Journal of Stem Cells & Regenerative Medicine
ISSN 0973 - 7154

EDITORIAL

JSRM Code: 014020100009

Induced pluripotent stem cells (iPS) derived disease models: *In vivo* to *in vitro* gaps

Induced pluripotent stem (iPS) cells are one of the most sought-after tools of regenerative medicine created by extra-physiological endeavours of reprogramming which help not only as promising avenues for therapy but also for recapitulating the disease pathology in a dish and also as modelling systems for studying organ/tissue behaviours. iPS cell based clinical trials having been started for treating age -related macular degeneration[1] and recently for Parkinson's[2] though seem promising, several hurdles such as genetic mutations in the cells[3] and adverse effects[4] remain obstacles to further progress.

Though the clinical applications are having several hurdles, iPS cells remain treasured tools of researchers all over the world to model diseases because previously unknown aspects of disease behaviour and molecular mechanisms governing them have been brought to light by such iPS technology-based disease models. A classic example being cancer stem cells (CSC)[5] which are otherwise very elusive and difficult to obtain from cancer tissues that are heterogenous in nature, through iPS technology we are able to obtain which help us recapitulate the unique cancer microenvironment of that individual thus throwing a hope to study the cancer behaviour and develop personalized medicine strategies.

One such effort has been reported in this issue of JSRM where Nekrasov and Kiselev describe previously unknown aspects of Huntington's disease (HD)[6] by employing iPS cells generated from HD patients' fibroblasts in which they report for the first time an impairment of mitochondrial trafficking in pathological neurons with endogenous mutant huntingtin. They conclude that impairments of mitochondrial trafficking and nuclear roundness being harbingers of the disease long before it manifests, providing a new insight for a probable early diagnosis in the future.

At this instance we wish to outline five aspects by which iPS based disease models with current technologies may fall short of their goal of reflecting in vitro, a mirror image of what happens in vivo (Figure 1).

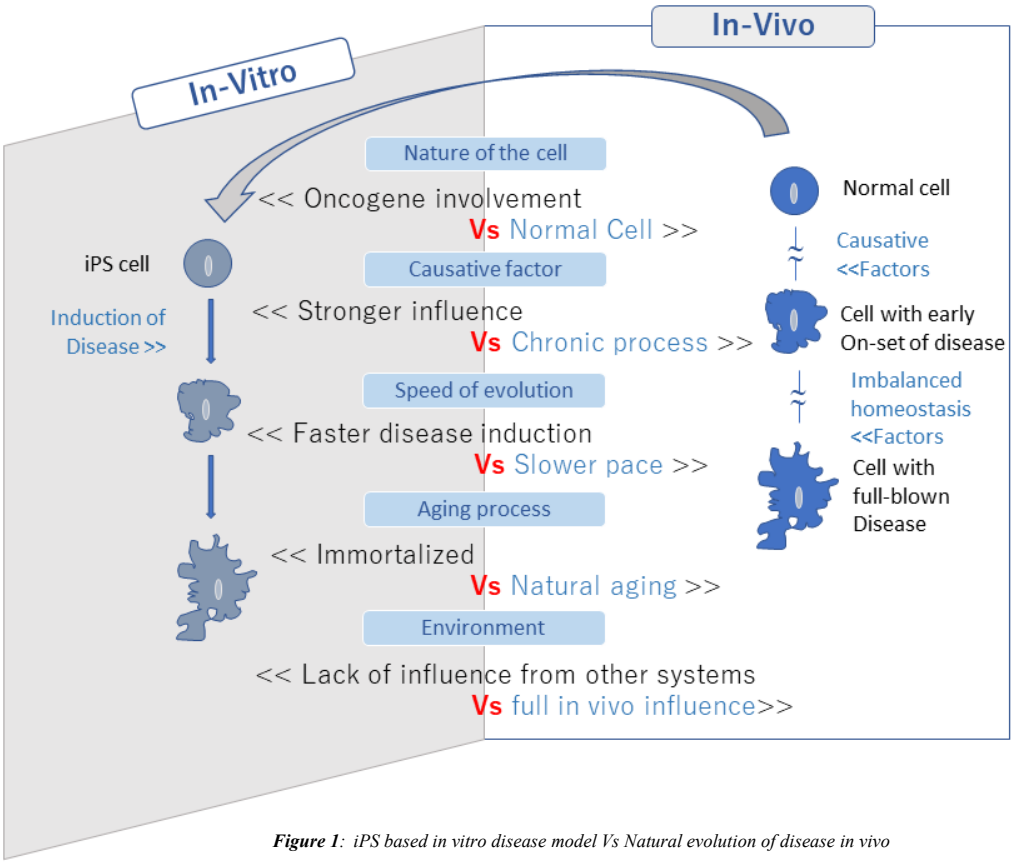

***Figure 1**: iPS based in vitro disease model Vs Natural evolution of disease in vivo*

i. Nature of the cell:

While the in vivo disease develops in an otherwise normal cell, the iPS derived cell has gone through an oncogene based non-physiological reprogramming before and during the process of induction of the disease.

ii. Causative factors:

In vivo causative factors in onset of any disease are highly complex and maybe even chronic while in vitro, disease is induced by definitive factors with a strong etiological influence[7].

iii. Speed of evolution:

The causative factors of in vitro models being strong and specific, the disease pathology is created at a faster pace which otherwise in vivo will be relatively slower.

iv. Aging process:

iPS cells by nature having been immortalized possess the capability for a long period of uncontrolled proliferation whereas the in vivo cells going through the pathophysiological disease process are amenable to the natural process of aging and exhibit relevant behaviour[8].

v. Environment:

In vitro disease models' cells lack what otherwise cells in vivo during pathophysiology would have as an environment and/or influence such as enzymes, hormones, diurnal rhythms, angiogenesis, physico-chemical factors etc., [9].

While understanding the limitations in iPS technology as mentioned above, further research into overcoming them to gain a much accurate insight into the process of evolution of diseases is essential.

References

1. Mandai M, Watanabe A, Kurimoto Y, Hirami Y, Morinaga C, Daimon T, Fujihara M, Akimaru H, Sakai N, Shibata Y, Terada M, Nomiya Y, Tanishima S, Nakamura M, Kamao H, Sugita S, Onishi A, Ito T, Fujita K, Kawamata S, Go MJ, Shinohara C, Hata KI, Sawada M, Yamamoto M, Ohta S, Ohara Y, Yoshida K, Kuwahara J, Kitano Y, Amano N, Umekage M, Kitaoka F, Tanaka A, Okada C, Takasu N, Ogawa S, Yamanaka S, Takahashi M. Autologous Induced Stem-Cell-Derived Retinal Cells for Macular Degeneration. N Engl J Med. 2017;376(11):1038-1046.
2. Barker RA, Parmar M, Studer L, Takahashi J. Human Trials of Stem Cell-Derived Dopamine Neurons for Parkinson's Disease: Dawn of a New Era. Cell Stem Cell. 2017;21(5):569-573.
3. Landmark IPSC clinical study on hold due to genomic issue [Internet] [cited 2018 Dec 31]. Available from: https://ipscell.com/2015/07/firstipscstop/
4. Adverse event in IPS cell (ips細胞) trial for vision loss in Japan: initial perspectives [Internet] [cited 2018 Dec 31]. Available from: https://ipscell.com/2018/01/adverse-event-in-ips-cell-trial-for-vision-loss-in-japan/
5. Chen L, Kasai T, Li Y, Sugii Y, Jin G, Okada M, Vaidyanath A, Mizutani A, Satoh A, Kudoh T, Hendrix MJ, Salomon DS, Fu L, Seno M. A model of cancer stem cells derived from mouse induced pluripotent stem cells. PLoS One. 2012;7(4):e33544
6. Nekrasov ED,Kiselev SL. Mitochondrial distribution violation and nuclear indentations in neurons differentiated from iPSCs of Huntington's disease patients. J Stem Cells Regen Med 2018; 14(2) : 80-85.
7. Xiao B, Ng HH, Takahashi R, Tan EK. Induced pluripotent stem cells in Parkinson's disease: scientific and clinical challenges. J Neurol Neurosurg Psychiatry. 2016;87(7):697-702.
8. Geissler S, Textor M, Kühnisch J, Könnig D, Klein O, Ode A, Pfitzner T, Adjaye J, Kasper G, Duda GN. Functional comparison of chronological and in vitro aging: differential role of the cytoskeleton and mitochondria in mesenchymal stromal cells. PLoS One. 2012;7(12):e52700.
9. Liu C, Oikonomopoulos A, Sayed N, Wu JC. Modeling human diseases with induced pluripotent stem cells: from 2D to 3D and beyond. Development. 2018;145(5). pii: dev156166

Acknowledgements

The editorial team wishes to acknowledge Prof. Masaharu Seno, Okayama University, Japan for his inputs to this article.