, which includes *TAL1*, *TAL2*, *LYL1*, *LMO2*, *TLX1/HOX11* and *TLX3/HOX11L2* [2, 16–20]. 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 shown that T-ALL cases can be classified into several subgroups that are mutually exclusive, based on the expression of oncogenic transcription factors [21–23]: (1) the *TAL*-positive subgroup (expressing *TAL1* or *TAL2* together with *LMO2* or *LMO1*); (2) the *TLX*-positive subgroup (expressing *TLX1* or *TLX3*); (3) the *NKX2-1*-positive subgroup; (4) the *HOXA*-positive subgroup; and (5) the *LMO2/LYL1*-positive subgroup. These findings indicated that these transcription factors delineate distinct molecular pathways in T-ALL cells (called “type A abnormalities”) [24–26]. Among them, *TAL*-positive T-ALL is the largest subgroup, accounting for 40–60% of all cases. Additionally, early T-cell precursor (ETP) ALL/immature T-ALL has been defined based on the expression of genes that are present in normal ETP cells [27, 28]. This category overlaps with the type A abnormality and thus is not an exclusive criterion.

In addition to these abnormalities, other types of genetic alterations that are commonly observed across different subgroups of T-ALL have been reported (called “type B abnormalities”) [24–26]. As an example, the activating mutations of *NOTCH1* and inactivating mutations of *FBXW7*, both of which lead to the constitutive activation of NOTCH1 protein, are found in over 50% of T-ALL cases [29, 30]. NOTCH1 primarily activates the *MYC* oncogene in T-ALL cells, thereby driving cell proliferation [31–33]. Similarly, genetic mutations or deletions in the cell cycle regulator *CDKN2A/CDKN2B* are frequently found in T-ALL [34]. 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) [35, 37, 38], 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 abnormalities [24–26].

## Molecular functions and roles of TAL1 in normal hematopoiesis

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 [41].

In normal hematopoiesis, TAL1 is required for the specification of the blood lineage and maturation of several hematopoietic cells [39]. 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 [3, 4]. Subsequent studies revealed that *Tal1* is also required for definitive hematopoiesis, in particular for the specification of blood lineages [5–9]. A study using conditional knockout mice indicated that *Tal1* is required for the maturation of erythrocytes and megakaryocyte lineages [42]. 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 [43], while others reported that TAL1 is required for the function of short-term HSCs and progenitor cells [44]. The lack of a phenotype in adult HSCs of the knockout mice could be partially explained by functional redundancy with the LYL1 protein [45], 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”) [46]. 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.

Importantly, *TAL1* and other stem cell transcription factors, including *LMO2*, *GATA2* and *LYL1*, are transcriptionally silenced during normal lymphocyte development [47–49]. The expression of murine *Tal1* is not detectable in the stages of double-negative (DN) 4 or double-positive (DP) thymocytes. Although the mechanism of gene silencing of *TAL1* has not been fully elucidated yet, it could be associated with the upregulation of transcriptional repressors and/or mediated by epigenetic mechanisms.

In contrast, E-proteins are functionally or transcriptionally upregulated during T-cell development [40, 49]. The silencing of *TAL1* and *LMO2* could result in the formation of E-protein dimers, which can regulate genes required for T-cell differentiation, such as *RAG1*, *RAG2* and *PTCRA* [40, 49, 50]. Thus, the stage-specific regulation of bHLH family transcription factors is critical for normal T-cell development by switching the transcriptional program.

### Transcriptional targets of TAL1 in normal hematopoietic cells

In normal HSCs and progenitor cells, TAL1 regulates several genes involved in HSC or progenitor function. One example is the receptor tyrosine kinase *c-KIT*, which is expressed in HSCs and is essential for definitive hematopoiesis. This gene has been identified as a direct target of the TAL1 complex [51]. The expression pattern of *c-KIT* during T-cell development is similar to that of *TAL1*, which is expressed in progenitor cells and silenced during the DN stage of thymocytes [47]. TAL1 also negatively regulates the expression of *CDKN1A/p21* in HSCs, which is an inhibitor of the cell cycle [52], possibly contributing to HSC quiescence. The regulation of *c-KIT* and *CDKN1A* explains in part the role of TAL1 in normal HSCs. Additionally, a recent study has shown that TAL1 directly represses the *DDIT4* gene, an inhibitor of mTORC1, in HSCs and the progenitor cells [53]. Knockdown of *TAL1* was shown to repress the phosphorylation of mTOR targets, such as 4EBP1 and S6K proteins, which are required for protein synthesis during cell growth and proliferation. This finding provides insights into the link between the TAL1 and mTOR signaling pathways.

On the other hand, TAL1 can regulate a different set of genes in the erythro-megakaryocyte lineages. These genes include the  $\alpha$ - and  $\beta$ -*globin* gene clusters and its regulator, *KLF1*, that are uniquely expressed and required for the function of red blood cells [54–56]. Similarly, the *EPB42* and *glycophorin A (GYPA)* genes, which are abundantly expressed in erythroid cells, are regulated by TAL1 [54, 57]. *UBE2H*, which encodes an E2-ubiquitin conjugase during erythrocyte differentiation, is a target of TAL1 [58]. Additionally, the *MEF2C* gene, which encodes a transcription factor, has been reported to be directly regulated by TAL1 during megakaryocytes differentiation [59].

In addition, it is noteworthy that TAL1 regulates several other hematopoietic transcription factors in normal hematopoietic cells, including *LMO2*, *RUNX1*, *GATA2*, *MYB* and *FLII* [60–63]. These transcription factors regulate each other, thus forming a densely connected autoregulatory loop structure. This transcriptional circuitry is likely important for the maintenance of gene expression programming [64]. Together with its potential as a reprogramming factor, TAL1

is considered a master transcription factor that characterizes the cell fate and identity of normal HSCs and progenitor cells.

### Oncogenic roles of TAL1 in T-cell leukemogenesis

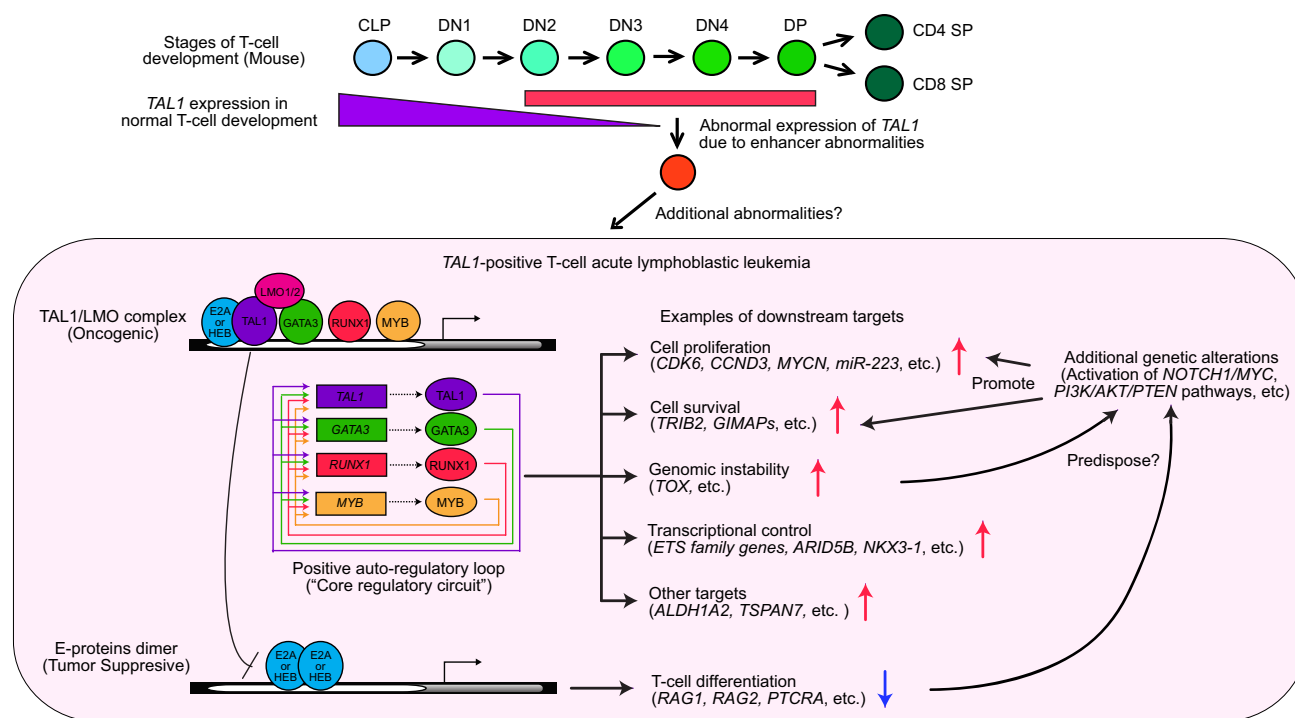
TAL1 plays an indispensable role in normal hematopoiesis, and its expression progressively decreases during T-cell development. In contrast, this factor has been implicated as an oncogene in T-ALL (Fig. 1). The *TAL1* gene is overexpressed in approximately half of T-ALL cases through chromosomal translocations, intrachromosomal rearrangements, or somatic mutations in an intergenic element [2, 65–68], which in turn replaces the regulatory element.

### Mechanisms of activation of TAL1 in T-ALL

The chromosomal translocation involving the regulatory element of the *T-cell receptor (TCR)* gene [14q11.2 (*TRA*, *TRD*), 7q34 (*TRB*) and 7p14 (*TRG*)] is a hallmark of T-ALL [1]. *TAL1* was originally identified as the “stem cell leukemia (*SCL*)” gene from the chromosomal translocation t(1;14)(p33;q11) in a T-ALL cell line [2]. This type of chromosomal translocation event leads to the abnormal expression of a translocation partner gene under the control of the *TCR* regulatory element. Another mechanism that drives *TAL1* expression is the intrachromosomal rearrangement called “*SIL-TAL1* fusion” or “*SIL-TAL1* deletion” [65, 68]. In this instance, the sub-microscopic interstitial deletion including the 5' untranslated region between the *TAL1* and *SIL* genes leads to the abnormal expression of *TAL1* under the *SIL* gene regulatory element. In addition to those structural abnormalities, Mansour et al. and Navarro et al. recently discovered heterozygous somatic mutations within a noncoding intergenic element prior to the *TAL1* transcription start site, which introduces a *MYB*-binding motif and generates a new enhancer driving *TAL1* expression (named *MuTE*) [67, 69]. This is one of the first examples of enhancer mutations in cancer. Importantly, all of these mechanisms lead to the expression of wild-type TAL1 protein. Thus, an abnormal ectopic expression but not a functional alteration is the oncogenic mechanism of TAL1.

### Inhibition of E-protein functions and differentiation block

The oncogenic properties of TAL1 have also been characterized. Early studies using animal models have shown that *Tal1* overexpression in murine T-cells results in a differentiation block at the DN or DP stage of thymocytes and, subsequently, T-ALL [10, 11]. One of the critical mechanisms



**Fig. 1** Model of leukemic transformation induced by TAL1 in T-ALL. *TAL1* is normally silenced during T-cell development. In human T-ALL cells, *TAL1* is abnormally expressed due to enhancer abnormalities such as chromosomal translocation, intrachromosomal rearrangement, or mutations in the enhancer. The cells may acquire additional genetic abnormalities to be fully transformed. In *TAL1*-positive T-ALL cells, TAL1 protein forms a large complex with several transcription factors and coordinately regulates downstream target genes, which affect several different cellular machineries. TAL1, GATA3, RUNX1 and MYB positively regulate each other, thus form-

ing a positive auto-regulatory loop (“core regulatory circuit”). TAL1 also inhibits E-protein functions, thereby leading to a differentiation block. Those mechanism may predispose the cells to acquire additional abnormalities such as mutations in the NOTCH1 and PIK3/AKT/PEN pathways, which also promote cell proliferation and survival in T-ALL cells. Stages of mouse T-cell development are shown: *CLP* common lymphoid progenitors, *DN* CD4<sup>-</sup> CD8<sup>-</sup> double negative, *DP*, CD4<sup>+</sup> CD8<sup>+</sup>, double positive, *SP* single positive (CD4<sup>+</sup> or CD8<sup>+</sup>)

involved is the disruption of the T-cell differentiation machinery via inhibition of E-proteins. TAL1 overexpression is thought to result in a sequestration of E-proteins into the TAL1-E-protein heterodimer and thus indirectly inhibit the transcription of genes regulated by E-protein–E-protein dimers [70]. In human and mouse T-ALL cells, the expression levels of *RAG1*, *RAG2* and *PTCRA* are often repressed and can be upregulated after *TAL1* knockdown [71–73]. Similarly, *CD4*, *TCR-alpha* and *CD69* genes have been reported to be repressed by TAL1 [49, 71, 74]. Thus, ectopic *TAL1* expression affects the T-cell differentiation program.

Importantly, earlier studies have shown that genetic knockout of the E-protein *E2a* causes a differentiation block and T-ALL [75], which are similar to the phenotypes observed in the *Tall*-transgenic model. A haplo-insufficient genetic background of E-proteins (*E2a* or *Heb*) significantly accelerates tumor onset and increases overall disease penetrance in *Tall*-transgenic mice [71]. Those studies clearly implicate E-proteins as tumor suppressors in the context of T-ALL. Additionally, overexpression of the mutant form of Tall protein, which lacks a DNA-binding ability but can

still bind to E-proteins, is able to induce T-ALL [76]. Thus, this result suggests that inhibition of the E-protein-mediated transcriptional program is one of the primary mechanisms of T-cell leukemogenesis.

### Collaborating oncogenic pathways of TAL1

Although these studies demonstrated the abilities of TAL1 and E-proteins to act as an oncogene and a tumor suppressor, respectively, the overexpression of *TAL1* alone may not be sufficient to fully transform thymocytes. In the *Tall*-transgenic mice model, only approximately 30% of animals develop T-ALL after a latent period of typically more than 100 days [71], which suggests that additional abnormalities might be required. In this regard, either the *LMO1* or *LMO2* gene, which encodes another component of the TAL1 complex, is abnormally expressed in almost all *TAL1*-positive human T-ALL cases due to enhancer abnormalities, such as mutations in the enhancer or chromosomal translocation [18, 77, 78]. In murine studies, *Tall/Lmo2*-double transgenic mice show a significant acceleration of tumor onset and an

increase in disease penetrance compared with single transgenic animals [11, 79, 80], demonstrating a collaborating effect. A recent structural study showed that LMO2 binding strengthens the TAL1-E2A heterodimer formation by introducing new hydrogen bonds [81]. These studies indicate that TAL1 requires either LMO1 or LMO2 to also be expressed to exert its full oncogenic ability.

Another collaborating oncogene is *NOTCH1*. In murine T-ALL models, the *Notch1* gene is mutated in over 50% of cases, similar to human T-ALL [11, 82]. Interestingly, the frequency of *Notch1* mutations in the *Tal1*-transgenic model is higher (over 75%) than that in T-ALL developed using other murine models (e.g., mutation of *Tp53* or *Atm*) [82]. Several studies have demonstrated that TAL1 and NOTCH1 regulate a different set of genes [32, 83] but also share the same targets, such as *CDK6* and *TRIB2* [41, 84–86]. Thus, these two T-ALL oncogenes compensate and potentiate each other to synergistically promote T-cell leukemogenesis.

Additionally, recent genome-wide studies have revealed that several genes are more frequently mutated in the *TAL1*-positive T-ALL subgroup than in other subgroups [35]. For instance, mutations in the genes mediating the PI3K-PTEN-AKT-mTOR pathway, including *PTEN*, are observed in approximately half of *TAL1*-positive human T-ALL cases [35, 37, 38], while these mutations are less frequently found in *TAL1*-negative cases. This finding suggests potential collaborating effects or a requirement of this pathway and could also coincide with the fact that TAL1 affects the mTOR pathway in normal HSCs via the repression of *DDIT4* [53]. Similarly, mutations in the *USP7* gene are more frequently found in *TAL1*-positive cases [35], suggesting a potential collaborating role of this gene.

### Transcriptional targets of TAL1 in T-ALL cells: protein-coding genes

Besides the inhibition of E-protein functions, TAL1 exerts its oncogenic ability by directly regulating target genes in T-ALL cells, including protein-coding genes and non-coding RNAs. Because TAL1 is normally silenced during T-cell development, TAL1 may not have any physiological targets in normal T-cells. Thus, activation of target genes by TAL1 in T-ALL cells could be aberrant. Such genes would be responsible for the pathogenesis of T-ALL. In this regard, we and other groups have identified several genes directly regulated by TAL1 in human T-ALL cells.

### Hematopoietic transcription factors forming the core regulatory circuit

The Look, Young and Sanda laboratories and the Brand laboratory independently performed a genome-wide analysis

for the identification of TAL1 targets in T-ALL cells, using ChIP-seq and gene expression analysis [41, 87]. These studies demonstrated that TAL1 regulates several other hematopoietic transcription factors, including *GATA3*, *RUNX1*, *MYB* and the *ETS* family of genes. For example, TAL1 binds to the *RUNX1* enhancer (*eRI*), located in intron 1 of the *RUNX1* gene, which has been previously reported to be active in normal HSCs and progenitors [61, 88]. Similarly, TAL1 binds to the *GATA3* and *MYB* regulatory elements. TAL1 also binds to its own enhancer region in cases of *TAL1* enhancer mutations (*MuTE*) [41, 67]. Independently, Thoms et al. reported that the TAL1 complex regulates the ETS family transcription factor *ERG* through an enhancer region in T-ALL cells [89]. *ERG* overexpression maintains T-ALL cell proliferation, and transgenic mice with *Erg* overexpression develop T-ALL. Of note, *ERG* directly interacts with TAL1, *RUNX1*, and *GATA2*, and this complex coordinately regulates their common targets in normal human HSCs and progenitors [63, 90]. In our previous study, other ETS family genes, including *ETS1*, *ETV5* and *ETV6*, have also been found to be regulated by TAL1 in T-ALL cells [41].

Importantly, these transcription factors often co-occupy the same regulatory elements in T-ALL cells, including the enhancers of their own genes. For example, the *eRI* and *MuTE* regions are co-bound by TAL1, *GATA3*, *RUNX1*, *MYB* and the ETS family proteins [41]. Similarly, *GATA3* and *MYB* enhancers are bound by these factors. Additionally, the genes regulated after knockdown of *TAL1* closely overlaps with those after knockdown of *GATA3*, *RUNX1* or *MYB* [41]. Thus, these complexes of transcription factors are orchestrated in an auto-regulatory loop and coordinately regulate downstream gene expression in T-ALL cells. Of note, a recent study using murine models demonstrated that a genetic loss of *Runx1* significantly delays the tumor onset of *Tal1*-induced T-ALL [91]. Knockdown of *RUNX1* in human T-ALL cell lines inhibits cell growth. These results demonstrate the requirement of *RUNX1* in the context of *TAL1*-positive T-ALL, which is in marked contrast to its tumor-suppressive role in myeloid malignancies.

Furthermore, it is noteworthy that the enhancers of *TAL1*, *GATA3*, *RUNX1* and *MYB* are all associated with a super-enhancer, which is a cluster of enhancers characterized by a high level of active histone marks [92]. This finding suggests that TAL1 and its regulatory partners need to be highly expressed to maintain the transcriptional program in T-ALL cells. This type of structure has been termed as the “core regulatory circuit” and is considered to maintain the state of normal or malignant cells [41, 93, 94]. One example is *Oct4*, *Sox2* and *Nanog* that form an interconnected auto-regulatory loop in embryonic stem cells [93]. These findings indicate that TAL1 functions as a master transcription factor and that the core regulatory circuit controls an extensive transcriptional regulatory network in T-ALL.

## Other transcription regulators

Several other transcriptional regulators have been implicated as TAL1 targets in T-ALL cells. Our group has recently performed a comprehensive analysis using RNA-seqs after *TAL1* knockdown and each of its regulatory partner proteins [95]. This analysis identified several high-confidence targets of TAL1, including *ARID5B*. *ARID5B* is a member of the ARID family of transcription factors. The enhancer controlling *ARID5B* expression (−135 k enhancer) is directly activated by the TAL1 complex and is associated with a super-enhancer in T-ALL cells but not in normal T-cells. Although the molecular function of *ARID5B* remains unclear, its genome-wide binding profiling demonstrates that *ARID5B*-bound regions are predominantly associated with active histone marks in T-ALL cells. As an example, *ARID5B* positively regulates the expression of *TAL1* and its regulatory partners (*GATA3*, *RUNX1* and *MYB*) as well as the *MYC* oncogene in T-ALL cells. Therefore, *ARID5B* may serve as a transcriptional activator that enhances or consolidates the regulatory network initiated by the TAL1 complex. In addition, *ARID5B* overexpression in zebrafish leads to thymus retention, radio-resistance and differentiation arrest, some of which can result in T-ALL [95]. These results indicate that *ARID5B* plays critical oncogenic roles as a second-tier factor of TAL1 in T-ALL.

Similarly, the *NKX3-1* gene, which encodes an NKL homeobox transcription factor, has been reported as a downstream target of the TAL1 complex in T-ALL cells [94, 96, 97]. *NKX3-1* is normally expressed in prostate and testis and plays substantial roles in several fundamental cellular processes, such as stem cell maintenance, embryogenesis and cell proliferation [98, 99]. *NKX3-1* is required for T-ALL cell proliferation and maintenance in mice [96]. The downstream analysis of *NKX3-1* revealed that it regulates *MYCN* and a homeobox gene, *SIX6*. These results indicate there is a critical role of *NKX3-1* as a downstream target of TAL1.

The oncogene *MYCN* has also been reported as a TAL1 target in T-ALL cells [100]. Silencing of *MYCN* induces apoptosis in *TAL1*-positive T-ALL cells, implying its oncogenic role. *MYCN* is normally expressed in HSCs and progenitor cells but is silenced during the DN stage of thymocytes [47], which is similar to the *TAL1* expression pattern. Thus, *MYCN* could be a physiological target of TAL1 in normal hematopoietic cells. However, *MYCN* is also overexpressed in *TAL1*-negative, *LYL1*-positive T-ALL cases that typically show the ETP/immature T-ALL phenotype [21], suggesting that *MYCN* could be regulated by other transcription factors in progenitor cells. In most T-ALL cases, another *MYC* oncogene (*MYC/c-MYC*) is highly expressed due to activating mutations of *NOTCH1* and serves as a driver oncogene [31–33]. Hence,

the significance of *MYCN* overexpression in the pathogenesis of *TAL1*-positive T-ALL remains unclear.

Additionally, NF- $\kappa$ B signaling has been reported to be regulated by the TAL1 complex in T-ALL. Poglio et al. reported that the NF- $\kappa$ B pathway contributes to rapid T-ALL growth in xenografts [101]. Increased NF- $\kappa$ B activity is observed in pre-malignant thymocytes and tumors in *Tall*-transgenic mice [102]. As a potential mechanism, TAL1 has been shown to repress the transcription of the *NFKB1* (*p105/p50*) gene by directly binding to its promoter [103]. The reduced expression of p50, the processed form of p105, results in the formation of the atypical p65/c-REL complex rather than the classic p65/p50 NF- $\kappa$ B dimer and thus, upregulates p65/c-REL target genes.

## Cell cycle regulators

One of the common phenotypes observed in T-ALL is the abnormal proliferation of immature thymocytes. Previous studies have shown that CDK6 and its substrate Cyclin D3 are required for T-ALL development [104–106]. Choi et al. reported that genetic knockout of *Cyclin D3* inhibits both the initiation and maintenance of murine T-ALL driven by *Notch1* [106]. More recently, the same group has reported that most T-ALL cells predominantly express *CDK6* and *Cyclin D3*, while a low level of other *D-type cyclins* and *CDK4* have been found [107]. In addition to cell cycle regulation, increased expression of the Cyclin D3-CDK6 complex is associated with the capacity of enzymes involved in glycolysis, which reprograms the cell for the pentose phosphate and serine pathways rather than glycolysis.

In this regard, TAL1 has been known to directly regulate *CDK6* to supplement this factor, where it can also suppress the transcription of *CDKN2A/p16*, which inhibits CDK6-Cyclin D3 function, in T-ALL cells [87, 108]. Our previous dataset also confirmed that both the *CDK6* and *CCND3* gene locus are bound by the TAL1 complex [41]. In particular, the *CDK6* gene is associated with a super-enhancer and is highly expressed in *TAL1*-positive human T-ALL cells [92]. These studies indicate that TAL1 could promote cell proliferation via the upregulation of *CDK6* and *CCND3*. However, it should be noted that the cell cycle arrest phenotype after *TAL1* knockdown in T-ALL cells is generally very subtle [41]. This effect could be in part explained by the compensatory mechanism by CDK4 and other upstream oncogenic transcription factors. For example, the *CDK6* and *CDK4* genes are known to be regulated by NOTCH1 in T-ALL cells [83, 84]. Nevertheless, these findings indicate an essential role of *CDK6* in the initiation and maintenance of T-ALL driven by two oncogenes.

## Pro-survival factors

Resisting cell death is another important hallmark of cancer [109]. Anti-apoptotic BH3 proteins, such as BCL2, BCL-XL and MCL1, are often highly expressed in T-ALL, thereby preventing apoptotic cell death [110, 111]. It is, however, noteworthy that these proteins are also expressed at specific stages in normal T-cells. For example, *BCL2* is highly expressed in normal ETP cells as well as in ETP ALL, whereas *BCL-XL* is highly expressed in the DP stage of normal thymocytes as well as in non-ETP T-ALL [110, 112]. In our previous study, we extensively searched for the possibility of the regulation of these BH3 proteins by TAL1, but no strong evidence was discovered to confirm this hypothesis. Thus, the upregulation of those proteins may reflect the differentiation stage, where T-ALL cells arise.

On the other hand, certain TAL1 targets have known to indirectly affect apoptosis pathways. The Sicinski laboratory has shown that the depletion of *Cyclin D3* or *CDK6* triggers apoptotic cell death in human T-ALL cells through an increase in reactive oxygen species [106, 107]. In addition, we previously performed a loss-of-function RNA interference screen for *TAL1*-positive T-ALL cells [41]. Among the high-confidence targets that were directly regulated by TAL1, the *TRIB2* gene was selected as a factor that is required for cell growth and survival. *TRIB2* belongs to the *Tribbles* gene family and encodes a pseudokinase domain that is incapable of catalyzing protein phosphorylation but may act as an adaptor protein [113]. Subsequent studies by us showed that *TRIB2* enhances resistance to cytotoxic drugs and upregulates the expression of the XIAP anti-apoptotic protein but not of other anti-apoptotic proteins [114]. Interestingly, *TRIB2* also positively regulates the expression of *TAL1*, *GATA3*, *RUNX1* and *MYB* and inhibits *E2A*, thus indicating that this factor reinforces the TAL1-induced transcriptional program as a second tier in T-ALL cells. Of note, *TRIB2* is also a NOTCH1 target in T-ALL [85, 86]. Ablation of *TRIB2* shortened T-ALL tumor onset and accelerated the penetrance in a Notch-driven T-ALL mice model, possibly through the negative regulation of MAPK signaling or C/EBP- $\alpha$  [115, 116].

## DNA damage repair factors

Mouse studies have shown that TAL1 induces T-ALL after a long latent period [71], which suggests that pre-leukemic cells initiated by *TAL1* overexpression may require an accumulation of genetic abnormalities for full leukemic transformation. In general, an enhanced genotoxicity or compromised DNA repair machinery contributes to this mechanism [109]. For example, *KU70/KU80* (*XRCC6/XRCC5*)-deficient mice develop T-cell malignancies [117], because impaired nonhomologous end joining (NHEJ) machinery facilitates

chromosomal deletions, transversions and translocation in early leukemic cells. Similarly, mice deficient in *Tp53* or *Atm* frequently develop T-cell malignancies [82, 118].

In this regard, the *TOX* gene has been reported as a TAL1 target in T-ALL [41, 119]. *TOX* protein binds directly to the dimeric KU70/80 and suppresses the recruitment of this complex to the DNA breaks. This suppression impedes the formation of the full DNA-PK complex, which is an essential machinery during the NHEJ repair. Thus, *TOX* upregulation possibly elevates genomic instability and expands the initiating pool of transformed clones via suppressing the NHEJ repair pathway. In a zebrafish model, overexpression of human *TOX* was found to accelerate *Myc*-driven T-ALL onset [119]. *TOX* sustains leukemic cell proliferation following transformation, as interpreted from its indispensable roles in T-ALL xenograft growth in mice. These studies indicated an oncogenic role of *TOX* in T-ALL development.

## Other TAL1 target genes

Despite the regulatory roles of the TAL1 complex as well as its landmark targets having been well elucidated in T-ALL, the functions of several TAL1 downstream genes remain uncharacterized. *TSPAN7/CD231* is one of the first examples reported as a TAL1 target in human T-ALL cells [120]. This gene encodes a cell surface protein that was originally named “T-cell acute lymphoblastic leukemia antigen (TALLA-1)”. Exogenous transfection of *TAL1*, *LMO* and *GATA3* can induce *TSPAN7* protein expression in a T-ALL cell line [121]. Importantly, *TSPAN7* is specifically and highly expressed in T-ALL cells compared with normal peripheral blood [122]. Although the biological function of *TSPAN7* is largely unknown, this protein can be a feasible therapeutic target for T-ALL.

Another gene that was identified as a TAL1 target in human T-ALL is the *ALDH1A2* gene [123]. The TAL1 complex binds within the intron of *ALDH1A2* gene, initiating the transcription of the shortest variant of this gene. This variant is specific to T-ALL and is highly expressed in T-ALL cell lines and primary cases. *ALDH1A2* canonically encodes a major enzyme that synthesizes retinoic acid. *ALDH1A2*-knockout mice show reduced production of retinoic acid and eventually develop hypoplasia or aplasia in the thymus and parathyroid glands [124], indicating that *ALDH1A2* activity is indispensable for the development of these organs. Interestingly, forced expression of *ALDH1A2* enhances cell proliferation and drug resistance in chronic myeloid leukemia cells [125, 126]. Moreover, genes that are highly associated with *ALDH1A2* in primary T-ALL expression profiles mostly benefit cell proliferation [127]. Treatment with an *ALDH1A* inhibitor and a retinoic acid signaling agonist are more effective against T-ALL than B-cell lineage malignancies [127]. These results suggest potential oncogenic roles of

ALDH1A2 in T-ALL pathogenesis. It is also noteworthy that ALDH activity has been implicated as a stem cell marker in both normal and cancer stem cells.

The other example of TAL1 targets in T-ALL cells is the *GIMAP* gene cluster [128], which consists of seven genes (*GIMAP1*, *GIMAP2*, *GIMAP4*, *GIMAP5*, *GIMAP6*, *GIMAP7* and *GIMAP8*) that belong to the same gene family. Some of the *GIMAP* genes have been implicated in the T-cell survival-death decision [129]; however, their molecular functions have not been elucidated yet. Our group has shown that the TAL1 complex binds to the enhancer located between the *GIMAP6* and *GIMAP2* genes in human T-ALL cells, and this enhancer is associated with a super-enhancer [128]. This element is also bound and regulated by NOTCH1 [130]. Interestingly, knockdown of a member of the TAL1 complex or genetic knockout of the enhancer results in the concurrent downregulation of all *GIMAP* genes, indicating that a single enhancer can control all *GIMAP* genes. Notably, this enhancer can be activated in HSCs and progenitors in zebrafish. Similar to the expression pattern of *Tal1*, the expression of mouse *Gimap* genes are found in HSCs and repressed during thymocyte differentiation. Hence, *GIMAP* gene expression is associated with *TAL1* expression. Importantly, the concomitant overexpression of *GIMAP5* and *GIMAP7* significantly accelerates tumor onset of T-ALL driven by *Myc* in zebrafish. Although further characterization of the molecular functions of GIMAPs is required, the *GIMAP* genes contribute to T-cell leukemogenesis as a downstream effector of TAL1 and NOTCH1.

### Transcriptional targets of TAL1 in T-ALL cells: non-coding RNAs

Over the last decade, a large proportion of the human genome (> 75%) was discovered to be actively transcribed, but not all of the resulting transcripts encode proteins [131–134]. The non-coding transcription products include microRNAs (miRNAs), long non-coding RNAs (lncRNAs), small nuclear RNAs (snRNAs) and circular RNAs (circRNAs). Recent studies have demonstrated that these non-coding substances not only embrace key functions in normal development but also play critical roles in the pathogenesis of cancer [135–138].

For example, Wendel et al. have shown that *miR-19* from the *miR-17~92* cluster is sufficient to promote leukemogenesis in *Notch1*-induced T-ALL [139]. Regarding lncRNAs, Wallaerts et al. performed an expression profile in primary T-ALL cases, which was able to classify T-ALL subgroups based on their expression pattern [140]. Trimarchi et al. have reported that *LUNARI* (leukemia-induced noncoding activator RNA1) was a NOTCH1 target that plays an oncogenic role by regulating *IGF1R* expression [141].

Meanwhile, Wang et al. reported *NALT* (*Notch1-associated lncRNA in T-ALL*) as a lncRNA-regulating *NOTCH1* expression through cis-regulation, mainly involved in cell proliferation [142]. On the other hand, we have reported several miRNAs and lncRNAs as downstream of TAL1 in T-ALL cells. However, compared with protein-coding genes, very little is known regarding these molecules.

### miRNAs regulated by TAL1 in T-ALL

In the case of the *TAL1*-positive subgroup of T-ALL, Mansour et al. along with us previously performed a comprehensive identification of miRNAs directly regulated by TAL1 [143]. This study discovered 22 miRNAs that were significantly up or downregulated after *TAL1* knockdown, and among them, five (*miR-223*, *miR-181a*, *miR-29c*, *miR-26a* and *miR-620*) exhibited TAL1 binding near the miRNA loci. Among the shortlisted miRNAs, *miR-223* was the most promising downstream target based on its differential expression after *TAL1* knockdown and its contribution to cell viability of *TAL1*-positive T-ALL cells. The expression pattern of *miR-223* is similar to that of TAL1, which is high during the ETP stage and decreases after the DN3 stage. Importantly, *miR-223* inhibits the mRNA of the ubiquitin ligase *FBXW7* in a sequence-specific manner, which results in upregulation of its substrate oncoproteins including MYC, MYB, Cyclin E and NOTCH1. Hence, the *TAL1-miR223* axis supports cell proliferation and survival by indirectly regulating these oncoproteins.

### lncRNAs regulated by TAL1 in T-ALL

Our group has recently performed a comprehensive identification of lncRNAs expressed in *TAL1*-positive T-ALL cells by developing a bioinformatics pipeline and RNA-seq analysis with deep coverage [73]. We selected a list of putative lncRNAs that are directly activated by TAL1 and their regulatory complex partners. From this study, two novel lncRNAs that are aberrantly expressed in T-ALL cells but not in normal thymocytes were identified. One lncRNA is the *ARID5B Inducing Enhancer Associated Long non-coding RNA (ARIEL)* (originally named *XLOC\_005968*), which is located in the *ARID5B* –135 k enhancer locus and is directly activated by the TAL1 complex. This transcript was specifically expressed in several *TAL1*-positive T-ALL cell lines and primary leukemia samples but not in normal hematopoietic cells. The other novel lncRNA (*XLOC\_030252*) is located between the *FAM49A* and *MYCN* gene locus and is expressed in not only *TAL1*-subtypes but also in *TLX*-subtype T-ALL samples. This lncRNA is also expressed in normal hematopoietic progenitor cells and in the early stages of thymus development, suggesting that it is a physiological



target of TAL1 and may play a role in normal hematopoiesis as well.

Meanwhile, we have also reported lncRNAs that are negatively regulated by TAL1, including a known lncRNA *lnc-OAZ3-2:7*, which is located near the *RORC* gene. Both *lnc-OAZ3-2:7* and *RORC* are expressed in normal thymocytes but are downregulated in *TAL1*-positive T-ALL cells, suggesting that they are repressed by TAL1, possibly through inhibition of E-proteins, and may play a role in T-cell differentiation.

## Conclusions and future perspectives

TAL1 is a classic example of an oncogene that was identified from a chromosomal translocation in acute leukemia. The studies on TAL1 provided several novel insights into cancer genetics, including the discovery of intrachromosomal rearrangements and mutations in the enhancer, which replace or create a regulatory element. Furthermore, recent studies have revealed TAL1 as a master transcription factor that forms a core regulatory circuit and is driven by super-enhancers. Comprehensive analysis clarified the regulatory elements and downstream targets controlled by TAL1 in T-ALL cells. All of these studies implicate TAL1 as a critical transcription factor at the top of the transcriptional hierarchy.

However, there are several questions that remain unelucidated. First, our current understanding of the regulatory network is mostly based on the function of protein-coding genes. However, our previous analysis demonstrated that approximately half of TAL1-bound regions are located in the intergenic elements, many of which do not reside near protein-coding genes. Hence, we have not yet clarified all of the targets of TAL1. Second, related to this question, the involvement of non-coding RNAs is largely unknown. Although we have identified several miRNAs and lncRNAs that are directly regulated by TAL1 in human T-ALL cells, it is difficult to elucidate their physiological functions, because the sequence of non-coding RNAs are poorly conserved among species in general, and thus, animal models may not be used. In other words, studying non-coding RNAs is critical to explaining the pathogenesis of human T-ALL, which is not observed in animal models. Third, we have not answered the most fundamental question: why does TAL1 expression cause leukemia specifically in T-cells? To address this point, more detailed analysis of the regulatory network in the context of T-cells is necessary. Lastly, although we and others have identified several downstream targets of TAL1 that contribute to leukemogenesis, we still do not have feasible therapeutic targets. More extensive investigations are necessary to develop novel therapeutics for T-ALL.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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