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EDITORIAL

The rebirth of iPSCs: Towards a healthier epigenetic landscape

KEYWORDS

Cell replacement;
Differentiation;
Epigenetics;
iPSCs;
SCNT

Abstract It is well recognized that transcription factor-induced iPSCs carry an aberrant genetic and epigenetic makeup. However, it is not clear whether these defects are developed de novo due to the reprogramming process or inherited from the somatic source cells. Ma and colleagues presented convincing data that iPSCs derived through transcription factor over-expression carry a higher incidence of the epigenetic flaws in comparison with those generated through SCNT. The authors conclude that 1) the source of the epigenetic aberrations is more related to the reprogramming protocol, and less to the intrinsic abnormality of the somatic source cells; 2) SCNT based protocol is superior to that involving a cocktail of transcription factors. These important findings by Ma and colleagues will certainly steer future research towards understanding the mechanisms underpinning the SCNT reprogramming. With these efforts a whole array of unknown factors is expected to emerge, which regulate the onset of early embryonic development and can be applied to induce iPSCs with a healthier epigenetic landscape.

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Induced pluripotent stem cells (iPSCs) and their differentiated derivatives hold great promise for future autologous cell therapy and disease modeling. Since the breakthrough discovery made by Yamanaka et al,^{1,2} much effort has been devoted to study the biological property of iPSCs regarding its genetic stability, epigenetic fitness, as well as the safety and efficacy of its differentiated products in comparison with embryonic stem cells (ESCs). It was well recognized early on that transcription factor-induced iPSCs carry an aberrant genetic and epigenetic makeup. However, it is not clear whether these defects are developed de novo due to the reprogramming process or inherited from the somatic source cells.³ Accumulated experimental evidence indicates that the major difference between iPSCs and ESCs is

the incomplete removal of the epigenetic memory of somatic cells, which may negatively affect the pluripotency and lineage potential of the iPSCs. On the other hand other genetic and epigenetic aberrations of the iPSCs may jeopardize the fidelity of the pathophysiological phenotype when iPSCs are used for disease modeling. Furthermore, one major safety concern over the present iPSC products is their tumorigenic potential due to the oncogenic property of the transcription factors used in the reprogramming protocol and the significant similarities between iPSCs and cancer cells with respect to overall gene expression profiles and epigenetic signatures.⁴ It is apparent that an alternative reprogramming protocol, free of the previously mentioned flaws, needs to be invented before rendering iPSC products meaningful to future clinical therapy and disease modeling. Towards that end Ma and colleagues conducted a methodical study comparing transcription

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factor-induced reprogramming with that induced by somatic cell nuclear transfer (SCNT). In their research report published recently in *Nature*.⁵ Ma and colleagues presented convincing data that iPSCs derived through transcription factor over-expression carry a higher incidence of the epigenetic flaws in comparison with those generated through SCNT. The authors conclude that 1) the source of the epigenetic aberrations is more related to the reprogramming protocol, and less to the intrinsic abnormality of the somatic source cells; 2) SCNT based protocol is superior to that involving a cocktail of transcription factors. Since this study tested only one type of human cells with fetal origin, these initial results have yet to be validated through reprogramming studies of cells from multiple embryonic and adult tissues. Nevertheless, these important findings by Ma and colleagues will certainly steer future research towards understanding the mechanisms underpinning the SCNT reprogramming. With these efforts a whole array of unknown factors is expected to emerge, which regulate the onset of early embryonic development and can be applied to induce iPSCs with a healthier epigenetic landscape.

Disclosure

The author declares no conflict of interest.

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