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On the Origin of ETP Leukemias

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Early T-cell precursor acute lymphoblastic leukemia was initially believed to originate from the transformation of lympho-myeloid thymic precursors. Rigorous proofs, however, have been lacking. In a recent Cancer Cell issue, Christopher Booth and colleagues provide novel insights into this issue.

The cancer stem cells model postulates tumors to originate from rare malignant cells, which are able to initiate and propagate the disease since they are endowed with a self-renewal capacity. A corollary of this model implies that oncogenic mutations can either transform normal hematopoietic stem cells, hijacking their intrinsic self-renewal, or alternatively target more differentiated progenitor cells, conferring on them the self-renewal they do not have intrinsically. Defining the so-called cell of origin is key to exploring disease biology and identifying new therapeutics. In certain hematological malignancies, however, this task remains challenging. This is the case for early T-cell precursor acute lymphoblastic leukemia (ETP-ALL), a distinct subtype of T-ALL that is associated with a high risk of treatment failure. Characterized by a distinctive immunophenotype (absent/reduced expression of T-lymphoid markers and expression of 1 or more myeloid or stem cells markers), this leukemia was originally named ETP-ALL because its transcription profile resembled that of murine ETP,[1] namely immature thymocytes that migrate from the bone marrow to the thymus and possess a lympho-myeloid differentiation potential. Subsequent gene expression analysis, however, revealed that the ETP-ALL signature is more similar to the signature of normal hematopoietic and myeloid leukemia stem cells, suggesting ETP-ALL to be a stem cell leukemia.[2] The mutational landscape is also closer to myeloid tumors. In contrast to other T-ALL subtypes, ETP-ALL are less likely to present mutations of *NOTCH1* receptor but they frequently mutate components of the RAS signaling pathway (such as FLT3), genes encoding transcription factors involved in hematopoietic development (such as *RUNX1*), and genes encoding histone modifiers (such as the polycomb repressive complex 2 component, *EZH2*).[2,3] Although the mutational landscape has been extensively characterized, it remains to be fully determined which genetic lesions are sufficient to initiate the disease, how do they cooperate in vivo, and which population(s) they transform.

In a recent Cancer Cell issue, Christopher Booth and colleagues provide some answers to these questions, providing a model of ETP-ALL development whereby *Ezh2* and *Runx1* inactivation cooperatively establish a preleukemic reservoir in early thymic progenitors, which are next turned into leukemia-propagating cells following subsequent acquisition of FLT3 mutations.[4]

Modeling the association between *RUNX1* and *EZH2* mutations, frequently observed in ETP-ALL, the researchers used a Rag1-Cre-driven conditional knockout model to inactivate *Runx1* and *Ezh2* in early thymic progenitors but not in hematopoietic stem cells. Whereas the inactivation of either 1 of the 2 genes did not affect thymic development, the inactivation of both genes expanded ETP progenitors, blocking T-cell differentiation. In sharp contrast to this phenotype, the Mx1-Cre-driven deletion of both genes in the hematopoietic stem/progenitor cell compartment drove the development of a fatal myelodysplastic syndrome. Interestingly, the expression profile of mutant ETP cells recapitulated transcriptional features of ETP-leukemias, namely myeloid and hematopoietic stem cells' signatures, increased expression of genes associated with cytokine signaling and lack of a *Notch1* signature. Despite this, *Runx1* and *Ezh2* double mutant mice did not show signs of leukemia development, thus indicating that additional oncogenic events are necessary to fully transform the expanded pool of mutant ETP cells. Mutations in RAS signaling pathway components, such as *FLT3*, are intriguing candidates in this context: rare in other T-cell leukemia, they are frequently observed in ETP-ALL where they are often associated with mutations in genes involved in epigenetic and transcriptional regulation, such as *EZH2* and *RUNX1*. Consistently, *Runx1*;*Ezh2* double mutant mice bearing *FLT3*-ITD activating mutations developed a highly penetrant and aggressive ALL expressing myeloid markers and showing an

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Funding/support: None.
Disclosure: The authors have indicated they have no potential conflicts of interest to disclose.

HemaSphere (2018) 2:3(e48)
Citation: Tesio M. On the Origin of ETP Leukemias. *HemaSphere*, 2018;2:3. http://dx.doi.org/10.1097/HS9.0000000000000048

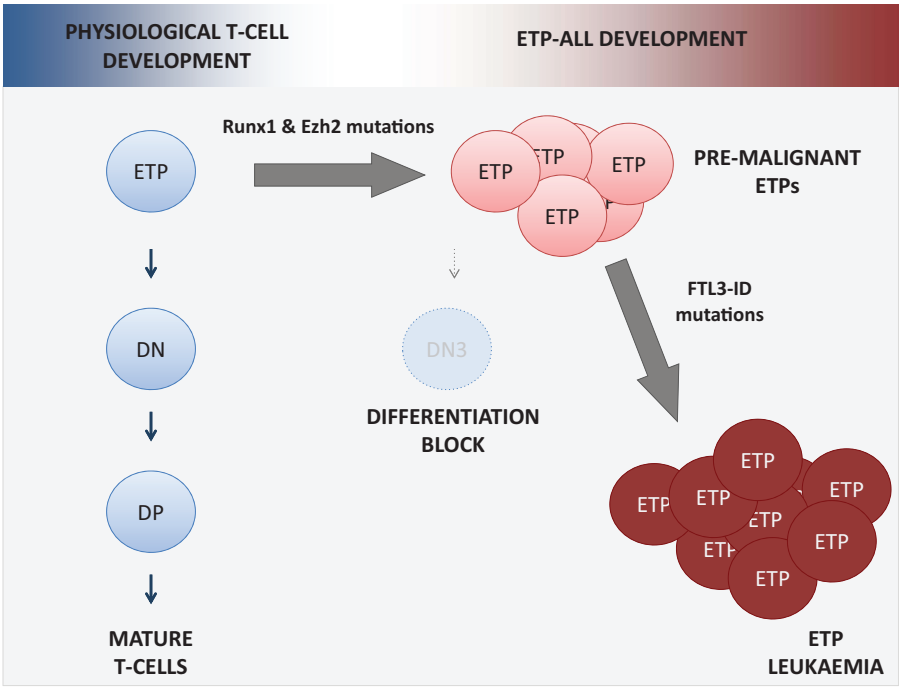

Figure 1. **Booth et al model for ETP-ALL initiation and development.**

immunophenotype characteristic of ETP-leukemias. Transplantation assays next indicated that the leukemia propagating potential resides in triple mutant ETP cells, as only these cells but not more differentiated T-cell progenitor cells could engraft and propagate leukemias in transplanted recipients. Although serial transplantation assays would have strengthened the authors' results, the data provided are intriguing, as they suggest a model whereby *Runx1* and *Ezh2* alterations act as founder mutations, expanding the pool of ETP cells, which become able to propagate ETP leukemias upon acquisition of *FLT3*-ITD activating mutations (Fig. 1).

In addition to providing novel insights into the mechanisms driving ETP-ALL initiation and transformation, this model represents an interesting preclinical tool for evaluating novel therapeutic approaches. In keeping with the epigenetic changes induced by *Ezh2* loss in ETP cells (ie, loss of H3K27me3 repressive histone marks and consequential increase in H3K27ac marks), ETP-propagating leukemia cells were targeted by bromodomain inhibitors, such as JQ-1. As such, these compounds may potentially be useful drugs in ETP-ALLs presenting mutations in components of the polycomb repressive complex 2.

In identifying leukemia-propagating activity in the ETP compartment, this model differs from 2 previous studies, in which hematopoietic progenitors[5] or double negative thymocytes (more differentiated thymic progenitors still retaining myeloid differentiation potential)[6] were postulated to be the target of transformation. A possible explanation for these discrepancies involves differences in the oncogenetic lesions that were examined in these studies. This emphasizes the possibility that, in T-ALLs, the complex genetic heterogeneity might reflect heterogeneity in leukemia-initiating cells of different origins. Futures studies will be necessary to translate these interesting findings into the human disease. In this regard, it will be particularly important to investigate the nature and hierarchical organization of leukemia-initiating cells in primary patient samples, especially for those T-ALL subtypes, such as ETP-ALL, which are associated with a high risk of treatment failure.

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