Genetic insights in *ETV6/RUNX1*-positive B-cell precursor acute lymphoblastic leukaemia

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SUMMARY

Acute lymphoblastic leukaemia, a clinically and biologically heterogeneous disease, represents the most common malignant disease in childhood. Approximately 20-25% of B-cell precursor acute lymphoblastic leukaemia in childhood carry the cryptic chromosomal translocation t(12;21)(p13;q22). This translocation combines two transcription factors and essential regulators of normal haematopoiesis, ETV6 and RUNX1, into the fusion oncogene *ETV6/RUNX1* (formerly known as *TEL/AML1*). Recent studies in various animal models have strengthened the view that *ETV6/RUNX1*-positive cells give rise to pre-leukemic clones with a differentiation block in the pro/pre-B stage of B-cell development that, after acquisition of additional mutations, may transform into full malignancy. Despite the favourable prognostic parameters of this B-cell precursor acute lymphoblastic leukaemia subgroup, relapse and resistance to chemotherapeutics do occur and increased knowledge of the molecular mechanisms underlying *ETV6/RUNX1*-driven leukaemia is essential to develop novel therapeutic strategies to selectively target *ETV6/RUNX1*-positive leukaemia. In this manuscript, an overview of the most recent genetic insights in *ETV6/RUNX1*-positive B-cell precursor acute lymphoblastic leukaemia is given.

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INTRODUCTION

The cryptic t(12;21)(p13;q22) translocation was first described in 1995 and is recognised as the most common structural chromosomal abnormality in paediatric B-cell precursor acute lymphoblastic leukaemia (BCP-ALL) occurring in ~25% of children diagnosed with ALL.[1,2] On the contrary, it is only observed in 1-4.4% of adult BCP-ALL.[3] The translocation gives rise to the fusion of Runt-related transcription factor 1 (*RUNX1*; formerly known as *AML1*) and ETS variant 6 (*ETV6*; formerly known as *TEL*). This rearrangement is not detectable by conventional cytogenetic analysis as the G-banding pattern and size of the translocated regions between chromosome 12 and 21 are identical. Nevertheless, *ETV6/RUNX1*-positive BCP-ALL patients can easily be identified by fluorescence in situ hybridisation (FISH) and/or reverse transcription polymerase chain reaction (RT-PCR) analysis.[3,4]

The identification of *ETV6/RUNX1* genomic sequences in neonatal blood spots and the fact that monozygotic twin pairs with concordant leukaemia share the exact same fusion gene sequence and unique genomic breakpoints, clearly suggests that this translocation can originate *in utero*.[5] However, the low concordance rate in monozygotic twins (around 5–10%), a prolonged postnatal latency between fusion formation and disease presentation (up to fourteen years) and the presence of this fusion protein in cord blood at a higher frequency than the risk of developing the corresponding leukaemia, hints towards the fact that this translocation *per se* cannot induce overt leukaemia.[6] Malignant progression depends on the acquisition of additional oncogenic, postnatal

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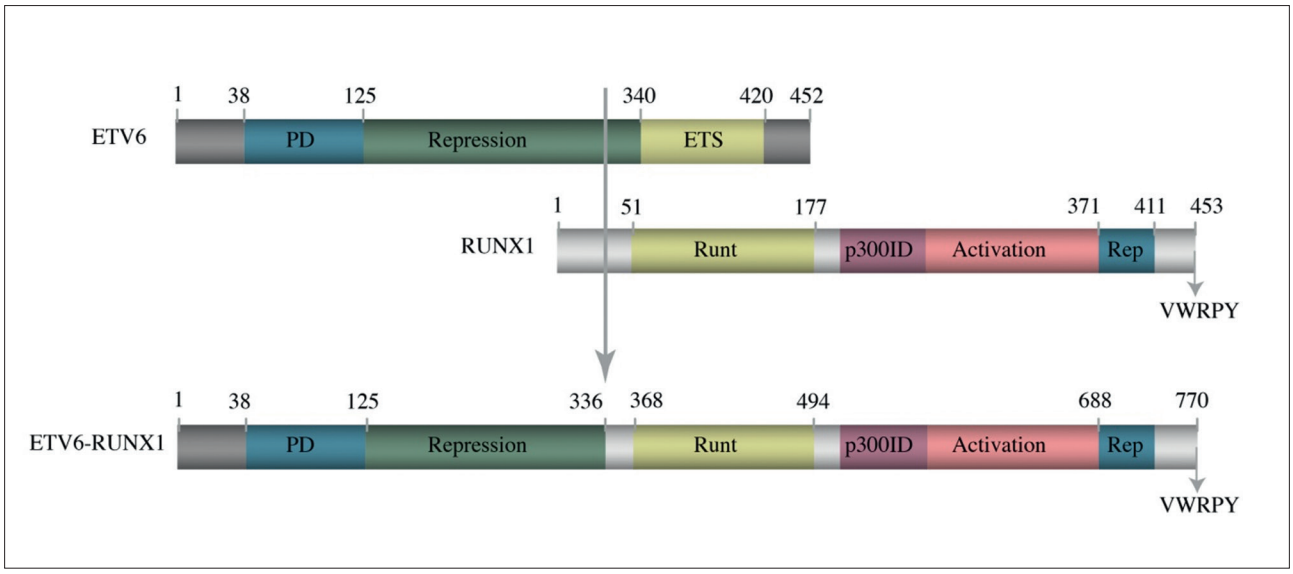

FIGURE 1. Schematic presentation of full-length ETV6, RUNX1 and ETV6/RUNX1 proteins.[26] Arrows indicate fusion points between ETV6 and RUNX1 sequences. Amino acids that border the key functional domains are numbered with number 1 corresponding to the first methionine. *Adapted with permission from Macmillan Publishers Ltd: Oncogene, doi:10.1038/sj.onc.1207672, copyright 2004.*

genetic events.[5,7,8] This concept was further confirmed using transplantation of bone marrow (BM) cells expressing the *ETV6/RUNX1* fusion protein in a mouse model, where the ETV6/RUNX1 expression affected the normal haematopoietic differentiation. Although the impaired haematopoietic differentiation led to the *in vivo* accumulation and persistence of B-cell progenitors and an increased self-renewal capacity, no leukaemia induction was observed during an observation period of over one year.[9]

During lymphocyte development, immunoglobulin and T-cell receptor genes undergo somatic DNA rearrangements.[10] This process is mediated by recombination-activating gene proteins, such as RAG1 and RAG2, which recognise and bind recombination signal sequences (RSSs) that are located adjacent to the site of recombination. Notably, off-target RAG activity is an important driver of leukaemia, as exemplified by the frequent identification of RSS sites in close proximity of the genomic breakpoints of somatic deletions in human leukaemias.[11-14] Similarly, aberrant RAG recombinase activity has also been identified as a dominant mechanism of tumour suppressor inactivation as secondary genetic events in *ETV6/RUNX1*-positive BCP-ALL.[15]

Commonly observed genetic alterations in the *ETV6/RUNX1* rearranged leukaemias include deletions of transcription factor genes (such as *PAX5, EBF1* or the wild-type copy of *ETV6*), cell cycle regulators (e.g. *CDKN2A*), recombination-activating enzymes (e.g. *RAG1* or *RAG2*), lymphoid signalling molecules (e.g. *BTLA, CD200* or *TOX*), alterations of transcriptional co-activators (e.g. *TBL1XR1*), the glucocorticoid receptor *NR3C1* and the apoptosis regulator *BTG1*.[15-19]

Although this BCP-ALL subtype is generally associated with a good prognosis with event-free survival rates approaching 90% with contemporary treatment protocols, late relapses and resistance to chemotherapy do occur.[20-22]

The late occurrence of relapse, together with clonal variation between initial and relapse leukaemias suggests that ETV6/RUNX1-expressing pre-leukaemia sub-clones, which are not fully malignant at initial diagnosis, resist treatment and acquire additional genomic aberrations, which may be necessary for the manifestation of relapse.[23-25] Genome-wide copy number analysis of matched diagnosis and relapse leukaemias, revealed particular alterations exclusively present or more abundant at relapse such as deletions of *IKZF1, EBF1, CDKN2A, NR3C1* and *NR3C2* genes, which might be either predictive or characteristic of relapse.[25]

MOLECULAR STRUCTURE AND FUNCTION OF ETV6/RUNX1

RUNX1

RUNX1 is located at chromosome 21q22.12 (Chr 21: 34,787,801-36,004,667 reverse strand GRCh38) and encodes the α-subunit of the core-binding factor (CBFα). The RUNX1 protein consists of two large functional domains: the highly conserved Runt domain which mediates both DNA binding and heterodimerization with the β-subunit (CBFβ) and the distal transactivation domain (*Figure 1*). The RUNX1 protein

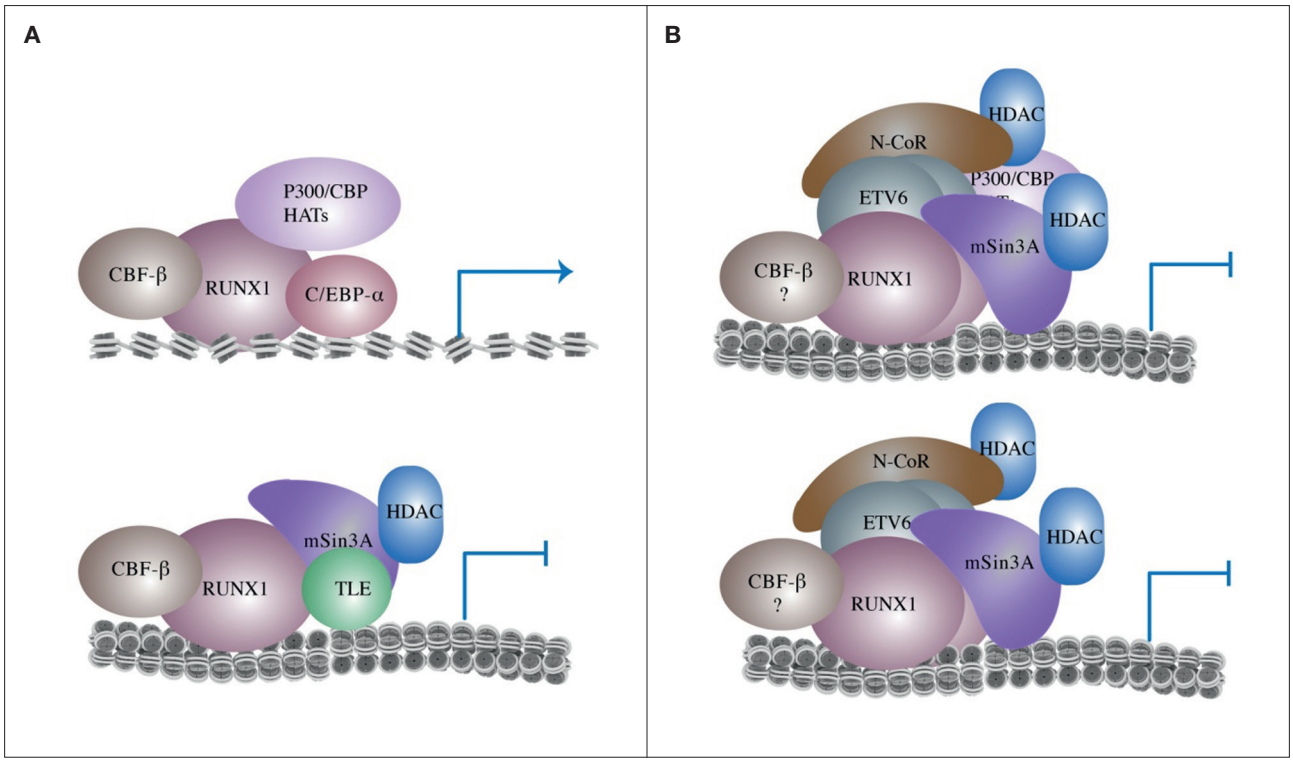

FIGURE 2. Molecular mechanism of wild type RUNX1 and ETV6/RUNX1.[26] The transcription factor RUNX1 either activates or represses its target genes by recruitment of p300 or mSin3A/HDAC, respectively **(A)**. By contrast, the abilities of the ETV6 moiety of ETV6/RUNX1 to recruit and bind to nuclear receptor corepressor/HDAC complex (N-CoR) and mSin3A allow formation of a very stable repressor complex **(B)**. *Adapted with permission from Macmillan Publishers Ltd: Oncogene, doi: 10.1038/sj.onc.1207672, copyright 2004.*

is a transcription factor with activating and repressing abilities depending on recruitment of p300 or mSin3A/HDAC, respectively. The latter is a multi-protein co-repressor complex known to silence gene expression by deacetylating histones. Its association with these cofactors may also be dependent on the regulatory region of RUNX1 target genes and/or cell context (*Figure 2A*).[26] Homozygous disruption of RUNX1 activity in mice (RUNX1$^{-/-}$) result in mid-gestation embryonic lethality and affects all definitive haematopoietic lineages indicating that this transcription factor is a master regulator for the formation of definitive haematopoietic stem cells during haematopoietic development.[27]

ETV6

ETV6 is located at chromosome 12p13.2 (Chr 12: 11,649,854-11,895,402 forward strand GRCh38) and encodes a member of the Ets family of transcription factors harbouring different functional domains such as an N-terminally located oligomerisation pointed domain (PD) (also known as SAM or HLH domain), a central repression domain and a c-terminal ETS domain which mediates DNA binding (*Figure 1*).[26] While RUNX1 is capable of either activating or repressing its target genes, ETV6 is generally considered to act as a transcriptional repressor. ETV6 protein localisation is confined to both nucleus and cytoplasm whereas RUNX1 is found only in the nucleus. *ETV6* knockout in mice (ETV6$^{-/-}$) is embryonic lethal, due to defects in yolk sac angiogenesis. Moreover, in mouse chimeras, which were constructed by injection of neoR-*ETV6*$^{-/-}$ embryonic stem cells in wild type blastocysts, low numbers of *ETV6*$^{-/-}$ haematopoietic progenitor cells detected in the BM suggest that ETV6 is required for homing of haematopoietic progenitors cells to the BM.[28]

ETV6/RUNX1 FUSION

Rearrangement of *RUNX1* and *ETV6* genes with multiple partners has been found in different types of lymphoid and myeloid leukaemias.[29] However, the only known translocation involving *RUNX1* in BCP-ALL is the t(12;21)(p13;q22) (*ETV6/RUNX1*).[30] This fusion gene encodes a chimeric transcription factor which comprises the N-terminal *ETV6* sequence containing the Pointed/SAM and the central repression domain, and nearly the entire *RUNX1* sequence with all known functional regions (*Figure 1*).[1,2] The ETV6 moiety of the fusion protein is responsible for the recruitment

of the nuclear receptor corepressor/HDAC complex (N-CoR) and other corepressor complexes including SMRT and mSin3A. Given that the fusion protein only possesses the DNA binding domain of RUNX1, it would be able to bind to the promoter and enhancer regions of RUNX1 target genes and repressing transcription of these genes (*Figure 2B*).[31,32] Using *in vitro* promoter-reporter assays, this hypothesis was confirmed as illustrated by the ability of ETV6/RUNX1 fusion protein to repress the regulatory regions of haematopoietic-specific genes. In addition, the histone deacetylase inhibitor Trichostatin A could rescue the observed repression.[33,34]

The ETV6 domain, encoded in the fusion protein, confers the ability for homo- or oligomerisation, allowing simultaneous and high affinity binding to multiple RUNX1 DNA-binding sites present in target-gene promoters.[26] In addition, the fusion might hamper normal ETV6 transcriptional regulation through dimerization with, and thus sequestering wild type ETV6 and/or regulatory cofactors.[35,36]

In vivo experiments using transplantation of BM cells with ETV6/RUNX1-expressing vectors in a mouse model showed that the ETV6/RUNX1 fusion protein impairs the normal haematopoietic development and differentiation program of B-lymphocytes resulting in accumulation of early B-cell progenitors. Remarkably, the impact of ETV6/RUNX1 expression appears to be selective for B lymphoid lineages since no block in differentiation of other lineages was observed.[9,37]

PERTURBED PATHWAYS IN *ETV6/RUNX1*-POSITIVE BCP-ALL

Genome-wide transcriptome profiling has provided new insights into the mechanisms driving the development of *ETV6/RUNX1* leukaemias. Studies comparing *ETV6/RUNX1*-positive and negative patients or cell lines revealed aberrant expression of genes involved in differentiation, apoptosis, signal transduction, PI3K/AKT/mTOR signalling and immune responses.[38-40]

Several of these findings were subsequently validated *in vitro* using *ETV6/RUNX1*-positive cell line models, such as REH and AT-2. For example, down-regulation of the fusion product, resulted in a clear inhibition of the PI3K/AKT/mTOR signal pathway, suggesting that this signalling cascade is truly involved in the pathogenesis of *ETV6/RUNX1*-positive childhood leukaemia.[38,39] Given the central role of the PI3K/AKT/mTOR signalling pathway in many cellular activities critical for neoplastic behavior, it is likely that its aberrant activation is not only essential for initiation, but also for the maintenance of *ETV6/RUNX1*-positive leukaemias.[41,42]

In addition, the role of this fusion protein in B-cell differentiation, cell survival and cell renewal capacity was further confirmed by *in vivo* experiments. The ability of ETV6/RUNX1 to block B-cell differentiation through down-regulation of the IRF3-IFNα/β pathway was demonstrated in mouse and human primary haematopoietic precursor cells, which was rescued by treatment of ETV6/RUNX1 expressing cells with IFNα/β.[43] The repopulation capacity of ETV6/RUNX1-supressed REH cells in xenotransplantation NOD/SCID mouse models was diminished as these mice developed leukaemia significantly later than the mice which received the negative control cells.[38,39] Furthermore, an inhibitory impact of ETV6/RUNX1 on the response to TGF-beta was shown in both murine and human model systems. The cells expressing the ETV6/RUNX1 fusion protein showed reduced sensitivity to TGFβ-mediated inhibition of proliferation.[44] These studies provided additional evidence for the role of the ETV6/RUNX1 fusion gene in sustaining the leukaemia process.

UNIQUE LONG NON-CODING RNA EXPRESSION SIGNATURE IN ETV6/RUNX1-DRIVEN BCP-ALL

Overwhelming evidence indicates that long non-coding RNAs (lncRNA) have essential roles in tumorigenesis. Nevertheless, their role in the molecular pathogenesis of paediatric BCP-ALL has not been extensively explored. In a recent comprehensive analysis of the lncRNA transcriptome in *ETV6/RUNX1*-positive BCP-ALL, a unique ETV6/RUNX1 lncRNA signature was established and the transcriptional and phenotypic consequences of lncRNA modulation in the context of ETV6/RUNX1 rearranged leukaemia was analysed. This set of experiments revealed that lnc-NKX2-3-1, lnc-TIMM21-5, lnc-ASTN1-1 and lnc-RTN4R-1 were truly regulated by the oncogenic fusion protein. Moreover, sustained inactivation of lnc-RTN4R-1 in ETV6/RUNX1 positive cells reduced cell viability and caused profound changes in gene expression. Hence, lnc-RTN4R-1 was identified as an lncRNA that might be functionally implicated in the biology of this prevalent subtype of human leukaemia.[45]

CONCLUSION

The *ETV6/RUNX1* rearrangement, the most common genetic abnormality in childhood BCP-ALL, is usually associated with a favourable outcome. Late relapses and chemotherapy resistance remain a problem, indicating the need for identification of additional prognostic markers in this subtype of BCP-ALL. Genome-wide profiling studies have shown that *ETV6/RUNX1*-positive leukaemias are characterised by a unique coding and non-coding gene expression signature with differential expression of genes involved in differentiation, apoptosis, signal transduction and immune response. Overall, these data provide new insights into the mechanisms

KEY MESSAGES FOR CLINICAL PRACTICE

1. The cryptic t(12;21)(p13;q22) translocation is the most common structural chromosomal abnormality in paediatric BCP-ALL, occurring in ~25% of cases.
2. Despite the favourable outcome for most patients, late relapses and chemotherapy resistance occur in this leukaemia subtype and novel therapeutic strategies are needed.
3. The *ETV6/RUNX1* fusion gene gives rise to pre-leukemic clones with a differentiation block in the pro/pre-B stage of B-cell development that, after acquisition of additional mutations, may transform into full malignancy.
4. Aberrant RAG recombinase activity has also been identified as an important secondary genetic event in *ETV6/RUNX1*-positive BCP-ALL.
5. Genome-wide transcriptome profiling revealed aberrant expression of genes involved in differentiation, apoptosis, signal transduction, PI3K/AKT/mTOR signalling and immune responses.
6. A unique lncRNA expression signature is associated with *ETV6/RUNX1*-positive BCP-ALL and lnc-RTN4R-1 is identified as an lncRNA that might be functionally implicated in the biology of this leukaemia subtype.

driving the development of *ETV6/RUNX1* leukaemias, which may lead to the development of novel therapeutic strategies.

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