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Acute myeloid/T-lymphoblastic leukaemia (AMTL): A distinct category of acute leukaemias with common pathogenesis in need of improved therapy

Alejandro Gutierrez[1,*] and **Alex Kentsis**[2,*]

[1]Division of Hematology/Oncology, Boston Children's Hospital, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA

[2]Molecular Pharmacology Program, Sloan Kettering Institute, and Department of Pediatrics, Weill Cornell Medical College, Memorial Sloan Kettering Cancer Center, New York, New York, USA

Summary

Advances in the classification of acute leukaemias have led to improved outcomes for a substantial fraction of patients. However, chemotherapy resistance remains a major problem for specific subsets of acute leukaemias. Here, we propose that a molecularly distinct subtype of acute leukaemia with shared myeloid and T cell lymphoblastic features, which we term acute myeloid/T-lymphoblastic leukaemia (AMTL), is divided across 3 diagnostic categories owing to variable expression of markers deemed to be defining of myeloid and T-lymphoid lineages, such as myeloperoxidase and CD3. This proposed diagnostic group is supported by i) retained myeloid differentiation potential during early T cell lymphoid development, ii) recognition that some cases of acute myeloid leukaemia (AML) harbour hallmarks of T cell development, such as T-cell receptor gene rearrangements and iii) common gene mutations in subsets of AML and T cell acute lymphoblastic leukaemia (T-ALL), including *WT1, PHF6, RUNX1* and *BCL11B*. This proposed diagnostic entity overlaps with early T cell precursor (ETP) T-ALL and T cell/myeloid mixed phenotype acute leukaemias (MPALs), and also includes a subset of leukaemias currently classified as AML with features of T-lymphoblastic development. The proposed classification of AMTL as a distinct entity would enable more precise prospective diagnosis and permit the development of improved therapies for patients whose treatment is inadequate with current approaches.

Keywords

acute leukaemia; classifications; AML; ALL

[*]Correspondence to: Professor Alex Kentsis, Memorial Sloan-Kettering Cancer Center, Sloan Kettering Institute, 1275 York Ave, Box 223, New York, NY 10065-6007, USA, Tel: 1-646-888-2593, kentsisresearchgroup@gmail.com And Dr. Alejandro Gutierrez, Division of Hematology/Oncology, Boston Children's Hospital, Dana-Farber Cancer Institute, Boston, Massachusetts, USA. alejandro.gutierrez@childrens.harvard.edu.

DR. ALEJANDRO GUTIERREZ (Orcid ID : 0000-0002-0249-9007)

PROF. ALEX KENTSIS (Orcid ID : 0000-0002-8063-9191)

Introduction

Acute leukaemias are aggressive neoplasms characterized by the pathological accumulation of immature haematopoietic progenitors. Improvements in clinical outcomes for patients with acute leukaemias treated with modern chemotherapy regimens have been variable. The introduction of molecularly targeted therapies has had a major impact on a small subset of genetically-defined acute leukaemias. For example, arsenic trioxide and retinoic acid, which target the PML-RARA fusion oncoprotein via distinct mechanisms (de The, 2015), can now cure the majority of patients with acute promyelocytic leukaemia without exposure to cytotoxic chemotherapies (Lo-Coco *et al*, 2013). However, clinical outcomes for a substantial fraction of acute leukaemias have seen little improvement despite the application of treatment regimens that are among the most intensive and toxic used for any disease. Consequently, improving clinical outcomes for these patients will require linking an improved molecular understanding to the application of effective targeted therapies.

Classification of acute leukaemias

Acute leukaemias have traditionally been classified based on the normal cell types most closely resembling the leukaemic cell population. Lymphoblastic leukaemias are those with evidence of differentiation arrest at immature stages of B- or T-cell lymphoid development, whereas acute myeloid leukaemias encompass malignancies with immunophenotypic features that lie along a broad spectrum of haematopoietic progenitors, ranging from minimally differentiated leukaemias to those with evidence of granulocytic, monocytic, erythroid or megakaryocytic differentiation. Although this classification scheme is intuitive, lineage assignment is complicated by the high frequency of aberrant differentiation states in acute leukaemias. Indeed, the simultaneous expression of markers that are not known to be co-expressed in any normal haematopoietic progenitor is common. To address the requirement for consistent diagnostic criteria for the successful performance and interpretation of clinical trials, the World Health Organization (WHO) has devised a classification scheme that allows most acute leukaemias to be unambiguously classified as specific diagnostic entities, which has been regularly revised (Swerdlow *et al* 2008; Arber *et al*, 2016).

The genetics of leukaemia are beginning to be incorporated into the WHO classification, with increasing weight being given to specific chromosomal translocations and, in some cases, somatic gene mutations, as disease-defining genetic lesions (Arber *et al*, 2016). Thus, the presence of a characteristic genetic feature can define a disease, independent of the phenotypic lineage which can be difficult to assign in practice. For example, leukaemias with *FGFR1* translocations that can present with T cell lymphoblastic or myeloid markers are defined as a single diagnostic entity, regardless of the immunophenotype of the presenting leukaemic cells (Arber *et al*, 2016; Macdonald *et al*, 2002). Similarly, acute myeloid leukaemia (AML) cases with t(8;21) translocations exhibit aberrant expression of CD19, a marker typically associated with B cell lymphoid malignancies, due to lineage-inappropriate PAX5 expression induced by the *RUNX1-RUNX1T1* (previously termed *AML1-ETO*) oncogene (Walter *et al*, 2010). While we anticipate that genomic classification will have an increasingly important role in defining leukaemia subsets in the future, the

current diagnostic classification for most acute leukaemias does not rely on genetic mutations. Thus, phenotypic lineage assignment remains a central component of diagnostic classification and treatment assignment for most patients with acute leukaemia.

The current WHO classification considers strong expression of a small number of immunophenotypic markers to be lineage-assigning: myeloperoxidase (MPO) or at least two monocytic markers (CD11c, CD14, CD64 or lysozyme) for myeloid lineage; surface or cytoplasmic CD3 expression for T cell lineage; and CD19 with at least one additional B cell marker (CD79a, cytoplasmic CD22, or CD10) for B cell lineage (Arber *et al*, 2016). While the specificity of these markers is widely agreed upon, some prominent clinical trials groups use subtly different criteria for lineage assignment (Dworzak *et al*, 2017). Nevertheless, it is recognized that these classification schemes are imperfect, and the strict application of the WHO criteria for lineage assignment is not required to make a diagnosis of AML, T cell acute lymphoblastic leukaemia (T-ALL) or B cell acute lymphoblastic leukaemia (B-ALL) unless a diagnosis of mixed phenotype acute leukaemia (MPAL) is also being considered (Arber *et al*, 2016). Thus, while MPALs that meet formal criteria for assignment to two distinct lineages are very rare, leukaemias classified as AML, T-ALL or B-ALL based on their predominant morphology and immunophenotype commonly co-express markers that indicate aberrant differentiation towards another lineage.

Acute myeloid/T-lymphoblastic leukaemia (AMTL): Acute leukaemias with shared T cell lymphoid and myeloid features

The classical model of haematopoiesis postulates an early binary split between common myeloid and lymphoid progenitors that subsequently give rise to both B- and T-cell lymphocytes. However, more recent work using clonal tracking assays has shown the existence of progenitors that retain T cell/myeloid or B cell/myeloid bi-lineage potential. By contrast, individual progenitors whose potential is restricted to T cell and B cell (but not myeloid) lineages have been difficult to identify (Kawamoto *et al*, 2010). These findings fit the clinical observation that MPALs most commonly present with B cell/myeloid or T cell/ myeloid marker co-expression, whereas B/T cell MPALs are very rare (Matutes *et al*, 2011).

Here, we propose AMTL as a molecularly distinct subtype of acute leukaemias associated with shared T cell lymphoid and myeloid features. Expression of markers deemed to be defining of the myeloid and T cell lymphoid lineages, including myeloperoxidase and CD3, is variable in this disease, resulting in its separation across three diagnostic categories in the current WHO classification scheme: early T cell precursor (ETP) T-ALL, T/myeloid MPAL, and a specific subset of AML harbouring hallmarks of T-lymphoblastic differentiation.

This proposed diagnostic entity overlaps with subsets of ETP T-ALL, which is characterized by differentiation arrest at early stages of T cell development. While a number of biomarkers have been described to identify these cases (Coustan-Smith *et al*, 2009; Gutierrez *et al*, 2010; Homminga *et al*, 2011; Zuurbier *et al*, 2014), these are most commonly defined clinically using an immunophenotypic classifier that includes absent expression of CD1a and CD8, CD5 expression that is substantially lower than that of normal peripheral blood T cells, and the presence of one or more markers of myeloid or haematopoietic progenitors (CD117,

CD34, HLA-DR, CD13, CD33, CD11b or CD65) (Conter *et al*, 2016; Coustan-Smith *et al*, 2009; Patrick *et al*, 2014). Currently, ETP is classified as a subtype of T-ALL due to the expression of CD3, but has a genetic mutational profile that is similar to those observed in myeloid malignancies, such as AML, whereas mutations characteristic of other subtypes of T-ALL, such as *CDKN2A* deletions, are less common (Gutierrez *et al*, 2010; Van Vlierberghe *et al*, 2011a; Zhang *et al*, 2012).

While similarities between ETP T-ALL and AML have been previously recognized (Van Vlierberghe *et al*, 2011a; Zhang *et al*, 2012; Zuurbier *et al*, 2014), we propose that the biological overlap of AMTL is not with AML *per se*, but with a specific subset of AML cases that also exhibit T cell lymphoid features. Namely, a subset of AMLs has long been recognized to harbour clonal T-cell receptor (TCR) or immunoglobulin (Ig) gene rearrangements, indicating activity of the RAG recombinase that is responsible for generating somatic V(D)J recombination at these loci at specific stages of lymphoid development (Norton *et al*, 1987; Parreira *et al*, 1992; Schmidt *et al*, 1992). These AML cases can also express the lymphoid marker terminal deoxynucleotidyltransferase (TdT, also known as DNTT), which generates diversity at the TCR and Ig genes by mutating the junctions of rearrangements during V(D)J recombination (Drexler *et al*, 1993; Patel *et al*, 2013). Non-megakaryoblastic AMLs with TCR rearrangements typically co-express phenotypic markers of T-lymphoblastic differentiation, such as CD7, CD2 and CD4 (Schmidt *et al*, 1992). We postulate that this is the subset of AMLs that also harbour mutations that are commonly observed in a distinct subset of T-ALL, including *WT1, PHF6, RUNX1* and *BCL11B* (The Cancer Genome Atlas Research Network, 2013; Della Gatta *et al*, 2012; Ding *et al*, 2012; Klco *et al*, 2015; Tosello *et al*, 2009; Van Vlierberghe *et al*, 2010; Van Vlierberghe *et al*, 2011b; Zhang *et al*, 2012). Thus, a similar group of acute leukaemias exhibit shared features of myeloid and T cell lymphoid differentiation, and shared genetic mutations, which will need to be formally assessed in future studies.

Potential mechanisms for combined T-lymphoblastic and myeloid differentiation in acute leukaemia

At least two non-mutually exclusive mechanisms can explain the development of acute leukaemias with differentiation potential shared with myeloid and T-lymphoid lineages:

1. *Transformation of normal haematopoietic progenitors with T-lymphoblastic and myeloid bi-lineage potential.* While studies of endogenous haematopoiesis have revealed limited evidence of a putative normal progenitor whose fate is restricted to T-lymphoid and myeloid lineages, the identification of such a progenitor may have been hindered by differences in the lifespan of mature myeloid versus T-lymphoid cells. Nevertheless, even if a normal progenitor whose differentiation fate is restricted to T-lymphocytes and myeloid cells is lacking, such leukaemias can arise from cells that retain multi-lineage potential, even though their fate is normally restricted to a single lineage by microenvironmental signals. Immature intrathymic T cell progenitors at early double-negative stages of differentiation represent one potential cell of origin for such leukaemias. Indeed, the most immature intrathymic T cell progenitors retain myeloid (but not B-lymphoid)

potential until they progress through a BCL11B-dependent commitment to the T cell lineage (Balciunaite *et al*, 2005; Ikawa *et al*, 2010; Li *et al*, 2010) (Figure 1). Further, lineage tracing studies have demonstrated that immature T cell progenitors give rise to some macrophages and neutrophils harbouring TCR gene rearrangements *in vivo* (Bell & Bhandoola, 2008; Wada *et al*, 2008). Ectopic expression of *Myc* and *Bcl2* in mouse early double-negative T cell progenitors can drive development of acute leukaemias with variable expression of markers of myeloid and T-lymphoid lineages (Riemke *et al*, 2016), demonstrating that early T cell progenitors can function as the potential cell of origin of AMTL.

2. *Induction of aberrant trans-differentiation by leukemogenic mutations.* It is now established that specific gene mutations can induce T cell lymphoid or myeloid differentiation. For example, activation of NOTCH1 signalling in mouse bone marrow cells causes aberrant T cell differentiation independent of thymic microenvironmental signals (Pui *et al*, 1999). Likewise, mutations inactivating *Runx1* in haematopoietic progenitors cause, aberrant myeloid differentiation (Goyama *et al*, 2013). Thus, aberrant trans-differentiation of AMTL cells can in principle, occur as a result of combinations of mutations that cooperatively result in combined myeloid and T-lymphoid lineage commitment with differentiation arrest (Figure 1). These mutations include genes encoding regulators of chromatin and DNA remodelling, and transcription factors with key functions in controlling lymphoid and myeloid cell fate specification. Future studies using emerging approaches for combinatorial gene editing and conditional gene manipulation *in vivo* may reveal how the specific combinations of mutations in specific cell progenitor populations cooperate to induce AMTL and other non-canonical leukaemia subtypes.

Identification of Acute Myeloid/T-Lymphoblastic Leukaemia

To a first approximation, AMTL can be defined as acute leukaemias that fit the diagnostic criteria of ETP T-ALL or of T/myeloid MPALs, together with AMLs with clonal TCR gene rearrangements and evidence of T-lymphoid differentiation (CD3, CD7, CD2 or CD4 expression). However, we note that aberrant expression of CD4 and CD7 is relatively common in acute megakaryoblastic leukaemia (AMKL), a subtype of AML that is molecularly distinct from AMTL (de Rooij *et al*, 2017). Therefore, AMKL should be excluded from the definition of AMTL, based on absence of megakaryblastic morphology and expression of the platelet markers CD41 or CD61. Thus, our initial proposal for AMTL as a diagnostic entity includes all cases currently classified as ETP T-ALL and T/myeloid MPALs, together with the subset of AMLs with TCR rearrangements and expression of T-lymphoblastic markers.

Given the variability in cell surface marker expression in acute leukaemias, we propose that clinical genomic profiling will enhance the classification of AMTL as a specific diagnostic entity. Indeed, ETP T-ALLs harbour mutations of several genes that are commonly mutated in myeloid neoplasms, such as *RAS* family members, *ETV6*, *MEF2C* and *EZH2*, but whose mutations are rare in other T-ALL subtypes, (Homminga *et al*, 2011; Van Vlierberghe *et al*,

2011a; Zhang *et al*, 2012; Zuurbier *et al*, 2014). We also suggest that the subset of AML cases harbouring clonal TCR gene rearrangements should demonstrate substantial overlap with those AML cases harbouring mutations that are common in T-ALL, such as *WT1, RUNX1, PHF6* and *BCL11B* (The Cancer Genome Atlas Research Network, 2013; Ding *et al*, 2012; Klco *et al*, 2015; Zhang *et al*, 2012). We anticipate that future investigation will lead to an improved classifier of AMTL based on both immunophenotypic and genetic diagnostic markers.

Conclusions

We propose acute myeloid/T-lymphoblastic leukaemia (AMTL) as a new diagnostic entity for acute leukaemias with shared myeloid and T cell lymphoblastic features. Defining the detailed molecular mechanisms of aberrant cell differentiation may lead to the development of improved therapies by targeting specific molecular dependencies in these cells. For example, mutant transcription factors function in the context of corepressor and coactivator complexes, which have specific enzymatic functions, such as histone deacetylase (HDAC) inhibitors (Haberland *et al*, 2009). Isoform-specific HDAC inhibitors are beginning to be developed (West & Johnstone, 2014), and specific inhibitors may warrant therapeutic investigation in AMTL with dysregulation of MEF2 family members, for example. Likewise, specific mutations may engender synthetic lethal dependencies, such as, for example, inhibition of the EZH2 methyltransferase in cases of cancers with mutations of genes encoding components of the SWItch/Sucrose Non-Fermentable/BRG1-associated factors (SWI/SNF/BAF) chromatin remodelling complex (Kim *et al*, 2015). Recently, acetyltranferase inhibitors have been found to have therapeutic efficacy in CBP-deficient lymphomas (Ogiwara *et al*, 2016). Finally, many leukaemias exhibit aberrant resistance to mitochondrial apoptosis, conferring resistance to intensive combination chemotherapies, such as those used for treatment of refractory AML and T-ALL. Recent data suggest that AMTLs are particularly susceptible to inhibitors of BCL2 (Chonghaile *et al*, 2014; Pan *et al*, 2014), and emerging inhibitors of other regulators of intrinsic apoptosis are expected to offer useful therapeutic strategies for AMTL patients as well.

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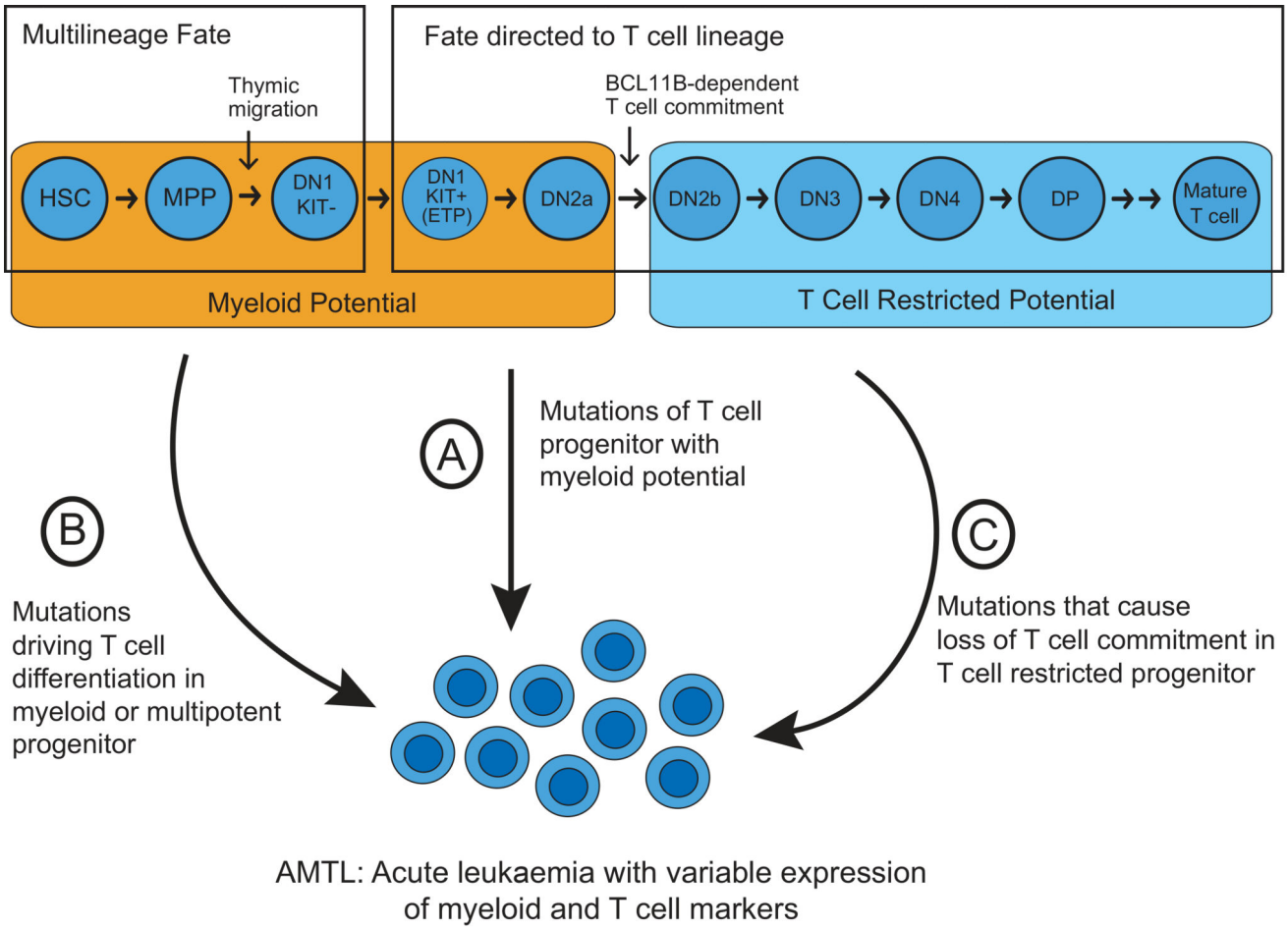

Figure 1. Potential mechanisms leading to acute leukaemia with shared myeloid and T-lymphoblastic features

The fate of multipotent haematopoietic progenitors first entering the thymus is directed to the T cell lineage via thymic microenvironmental signals, but these cells retain myeloid potential until BCL11B-dependent commitment to the T cell lineage at the DN2a to DN2b transition (Hosokawa & Rothenberg, 2017). Such T cell progenitors with myeloid potential can function as a cell of origin of AMTL (Riemke *et al*, 2016) (A). Alternatively, AMTL can in principle arise from mutations that induce aberrant T cell differentiation in myeloid or multipotent haematopoietic progenitors (B), or from mutations in T cell restricted progenitors leading to their myeloid differentiation (C). Note that the developmental stages shown (top) are based on mouse T cell development, because human early T cell development is less well-defined.

AMTL: acute myeloid/T-lymphoblastic leukaemia; DN: CD4/CD8 double-negative T cell progenitor; DP: CD4/CD8 double-positive T cell progenitor; ETP: early T cell precursor; HSC: haematopoietic stem cell; MPP: multipotent progenitor.