EDITORS' CHOICE | CANCER

From MDS/AML to iPSC and back again

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Abstract

iPSC lines derived from MDS and AML patient samples can map clonal evolution, disease progression and regression, and identify disease stage–specific medication effects.

Acute myeloid leukemia (AML) is an aggressive clonal blood and bone marrow cancer that can arise de novo or from preexisting hematologic diseases, such as myelodysplastic syndromes (MDS). It is now well established that AML evolves from hematopoietic stem and progenitor cells (HSPCs) through the step-wise accumulation of multiple genetic changes. However, functional studies of the evolution from MDS to AML are limited by the relative inability of primary MDS cells to grow and transplant. Patient-derived induced pluripotent stem cells (iPSCs) are being evaluated as potential platforms for studying cancer progression,

genetics, and treatment, including a recent report by Kotini *et al*. investigating iPSCs derived from patients with myeloid diseases.

Using primary MDS and AML patient samples, Kotini *et al*. developed a reprogrammed panel of patient-derived iPSC lines spanning the entire myeloid disease spectrum, including normal, preleukemic, MDS, and AML stages. Notably, the reprogramming potential of each patient sample was mutation-specific. The investigators selected iPSC lines representative of different disease stages and used a hematopoietic differentiation protocol to characterize the phenotype of each disease stage–specific line. Hematopoietic progenitor cells (HPCs) derived from these iPSC lines demonstrated graded disease stage–specific changes in dysplasia, progenitor loss, differentiation block, cell growth rate, gene expression, and engraftment in NOD/SCID/IL-2rγ^{null} mice that mapped the phenotypic transformation from normal HSPCs to fulminant and serially transplantable leukemia. Next, the investigators used genome-editing methods to model clonal evolution and showed that iPSC lines from distinct disease stages could be transitioned forward or backward through the introduction or correction of specific mutations. Last, iPSC-derived HPCs showed disease stage–specific responses to drug treatment.

This study used cell reprogramming and genetics to develop a panel of patient-derived, disease stage–specific iPSC lines that provides a phenotypic roadmap of myeloid disease progression and can be custom tailored through genome editing approaches. The small number of primary patient samples and inability of some cells with specific mutations to reprogram are limitations; overall, however, stage-specific iPSC lines represent a powerful new tool for functional studies of myeloid diseases, demonstrating proof of principle that treatment effects can be studied in these models with potentially broader cancer applicability.

Highlighted Article

A. G. Kotini, C. J. Chang, A. Chow, H. Yuan, T. C. Ho, T. Wang, S. Vora, A. Solovyov, C. Husser, M. Olszewska, J. Teruya-Feldstein, D. Perumal, V. M. Klimek, A. Spyridonidis, R. K. Rampal, L. Silverman, E. P. Reddy, E. Papaemmanuil, S. Parekh, B. D. Greenbaum, C. S. Leslie, M. G. Kharas, E. P. Papapetrou, Stage-specific human induced pluripotent stem cells map the progression of myeloid transformation to transplantable leukemia. *Cell Stem Cell* **20**, 315–328.e7 (2017). UC-eLinks Google Scholar

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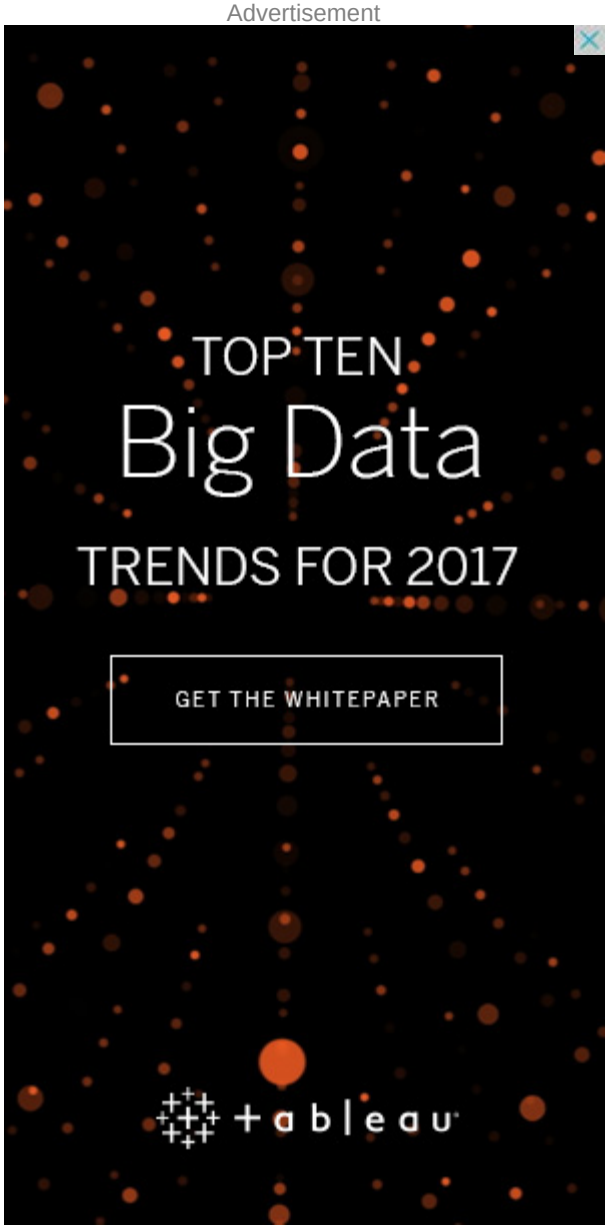

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