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Molecular Biology of Childhood Leukemia

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Abstract

Childhood hematological malignancies (HM) exhibit profound genetic and biological heterogeneity. Many sporadic and familial HM have a heritable predisposition. Genomic sequencing has revised the taxonomy of lymphoid and myeloid leukemias, indicating the importance of accurate molecular diagnosis in disease management. Notable examples include the identification of gene expression–based subtypes of acute lymphoblastic leukemia (ALL), identification of diverse rearrangements of *NUP98* in high-risk acute myeloid leukemia (AML), characterization of the interplay of cell-of-origin and genomic alterations in lineage-ambiguous leukemias, and the prognostic importance of DNA methylation in juvenile myelomonocytic leukemias. These insights provide therapeutic opportunities, including kinase inhibition in Ph-like ALL, menin inhibition in *KMT2A*-rearranged AML, histone deacetylase inhibition in *MEF2D*-rearranged ALL, and FLT3 inhibition in T-lineage and myeloid leukemias. We provide an overview of the molecular foundation and classification of childhood leukemias, focusing on recent scientific advances, and discuss potential therapeutic implications.

INTRODUCTION

Childhood hematological malignancies (HM) are caused by the interaction of inherited and somatic genetic alterations occurring at a specific stage of hematopoietic development. Greaves & Janossy (1978) postulated that "most cells and particularly stem cells probably have all the inherent 'information' which is necessary for malignancy and that the change which permits clonal selection and resultant malignancy is a normally rare event, or series of events resulting in disruption of regulatory mechanisms. . .which regulate the sequential expression of different gene programmes in differentiation in concert with mitotic cycles" (p. 224). Subsequent research has elucidated many of these "rare events" using diverse experimental strategies. These include twin and neonatal backtracing studies that have examined the timing of origin of leukemogenesis (Wiemels et al. 1999); genomic analyses of large cohorts of childhood leukemia samples that have defined the nature and sequence of somatic alterations that define distinct subtypes of leukemia; genomic analyses of sequential diagnostic, remission, and relapse samples that have dissected the relationship of genetic heterogeneity and clonal evolution and, in doing so, have revised the concept of the cancer stem cell (Mullighan et al. 2008b, Shlush et al. 2017); mouse models that have provided insight into the mechanism by which founding and cooperating lesions drive leukemogenesis (Downing 2003); and analyses of the germline that have expanded our appreciation of the importance of heritable predisposition to leukemia (**Figure 1**) (Zhang et al. 2015).

HM account for 40% of childhood cancer. Children younger than 15 years have a three-times-higher prevalence of leukemia than lymphoma, while adolescents are twice as likely to have lymphoma (Ward et al. 2014). In total, 80% of leukemias in childhood are acute lymphoblastic leukemia (ALL), of which 85% are B progenitor and 15% are T-lineage. Acute myeloid leukemia (AML) comprises 15% of pediatric leukemia, while mixed phenotype acute leukemia (MPAL), juvenile myelomonocytic leukemia (JMML), and chronic myeloid leukemia comprise the remaining cases. The peak incidence of B cell ALL (B-ALL) is 2–6 years of age, while T cell ALL (T-ALL) and AML show a relatively constant incidence throughout childhood.

In contrast to many adult malignancies, childhood HM have relatively sparse mutational landscapes and are often initiated by chromosomal rearrangements that perturb hematopoietic differentiation and self-renewal. For example, rearrangements of *KMT2A* (MLL) commonly occur in utero and may be sufficient for malignant transformation, with leukemia commonly manifesting in infancy (Andersson et al. 2015). Most leukemia fusion oncoproteins require additional genomic alterations to cause clinical disease, as indicated by (*a*) the long latency from acquisition of fusion events until overt leukemia; (*b*) the presence of detectable *ETV6-RUNX1* or *RUNX1-RUNXT1* fusions detected on dried newborn blood spots at a rate much higher than the incidence of ALL or AML, respectively; and (*c*) the observation of secondary DNA alterations at diagnosis (Bateman et al. 2010, Wiemels et al. 2002). Collectively, these alterations typically perturb hematopoietic differentiation, tumor suppression, chromatin modeling, and signaling pathways, although the nature of genetic alteration and genes affected varies between subtypes and cases.

HERITABLE SUSCEPTIBILITY TO LEUKEMIA

There is increasing evidence for genetic predisposition for many subtypes of childhood HM, including (*a*) rare constitutional syndromes with increased risks for leukemia; (*b*) familial cancer syndromes; (*c*) noncoding DNA polymorphisms that subtly influence risk of HM, particularly ALL; and (*d*) a growing number of genes harboring germline nonsilent variants presumed to confer risk of sporadic HM. Examples of each are described below.

Children with constitutional syndromes such as Down syndrome, Noonan syndrome, neurofibromatosis type 1, ataxia-telangiectasia, Fanconi anemia, and other bone marrow failure

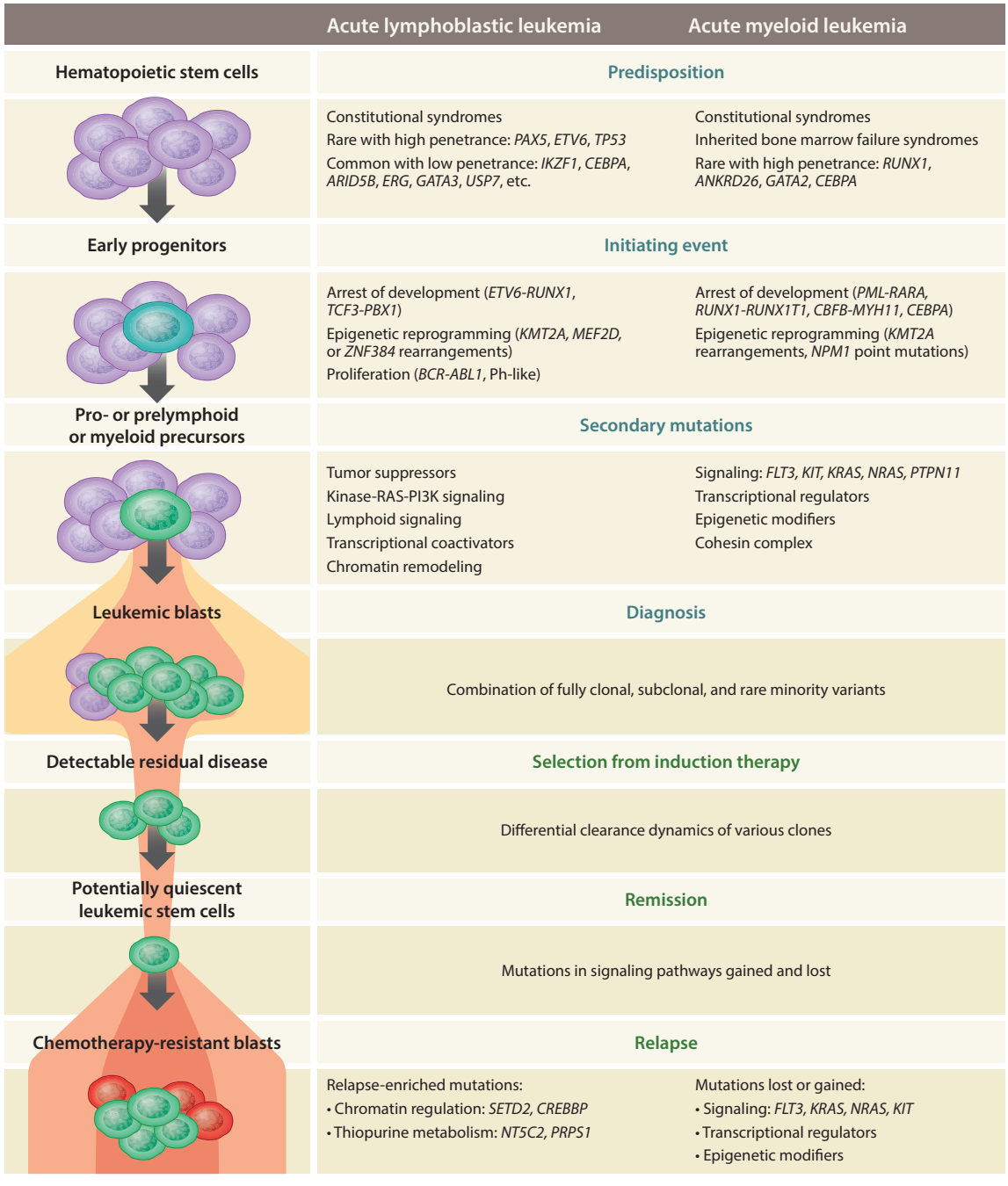

Figure 1

Model of leukemogenesis and clonal evolution from diagnosis through relapse. Purple cells represent healthy hematopoietic progenitors. Green cells represent malignancy. Red cells represent clonal evolution driven by therapeutic pressure.

syndromes (severe congenital neutropenia, dyskeratosis congenita, Shwachman-Diamond syndrome, and Diamond-Blackfan anemia) have an increased risk of leukemia. The spectrum of risk is syndrome specific. For example, Down syndrome is associated with a markedly increased risk of AML and B-ALL, Noonan syndrome and neurofibromatosis type 1 have increased risk of JMML (discussed below), ataxia-telangiectasia increases T-ALL risk, and bone marrow failure syndromes primarily increase risk of AML (Hasle et al. 2000, Rafei & DiNardo 2019, Reiman et al. 2011, Strullu et al. 2014).

Familial cancer syndromes such as Li-Fraumeni syndrome, constitutional mismatch repair deficiency syndrome, or DNA repair syndromes (Bloom, Werner, and Nijmegen breakage) have increased incidence of malignancy in general as the primary manifestation of disease. Familial predisposition specific to leukemia is uncommon, but genomic analyses of kindreds have identified multiple leukemia-subtype-associated nonsilent germline variants that are also present in the germline of sporadic leukemia cases. Key examples in B-ALL are *TP53* germline mutations and low-hypodiploid B-ALL, *ETV6* variants and hyperdiploid ALL, and *PAX5* mutations and B-ALL with dicentric/isochromosome 9 (Holmfeldt et al. 2013, Moriyama et al. 2015, Noetzli et al. 2015, Shah et al. 2013). These susceptibility genes are targets of somatic mutation in ALL: *ETV6* and *PAX5* are rearranged, amplified/deleted, and mutated in B-ALL (Gu et al. 2019, Mullighan et al. 2007). Moreover, germline variants of *IKZF1* are observed in familial B-ALL and immunodeficiency (Churchman et al. 2018, Kuehn et al. 2016), and somatic *IKZF1* alterations are enriched in *BCR-ABL1*, Ph-like, and *DUX4*-rearranged B-ALL (Mullighan et al. 2008a, 2009; Zhang et al. 2016).

Germline mutations in hematopoietic transcription factors such as *CEBPA*, *GATA2*, *RUNX1*, and *ANKRD26* cause familial AML and myelodysplastic syndrome, potentially through impaired hematopoietic differentiation of progenitor cells (Noris et al. 2011, Sakurai et al. 2014). The relative risk of AML is variable, with presentation common in adolescence and young adulthood (Spinner et al. 2014, Tawana et al. 2017). Patients with *CEBPA* mutations demonstrate near complete penetrance, with decreasing relative risk for *RUNX1*, *GATA2*, and *ANKRD26* mutations, respectively (Tawana et al. 2015). Additional inherited variants implicated in pediatric AML or myelodysplastic syndrome include *DDX41*, *SRP72*, *ETV6*, *SAMD9*, and *SAMD9L* (Rafei & DiNardo 2019, Schwartz et al. 2017). Germline variants in familial AML are associated with characteristic somatic mutations, such as acquisition of *ASXL1* in cases with germline *GATA2* or *ANKRD26* variants and enrichment of somatic mutations affecting the remaining wild-type allele in patients with germline *RUNX1* or *CEBPA* alterations (Brown et al. 2020, Micol & Abdel-Wahab 2014, Pabst et al. 2008, Perez Botero et al. 2015). In a subset of familial leukemia syndromes, patients can present with symptomatic thrombocytopenia without leukemia (*RUNX1*, *ANKRD26*, and *ETV6* variants) or with clinically significant immunodeficiency (*GATA2* variants) (Ostergaard et al. 2011, Rafei & DiNardo 2019). While most familial leukemia is subtype specific, *RUNX1* variants can lead to T-ALL in addition to AML, and *ETV6* variants predispose to myelodysplastic syndromes in addition to the more common B-ALL (Brown et al. 2020, Feurstein & Godley 2017).

Genome-wide association studies have identified at least 13 loci with primarily noncoding variants associated leukemia, particularly B-ALL. The relative risk associated with these variants is modest compared with constitutional syndromes or familial leukemia. Risk variants are frequently at/near hematopoietic transcription factor or tumor-suppressor genes, including *ARID5B*, *BAK1*, *CDKN2A/CDKN2B*, *BMI1-PIP4K2A*, *CEBPE*, *ELK3*, *ERG*, *GATA3*, *IGF2BP1*, *IKZF1*, *IKZF3*, *USP7*, and *LHPP* (Gocho & Yang 2019, Papaemmanuil et al. 2009, Trevino et al. 2009). Several variants display ancestry and ALL-subtype-specific associations, such as *GATA3* with Hispanics and Ph-like B-ALL, *ERG* with African Americans and *TCF3-PBX1* B-ALL, and *USP7* with African Americans and T-ALL with *TAL1* deregulation (Perez-Andreu et al. 2013; Qian et al. 2019a,b).

Finally, germline genomic analysis has identified additional susceptibility variants in sporadic hyperdiploid B-ALL (*NBN*, *ETV6*, *FLT3*, *SH2B3*, and *CREBBP*), Down syndrome–associated B-ALL (*IKZF1*, *NBN*, and *RTEL1*), and T-ALL (Fanconi-BRCA pathway mutations) (de Smith et al. 2019, Pouliot et al. 2019, Winer et al. 2020). These discoveries notwithstanding, currently known inherited susceptibility variants explain only a minority of cases of childhood HM.

ACUTE LYMPHOBLASTIC LEUKEMIA

Children with ALL have an overall survival approaching 90% on current clinical protocols (Jeha et al. 2019, Maloney et al. 2020). However, therapy results in substantial short- and long-term morbidity, and high-risk subtypes continue to have poor survival (Schultz et al. 2014). This section provides an overview of the current genetic classification of ALL in children, with an emphasis on newly described subtypes and key alterations of cellular pathways and genes (**Table 1**).

Genomic Subtypes of B Cell Acute Lymphoblastic Leukemia

B-ALL has historically been classified by gross karyotypic chromosomal alterations, including aneuploidy or common chromosomal translocations. Hypodiploidy, defined as less than 44 chromosomes for B-ALL treatment purposes, carries a poor prognosis (Harrison et al. 2004). Near-haploid cases (24–31 chromosomes) have frequent mutations targeting receptor tyrosine kinase or Ras signaling, while low-hypodiploid cases (32–39 chromosomes) have nearly universal deletion/mutation of *TP53*, which are germline in over half of childhood low-hypodiploid ALL cases (Holmfeldt et al. 2013). In contrast, high hyperdiploidy (>50 chromosomes) confers an excellent prognosis. The most common translocation in B-ALL in children is t(12;21)(p13;q22), leading to the *ETV6-RUNX1* fusion, which is typically cryptic by conventional karyotyping and is a favorable prognostic marker. Recurrent translocations that are apparent by karyotyping include t(1;19)(q23;p13) encoding *TCF3-PBX1*, t(9;22)(q34;q11.2) encoding *BCR-ABL1*, and rearrangements of *KMT2A* at 11q23 involving multiple partners, most commonly t(4;11)(q21;q23) encoding *KMT2A-AFF1*, which occurs in infant ALL and portends dismal prognosis.

Genomic sequencing has facilitated discovery of additional subtypes of B-ALL across the age spectrum (**Figure 2*a***). Ph-like (*BCR-ABL1*-like) ALL, defined by a gene expression pattern that is similar to *BCR-ABL1*-positive ALL (Den Boer et al. 2009, Mullighan et al. 2009), is associated with high-risk disease and poor outcomes. It is driven by diverse alterations activating kinase signaling, including rearrangements (*CRLF2*, *JAK2*, *EPOR*, and ABL-class tyrosine kinase genes) or point mutations in JAK-STAT and Ras signaling pathways (**Figure 3**) (Roberts et al. 2014). Activating kinase alterations confer cytokine-independent proliferation, which is blocked by ABL1 inhibitors for ABL-class fusions or JAK inhibition for JAK-STAT pathway mutations (Roberts et al. 2014, 2017). Anecdotal reports of efficacy of tyrosine kinase inhibitors (TKIs) in Ph-like ALL led to prospective studies examining effects of TKIs frontline or in relapsed Ph-like ALL (Roberts et al. 2014, Tanasi et al. 2019, Weston et al. 2013). However, the clinical efficacy of single-agent TKI therapy in Ph-like ALL is variable, with dramatic responses in *ETV6-NTRK3* ALL and ABL-class Ph-like ALL (Nardi et al. 2020, Roberts et al. 2018, Tanasi et al. 2019), but variable-to-poor efficacy in JAK-STAT-driven ALL, particularly *CRLF2*-rearranged ALL. Thus, therapeutic approaches are needed for targeted activation of parallel signaling pathways (e.g., PI3K or BCL2 inhibitors) or for directly targeting deregulated receptors with immunotherapeutic approaches (Qin et al. 2015, Roberts et al. 2017, Tasian et al. 2012).

Additional subtype-defining alterations in B-ALL include those involving the transcription factors *DUX4*, *ERG*, *MEF2D*, *ZNF384*, and *PAX5* (Gu et al. 2019, Yasuda et al. 2016). *DUX4*, a double

Table 1 Key genetic subtypes in pediatric ALL

Category	Age	Description
B cell precursor ALL		
Hyperdiploidy with more than 50 chromosomes	Children ≫ adults	Excellent prognosis; mutations in Ras signaling pathway and histone modifiers
Near-haploid	Children > adults	24–31 chromosomes; poor prognosis; Ras-activating mutations; inactivation of *IKZF3*
Low-hypodiploid	Children < adults	32–39 chromosomes; poor prognosis; *TP53* mutations (somatic and germline)
iAMP21	Older children	Complex alterations of chromosome 21; requires high-risk therapy for good outcomes
t(12;21)(p13;q22) encoding *ETV6-RUNX1*	Children ≫ adults	Excellent prognosis; cryptic rearrangement that is detectable by FISH
ETV6-RUNX1–like	Children > adults	Absence of *ETV6-RUNX1* fusion; mutations or rearrangements of *ETV6* or *IKZF1*
t(1;19)(q23;p13) encoding *TCF3-PBX1*	Children and adults	Increased incidence in African Americans; favorable prognosis
t(9;22)(q34;q11.2) encoding *BCR-ABL1*	Children ≪ adults	Historically poor prognosis, improved with TKIs; common deletions of *IKZF1*
Ph-like	Children < adults	Kinase-activating lesions; poor outcomes; potentially amenable to kinase inhibition
CRLF2-rearranged (*IGH-CRLF2*; *P2RY8-CRLF2*)	Children and adults	Common in Down syndrome and Ph-like ALL; associated with *IKZF1* deletion and *JAK1/2* mutation
KMT2A (*MLL*)-rearranged	Infants ≫ children to adults	Common in infant ALL; dismal prognosis; few cooperating mutations, commonly in RAS signaling pathway
DUX4-rearranged and *ERG*-deregulated	Children and adults	Distinct gene expression profile; majority have focal *ERG* deletions and favorable outcome despite *IKZF1* alterations
MEF2D-rearranged	Children and adults	Distinct gene expression profile; potential sensitivity to HDAC inhibition
ZNF384-rearranged	Children and adults	Pro-B-ALL phenotype; expression of myeloid markers; increased expression of *FLT3*
*PAX5*alt	Children > adults	*PAX5* fusions, mutations, or amplifications; intermediate prognosis
PAX5 P80R	Children < adults	Frequent signaling pathway alterations
IKZF1 N159Y	Children and adults	Rare; unknown prognosis
NUTM1-rearranged	Children	Rare; exclusively in children; excellent prognosis
t(17;19(q22;p13) encoding *TCF3-HLF*	Children and adults	Rare; dismal prognosis
BCL2/MYC-rearranged	Children ≪ adults	Poor prognosis
T-lineage ALL		
TAL1 deregulation	Children and adults	Enrichment of mutation in PI3K signaling pathway
TLX3 deregulation	Children and adults	Poor prognosis; frequent cooperating mutations in ubiquitination and ribosomal genes
HOXA deregulation	Children and adults	Frequent mutations in JAK-STAT pathway; *KMT2A* rearrangements
TLX1 deregulation	Children > adults	Favorable prognosis
LMO2/LYL1 deregulation	Children and adults	Poor prognosis; enriched for ETP-ALL; frequent cooperating mutation in JAK-STAT
NKX2–1 deregulation	Children and adults	Frequent cooperating mutation in ribosomal genes
NUP214-ABL1 with 9q34 amplification	Children and adults	Neutral prognosis, in contrast to kinase driven B-ALL; potentially amenable to TKIs

Abbreviations: ALL, acute lymphoblastic leukemia; FISH, fluorescence in situ hybridization; iAMP, intrachromosomal amplification; TKI, tyrosine kinase inhibitor.

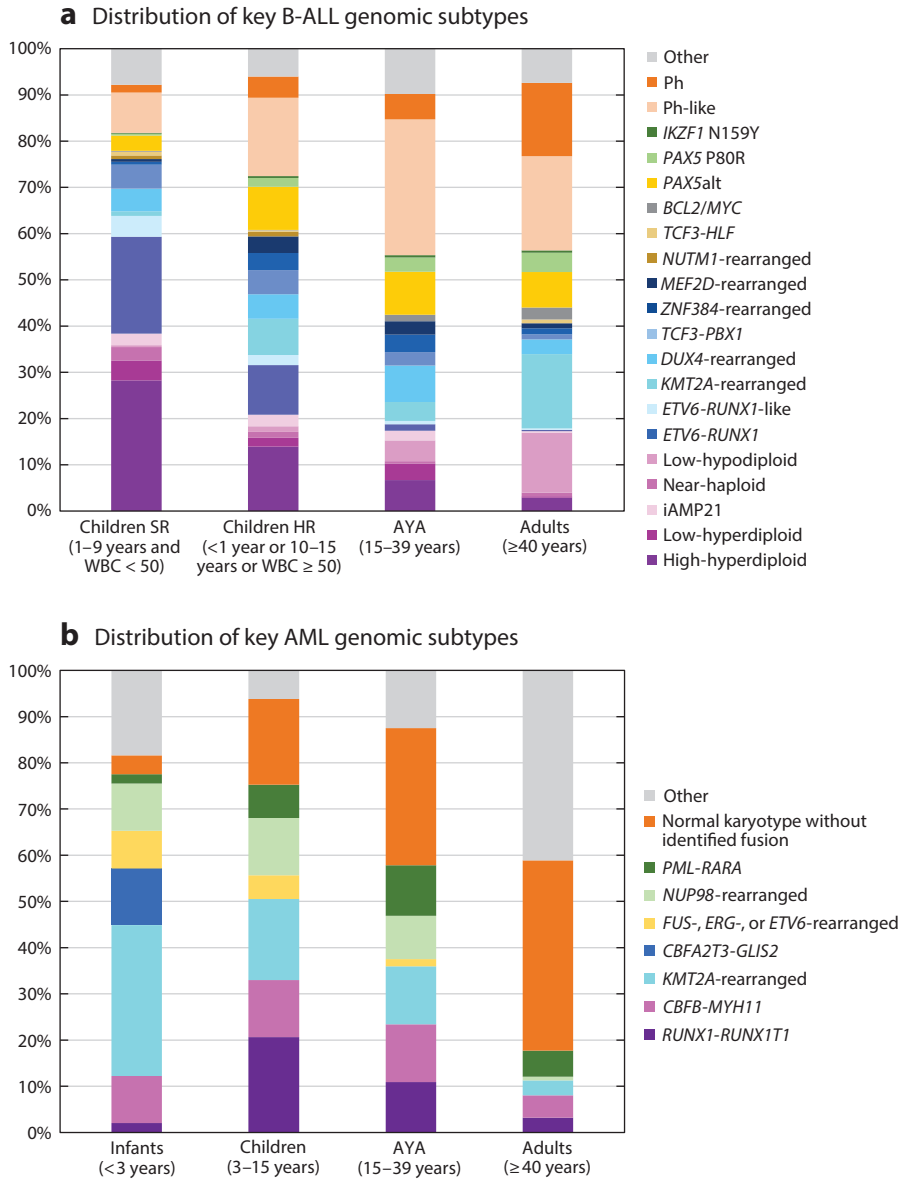

Figure 2

Age distribution of genomic subtypes of B-ALL and AML. (*a*) The prevalence of B-ALL subtypes varies between children with SR B-ALL, children with HR B-ALL, AYA with B-ALL, and adults (age ≥ 40 years) with B-ALL (Gu et al. 2019). WBC is measured in 10^9 cells/L. (*b*) The prevalence of key AML genomic subtypes also varies greatly between infants, children, AYA, and adults, emphasizing the critical nature of pediatric-specific therapeutic development approaches for AML (Bolouri et al. 2018). Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; AYA, adolescents/young adults; B-ALL, B cell ALL; HR, high risk; iAMP, intrachromosomal amplification; SR, standard risk; WBC, white blood cell count.

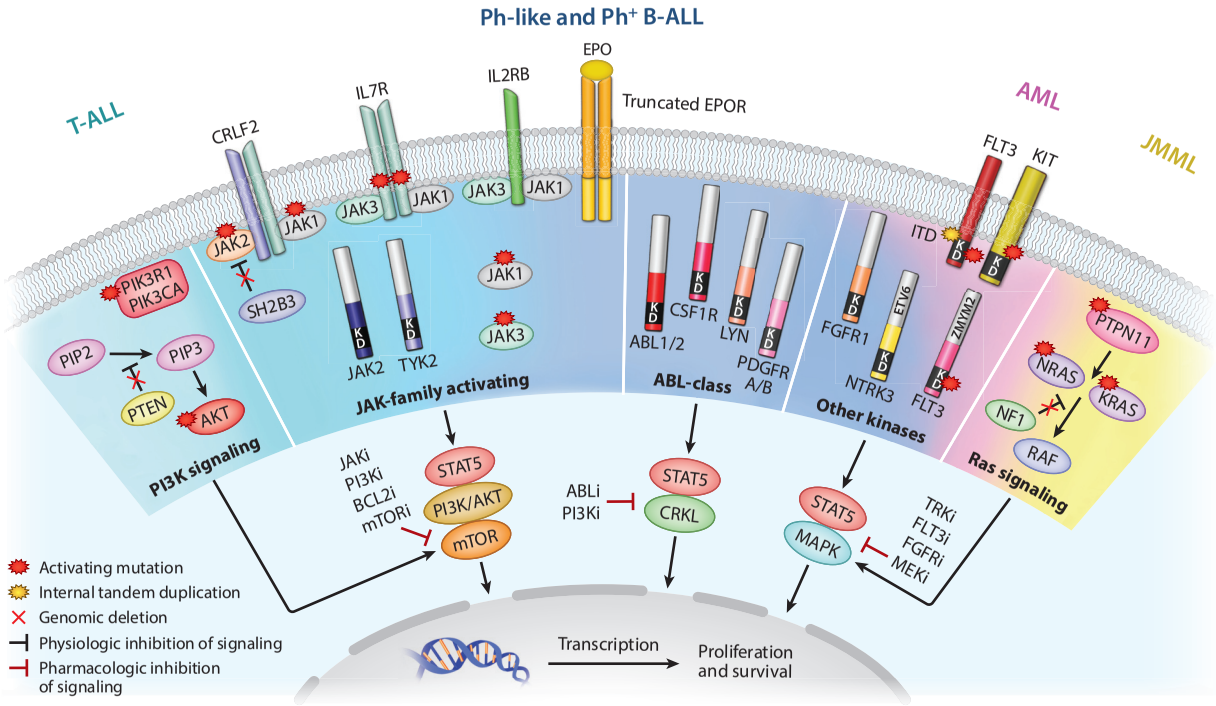

Figure 3

Signaling pathways altered in pediatric leukemia. Mutations in signaling pathways occur at different frequencies in pediatric leukemia subtypes. PI3K pathway mutations are the most common signaling abnormality in T-ALL. Deregulation of JAK signaling occurs in T-ALL, particularly ETP-ALL, and Ph-like ALL. Alterations of JAK, ABL, and other (FGFR1, FLT3, NTRK3) signaling pathways are hallmark events in Ph^+ and Ph-like ALL. Activating mutations (*red stars*), fusion genes (*rectangles within the cell*), or genomic deletions (*red crosses*) cause overexpression of cytokine receptors (e.g., CRLF2, IL7R, and EPOR) or constitutive activation of tyrosine kinases (e.g., JAK2, TYK2, ABL1, PDGFRA, NTRK3). Pathologically activated signaling in AML most commonly occurs through ITD of FLT3 or point mutations causing constitutive activation of FLT3 or KIT. The Ras pathway is a recurrent target of mutation across pediatric acute leukemia subtypes, most commonly AML, but it is the definitive driver in JMML. Simplified downstream signaling pathways are shown, although regulation and activation are interconnected. Potential opportunities for therapeutic inhibition of signaling pathways are shown. Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; B-ALL, B cell ALL; ETP, early T cell precursor; i, inhibitor; ITD, internal tandem duplication; JMML, juvenile myelomonocytic leukemia; Ph, Philadelphia chromosome; T-ALL, T cell ALL.

homeobox, is rearranged to strong enhancers at *IGH*, leading to overexpression of C-terminal-truncated DUX4. DUX4 binds to and deregulates expression of the ETS-family transcription factor *ERG*, often with expression of novel coding and noncoding *ERG* transcripts (Lilljebjorn et al. 2016, Zhang et al. 2016). *MEF2D* is rearranged to multiple partners, most commonly *BCL9*, and results in dysregulation of *MEF2D* target genes and increased *HDAC9* (histone deacetylase 9) expression (Ohki et al. 2019). Increased *HDAC9* expression has suggested a vulnerability to HDAC inhibition, which has been confirmed in vitro using panobinostat (Gu et al. 2016). *ZNF384* rearrangements have been identified in 5% of B-ALL, most commonly in adolescents (Gocho et al. 2015, Gu et al. 2016, Shago et al. 2016). B-ALL cases with *ZNF384* rearrangements are characterized by a distinct transcriptional profile, early B cell phenotype, and frequent coexpression of nonspecific myeloid markers (Hirabayashi et al. 2017). Experimental modeling of *ZNF384* rearrangements with *EP300* or *CREBBP* show reduced HDAC activity leading to impaired histone acetylation at K9 and K27 residues, suggesting another potential therapeutic role for HDAC inhibition (Qian et al. 2017).

Researchers have also identified distinct subgroups defined by point mutations in transcription factors *PAX5* or *IKZF1* as the putative driving event in leukemogenesis (Gu et al. 2019, Li et al. 2018). PAX5 p.Pro80Arg defines a B-ALL subtype with differentiation arrest at very early B cell progenitor state and loss of the wild-type *PAX5* allele (Passet et al. 2019). A similar example is a rare B-ALL subtype defined by a point mutation *IKZF1* causing p.Asn159Tyr, which leads to nuclear mislocalization and aberrant intercellular adhesion (Churchman et al. 2015, Gu et al. 2019). Finally, a subgroup of B-ALL labeled *ETV6-RUNX1*-like has a gene expression profile consistent with *ETV6-RUNX1* without RNA or DNA evidence of the fusion that contains alterations of both *ETV6* and *IKZF1* (Lilljebjorn et al. 2016).

Key Pathways Recurrently Altered in B Cell Acute Lymphoblastic Leukemia

Mutations in hematopoietic transcription factors resulting in arrested maturation occur frequently in B-ALL as either translocations, focal deletions/amplifications, or sequence mutations (Kuiper et al. 2007, Mullighan et al. 2007, Roberts & Mullighan 2019). The genes *PAX5*, *IKZF1*, *EBF1*, and *ETV6*, encoding regulators of lymphoid development, are commonly altered as secondary events. These alterations are important in leukemogenesis but have context-dependent associations with prognosis. *IKZF1* alterations overall are a strong negative prognostic factor in kinase-driven (BCR-ABL1 and Ph-like) but not *DUX4*-rearranged ALL (Hamadeh et al. 2019, Stanulla et al. 2018). Activation in signaling pathways is a hallmark of *BCR-ABL*, *BCR-ABL*-like, and hypodiploid ALL, and includes cytokine receptors, tyrosine kinases, the JAK-STAT pathway, and the Ras pathway (Holmfeldt et al. 2013, Roberts et al. 2014). Additionally, alterations of tumor-suppressor and cell cycle regulation genes (*TP53*, *RB1*, and *CDKN2A/CDKN2B*) exist as both sequence mutations and focal deletions, and mutations in genes that influence chromatin remodeling (*CREBBP*, *EZH2*, *SETD2*, and *KMT2D*) may influence risk of relapse (Mar et al. 2014, Mullighan et al. 2011, Waanders et al. 2020).

Genetic Basis of T Cell Acute Lymphoblastic Leukemia

Pediatric T-ALL is characterized by alterations of core T lymphoblast transcriptional pathways and disruption of cell cycle control. Gene expression profiling enables classification of over 90% of T-ALL into core subgroups defined by deregulation of T-ALL transcription factors *TAL1*, *TAL2*, *TLX1*, *TLX*, *HOXA*, *LMO1/LMO2*, *LMO2/LYL1*, or *NKX2–1* (**Table 1**) (Ferrando et al. 2002, Gianni et al. 2020). The pathways are most commonly deregulated by structural variants

or small deletions, placing the gene expression under control of strong promoters or enhancers near T cell receptor loci (Liu et al. 2017). More recently described mechanisms for deregulation include small insertion/deletion mutations upstream of *TAL1*, which lead to a new binding motif for MYB or TCF1/TCF2 and a subsequent change to *TAL1* expression levels (Liu et al. 2017, Mansour et al. 2014). A similar mechanism has been described for other oncogenes in T-ALL, including *LMO2* (Abraham et al. 2017). The second core transcriptional pathway mutated in most T-ALL cases is aberrant activation of *NOTCH1*, a critical transcription factor for T cell development (Yui & Rothenberg 2014). Constitutive *NOTCH1* activity, caused by activating *NOTCH1* mutations (75% of cases) or inhibitor mutations in the negative regulator *FBXW7* (25% of cases), promotes uncontrolled cell growth, partially through increased expression of *MYC* (Herranz et al. 2014, Palomero et al. 2006, Weng et al. 2004). The third core alteration observed in pediatric T-ALL is deletion of tumor-suppressor loci, primarily *CDKN2A/CDKN2B* (80% of cases), and less commonly *CDKN1B*, *RB1*, and *CCND3* (Hebert et al. 1994, Liu et al. 2017).

In addition to the core alterations above, T-ALL has frequent derangement of additional transcriptional regulators *MYB*, *LEF1*, and *BCL11B*; ribosomal function; ubiquitination through loss-of-function *USP7* mutations; RNA processing; signaling pathways; and epigenetic modifiers such as *PHF6*, *KDM6A*, and genes of polycomb repressive complex 2 (*EED*, *SUZ12*, and *EZH2*) (Liu et al. 2017). The signaling pathway most commonly activated is PI3K-AKT through loss of the negative regulation by PTEN (**Figure 3**) (Palomero et al. 2007). JAK-STAT pathway activation can occur through gain-of-function *IL7R*, *JAK1*, *JAK3*, or *STAT5B* mutations or loss-of-function alterations in the JAK-STAT regulator *PTPN2* (Kontro et al. 2014, Zenatti et al. 2011), while mutations in RAS-MAPK signaling are less common.

ACUTE MYELOID LEUKEMIA

Acute myeloid leukemia comprises 15–20% of pediatric leukemia cases. While overall survival for children with AML has approached 70% in recent trials, outcomes are heavily dependent on genomic subgroup, and progress has lagged behind improvements seen in ALL (Rubnitz et al. 2010, 2019; Zwaan et al. 2015). Development of all-*trans* retinoic acid and arsenic trioxide for acute promyelocytic leukemia (APML) has provided patients with substantially more effective, less toxic therapy for this previously high-risk subtype (Bally et al. 2012). However, apart from APML, the treatment of AML has not changed significantly in the last 25 years. In this section, we focus on the unique features of childhood AML and highlight potential therapeutic vulnerabilities.

There is marked variation in the mutational spectrum of AML according to age (**Figure 2*b***). Many mutations common in adult AML are nearly absent (*DNMT3A*, *RUNX1*, and *IDH1*) or uncommon (*TET2*, *NPM1*, and *IDH2*) in pediatric AML (Cancer Genome Atlas Res. Netw. et al. 2013, Tarlock & Meshinchi 2015). Conversely, frequency of *KMT2A* rearrangement is inversely related to age, and high-risk pediatric AML fusions *CBFA2T3-GLIS2*, *NUP98-NSD1*, and *NUP98-KDM5A* are exceedingly rare in adults (de Rooij et al. 2017, Struski et al. 2017). Within the pediatric age group, there are distinct patterns of alterations. Children younger than 2 years of age have high rates of *CBFA2T3-GLIS2* or *KMT2A* rearrangements with very few additional alterations, while the low-risk fusion *RUNX1-RUNX1T1* is uncommon in infants (Bolouri et al. 2018, Radtke et al. 2009).

Fusion Proteins in Acute Myeloid Leukemia

The most common karyotype abnormalities in pediatric AML are t(8;21)(q22;q22.1), inv(16)(p13.1q22), t(16;16)(p13.1;q22), and rearrangements of chromosome 11q23. Other

Table 2 Key genetic subtypes in pediatric AML

Category	Age	Description
t(15;17)(q24;q21) encoding *PML-RARA*	Infants < children and adults	APML; excellent prognosis; managed with ATRA and ATO
t(8;21)(q24;q22) encoding *RUNX1-RUNX1T1*	Infants ≪ children > adults	Good prognosis; improved outcomes with increased therapy intensity
inv(16)(p13.1q22) or t(16;16)(p13.1;q22) encoding *CBFB-MYH11*	Infants and children > adults	Good prognosis; improved outcomes with increased therapy intensity
KMT2A (*MLL*)-rearranged	Infants > children > adults	Prognosis dependent on fusion partner; few cooperating mutations
NUP98-rearranged	Older children	Poor prognosis; common partners *KDM5A* and *NSD1*; deregulation of HOX genes
Normal karyotype without identified fusion	Infants < children < adults	Frequent alterations of *CEBPA* or *NPM1*
t(1;22)(p13;q13) encoding *RBM15-MKL1*	Infants ≫ children	Common in AMKL; good prognosis
inv(16)(p13q24) encoding *CBFA2T3-GLIS2*	Infants ≫ children	Poor prognosis; common in AMKL; deregulation of HOX genes
t(6;9)(p22;q34) encoding *DEK-NUP214*	Infants < children and adults	Poor prognosis; frequent FLT3-ITD
t(7;12)(q36;p13) encoding *MNX1-ETV6*	Infants > children > adults	Poor prognosis; infants
t(8;16)(p11;p13) encoding *KAT6A-CREBBP*	Children < adults	Intermediate prognosis; reports of spontaneous resolution
inv(3)(q21q26) or t(3;3)(q21;q26) overexpressing *MECOM*	Children < adults	Poor prognosis; frequent monosomy 7; frequent Ras pathway mutations
FLT3-ITD	Infants ≪ children < adults	Poor prognosis with high allelic ratio; often subclonal; targetable with kinase inhibition

Abbreviations: AMKL, acute megakaryoblastic leukemia; AML, acute myeloid leukemia; APML, acute promyelocytic leukemia; ATO, arsenic trioxide; ATRA, all-*trans* retinoic acid.

translocations are hallmarks of specific AML subtypes, such as t(15;17)(q24;q21) and variant *RARA* rearrangements, which are pathognomonic for APML, as well as t(1;22)(p13;q13), associated with megakaryocytic leukemia (**Table 2**).

Chimeric fusion transcripts *RUNX1-RUNX1T1*, resulting from t(8;21)(q22;q22.1), and *CBFB-MYH11*, resulting from inv(16)(p13.1q22) or t(16;16)(p13.1;q22), confer a good prognosis in both pediatric and adult AML (von Neuhoff et al. 2010). The RUNX1 and CBFB proteins are components of the core binding factor heterodimeric transcription factor complex, which is critical for efficient transcription of regulators of granulocyte development (Downing 2003). *RUNX1-RUNX1T1* and *CBFB-MYH11* interfere with the core binding factor complex, blocking hematopoietic development. Translocations of *KMT2A* located on chromosome 11q23 occur in greater than 50% of AML cases in patients less than 1 year old, but decrease to 10% in teenagers with AML. *KMT2A* rearrangement causes overexpression of HOX genes, leading to increased self-renewal and inhibition of maturation (C. Meyer et al. 2013). In contrast to ALL, where any rearrangement involving *KMT2A* is high risk, prognosis for *KMT2A* rearrangement in AML may depend on the translocation partner (Balgobind et al. 2011). Recent progress in understanding protein-chromatin complexes required for maintenance of malignant self-renewal in

KMT2A-rearranged leukemia or *NPM1*-mutant AML (described below) may offer therapeutic opportunities through inhibition of the critical menin-MLL (*KMT2A*) interaction (Grembecka et al. 2012, Krivtsov et al. 2019, Kuhn et al. 2016).

Uncommon chromosomal rearrangements include t(6;9)(p22;q34), t(10;11)(p12;q21), and t(16;21)(p11;q22), which harbor chimeric fusion genes *DEK-NUP214*, *PICALM-MLLT10*, and *FUS-ERG*, respectively. The fusion *DEK-NUP214* occurs in 2% of pediatric AML, is highly associated with *FLT3* internal tandem duplication (ITD), and confers a poor prognosis (Tarlock et al. 2014). *PICALM-MLLT10* occurs in both T-ALL and AML. Leukemia with this translocation shows elevations in *HOXA* gene expression through aberrant MLLT10-mediated dysregulation of methylation, which may be blocked by XPO1 inhibitors currently under development (Alexander et al. 2016, Conway et al. 2015). AML with the dismal prognostic FUS-ERG oncoprotein may proliferate through transcriptional repression of the retinoic acid signaling pathway, suggesting all-*trans* retinoic acid treatment as an avenue of future therapeutic research (Noort et al. 2018, Sotoca et al. 2016).

Fusion genes have also been identified in AML cases with a normal karyotype. The fusion transcript *CBFA2T3-GLIS2* results from a cryptic inversion of chromosome 16, is common in acute megakaryoblastic leukemia but can occur throughout AML phenotypes, is exclusive to children less than 3 years old, and shows a poor prognosis (Gruber et al. 2012, Masetti et al. 2013). Similar to *KMT2A*-rearranged leukemia, *CBFA2T3-GLIS2* may be sufficient for malignant transformation without cooperating mutations (Smith et al. 2020). Cryptic fusions involving *NUP98* with multiple partners have been identified as recurrent in 4% of pediatric AML, including a subset of cases with erythroid phenotype (Iacobucci et al. 2019); indicate poor prognosis; and are associated with primary chemotherapy resistance (McNeer et al. 2019, Struski et al. 2017). *NUP98* fusions alter transcription in part through chromatin regulation, leading to increased methylation of H3K4 (Franks et al. 2017, Rio-Machin et al. 2017). This group of fusion proteins may offer targets for therapeutic development through disruption of pathogenic histone-modifying complexes (Xu et al. 2016).

Gene Mutations in Acute Myeloid Leukemia

Genes in signaling pathways are frequently mutated in pediatric AML. Two of the most common, *FLT3* and *KIT*, belong to the class III receptor tyrosine kinase family (**Figure 3**). *FLT3*-activating lesions are present in 15–20% of pediatric AML (Schuback et al. 2013). The prognostic influence of ITDs and point mutations in *FLT3* are distinct, as only *FLT3*-ITD carries poor prognosis in children (Meshinchi et al. 2006). Targeted inhibitors of FLT3 have been used in both relapsed and frontline AML protocols. The utility of FLT3 inhibition depends on the ITD allelic ratio, emphasizing the necessity of nuanced understanding of clonal mutational structure to guide precision therapy. Point mutations in *KIT* (10–15%) and the Ras pathway (25–30%) are common and largely nonoverlapping. *KIT* and Ras pathway mutations do not contribute prognostic information at diagnosis (Klein et al. 2015). Mutations of signaling genes in AML are likely secondary events, as evidenced by their inability to independently generate leukemia in mouse models, the frequent subclonal nature at diagnosis, and examples of both acquisition and loss at relapse (Bachas et al. 2010, Farrar et al. 2016).

Alterations of genes involved in hematopoietic development, such as transcription factors *CEBPA* (4–8%) and *WT1* (8–14%), may confer prognosis. As in adults with AML, *CEBPA* compound heterozygous mutations confer good prognosis in children (Hollink et al. 2011). *WT1* mutations, which also occur in 10% of T-ALL cases, usually occur as small frameshift insertions at

exons 7 or 9 (Bolouri et al. 2018, Liu et al. 2017). Data suggesting prognostic impact of *WT1* mutations or *WT1* expression levels in AML are conflicting (Ho et al. 2010). *NPM1* encodes a nuclear shuttling protein involved in various cellular processes, including ribosome biogenesis and centrosome duplication. Altered *NPM1* occurs in 4–8% of pediatric AML, most commonly occurring as a small insertion at exon 12, causing loss of the nuclear localization signal, leading to cytoplasmic mislocalization. *NPM1* mutations occur more commonly in cytogenetically normal AML and confer a good prognosis in patients without *FL3*-ITD (Brown et al. 2007).

Collectively, mutations in genes influencing epigenetic regulation occur in up to 20–25% of pediatric AML cases. However, alterations in individual genes *IDH1*, *IDH2*, *EZH2*, *EP300*, *CREBBP*, *ASXL2*, *TET2*, *SETD2*, and *DNMT3A* are each observed in less than 3% of childhood AML cases (Tarlock & Meshinchi 2015). These mutations influence chromatin structure and DNA expression through a wide range of mechanisms, such as DNA methylation, histone acetylation, and histone lysine methylation, emphasizing the complexity of precision drug development for epigenetic machinery.

UNCOMMON LEUKEMIA SUBTYPES

Lineage-Ambiguous Leukemia

While currently classified as a subtype of T-ALL, early T cell precursor ALL (ETP-ALL) is a form of hematopoietic stem cell leukemia, with clinical and biological features distinct from T-ALL. ETP-ALL is defined by an immature hematopoietic immunophenotype with a lack of core T cell antigen expression and aberrant expression of stem- or myeloid-associated markers (Coustan-Smith et al. 2009). ETP-ALL exhibits high rates of induction failure, but recent risk-adapted pediatric studies have mitigated the poor prognosis (Coustan-Smith et al. 2009, Patrick et al. 2014, Winter et al. 2018). This subtype is characterized by frequent mutations in cytokine receptor and Ras signaling pathways or developmental pathways (*RUNX1*, *ETV6*, *GATA3*, *IKZF1*, *EP300*), as well as frequent loss-of-function mutations in epigenetic regulatory genes *PHF6* and *KDM6A* and members of polycomb repressor complex through *EED*, *EZH2*, and *SUZ12* (Liu et al. 2017, Zhang et al. 2012). This high rate of mutations in cytokine receptor and epigenetic regulators, along with gene expression profiling, suggests that ETP-ALL shares certain features with AML. Frequent mutations in the JAK-STAT pathway led to the hypothesis and subsequent demonstration that ETP-ALL is sensitive to JAK-STAT inhibition, but the sensitivity is surprisingly independent of sequence mutations in the JAK-STAT pathway (Maude et al. 2015).

Rarely, acute leukemia has distinctive features of both myeloid and lymphoid leukemia and so is classified as MPAL (Arber et al. 2016). Recent studies have shown that the B/myeloid-subtype MPAL has a mutational profile akin to B-ALL, with frequent *ETV6* and *PAX5* deletions and RNA expression patterns similar to B-ALL (Alexander et al. 2018). *ZNF384* fusions are found in almost half a pediatric B/myeloid MPAL, implying a role for *ZNF384* in early hematopoietic development and, when fused with a variety of 5′ partners, in maintaining multipotent potential in malignant hematopoietic precursors (Alexander et al. 2018). *ZNF384* fusions are not found in adult B/myeloid MPAL, demonstrating the biologic variation across the age spectrum (Takahashi et al. 2018). The *ZNF384* fusion partners, secondary genomic alterations, and transcriptional profiles of *ZNF384*-rearranged leukemias diagnosed as B-ALL are identical to those of *ZNF384*-rearranged leukemias diagnosed as B/myeloid MPAL, suggesting that *ZNF384* rearrangement defines a distinct subtype of leukemia of variable and ambiguous lineage. T/myeloid MPAL, similar to ETP-ALL, has frequent mutually exclusive alterations in the transcription factors *WT1*, *RUNX1*, *CEBPA*, and *ETV6*, as well as a high proportion of cases with *FLT3*-ITD,

without a hallmark fusion event (Alexander et al. 2018, Zhang et al. 2012). Distinct phenotypic subpopulations within MPAL cases share the same mutational profile, with RNA and chromatin accessibility profiles similar to hematopoietic stem cells (Alexander et al. 2018, Granja et al. 2019). Thus, the phenotypic diversity is the result of the acquisition of DNA alterations and modified epigenetic states in immature hematopoietic progenitors that maintain lineage plasticity.

Ras Pathway–Driven Leukemia

JMML is an uncommon malignancy of granulocyte and monocyte lineage, typically occurring in young children, that presents with splenomegaly and hepatomegaly and can have pulmonary or abdominal infiltrates with only mildly increased bone marrow blasts (Arber et al. 2016). Clinical prognostic factors are age, hemoglobin F, and platelet count. Even across prognostic subgroups, JMML can spontaneously regress or recur. JMML is driven by, and partially defined by, mutations causing constitutive activation of the Ras pathway (*NF1*, *NRAS*, *KRAS*, *PTPN11*, or *CBL*), in contrast to ALL and AML, which have recurrent subclonal cooperating Ras mutations. Given this fundamental dependence on Ras pathway, trials evaluating MEK inhibition for JMML are enrolling (**https://www.clinicaltrials.gov** identifier NCT03190915). Additional mutations are uncommon but can involve tumor suppression (*SETBP1*), the JAK-STAT pathway (*SH2B3*), or epigenetic regulators (*ASXL1*, *DNMT3A*, and *EZH2*), and confer a worse prognosis when present (Stieglitz et al. 2015). Recently, multiple groups simultaneously demonstrated improved JMML risk stratification with analysis of DNA methylation patterns, with the lowest DNA methylation predicting high rates of survival (Lipka et al. 2017, Stieglitz et al. 2017). Increased examination of epigenetic contribution to leukemia pathogenesis, prognosis, and, potentially, treatment is a critical area of future study across leukemia subtypes.

CLONAL EVOLUTION AND RELAPSE

Molecular classification of tumor genomics is predicated on discovering clonally predominant alterations through examination of bulk tumor cells at a single point in time. However, the subclonal complexity of leukemia at diagnosis is now well established, and the clonal dynamics that occur during therapy and at relapse have been explored through deep sequencing and, more recently, single-cell analysis (Anderson et al. 2011, De Bie et al. 2018). Chimeric fusions, when present, are usually clonal leukemia–initiating lesions that are retained throughout disease progression. Alterations of signaling genes (*FLT3*, *KRAS*, or *NRAS*) are often subclonal and frequently lost or gained from diagnosis to relapse in both ALL and AML (Farrar et al. 2016, Ma et al. 2015).

In B-ALL, mutations in genes such as the histone acetyl transferase *CREBBP*, histone methyltransferase *SETD2*, and corticosteroids receptors *NR3C1* and *NR3C2* are enriched at relapse (Li et al. 2020, Mar et al. 2014, Mullighan et al. 2011, Waanders et al. 2020). Rare relapse-initiating subclones can exist at diagnosis with distinct biology and resistance to chemotherapy (Dobson et al. 2020). Other relapse-specific mutations such as *PRPS1*, *PRSP2*, *NT5C2*, or *MSH6*, each influencing thiopurine metabolism, may only emerge during therapy, driven by selective therapeutic pressure (Li et al. 2020, 2015; J.A. Meyer et al. 2013; Waanders et al. 2020). These mutations confer chemotherapy resistance and may have implications for disease monitoring and therapeutic decisions (Li et al. 2015, J.A. Meyer et al. 2013). Inherited genomic variants in specific ethnic and racial groups also contribute to relapse risk through differential drug metabolism or acquisition of distinct somatic mutations (Karol et al. 2017; Yang et al. 2011, 2015). Monitoring the dynamics of mutation clearance during induction therapy, or monitoring for emergence of relapse-associated mutations, may identify patients who could benefit from early modification of therapy.

Leukemia exhibits profound phenotypic, clinical, and molecular diversity in children, with a profile of genomic alterations distinct from adults, with individual cases demonstrating clonal complexity. Such heterogeneity contributes to the challenge of effective therapeutic development. In spite of this biologic intricacy, researchers continue to offer hope by uncovering the molecular basis of pediatric leukemia, extending insight into potential vulnerabilities specific to malignant cells and exploring novel therapeutic approaches.

SUMMARY POINTS

1. Inherited susceptibility to pediatric leukemia associated with constitutional syndromes or highly penetrant germline alterations is uncommon, but large-scale genomic analyses are identifying diverse low-penetrance noncoding risk alleles and nonsilent variations, frequently in or near transcription factor genes known to be important in hematopoietic development.
2. Pediatric B cell acute lymphoblastic leukemia (B-ALL) and acute myeloid leukemia (AML) have different patterns of mutation than adults in both the founding genetic alteration and the acquisition of secondary mutations.
3. Novel subtypes of B-ALL have been defined through whole-genome and RNA sequencing, including kinase-driven Ph-like ALL; transcription factor fusions involving *DUX4*, *MEF2D*, and *ZNF384*; and specific point mutations in transcription factors *PAX5* and *IKZF1*, which can be identified on the basis of either DNA alteration or gene expression profile.
4. Recently characterized AML oncoproteins enriched in pediatric or adolescent/young adult populations, such as *NUP98* rearrangements, *FUS/ERG/ETV6* rearrangements, or *CBFA2T3-GLIS2* fusions, carry poor prognosis and demand pediatric-specific therapeutic development.
5. Lineage-ambiguous leukemia subtypes ETP (early T cell precursor)-ALL and T/myeloid MPAL (mixed phenotype acute leukemia) are forms of immature, progenitor cell leukemias that share genomic profiles; *ZNF384* rearrangements define a biological subgroup of leukemia that can have the phenotype of B-ALL or B/myeloid MPAL.
6. Relapsed ALL is enriched for mutations in histone modifiers, glucocorticoid receptors, and genes involved in thiopurine metabolism, while mutations in signaling pathways are gained or lost without enrichment at relapse.

FUTURE ISSUES

1. Will increased understanding of inherited susceptibility to childhood leukemia through low-penetrance risk alleles lead to clinically actionable information?
2. How will we implement comprehensive genomic assessment for clinical use, requiring rapid and reliable results?
3. How can we efficiently evaluate genomic predictors of response to novel agents in preclinical development and in early-phase clinical trials?

4. Will inhibition of signaling pathways improve outcomes? Examples in clinical trials or advanced translational development include (*a*) kinase-driven B-ALL (outside of *ABL1* lesions); (*b*) Ras pathway–driven leukemias such as JMML (juvenile myelomonocytic leukemia) or AML with Ras pathway mutations; (*c*) leukemias with high-level expression of FLT3 (without *FLT3* mutations), such as ETP-ALL, or *ZNF384*-rearranged ALL or MPAL; and (*d*) PI3K inhibition in T-ALL subsets.
5. With the most common fusions in childhood leukemia involving transcription factors, when will targeting aberrant transcription factor activity become a clinical reality in pediatric leukemia?
6. Will assessment of epigenetic profiles (DNA methylation, histone methylation, histone acetylation) transition into the clinic for prognostic assessment or therapy selection?
7. How can researchers improve understanding of aberrant chromatin remodeling and develop therapies targeting specific changes rather than broad-based tools of histone deacetylase inhibitors or DNA methyltransferase inhibitors?
8. How will monitoring and detection of relapse-enriched and -specific mutations be implemented and alter therapeutic approaches to patients throughout therapy?

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