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On the origin of relapse in AML

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Abstract

Preexisting therapy-resistant leukemia stem cell populations underlie the cellular origin of relapse in acute myeloid leukemia.

Acute myeloid leukemia (AML) is associated with a poor prognosis and a high rate of relapse. Various relapse mechanisms have been described, including preexistence or acquisition of mutations resulting in drug resistance, minor subclones that are present at diagnosis and survive treatment, and clonal evolution from pools of preleukemic hematopoietic stem cells (HSC). Furthermore, AML is the prototypic cancer stem cell model, with rare multipotent leukemia stem cells (LSC) predicted to be responsible for relapse due to their inherent chemoresistance and self-renewal capacity. Although LSC gene expression signatures are predictive of relapse, the direct role of LSCs in relapse remains controversial.

Shlush *et al.* used combined genetic and functional analytic approaches to study the origins of relapse in AML. Paired diagnosis and relapse AML patient samples and patient-derived xenografts from these samples were used to sequence leukemic and normal cell subpopulations and determine preleukemic, leukemic, and relapse variants. The presence and frequency of variants in each patient allowed construction of phylogenetic lineage trees, and the pattern of relapse variants suggested a clonal change between diagnosis and relapse for most patients. Two principal origins of relapse were identified, termed relapse origin-primitive (ROp) and relapse origin-committed (ROc), that were both related to stem cell properties. In ROp, the cellular origin of relapse was preexisting rare LSCs with primitive hematopoietic stem/progenitor cell functional properties and phenotype. In ROc, relapse originated from LSCs in larger subclones that had a committed immunophenotype and retained stem cell–like or stemness transcriptional signatures.

This study confirms that at least two preexisting LSC populations sharing functional and transcriptional stemness properties constitute the cellular origin of relapse in AML. Assay-specific limitations in detecting ultra-rare variants raise the possibility of other cellular origins of relapse, including preleukemic HSCs. Nevertheless, these findings have major implications, including the importance of therapeutic approaches targeting stemness features, potential limitations of therapies that may fail to target relevant nondominant clones, and the need to consider clonal architecture and LSC subpopulations in disease monitoring.

Highlighted Article

1. Shlush LI, Mitchell A, Heisler L, Abelson S, Ng SWK, Trotman-Grant A, Medeiros JJF, Rao-Bhatia A, Jaciw-Zurakowsky I, Marke R, McLeod JL, Doedens M, Bader G, Voisin V, Xu C, McPherson JD, Hudson TJ, Wang JCY, Minden MD, Dick JE. Tracing the origins of relapse in acute myeloid leukaemia to stem cells. Nature. 2017; 547:104–108. [PubMed: 28658204]