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Stem Cell Research 2018 - Cell Reprogramming: Mirage or Reality?- Seyed Hadi Anjamrooz- Kurdistan University of Medical Sciences

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Introduction

In mammals, the zygote and early blastomeres are totipotent, whereas other cells possess less or no multi-lineage differentiation capacity . It is thought that by better understanding the mystery underlying this cell behaviour, based on the architecture and kinetics of the cell information content, the promise of regenerative medicine can be fulfilled. However, instead of focusing on this, scientists have tried to find other ways to generate specialized cells. Eventually, their efforts led to new technologies that ostensibly enabled somatic cells to be reprogrammed into target cells. Currently, a majority of scientists believe that such reprogrammed cells are a promising source of cells for use in regenerative medicine. However, this hope may not be realized as expected because claims for both in vivo and in vitro observations of cell plasticity have remained highly controversial. These discrepancies may relate in part to cell-detection and cell-tracking strategies or differences in the sources of the original cells, cell purification techniques, or the approaches used to distinguish different cell-transformation and response processes. Regardless of such contradictory evidence, the reprogramming process has been unsuccessful in many experimental instances that, because of the bias toward reporting "positive" results, either have been underreported or were reported but received less attention. This failure is only half of the story. The other half is that even in cases of apparently successful reprogramming of cells, in addition to faulty reprogramming, the overall magnitude of reprogramming has been notoriously low [see Table S1 in the Supplemental Data available with this article], and some of the claims have proven difficult to reproduce in other laboratories, despite the use of similar or identical experimental paradigms. Moreover, the published conclusions of some studies have not been convincingly supported by the presented data , and because of potential errors, such as flaws in the experimental design or misinterpretations of data, much refinement and characterization of reprogrammed cells as well as their functionality and durability are necessary. For example, some tissues exhibit high levels of autofluorescence that can account for false positive results. This property, rather than the incorporation of donor cells, might explain the detection of fluorescent protein marker expression in recipient tissues. Such auto-fluorescence can be particularly problematic when transdifferentiation of adult stem cells into non-autochthonous cell types is investigated in vivo. The fixation conditions and some auto-fluorophores, such as lipofuscin and flavin, may be responsible for the phenomenon of autofluorescence . The production of lipofuscin appears to be symptomatic of membrane damage or damage to mitochondria and lysosomes, which are not unexpected in the damaged tissue of the recipient or during cell manipulation. Even if the experimental design is perfect, the temporary expression of a limited set of marker genes, as used in most studies, is often insufficient evidence from which to conclude that a cell has been permanently converted to a true stem cell or a new state of cellular differentiation. This behaviour, also known as "cellular mimicry," may be spontaneous or can arise from a cellular stress response . The case in point is the activation of commonly used neural markers such as β-tubulin III, nestin, and NeuroD1 in skin or bone marrow-derived cells, which can reflect the cellular stress that occurs in response to removing cells from their particular microenvironments (or "niches") rather than demonstrating true trans-differentiation into the neural lineage . In another case, it was revealed that myogenic conversion following the overexpression of the MyoD gene in muscle-unrelated cells is temporary . Therefore, the dogma of irreversibility in cellular differentiation of terminally differentiated cells [34] appears to still be valid but not in as strict a form as previously thought. It is likely that cellular differentiation exhibits non-linear features of a bi-stable switch model of memory

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and mimicry, and either of these may predominate, depending on the external conditions [35]. Similarly, multipotent stem cells reversibly switch between states of dormancy and self-renewal [36]. Because quiescence has been postulated to protect stem cells from acquiring carcinogenic mutations, to hamper stem-cell exhaustion [36], and to increase cell resistance to anti-proliferative chemotherapeutic agents [37,38], it might make sense to postulate that the dormant state is the same state of temporary mimicry in which stem cells look like other cells. A similar dual property, known as meta-stability, has also been assumed for the pluripotent state [39]. Perhaps some of the contradictions and uncertainties in the literature related to the reliability of cell markers are attributable to the various cell-switch models noted above

Conclusion and Perspectives

In summary, based on CMD fluidity, some laboratory facts can be misleading. The future of regenerative therapy thus, in addition to unbiased factualism, depends on CMD-based regenerative strategies that are currently being developed. However, many details about the architecture and kinetics of the CMD during cell damage and repair must be deciphered if we expect to make significant progress in regenerative medicine.

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