

hESC – iPSC equivalence: a genetic, epigenetic, functional and immunogenic comparison.

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Introduction

ESC: Embryonic Stem Cell iPSC: induced Pluripotency Stem Cell

iPSC are very similar to ESC, but are they equivalent? Our goals are to determine which are the differences and similarities between this cell groups at different levels, enunciate the fields of future investigations and to obtain some conclusions that may help in better understanding of the hESC-iPSC equivalence question.

Genetic

Small number of genes differently expressed (Chin et al., 2010). Guenther et al., (2010) objected differences are due to laboratorial and statistic methods, and not consistent through different cellular lines (due to line variability).

Cellular lines heterogeneity and differences between early and late passages of iPSC might be the cause for some of the observed differences.

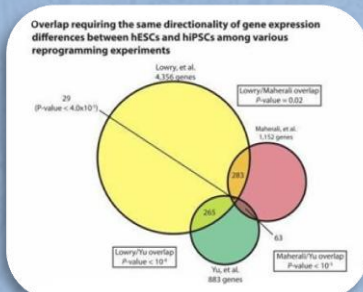


Figure 1. From Chin et al. (2010) Molecular analyses of hESC and iPSC.

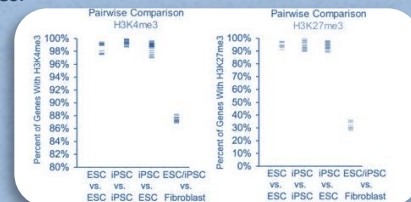
Epigenetic

iPSC have to acquire an ESC-like histone open methylation pattern.

Xie et al (2009) identified 71 Different Methylated Regions (DMR) between ESC and iPSC. Most were related to epigenetic memory, but some were exclusive from iPSC.

High levels of ARNm.

Pluripotent context.: low H3K27me3 and high H3K4me3 in promoters of actively transcribed genes. Alike at both cell types.



H3K9me3 is significantly different even at high passage → effects?

Figure 2. From Guenther, G., et al. (2010) Chromatin Structure and Gene Expression Programs of hESC and iPSC.

Functional

Proteomics: differences in less than 1% of proteins and fosforilation sites; no common functionality observed. The number of differences between iPS-ESC were the same than between ESC lines.

Differentiation: in vitro. Issues for testing pluripotency: ethical limitations, in vitro culture, line heterogeneity.

iPSC have shown the same differentiation potential than ESC, but are less efficient.

Epigenetic memory has been detected at high passages. It might affect long term.

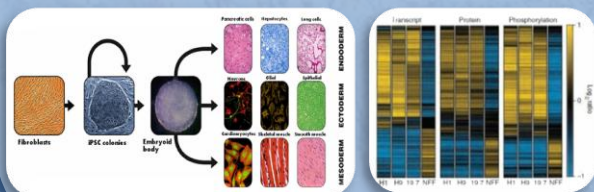


Figure 3. Differentiation potential of hiPSC.

Figure 4. From Douglas, HP., Et al. (2011) Proteomic and phosphoproteomic comparison of hES and iPSC cells.

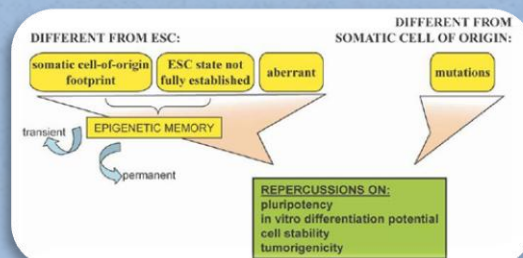
Immunogenic

Supposedly, iPSC does not generate immune response.

But it depends on the method of generation. Retrovirus can insert in transcriptionally active locations related with immune mediators. Immune response has been observed in murines. With lentivirus and plasmids no immune response has ever been observed. This is one of the main advantages of iPSC.

ESC depends of compatibility or syngeneic donators.

Immunogenicity in human iPSC has not been deeply studied yet. As each cell involves different proteins, further studies need to be made.



Bilic, J., Et al (2012) Concise review: iPSC vs ESC: Close Enough or Yet Too Far Apart?

Conclusions

Genetic: no concrete and recurrent differences

Epigenetic: the most controverted field. Differences observed, particularly regarding lysine methylation pattern, whose effects are not clear. Might affect cell functions.

Proteomic: negligible differences, with no common functionality. No distinction possible.

Functional: high number of study limitations. Very similar differentiation potential, ESC 's seems slightly higher.

Immunogenic: iPSC do not produce immunogenic response (some excepcons with retrovirus method). Cells obtained from ESC can produce IR if there is no HLA compatibility.

Future: standardize laboratorial methods. Deep study of incomplete reprogramming and epigenetic memory.

Methods

Bibliographic search at NCBI's PubMed.

Articles comparison. 4 months stage at Human Genetics lab

at E.O. Ospedale Galliera (Genoa, IT) practising iPSC

obtention from fibroblasts and neural differentiation.

Bibliography

•Chin MH, et al. Molecular Analyses of Human Induced Pluripotent Stem Cells and Embryonic Stem Cells. Cell Stem Cell, 2010. 7(2), pp 263–269.

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•Kim, K., et al. Epigenetic memory in induced pluripotency stem cells. NIH-PA, Nature, 2010. Nature 467, 285-290.