Genes & Diseases (2015) 2, 286–287

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VIEW ON NEWS

Direct lineage conversion with pluripotency factors: A risky detour through transient pluripotency?

Available online 10 August 2015

The advent of induced pluripotent stem cells (iPSCs) marked a giant step forward towards the reality of converting one type of primary somatic cells into different lineages capable of clinically repairing damaged tissues and organs. However, the major drawbacks of iPSCs hinder their quick translation to the bedside. These drawbacks include the time-, cost-, and labor-intensive process in production of clinical products from iPSCs, and the inherent risk of long-term tumorigenesis due to the forced expression of transcription factors associated with pluripotency, which are often implicated as aberrations within the cancerous gene circuitry.

The recent reports of the direct conversion of one somatic lineage into other types following a short-term pulse of pluritotent transcription factors pointed to a more efficient and more lineage–versatile alternative to those using only lineage-restricted transcription factors.[1,2] This new approach has also been applauded for its perceived safety merits due to need for fewer perturbations of the genes in the target cells and, perhaps, without generating "true" iPSCs. However, the question remains whether this short-term approach represents a mechanistically different method, which avoids the total erasure of restricted epigenetic imprints as does iPSCs generation, and whether it therefore bypasses the pluripotency stage.[3,4] Two recent articles published in the same issue of ***Nature Biotechnology*** offered some definitive answers.[5,6] Using different, but reliable lineage tracing methods, the two groups of scientists came to the same conclusion that the majority of the converted new lineage offspring cells did indeed come from the intermediate precursors reprogrammed through the short-term pulse of transcription factors. These precursors bear the genomic and proteomic hallmarks, as well as having biological properties, similar to those found in iPSCs. Although the short-term approach still has its merits of efficiency and simplicity when generating desired somatic lineages for research and clinical application, these fresh insights will certainly shape the guidebook for its clinical translation, which requires that the risk of tumorigenesis be examined with the same rigor as in the case of iPSC-derived lineage cells.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgments

Work in Dr. Jim Hu's laboratory was supported in part by a research grant from the Canadian Institutes of Health Research (MOP 125882).

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Peer review under responsibility of Chongqing Medical University.

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31 July 2015