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COMMENTARY

Challenges in the clinical application of induced pluripotent stem cells

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Abstract

The advent of human induced pluripotent stem cells has been heralded as a major breakthrough in the study of pluripotent stem cells, for these cells have yielded fundamental insights into the reprogrammability of somatic cell fates, but also because of their seemingly great promise in applications, including potential uses in cell therapy. Several recent reports in the scientific literature and mass media, however, have challenged this concept for reasons of biological function and business feasibility, presenting an important opportunity to re-examine the prospects for human induced pluripotent stem cells in medicine. In this commentary, I will outline a number of hurdles that will need to be cleared if these cells are to fulfil their clinical promise, and suggest avenues that might facilitate these important endeavours.

Clinical prospects for human induced pluripotent stem cells

The first reports of the generation of human induced pluripotent stem cells (hiPSCs) from fibroblasts [1,2] were greeted with great enthusiasm over their ability to mimic the properties and function of embryonic stem cells without entailing the ethical controversies and resourcing issues associated with the use of human blastocysts in derivation. In the several years since those first reports, new advances in the derivation of hiPSCs from various tissue sources (including those from human patients) and using diverse reprogramming techniques, and in their use as a pluripotent cell source in the induced differentiation of a wide array of somatic cell types, have appeared with almost startling rapidity. At least one biotech company (iPierian) has been founded to exploit the commercial potential of these reprogramming technologies, and the Japanese government has established an entire research institute dedicated to fundamental and applied iPSC research (Center for iPS Cell Research and Application, Kyoto University). Clearly, the early expectations surrounding iPSCs have been extraordinary.

A number of recent articles, however, have reported that hiPSCs are, in fact, notably distinct from human embryonic stem cells in terms of their gene expression, epigenetic profile, proliferative capacity and the susceptibility of their differentiated progeny to cellular senescence and apoptosis [3-6]. Additionally, the head of a prominent human embryonic stem cells firm (Geron) has publicly questioned the viability of commercialized therapeutic applications of autologous hiPSCs due to the regulatory requirements imposed by the US Food and Drug Administration [7]. The important question now is whether these barriers are high enough to preclude the translation of fundamental hiPSC discoveries into cellular therapies.

As for any innovation with potential medical applications, hiPSCs must satisfy a great number of criteria prior to their introduction into clinical practice. First and foremost come issues of safety and efficacy. The earliest methods for the induction of iPSCs relied on the use of viral vectors, which are encumbered by risks of insertional mutagenesis and transgene reactivation. Numerous alternative methods for inducing pluripotency without the use of gene insertion have been reported, and although their efficiency remains problematic, if the current rate of progress in methodology continues, these should make it possible to bypass some of the primary safety concerns. But others will still remain, such as the long-term karyotypic stability, appropriate *in situ* localization, and potential for wayward differentiation of somatic cells derived from hiPSCs. Several excellent overviews of the scientific challenges confronting cell therapy have described these issues in detail [8-11].

Of course, safety alone does not guarantee efficacy. Despite promising results from animal studies, the viability of the cell transplantation paradigm in human has been demonstrated in only a few contexts, mainly involving the use of hematopoietic stem cell transplants,

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autologous skin and cartilage grafts, or the autologous recellularization of decellularized or engineered tissue. For hiPSCs, or any stem cells used as a source of human somatic cells, to be therapeutically effective in transplantation it needs to be shown that their progeny will function normally in the intended site for significant periods of time, which will require extensive testing first in animals, and then in appropriately designed (ideally in randomized, double-masked, multi-site) clinical trials.

Such trials are inevitably costly, and the traditional strategy for drug development suggests one means of undertaking these development expenses is for well-funded companies to lead the way, motivated by the potential return on investment to be gained from a successful proprietary therapy. However, with few exceptions, the stem cell and regenerative medicine industry has remained inadequately capitalized to carry out large-scale clinical trials independently, and major pharmaceutical firms have tended to show more interest in the use of hiPSCs as a source of large, pure populations of specific somatic cells for use in drug compound screening and toxicology tests, than they have in therapeutic uses of stem cells and their derivatives.

This reluctance is due in part to the great many unanswered questions over the viability of cell therapy business models. At the production stage, issues of end-product standardization and purity, scalability, and timeliness have yet to be worked out. Similarly, delivery systems for ensuring integration of hiPSC-derived cellular populations must be developed and tested. Even beyond these technical issues lie a host of purely business concerns, including intellectual property, cost-effectiveness, and regulatory affairs. Interested readers are directed to comprehensive reviews of cell medicine business models [12,13].

Despite these many hurdles and the newness of the technology, there are already some glimmers of hope for clinical applications of hiPSCs. Diseases of the retina may offer an early test bed for hiPSC-derived cells, in the form of retinal pigmented epithelium, given the relative isolation of the tissue, and the small number of cells required [14]. A second intriguing possibility would be the use of hiPSCs to produce functional cells for use in extra-corporeal applications, such as mature hepatocytes for use in bio-artificial livers. If such early applications prove successful, it may help to allay concerns over safety and increase public and regulatory acceptance of the clinical use of hiPSCs, enabling them to establish a solid footing before attempts are made at treating more complex and deeply rooted disorders.

At the same time, it will be important for cell therapy pioneers to investigate alternative routes for funding their work, so as to ensure the standards of safety and efficacy expected of small molecules are also met by cellular applications. In countries with socialized healthcare, governments have a strong interest in obtaining access to low-cost and effective long-term remedies, and may prove willing to invest in research and development if the economics of the cell therapy strategy are shown to be attractive. Japan has taken some steps in this direction, both in establishing the first centre dedicated entirely to hiPSC research, with an emphasis on application, and by publishing a draft of what looks to be the world's first governmental regulations specifically focused on hiPSC-derived cell safety and quality [15].

As can be seen, a great many issues must be resolved before hiPSCs can be responsibly introduced to the clinic. But it is important to stress that such hurdles have confronted other fledgling technologies that subsequently revolutionized medicine as well. None of the difficulties confronting hiPSCs appears to be inherently insurmountable, and given the revolutionary advances that successful applications of reprogramming and cell transplantation might one day bring, it would seem that, for now, the sustained investment of sufficient effort, capital and time remain imperative.

Abbreviations

hiPSC, human induced pluripotent stem cell.

Competing interests

The author declares that he has no competing interests.

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