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Enhancing Leukemia Taxonomy

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Almost 10 years ago, a number of papers classified certain noncoding regulatory DNA regions as super-enhancers. These genomic regions consist of large clusters of enhancers densely occupied by transcription factors and transcriptional coactivators. Originally described in embryonic stem cells, super-enhancers were shown to be critical determinants of cell fate.[1,2] Since the initial discovery, numerous papers identified super-enhancers in both myeloid and lymphoid malignancies, demonstrating that they regulate key oncogenic drivers.

In a recent *Cancer Discovery* issue, Montefiori et al[3] extend these findings and identify super-enhancers endowed with a taxonomic value. The authors initially analyzed gene expression and genetic alterations in RNA sequencing data from 2573 adult and pediatric cases of acute leukemias, which included T-cell acute leukemia (T-ALL), acute myeloid leukemia (AML), mixed phenotype acute leukemia (MPAL), and B-cell acute leukemia. This analysis identified a cluster of 61 cases showing a distinct gene expression profile and immunophenotypic features (variable expression of myeloperoxidase, expression of myeloid/stem cell markers, and expression of the T-cell markers CD7 and cytosolic CD3). Constituted by a subset of T/myeloid MPAL, early T-cell precursor acute lymphoblastic leukemia (ETP-ALL), and a small number of poorly differentiated AML cases, this cluster was characterized by the ectopic, monoallelic expression of BCL11b, a transcription factor required during physiological T-cell development to promote T-cell differentiation and repress commitment toward the natural killer or myeloid lineage. Moreover, 80% of cases in this cluster harbored *FLT3* alterations.

By integrating genomic and epigenetic analyses, the authors next revealed that the ectopic BCL11b expression characterizing this cluster originates from the activation of 2 distinct types of super-enhancers. The first one, identified in a minority of the cases, is a de novo enhancer generated from a high-copy number amplification of a noncoding region distal to BCL11b. The second type, identified in the majority of the cases, consists of hematopoietic stem/progenitor (HSPC) super-enhancers juxtaposed to BCL11b following chromosomal rearrangements. As evidenced by chromatin conformation analysis, these enhancers established long range interactions with the BCL11b allele. Hence, these enhancers, which are physiologically active in primitive hematopoietic stem cells, are hijacked in a group of T/myeloid MPAL, ETP-ALL, and AML cases to drive the ectopic expression of BCL11b, not otherwise expressed in HSPC. These leukemias moreover did not show evidence of rearrangements at T-cell receptor receptor loci, which is characteristic of non-BCL11b deregulated cases. This further indicates that BCL11b ectopic expression precedes T-cell lineage commitment and occurs in HSPC. In line with this, in BCL11b-deregulated leukemia, BCL11b binding correlated with an HSPC gene expression signature.

The authors next set to analyze whether the super enhancer–mediated BCL11b deregulation in HSPC is a driver oncogenic event. To this end, they ectopically overexpressed BCL11b in human cord blood CD34+ progenitor cells and murine stem/progenitor cells. As evidenced in vitro, BCL11b overexpression was sufficient to block myeloid differentiation and drive T-cell differentiation even in the absence of Notch1 signaling, which in physiological conditions is indispensable to T-cell development. When combined to FLT3-ID mutations, frequently observed in BCL11b deregulated cases, the ectopic BCL11b expression drove the emergence of a subpopulation of cells displaying a T-cell immunophenotype characteristic of ETP-ALL and T/myeloid MPAL (cytoplasmic CD3 expression). Furthermore, in mouse lineage negative HSPCs, BCL11b and FLT3-ITD overexpression conferred self-renewal properties, thereby confirming the transformation potential of BCL11b overexpression.

Taken together, these data support a model whereby BCL11b deregulation, as results of enhancers hijacking in HSPC, is the driver genetic event in a subset of undifferentiated AML, ETP-ALL, and T/myeloid leukemias (Figure 1). Identifying a common etiology in these leukemias, the BCL11b-deregulating structural alterations identified in this study have a taxonomic value as they define a novel distinct subgroup of leukemias. This taxonomic criterion is likely to improve the classification of T/myeloid MPAL and ETP-ALL, which despite sharing

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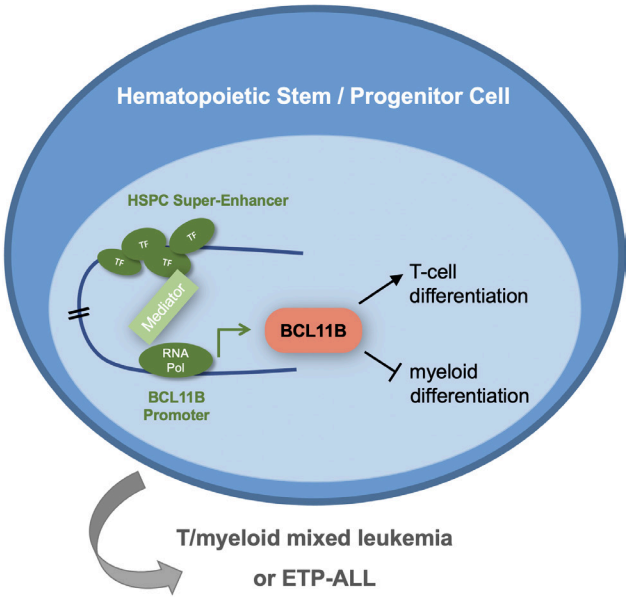

Figure 1. In a subset of undifferentiated AML, ETP-ALL and T/myeloid leukemias, the disease is driven by BCL11b ectopic expression in HSPC as result of hijacking of super enhancers active in these cells. ALL = acute leukemia; AML = acute myeloid leukemia; ETP = early T-cell precursor; HSPC = hematopoietic stem/progenitor cells; TF = transcription factor.

genomic alterations, stemness and lineage ambiguity features, remain classified by the World Health Organization as separate entities based on immunophenotypic criteria. Importantly, the identification of a super enhancers-mediated BCL11b deregulation is likely to help refine patients' risk stratification as, albeit analyzed in small cohort of ETP-ALL cases, BCL11b expressing leukemias showed a superior outcome versus non-BCL11b expressing leukemias. This aspect is particularly important to T/myeloid MPAL and ETP-ALL leukemias, which have a dismal prognosis. Last but not least, the study by Montefiori et al[3] brings novel insights into debated issues, namely the cell of origin of T/myeloid MPAL and ETP leukemias. Confirming a previous model from the same group, this study demonstrates that, at least in a subtype of MPAL and ETP-ALL, these leukemias originate from the transformation of HSPCs and not from the transformation of thymic progenitor cells, as proposed by other groups.[4,5]

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