Advances in Biological Regulation 74 (2019) 100647

Contents lists available at ScienceDirect

Advances in Biological Regulation

journal homepage: www.elsevier.com/locate/jbior

Multi-omic approaches to improve outcome for T-cell acute lymphoblastic leukemia patients

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ARTICLE INFO

Keywords:
T-cell acute lymphoblastic leukemia
Genomics
Transcriptomics
Proteomics
Personalized medicine
Interleukin-7 signaling

ABSTRACT

In the last decade, tremendous progress in curative treatment has been made for T-ALL patients using high-intensive, risk-adapted multi-agent chemotherapy. Further treatment intensification to improve the cure rate is not feasible as it will increase the number of toxic deaths. Hence, about 20% of pediatric patients relapse and often die due to acquired therapy resistance. Personalized medicine is of utmost importance to further increase cure rates and is achieved by targeting specific initiation, maintenance or resistance mechanisms of the disease. Genomic sequencing has revealed mutations that characterize genetic subtypes of many cancers including T-ALL. However, leukemia may have various activated pathways that are not accompanied by the presence of mutations. Therefore, screening for mutations alone is not sufficient to identify all molecular targets and leukemic dependencies for therapeutic inhibition. We review the extent of the driving type A and the secondary type B genomic mutations in pediatric T-ALL that may be targeted by specific inhibitors. Additionally, we review the need for additional screening methods on the transcriptional and protein levels. An integrated 'multi-omic' screening will identify potential targets and biomarkers to establish significant progress in future individualized treatment of T-ALL patients.

1. T-ALL subtypes and driving oncogenes

T-cell acute lymphoblastic leukemia (T-ALL) is the malignant expansion of immature, arrested T-cells at various stages of thymocyte development. The European Group for the Immunological Characterization of Leukemias (EGIL) distinguished three T-ALL subtypes by virtue of their expression of Cluster of Differentiation markers (CD-markers). These subtypes were denoted as early, cortical and mature T-ALL (Bene et al., 1995). The outcome of cortical T-ALL was found superior over the outcome of both other subtypes (Niehues et al., 1999; Pui et al., 1993).

The first T-ALL oncogenes were identified by resolving the translocations from T-cell receptor (TCR) gene enhancers or promoters to other chromosomes as a consequence of errors in VDJ recombination events. This led to the discovery of the *TAL1* oncogene for patients harboring the t(1; 14)(p34; q11) translocation (Begley et al., 1989; Finger et al., 1989), *LYL1* in a patient with a t(7; 19)(q34;

Abbreviations: T-ALL, T-cell acute lymphoblastic leukemia; EGIL, European group of immunological characterization of leukemias; CD, cluster of differentiation; TCR, T-cell receptor; ETP, early thymocyte progenitor; INDEL, insertion/deletion; IL-7R, interleukin-7 receptor; MAPK, mitogen-activated protein kinase; RTK, receptor tyrosine kinase; RPPA, reverse-phase protein array; IL-7, interleukin-7

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https://doi.org/10.1016/j.jbior.2019.100647
Received 25 July 2019; Received in revised form 20 August 2019; Accepted 23 August 2019
Available online 26 August 2019

Table 1
Oncogene rearrangements in T-ALL.

Oncogene activation	Enhancer/promoters	Incidence (%)	Associated subtype	Ref
TAL1, TAL2, LYL1	*TCRB (enh), TCRAD (enh), STIL (promoter), TCF7*[b], Myb-Enh mut.	27, < 1, < 1	TALLMO	(Aplan et al., 1992; Begley et al., 1989; O. Bernard et al., 1991; Brown et al., 1990; Finger et al., 1989; Mansour et al., 2014; Meijerink, 2010; Mellentin et al., 1989; Wang et al., 2000)
LMO1, LMO2, LMO3	*TCRB (enh), TCRAD (enh), MBNL1, STAG2*, Myb-Enh mut., 11q13 deletion	5, 12, < 1	TALLMO	(S. Chen et al., 2011; Hu et al., 2017; Z. Li et al., 2017; Meijerink, 2010; Rahman et al., 2017)
TLX1	*TCRB (enh), TCRAD (V-gene promoter), DDX30*[b]	5	Proliferative	(Dube et al., 1986, 1991; Hatano et al., 1991; Kennedy et al., 1991; Lu et al., 1991)
NKX2-1, NKX2-2	*TCRAD (enh), TCRB (enh)*	5	Proliferative	Homminga et al. (2011)
TLX3	*BCL11B (enh), TCRB (enh), TCRAD (V-gene promoter), CAPSL*	21	TLX	(Berger et al., 2003; O. A. Bernard et al., 2001; Ferrando et al., 2002; Hansen-Hagge et al., 2002; Su et al., 2004)
HOXA9/A10	*TCRB (enh)*	< 2	TLX/ETP-ALL	(Bergeron et al., 2006; Cauwelier et al., 2007; Soulier et al., 2005; Speleman et al., 2005)
MEF2C	*PITX2*	< 2	ETP-ALL	Homminga et al. (2011)
SP1	*BCL11B (enh)*	< 1	ETP-ALL	Homminga et al. (2011)
LMO2[b]	*BCL11B (enh)*	< 1	ETP-ALL	
NKX2.5	*BCL11B(enh), TCRAD (enh)*	< 1	ETP-ALL	(Homminga et al., 2011; Nagel et al., 2003; Przybylski et al., 2006)
LCK	*TCRB (enh)*	< 1	unknown	
MYB	*TCRB (enh), duplications*	< 2	unknown	(Clappier et al., 2007; Lahortiga et al., 2007; O'Neil et al., 2007b)
CCND2	*TCRB (enh)*	< 1	unknown	Clappier et al. (2006)

Oncogenic fusions	**Partner gene**	**Incidence**	**Associated subtype**	**Ref**
PICALM (*HOXA* act.)	*MLLT10*	3	TLX/ETP-ALL	(Dik et al., 2005; Homminga et al., 2011)
KTM2A (*HOXA* act.)	*MLLT1, ENL, MLLT10, MLLT4, MLLT6, CT45A4*	< 2	TLX/ETP-ALL	(Ferrando et al., 2003; Liu et al., 2017)
SET (*HOXA* act.)	*NUP214*	2	TLX/ETP-ALL	(Homminga et al., 2011; Quentmeier et al., 2009; Van Vlierberghe et al., 2008b)
SPI1	*STMN1, TCF7*	< 1	ETP-ALL (post-ETP)	Seki et al. (2017)
RUNX1	*AFF3, EVX*	< 1	ETP-ALL	(Homminga et al., 2011; Zhang et al., 2012)
ABL1	*BCR, EML1, ZMIZ1, NUP214 (episomal), SLC9A3R1, ETV6, MBNL1, ZBTB16*[a]	< 1	ETP-ALL/*TALLMO	(Barber et al., 2004; Bernasconi et al., 2005; B. Chen et al., 2018; Colleoni et al., 1996; De Braekeleer et al., 2011; De Keersmaecker et al., 2005; Fabbiano et al., 1998; Graux et al., 2004; Graux et al., 2009; Homminga et al., 2011; Liu et al., 2017; Quentmeier et al., 2005; Stergianou et al., 2005; Van Limbergen et al., 2001)
ETV6	*JAK2, NCOA2, INO80D, ABL1, CTNNB1*	< 1	ETP-ALL	(Liu et al., 2017; Zhang et al., 2012)
MLLT10 (*HOXA* act.)	*PICALM, XPO1, NAP1L1, DDX3X, KTM2A, FAM17A1, CAPS2, HNRNPH1*		TLX/ETP-ALL	(Bond et al., 2014; B. Chen et al., 2018; Homminga et al., 2011; Liu et al., 2017; Zhang et al., 2012)
NUP214	*ABL1 (episomal), SET, SQSTM1*	6	ETP-ALL	Zhang et al. (2012)
NUP98	*RAP1GDS1, CCDC28A, LNP1, PSIP1, DDX10, VRK1*	< 2	ETP-ALL	(B. Chen et al., 2018; Liu et al., 2017)

[a] *ABL1-ZBTB16* rearrangements found in 2 TALLMO patients.
[b] Unpublished unique rearrangement.

p13) translocation (Mellentin et al., 1989) and *TLX1/HOX11* in patients bearing t(10; 14)(q24; q11) translocations (Dube et al., 1991; Dube et al., 1986; Hatano et al., 1991; Kennedy et al., 1991; Lu et al., 1991). For *TAL1*, small deletions were identified in approximately 12–25% of pediatric patients that result in repositioning of the *TAL1* coding region behind the *STIL* gene promoter (Aplan et al., 1990; O. Bernard et al., 1991; Brown et al., 1990). Whereas *TAL1* abnormalities are predominantly associated with late cortical development (Macintyre et al., 1992), *TLX1*-rearranged patients mostly resemble early cortical thymocytes (Cave et al., 2004). Since these initial discoveries, extensive molecular and cytogenetic analyses have resolved many additional oncogenic rearrangements in nearly 80 percent of the T-ALL patients (Table 1) (Armstrong and Look, 2005; Belver and Ferrando, 2016; Iacobucci and Mullighan, 2017; Look, 1997; Meijerink et al., 2009; Raimondi et al., 1991; Rubnitz and Look, 1998; Van Vlierberghe and Ferrando, 2012).

The first genome-wide gene expression analysis that distinguished the T-ALL subtype from other leukemic types was performed by the group of Eric Lander (Golub et al., 1999). Shortly after, the gene signatures of immature, early and late cortical T-cell developmental stages in T-ALL patient samples could be distinguished that were characterized by ectopic expression levels of oncogenic transcription factors including *LYL1*, *TLX1/HOX11* or *TAL1*, respectively (Ferrando et al., 2002). Whereas expression of *TLX1* and *TAL1* are driven by chromosomal rearrangements, *LYL1*-positive T-ALL patients are devoid of *LYL1* rearrangements. Some early cortical T-ALL patients express the *TLX1*-related gene *TLX3/HOX11L2* due to a cryptic (5; 14)(q35; q32) chromosomal translocation in approximately 25 percent of pediatric T-ALL patients (O. A. Bernard et al., 2001; Ferrando et al., 2002). Later gene expression microarray studies distinguished at least four T-ALL groups, *i.e.* the immature, TLX, proliferative and TALLMO subtypes (Homminga et al., 2011; Soulier et al., 2005; Van Vlierberghe et al., 2008b). Identification of additional oncogenes extended previous observations that each subtype was characterized by specific oncogenic rearrangements that facilitate specific blocks in T-cell development and drive T-ALL. Each genetic subtype is discussed below.

1.1. Immature subtype (ETP-ALL)

Immature T-ALL patients are characterized by high expression levels of *BCL2*, *LYL1*, *LMO2*, *HHEX* and *MEF2C,* reflecting activation of self-renewal genes that are also expressed in hematopoietic stem cells (Homminga et al., 2011; McCormack et al., 2010). This profile matched with the immature T-ALL entity that was identified based on its resemblance to normal early thymocyte progenitor cells (ETP) (Bernt et al., 2016; Coustan-Smith et al., 2009; Zuurbier et al., 2014). This subtype was accordingly denoted ETP-ALL. In-depth molecular-cytogenetic analysis of immature/ETP-ALL patient samples revealed unique rearrangements of the *MEF2C* transcription factor in some patients while others contained *ETV6*-coupled fusions of the MEF2C co-factor NCOA2/TIFF (Homminga et al., 2011; Nagel et al., 2008; Strehl et al., 2008). Rearrangements that affect other *MEF2C* transcriptional regulators—including *SPI1*, *NKX2.5* and a *RUNX1-AFF3* fusion product—have also been reported in ETP-ALL (Table 1) (Homminga et al., 2011).

Since the introduction of next-generation sequencing, various additional fusions have been identified in ETP-ALL patients affecting *ETV6*, *KTM2A, RUNX1, ABL, MLLT10, NUP214* and *NUP98* (Table 1) (B. Chen et al., 2018; Liu et al., 2017; Zhang et al., 2012). A Japanese study on 121 pediatric T-ALL cases identified recurrent *SPI1* (encoding PU.1) fusions including *STMN1-SPI1* and *TCF7-SPI1* fusions in ETP-ALL patients that highly expressed *MEF2C*, *HHEX*, *FLT3* and *cKIT* (Seki et al., 2017). In contrast to most other ETP-ALL patients (Zhang et al., 2012), ETP-ALL cases bearing *SPI1* fusion products were characterized by recurrent activating *NOTCH1* mutations (Seki et al., 2017). Some ETP-ALL patients bear rearrangements that result in the activation of various members of the *HOXA* gene cluster (Table 1, *HOXA* act). Such *HOXA*-positive ETP-ALL patients were related to high intrinsic chemo-resistance and very poor outcome in the French GRAALL-2003 and -2005 studies (Ben Abdelali et al., 2013; Bond et al., 2016).

1.2. TLX subtype

Most patients that cluster in the TLX subtype are characterized by *TLX3* rearrangements (Homminga et al., 2011). Whereas some patients express the γδ TCR, other TLX patients have a more immature phenotype that lack TCR surface expression suggesting that this disease entity is associated with early γδ lineage of development (Berger et al., 2003; van Grotel et al., 2008). The TLX cluster also comprises patients with *HOXA*-activating events including *SET-NUP214*, *PICALM-MLLT10* or *MLL* fusion products (Homminga et al., 2011; Liu et al., 2017).

TLX3 rearrangements mostly reposition the *TLX3* oncogene from 5q35 in close proximity to the *BCL11B* enhancer at 14q32, thereby inactivating one functional allele of the *BCL11B* haplo-insufficient tumor suppressor gene (O. A. Bernard et al., 2001; L. Li et al., 2013). BCL11B is a critical transcription factor that commits early developing thymocytes to the αβ lineage of T-cell development (L.Li et al., 2010b; P. L. Li et al., 2010a; Yui et al., 2010). *TLX3-BCL11B* rearrangements may therefore impair αβ differentiation potential and consequently drive differentiation towards the γδ lineage. Some TLX patients also inactivate the second, non-rearranged *BCL11B* allele that may further block αβ lineage commitment potential (De Keersmaecker et al., 2010; Gutierrez et al., 2011; Wakabayashi et al., 2003). TLX3 itself may also switch off the TCR αβ lineage program. As a strong repressor (Della Gatta et al., 2012), TLX3 represses the *TRCA* enhancer in an ETS-dependent fashion thereby limiting *TCRA* recombination events (Dadi et al., 2012). As a significant number of *TLX3*-rearranged cases express cytoplasmic TCRB (van Grotel et al., 2008), it cannot be ruled out that *TLX3-BCL11B* rearrangements may initially have occurred in αβ lineage cortical thymocytes that subsequently diverged towards the γδ lineage as a consequence of BCL11B insufficiency and/or TLX3 expression (Asnafi et al., 2004). Some early studies reported an association of *TLX3* rearrangements with poor outcome (Ballerini et al., 2002; Cave et al., 2004; Ferrando et al., 2002; Gottardo et al., 2005; Mauvieux et al., 2002; van Grotel et al., 2006), but no such association has been reported for patients treated on contemporary

treatment protocols.

1.3. Proliferative subtype

T-ALL patients that express a proliferative gene signature are frequently characterized by *TLX1* or *NKX2-1* translocations (Homminga et al., 2011). Historically, *TLX1* translocated patients have been associated with superior outcome compared to patients from other T-ALL subtypes (Cave et al., 2004; Ferrando et al., 2004; Kees et al., 2003; Schneider et al., 2000). *TLX1* translocation breakpoints mostly occur downstream of *TLX1*, coupling the *TCRB* enhancer downstream of *TLX1* in *TCRB*-translocated patients. However, in *TCRAD* translocated patients the *TLX1* genomic breaks are positioned upstream and positions *TLX1* behind promoters of *TCRAD* V-gene segments, possibly because the *TCRAD* enhancer is repressed by TLX1 similar to the repressor function of TLX3 (Dadi et al., 2012). Various patients of the proliferative cluster contain translocations or inversions involving the *NKX2-1* or the homologous *NKX2-2* homeobox genes (Homminga et al., 2011). In these patients, ectopic *NKX2-1/2-2* oncogene expression levels are driven as consequence of their close proximities to *TCRB* or *TCRAD* enhancers (Homminga et al., 2011). The presence of recurrent *NKX2-1* aberrations in T-ALL has been confirmed in other studies (B. Chen et al., 2018; La Starza et al., 2013). Remarkably, most *TLX1*-rearranged patients also express low levels of *NKX2-1* in the absence of *NKX2-1* rearrangements implying direct regulation of *NKX2-1* by TLX1 (Homminga et al., 2011).

1.4. TALLMO subtype

Patients with a TALLMO gene expression profile represent nearly half of all pediatric T-ALL patients (Ferrando et al., 2002; Homminga et al., 2011; Liu et al., 2017; Soulier et al., 2005). Just as in normal hematopoietic erythroid precursors, TAL1 and TAL2 proteins form transcription complexes with E2A/HEB, RUNX1, GATA3, and MYB co-factors that are bridged by LMO1 or LMO2 in these T-ALL cells (Hsu et al., 1994; Porcher et al., 2017). In addition to recurrent *TAL1* translocations or *SIL-TAL1* deletions that drive ectopic TAL1 expression, other TALLMO patients bear alternative *TCRB* or *TCRAD* rearrangements that ectopically drive *TAL2*, *LYL1*, *LMO1*, *LMO2* or *LMO3* oncogenes (Ferrando et al., 2002; Hammond et al., 2005; Homminga et al., 2011; Homminga et al., 2012; McGuire et al., 1989; Mellentin et al., 1989; Nam and Rabbitts, 2006; Royer-Pokora et al., 1991; Simonis et al., 2009; Soulier et al., 2005; Van Vlierberghe et al., 2006). Almost a quarter of all TALLMO patients harbor a combination of 2 different aberrations that affect both members of *TAL1* and *LMO2* gene families. In addition, small insertion/deletion (INDEL) mutations have recently been identified that create strong MYB binding sites in or upstream of *TAL1*, *LMO1* or *LMO2* loci in nearly 6 percent of pediatric/young adult T-ALL patients (Liu et al., 2017). Recruitment of MYB at these sites results in the assembly of a TAL1 super-enhancer complex that strongly drives oncogene expression (Z. Li et al., 2017; Mansour et al., 2014; Rahman et al., 2017; Sengupta and George, 2017).

2. Non-driver mutations in T-ALL

In addition to the driving oncogenes or oncogene fusion products that characterize the four predominant T-ALL subtypes and that are denoted type A aberrations (Van Vlierberghe et al., 2008a), various other recurrent aberrations including point- or INDEL mutations, chromosomal gains and losses have been described for T-ALL (Belver and Ferrando, 2016; Iacobucci and Mullighan, 2017; Meijerink et al., 2009; Van Vlierberghe and Ferrando, 2012). These aberrations are not necessarily disease-initiating events as they mostly appear in leukemia subclones (Van Vlierberghe et al., 2008a). These mutations were accordingly denoted as type B mutations. These mutations provide advantages for oncogenesis, disease progression, relapse, or induce therapy resistance. Historic research and recent next-generation sequencing studies have now revealed over 100 genes that are recurrently mutated, amplified or deleted in T-ALL (Table 2) (B. Chen et al., 2018; Kunz et al., 2015; Y. Li et al., 2016; Liu et al., 2017; Richter-Pechanska et al., 2017; Van Vlierberghe et al., 2011; Zhang et al., 2012). The majority of these genetic alterations impact on cell cycle by inactivating cell cycle inhibitors or by loss of *Rb* (Liu et al., 2017), or ectopically activate signaling pathways that are important for T-cell development including NOTCH1 (Akhoondi et al., 2007; Malyukova et al., 2007; O'Neil et al., 2007a; Thompson et al., 2007; Weng et al., 2004), cytokine signaling cascades (Neumann et al., 2012; Paietta et al., 2004; Shochat et al., 2011; Van Vlierberghe et al., 2005; Zenatti et al., 2011) or their downstream pathways (Gutierrez et al., 2009; Kawamura et al., 1999; Mendes et al., 2014; Palomero et al., 2007; Yamamoto et al., 2006). Other mutations frequently involve (in)activation of transcriptional regulators, epigenetic reprogramming enzymes, components of ribosomes that affect protein translation, protein-modifying enzymes, or genes that are involved in the chromatin architecture and DNA looping, DNA repair or DNA synthesis. An overview of all mutations is listed in Table 2, along with the cellular processes they affect and notable associations.

While type B mutations occur in all T-ALL subtypes, ETP-ALL patients typically harbor the highest mutational load compared to the other subtypes (Y. Li et al., 2016; Zhang et al., 2012) and have been associated with an inferior steroid response (Maude et al., 2015). ETP-ALL is distinguished from other subtypes in the genetic landscape by the relative enrichment of specific type B events, which includes activating mutations in the tyrosine kinase receptor gene *FLT3*, mutations in the IL-7R (interleukin-7 receptor) signaling pathway (*i.e.* in *IL7R*, *JAK1* and/or *JAK3*) or recurrent 5q-deletions that affect the *NR3C1* gene locus (La Starza et al., 2016; Neumann et al., 2013a; Zhang et al., 2012). In contrast, ETP-ALL patients have a lower frequency of deletions affecting cell cycle regulators including *CDKN2A/B*, *CDKN1B* or *CDKN1C* and have lower incidences of NOTCH1-activating mutations (Y. Li et al., 2016; Liu et al., 2017; Seki et al., 2017). Although ETP-ALL was initially associated with extremely poor outcome (Allen et al., 2013; Coustan-Smith et al., 2009; Gutierrez et al., 2010a; Inukai et al., 2012; M. Ma et al., 2012; Neumann et al., 2012; Van Vlierberghe et al., 2013; Yang et al., 2012), treatment intensification in contemporary risk-adapted treatment protocols has improved outcome for

Table 2
Mutations in cellular pathways or processes in T-ALL.

Process/Pathway	Genes	Associations	Therapeutic compounds	Ref
Cell cycle	*CDKN2A/B, CDKN1B, CDKN1C, CCND3, RB*	Low in ETP-ALL	CDK4/6 inhibitors	(B. Chen et al., 2018; Clappier et al., 2006; Gutierrez et al., 2009; Y. Li et al., 2016; Liu et al., 2017; Richter-Pechanska et al., 2017; Seki et al., 2017; Soulier et al., 2005)
NOTCH signaling	*NOTCH1, FBXW7*	GPR, favorable	NOTCH inhibitors	(Akhoondi et al., 2007; Asnafi et al., 2009; Bond et al., 2014; Breit et al., 2006; B. Chen et al., 2018; Kox et al., 2010; Y. Li et al., 2016; Liu et al., 2017; Malyukova et al., 2007; O'Neil et al., 2007a; Richter-Pechanska et al., 2017; Seki et al., 2017; Thompson et al., 2007; Weng et al., 2004; Zuurbier et al., 2010)
IL7R-JAK-STAT	*IL7Ra, JAK1, JAK3, PTPN2, STAT5B*	Steroid resistance	JAK, MEK or PIM1 inhibitors	(Asnafi et al., 2009; Asnafi et al., 2010; Bains et al., 2012; Bandapalli et al., 2014; Bandapalli et al., 2013; Cante-Barrett et al., 2016; B. Chen et al., 2018; Delgado-Martin et al., 2017; Flex et al., 2008; Jeong et al., 2008; Kleppe et al., 2010; Kleppe et al., 2011; Kontro et al., 2014; Y. Li et al., 2016; Liu et al., 2017; Melao et al., 2016; Richter-Pechanska et al., 2017; Seki et al., 2017; Shochat et al., 2011; Zenatti et al., 2011; Zhang et al., 2012)
RAS-MEK-ERK	*N/K-RAS, NF1, PTPN11, BRAF*	Steroid resistance	MEK-inhibitors	(Balgobind et al., 2008; Cante-Barrett et al., 2016; B. Chen et al., 2018; Flex et al., 2008; Kawamura et al., 1999; Y. Li et al., 2016; Liu et al., 2017; Richter-Pechanska et al., 2017; Seki et al., 2017; Zhang et al., 2012)
PI3K-AKT	*PIK3R1, PIK3CA, PIK3CD, AKT*	Poor	AKT or mTOR inhibitor	(Cante-Barrett et al., 2016; Gutierrez et al., 2009; Y. Li et al., 2016; Liu et al., 2017; Seki et al., 2017)
PTEN	*PTEN*	Poor, therapy failure, relapse	PI3K, AKT or mTOR inhibitors	(Bandapalli et al., 2013; B. Chen et al., 2018; Flex et al., 2008; Gutierrez et al., 2009; Jenkinson et al., 2016; Jotta et al., 2010; Liu et al., 2017; Maser et al., 2007; Mendes et al., 2014; Palomero et al., 2007; Seki et al., 2017; Silva et al., 2008; Szarzynska-Zawadzka et al., 2019; Trinquand et al., 2013; Zuurbier et al., 2012)
Receptors and kinases	*ABL1, ALK, cKIT, FLT3, FAT1, ECT2L, SH2B3*	x	ABL-class tyrosine kinase inhibitors	(Y. Li et al., 2016; Liu et al., 2017; Neumann et al., 2013a,b; Neumann et al., 2013a,b; Paietta et al., 2004; Perez-Garcia et al., 2013; Richter-Pechanska et al., 2017; Seki et al., 2017; Van Vlierberghe et al., 2011; Van Vlierberghe et al., 2005; Zhang et al., 2012)
Transcription factors	*RUNX1, ETV6, BCL11B, WT1, PHF6, TCF7, LEF1, CTNNB1, GATA3, IKZF1, MYC, MYB, CREBBP, MLLT10*	x	BET inhibitors	(B. Chen et al., 2018; Clappier et al., 2007; De Keersmaecker et al., 2010; Della Gatta et al., 2012; Gutierrez et al., 2011; Gutierrez et al., 2010b; Homminga et al., 2011; Huether et al., 2014; Lahortiga et al., 2007; Y. Li et al., 2016; Liu et al., 2017; Richter-Pechanska et al., 2017; Seki et al., 2017; Tosello et al., 2009; Van Vlierberghe et al., 2010; Zhang et al., 2012)
Transcription co-factors	*EP300, MED12, SMARCA4, ATRX, CNOT1, CNOT3, CNOT6*	x	x	(B. Chen et al., 2018; De Keersmaecker et al., 2013; Y. Li et al., 2016; Liu et al., 2017; Richter-Pechanska et al., 2017; Seki et al., 2017)
Polycomb complex	*EED, SUZ12, EZH2, ASXL1*	x	x	(B. Chen et al., 2018; Huether et al., 2014; Ntziachristos et al., 2012; Richter-Pechanska et al., 2017; Seki et al., 2017; Zhang et al., 2012)
Epigenetic enzymes	*KDM6A, SETD2, KMT2A, KMT2D, KMT2C, DNMT3A, IDH1, IDH2*	x	HDAC or methyltransferase inhibitors	(B. Chen et al., 2018; Huether et al., 2014; Y. Li et al., 2016; Liu et al., 2017; Neumann et al., 2013b; Seki et al., 2017; Van Vlierberghe et al., 2013; Van Vlierberghe et al., 2011; Zhang et al., 2012)
Ribosomes	*RPL5, RPL0, RPL22, del6q*	x	ABT-199	(B. Chen et al., 2018; De Keersmaecker et al., 2013; Gachet et al., 2018; Girardi et al., 2018; Kampen et al., 2019; Y. Li et al., 2016; Liu et al., 2017; Rao et al., 2012; Seki et al., 2017)
Protein stability	*USP7, USP9X*	x	Bortezomib	(B. Chen et al., 2018; Huether et al., 2014; Liu et al., 2017; Richter-Pechanska et al., 2017; Seki et al., 2017)
Chromatine remodeling	*CTCF*	x	x	(B. Chen et al., 2018; Liu et al., 2017; Richter-Pechanska et al., 2017; Seki et al., 2017)

(*continued on next page*)

Table 2 (*continued*)

Process/Pathway	Genes	Associations	Therapeutic compounds	Ref
DNA repair	*P53, P53BP1, ATM, MSH2, MSH6, PMS2*	x	x	(B. Chen et al., 2018; Kawamura et al., 1999; Y. Li et al., 2016; Liu et al., 2017; Richter-Pechanska et al., 2017; Seki et al., 2017)
Adhesion	*DNM2*	x	x	(B. Chen et al., 2018; Ge et al., 2016; Y. Li et al., 2016; Liu et al., 2017; Neumann et al., 2013b; Richter-Pechanska et al., 2017; Seki et al., 2017; Tremblay et al., 2016; Zhang et al., 2012)
Steroid receptor	*NR3C1*	x	x	(La Starza et al., 2016; Y. Li et al., 2016)
Therapy resistance	*NT5C2*	Only observed in relapse	x	(Richter-Pechanska et al., 2017; Seki et al., 2017; Tzoneva et al., 2013)
Apoptosis	BCL2 protein expression[a]	ETP-ALL	ABT-199, ABT-737	(Chonghaile et al., 2014; Kawashima-Goto et al., 2015; Y. Li et al., 2016; Peirs et al., 2014; Suryani et al., 2014)

[a] No mutations for BCL2 have been reported.

ETP-ALL patients and is now comparable to the outcome of other T-ALL patients (Farah et al., 2018; Patrick et al., 2014; Wood et al., 2014; Zuurbier et al., 2014). The only exception is the *HOXA*-activated ETP-ALL group that still has a very poor outcome (Ben Abdelali et al., 2013; Bond et al., 2016). Other type B events that cluster with specific T-ALL subtypes include strong NOTCH1-activating mutations in *TLX3*-rearranged ALL, and activating *PIK3R1* or *PIK3CG* events, *PTEN*-inactivating mutations and inactivating *USP7* mutations in TALLMO subtype patients (Table 2). In contrast to NOTCH1-activating mutations, *PTEN*-inactivating events have been associated with poor outcome in various studies (Gutierrez et al., 2009; Jotta et al., 2010; Y. Li et al., 2016; Mendes et al., 2014; Paganin et al., 2018; Trinquand et al., 2013; Zuurbier et al., 2012) but not in the MRC UKALL2003 cohort (Jenkinson et al., 2016).

Mutations in genes encoding various IL-7R signaling molecules (*i.e. IL7R*, *JAK1/3*, *STAT5B*, *N/KRAS* or *AKT*) have been found in nearly 35% of pediatric T-ALL patients and are associated with inferior event free survival (Asnafi et al., 2010; Bains et al., 2012; Balgobind et al., 2008; Bandapalli et al., 2014; Cante-Barrett et al., 2016; B. Chen et al., 2018; Flex et al., 2008; Jeong et al., 2008; Kawamura et al., 1999; Kontro et al., 2014; Y. Li et al., 2016; Liu et al., 2017; Oliveira et al., 2019; Richter-Pechanska et al., 2017; Seki et al., 2017; Shochat et al., 2011; Zenatti et al., 2011; Zhang et al., 2012). These pathway mutations are predominantly found in ETP-ALL and TLX subtypes and occur in a near mutually exclusive manner (Cante-Barrett et al., 2016; Y. Li et al., 2016). Moreover, JAK-STAT and RAS/PTEN alterations are often identified in chemorefractory patients, and identified in higher frequencies at disease relapse. Similar to mutations affecting *IL7R*, these mutations predict for very poor outcome of relapsed T-ALL (Gianfelici et al., 2016; Richter-Pechanska et al., 2017). One of the explanations for this is that aberrant IL-7R signaling results in increased cellular resistance towards steroid treatment (Y. Li et al., 2016).

3. Combined *omic*-based targeted therapies: opportunities in T-ALL

Contemporary multi-agent and risk-adapted protocols have boosted survival rates to approximately 80 percent, with the number of toxic deaths now almost equaling the number of patients that relapse (Pieters et al., 2016). This proves that further treatment intensification is not feasible and there is an urgent need for targeted compounds in individualized treatment protocols for high-risk T-ALL patients. Given our profound understanding of pathogenic drivers and mutations in T-ALL, various targeted compounds could be implemented in the near future to improve outcome for refractory/relapsed T-ALL and may allow implementation in first-line treatment for high-risk T-ALL patients in the future.

Roughly 50% of all pediatric cancer patients present with a potentially druggable genetic event, with aberrations in NOTCH-, mitogen-activated protein kinase (MAPK)-, or receptor tyrosine kinase (RTK)-signaling and cell cycle control as potential targets for future T-ALL treatment regimens (Grobner et al., 2018). The question remains whether introduction of single targeted compounds in current chemotherapy backbones will improve treatment outcome. In adult metastasized carcinoma patients genomics-directed treatment strategies only yielded minimal prognostic benefits (Le Tourneau et al., 2015; Marquart et al., 2018; Massard et al., 2017). The effect of single targeted compound treatment might be disappointing in T-ALL since many of the targetable processes are the result of type B mutations that are frequently found at subclonal levels (X. Ma et al., 2018). Targeted inhibition should therefore not be expected to eradicate the complete leukemic burden. However, some subclonal mutations give rise to therapy resistance and could therefore still serve as essential targets for therapy. In the case of IL-7R pathway mutations, MEK and AKT are attractive targets for selective inhibitors that synergize with steroid treatment (Y. Li et al., 2016). Moreover, mutated subclones may actually reflect pathway dependency and/or drug sensitivity of the entire leukemic population. Therefore, the effect of combined treatment could extend beyond the elimination of mutated cells. For example, this has been implemented in the phase1/2 SeluDex trial in which dexamethasone treatment is given in combination with the MEK-inhibitor Selumetinib for relapse or refractory RAS-mutant BCP-ALL (Matheson et al., 2019) and is now open for relapsed/refractory T-ALL patients as well.

The observed benefit of combining targeted treatment with standard chemotherapeutics may extend beyond the treatment of patients that harbor specific (subclonal) mutations. Loh et al. demonstrated that in two out of three high risk-ALL cases no somatic mutations could be identified in tyrosine kinase-coding genes, despite their gene expression profiles that point to active kinase signaling (Loh et al., 2013). This indicates that patients with activated kinase signaling benefit from targeted therapy, especially those who lack druggable genetic targets. To decipher the full pathogenic program and to pinpoint novel biomarkers for both therapy and prognosis, an integrated approach that combines data on the genomic, transcriptomic and proteomic level may be required to identify additional druggable targets (Doll et al., 2019). This so-called ‘multi-omic’ approach could reveal other tumor targets, and therefore provides an opportunity to increase the detail and complexity of basket-trials for small numbers of patients or for individualized patient treatment programs (Worst et al., 2016) (Fig. 1). Refinement of treatment strategies, as a direct consequence of this advanced screening approach, could consequently improve outcome. Since for most hematological malignancies sufficient patient material can be obtained at diagnosis, testing on these three levels indeed seems feasible for T-ALL. In the next two paragraphs, we will highlight the current progress and application of transcriptome sequencing and proteomics in ALL.

3.1. Integration of transcriptome sequencing

In the last few years, great technological advances in sequencing have been applied not only to DNA analysis but to RNA as well. RNA-sequencing of the leukemia transcriptome has a prominent role in the identification of novel splice variants and fusion transcripts that drive or sustain tumorigenesis. As mentioned before, RNA-sequencing studies have led to the discovery of various novel and cryptic fusion transcripts in T-ALL (Atak et al., 2013; B. Chen et al., 2018; Gianfelici et al., 2016) and T-lymphoblastic lymphoma patients (Lopez-Nieva et al., 2019) that had not been identified earlier by genome sequencing or molecular-cytogenetic tests. The Total XVII protocol (NTC03117751) for the treatment of ALL at the St. Jude children's hospital integrates information from RNA

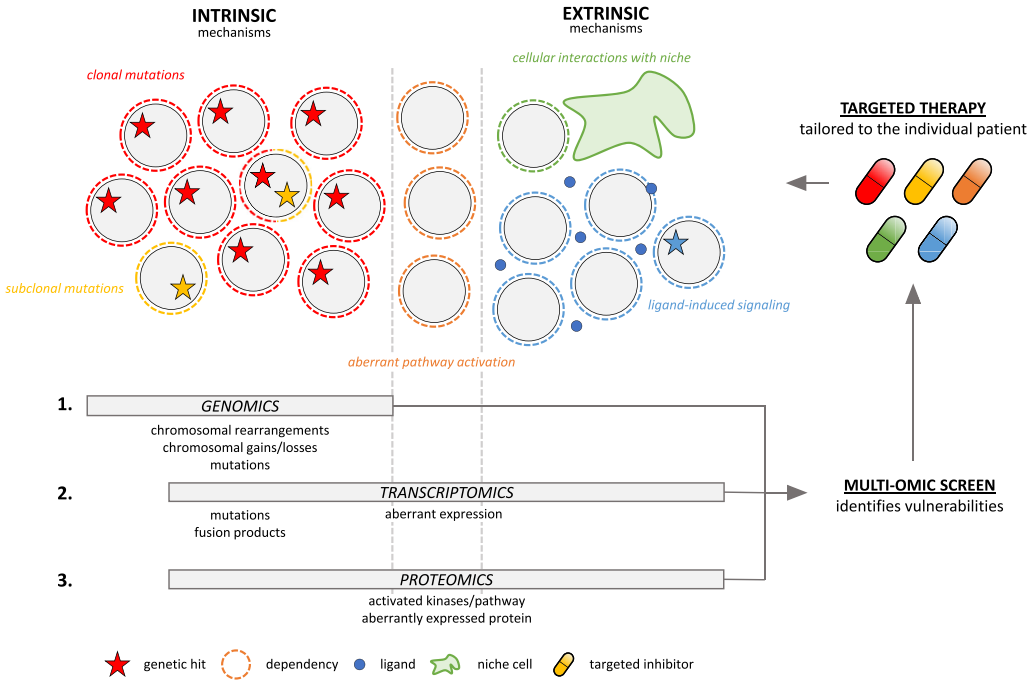

Fig. 1. Intrinsic mechanisms (e.g. by genetic hits (stars)), extrinsic mechanisms (e.g. by interaction with niche (green) or ligand-induced (blue)) and aberrant pathway activation with unknown cause (orange) involved in disease initiation, maintenance or drug resistance that may be observed in leukemic blasts. Integration of genomics, transcriptomics and proteomics identifies the vulnerabilities caused by these pathogenic events. As a result, it allows for the precise use of targeted compounds that (in combination with standard chemotherapeutics) can enhance treatment effectiveness and ultimately may improve survival.

sequencing with RT-PCR or FISH to detect potential druggable fusions at diagnosis that are then used for therapy stratification. While the pipeline for fusion detection from RNA-seq data will give results already at day 15 of the induction therapy, additional whole-genome sequencing information is available only at later stages of the treatment (Inaba et al., 2017).

Cancer cells rely on altered mechanisms of signal transduction that boost cell cycle progression and proliferation (Hanahan and Weinberg, 2011). When pathological pathway activation is not predicted by genomic aberrations, different approaches like transcriptome sequencing will be required to identify the *Achilles' heel* of the disease. Quantitative measurement of pathway activity inferred from target gene mRNA levels have been developed for various signaling pathways, e.g. the Oncosignal platform by Philips Healthcare, and provides a molecular phenotype of the tumor (Stolpe et al., 2019; van de Stolpe, 2019; van Ooijen et al., 2018; Verhaegh et al., 2014). It generates an automated and reliable quantitative readout of specific pathways that are highly activated in malignant cells that can support the choice of relevant small-molecule inhibitors. Furthermore, it can potentially predict therapy resistance due to the activation of compensatory/escape mechanisms.

3.2. Integration of proteomics

An additional way to discover novel oncogenic dependencies or identify new biomarkers is to analyze the cancer proteome. Mass spectrometry-based global proteomic analyses have been pivotal in the identification of changes in protein expression as well as in post-translational modifications, in particular phosphorylation (Cutillas, 2015; Jimenez and Verheul, 2014). These changes at the phospho-protein level reflect altered signal transduction that cannot be detected at the DNA or RNA level. Protein kinases are one of the major effectors of signal transduction. Nevertheless, direct quantification of activity levels of kinases has been challenging and requires *a priori* knowledge of the enzyme of interest. In the past decade, an increasing interest in post-translational modifications and their role in cancer led to development of workflows for the identification of alterations in protein phosphorylation levels as functional readout for enzyme hyper-activity. High-throughput phospho-proteome data can therefore provide direct information on pathway signaling. In 2013, Casado et al. demonstrated that kinase activity inferred from analysis of global phospho-proteome data of different hematological cancer cell lines correlates with differential drug responses (Casado et al., 2013). Phospho-proteomic analyses have also been applied to the identification of putative therapy response biomarkers in ALL (reviewed in (Lopez Villar et al., 2015; Lopez Villar et al., 2014)). In T-ALL, the phospho-proteomic studies investigating signal transduction have been limited to either a kinome microarray system—identifying differentially phosphorylated peptides for pediatric B-ALL versus T-ALL samples (van der Sligte et al., 2015)—or by using Reverse-Phase Protein Array (RPPA) that identified hyper-activation of the mTOR/STAT3 and LCK/calcineurin axes in pediatric ETP-ALL (Serafin et al., 2017b). Based on the latter study, the authors suggested LCK hyper-activity as possible resistance factor for steroid treatment in T-ALL (Serafin et al., 2017a). Both kinome array and RPPA are valuable tools but

can only detect changes in a subset of pre-defined proteins and therefore do not allow for screening of the entire (phospho)proteome. Unbiased mass spectrometry-based phospho-proteomic studies dedicated to T-ALL are necessary to unravel specific pathological signaling pathways and escape mechanisms. The identification and the degree of pathway activation with subsequent downstream effects will provide a rationale for therapy stratification and will lead to the identification of novel disease specific- or individualized biomarkers (Beekhof et al., 2019).

4. Functional screening into practice: IL-7R-signaling and steroid resistance

IL-7R pathway activation by interleukin-7 (IL-7) even in the absence of IL-7R pathway mutations has also been shown to confer steroid resistance in T-ALL patients (Delgado-Martin et al., 2017; Maude et al., 2015). This indicates that pathway activation (and subsequent drug responsiveness) can depend on the availability of growth factors, and may provide an underlying mechanism for increased therapy resistance for local, niche embedded leukemia cells. For patients that present with this so called 'IL-7 dependent steroid resistance' (Delgado-Martin et al., 2017), pathway inhibition by combined MEK or AKT inhibition with steroid treatment to restore steroid sensitivity may be equally effective as for patients that harbor IL-7R pathway mutations. Increase in the phosphorylation of STAT5 or the activation of downstream STAT5 target genes following IL-7 stimulation are important biomarkers to identify these patients for whom integration of phospho-proteomics and transcriptomics at diagnosis is needed.

Both proteomic and transcriptomic analyses have identified novel treatment targets or biomarkers that represent pathway activation downstream of the IL-7R before. For example, phospho-proteomic profiling of JAK3 mutated leukemia cells—that signal downstream of the IL-7R but do not impair steroid sensitivity in contrast to JAK1 mutations (Y. Li et al., 2016)—identified non-JAK-STAT druggable targets that were affected by mutant JAK3 signaling (Degryse et al., 2018). Combined pathway inhibition of these targets with Ruxolitinib or Tofacitinib (JAK-inhibitors) worked synergistically *in vitro* and *in vivo* (Degryse et al., 2018), indicating that proteomic profiling serves as a powerful tool to improve personalized medicine. Additionally, transcriptional and epigenetic research identified that the $STAT5B^{N642H}$ mutation—which leads to strong STAT5B pathway activation—increases its binding at regions that are also bound by epigenetic regulators such as EZH2 and SUZ12 (Bandapalli et al., 2014; Kontro et al., 2014; Pham et al., 2018). $STAT5B^{N642H}$ expressing T-cells showed a higher expression level and activity of the EZH2 target gene Aurora kinase B (Aurkb), yielding sensitivity for treatment with a specific Aurora Kinase B inhibitor (AT9283) (Pham et al., 2018). High *PIM1* expression downstream of STAT5 signaling has also been identified by transcriptional analysis, and PIM1 inhibition was demonstrated effective in (IL-7 mediated) JAK-STAT activated leukemias (de Bock et al., 2018; De Smedt et al., 2019; Ribeiro et al., 2018). The observations for JAK3 and STAT5 illustrate that pathway activation and dependency, as measured by proteomic and transcriptomic approaches, predict sensitivity to selective inhibitors and may improve outcome by optimization of personalized medicine. Additionally, screening at multiple levels provides additional biomarkers that can be used for targeted therapy regardless of signaling mutations. For example, RNA sequencing could reveal significant *PIM1* overexpression (in the absence of *JAK* or *STAT5B* mutations as determined by genomic screening) and could therefore provide a rationale for treatment with a selective PIM1-inhibitor for individual patients. As another example, phospho-proteomic results that point to activation of the AKT pathway in a T-ALL patient vouches for combination treatment with an AKT-inhibitor. Thus, 'multi-omics' screening approaches will excel the choice of targets to inhibit in personalized medicine. It will help clinicians to individualize treatment and optimize basket-trials in refractory/relapsed T-ALL patients. Moreover, a multi-omics functional screening with subsequent therapeutic consequences at the start of treatment might prevent (early) relapse, therefore significantly increasing the survival rate of T-ALL patients.

5. Concluding remarks

Given our profound understanding of genomic aberrations in T-ALL, we can now successfully identify oncogenic driving lesions in nearly 80% of T-ALL patients (Table 1). Additionally, patients frequently present with non-driver mutations at the subclonal level for which some relate to inferior outcome or therapy resistance (Table 2). At present, the majority of small-molecule inhibitors that could be applied in clinical trials target these subclonal mutations and may offer therapeutic effect if the mutation in the subclone is indicative for a vulnerability of the total leukemic population. Genomic screening in T-ALL should therefore not only focus on driving events, but also on identifying genetic aberrations for which a selective inhibitor combined with standard chemotherapeutics drugs can lead to a maximal treatment response. Integration of genomic sequencing, RNA sequencing and phospho-proteomics in a 'multi-omics' functional screening will uncover the complete *Achilles' heel* of the leukemia, allowing great improvement of personalized medicine and eventually patient outcome as a result of the precise use of targeted compounds (Fig. 1).

Declarations of interest

None.

Funding

This study received funding by Stichting Kinderen Kankervrij (KiKa219 and KiKa295) and KWF Kankerbestrijding (KWF2016_10355).

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