News Release

Title

Comparison of clonal architecture between primary and immunodeficient mouse engrafted acute myeloid leukemia cells

Key Points

- Primary AML cells including potentially chemotherapy-resistant clones engrafted in AML-PDX models
- Patients with AML cells engrafted in PDX mice had poorer outcomes than those without engraftment.
- AML-PDX mouse model is useful not only for drug discovery, but also for a more detailed understanding of clonal selection in AML.

Summary

Patient-derived xenografts (PDX) are widely used as human cancer models. Previous studies demonstrated clonal discordance between PDX and primary cells. However, in acute myeloid leukemia (AML)-PDX models, the significance of the clonal dynamics occurring in PDX remains unclear. By evaluating changes in the variant allele frequencies (VAF) of somatic mutations in serial samples of paired primary AML and their PDX bone marrow cells, we identify the skewing engraftment of relapsed or refractory (R/R) AML clones in 57% of PDX models generated from multiclonal AML cells at diagnosis, even if R/R clones are minor at <5% of VAF in patients. The event-free survival rate of patients whose AML cells successfully engraft in PDX models is consistently lower than that of patients with engraftment failure. We herein demonstrate that primary AML cells including potentially chemotherapy-resistant clones dominantly engraft in AML-PDX models and they enrich pre-existing treatment-resistant subclones.

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Research Background

Various chromosomal abnormalities and gene mutations are involved in the progression of acute myeloid leukemia (AML), and the acquisition of multiple gene abnormalities is necessary for the pathogenesis of AML. Patient-derived xenografts (PDX) are widely used as human cancer models and previous studies demonstrated clonal discordance between PDX and primary cells. However, in acute myeloid leukemia (AML)-PDX models, the significance of the clonal dynamics occurring in PDX remains unclear. In the present study, by generating 160 AML-PDX models from adult AML patients and tracking the dynamics of somatic mutations in

serial samples from primary AML cells and their PDX, we show their clonal architecture and the PDX-specific enrichment of AML clones with predictive power for characterizing clonal selection in parental patients.

Research Results

To compare the features of primary AML[*1] cells that successfully engraft and proliferate in PDX[*2] to those with engraftment failure, we generated AML-PDX models from 160 AML patients. PDX models from 105 patients (66%) were successfully established, whereas the engraftment of humanCD45+ cells was not confirmed in samples from the other 55 patients (34%). Successful engraftment was also associated with the M4-FAB type[*3], relapse/refractory (R/R) AML, and a higher risk in the European LeukemiaNet (ELN) risk classification[*4]. To obtain further insights into the genetic landscapes of engrafted primary AML cells, the mutation profiles of AML cells were analyzed. Among the evaluated genes that are frequently mutated in myeloid malignancies, mutations in the *FLT3, NPM1, IDH1,* and *WT1* genes were more frequently observed in engrafted patients than in those with engraftment failure. To investigate the clonal selection in AML-PDX models through propagation, changes in variant allele frequencies (VAF) were sequentially compared among primary AML cells, first engrafted or once passaged (P1-2) PDX models, and further passaged (P3-11) PDX models. Enriched genetic variants frequently included *FLT3, TP53, KRAS, TET2,* and *WT1* mutations. In contrast, clones harboring *NRAS* or *CEBPA* occupied small VAF at engraftment and then diminished through serial passages in PDX models. We attempted to establish whether clones that engraft and expand in PDX exert adverse effects on the clinical outcomes of patients, such as treatment resistance. We evaluated the responses of patients to chemotherapy according to the potential to engraft in PDX mice. Thirty-nine patients with successful engraftment into PDX had a significantly lower event-free survival (EFS) rate than 37 patients with engraftment failure (P=0.0004), with 2-year EFS rates of 20.0% and 53.5%, respectively. These results indicate that primary AML cells including potentially chemotherapy-resistant clones engraft in AML-PDX models.

Research Summary and Future Perspective

We elucidated the dynamics of clonal changes from primary patients to AML-PDX models. Primary AML cells including potentially chemotherapy-resistant clones engraft in AML-PDX models. The skewing of minor pre-existing treatment-resistant subclones in AML-PDX, which were under the detection limit in patients, predict clonal evolution at treatment resistance. These results will contribute to the application of AML-PDX models not only for drug discovery, but also a more detailed understanding of clonal selection in AML.

*1 Acute Myeloid Leukemia (AML)

AML is a cancer of the blood cells, characterized by the rapid growth of abnormal cancer cells in the bone marrow and blood and interfere with normal blood cell production. AML progresses rapidly and is typically fatal within weeks or months without any treatment.

*2 Patient-derived xenografts (PDX)
PDX are models of cancer where the cells from a patient's tumor are implanted into an immunodeficient or humanized mouse. PDX models are utilized for such as cancer research and drug discovery *in vivo*.

*3 FAB type
The French–American–British (FAB) classification systems refers to a series of classifications of hematologic diseases and it classified AML into eight subtypes according to cell-lineage and maturation status of leukemia cells.

*4 European LeukemiaNet (ELN) risk classification
The ELN risk classification is a risk stratification system, widely accepted, and has been shown to provide prognostic information in AML patients according to cytogenetics and gene mutations.

Publication

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