COMPARISON OF PLURIPOTENT STEM CELLS

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INTRODUCTION

Stem cells are unspecialized cells that are capable of self-renewal and can develop many different cell types. **Embryonic stem cells (ESCs)** are derived from early embryonic development of embryos fertilized *in vitro*. Other pluripotent stem cells can be obtained by reprogramming methods:

- **Induced pluripotent stem cells (iPSCs)** are reprogrammed from somatic cells by forcing them to express four transcription factors: Oct4, Sox2, Klf4 and c-Myc.
- **Nuclear-transfer-derived embryonic stem cells (NT-ESCs)** are reprogrammed inserting the nucleus of a somatic cell into an enucleated oocyte.

Both iPSCs and NT-ESCs have similar properties to ESCs, but they are not identical.

The **objective** of this bibliographic review is to compare different characteristics of ESCs, iPSCs and NT-ESCs to find similarities and differences among reprogrammed pluripotent cells and embryonic stem cells.

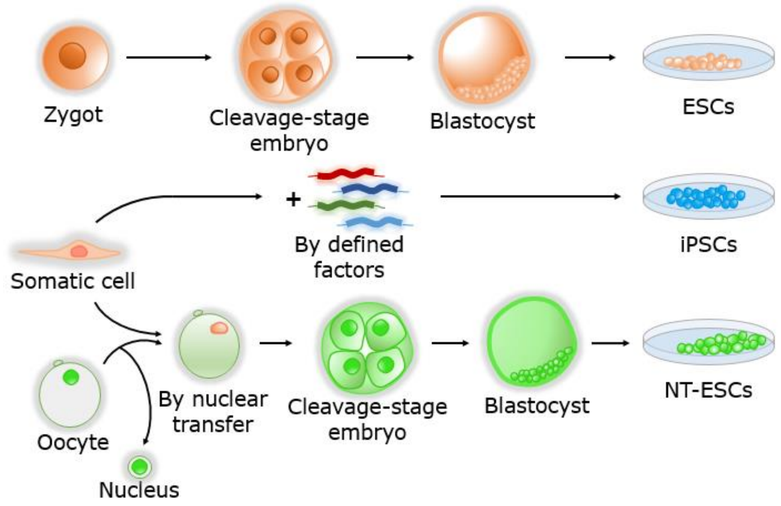

Figure 1. Obtaining ESCs and reprogrammed cells by defined factors (iPSCs) and nuclear transfer (NT-ESCs)

GENETIC CHARACTERISTICS

- Structural changes: no statistically significant differences were found for de novo copy number variations among hESCs, hiPSCs and NT-hESCs.
- Non-structural changes: more de novo coding unique mutations were confirmed in hiPSCs and NT-hESCs compared to hESCs, although no statistically significant differences were found among both reprogrammed cell types.

hiPSCs / NT-hESCs / hESCs

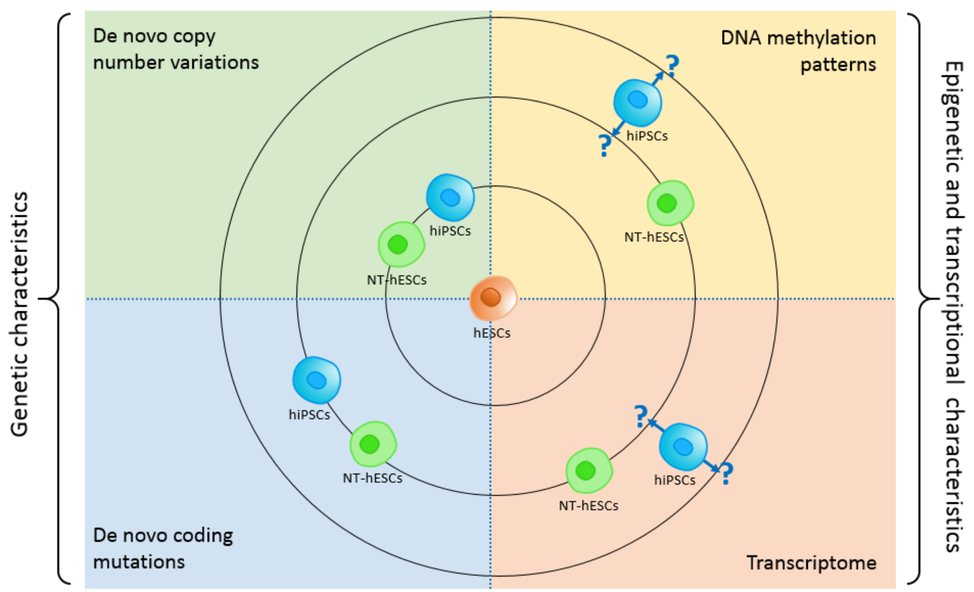

Figure 2. Comparison of genetic and epigenetic characteristics of various pluripotent stem cells. Relative similarity of human iPSCs (hiPSCs) and NT-ESCs (NT-hESCs) compared to human ESCs (hESCs)

EPIGENETIC AND TRANSCRIPTIONAL CHARACTERISTICS

DNA methylation patterns, involving imprinted genes and X chromosomal loci, and transcriptome showed very little difference among hESCs and NT-hESCs.

Nevertheless, results were not conclusive for hiPSCs: Johannesson *et al*. (2014) also found very little difference between the three cell types, whereas Ma *et al*. (2014) showed that hiPSCs retained more epigenetic memory and presented more random reprogramming errors comparing to NT-hESCs.

FUNCTIONAL CHARACTERISTICS

iPSCs / ESCs

Genetic and epigenetic variations –such as aberrant epigenetic statuses on certain loci or source cell memory– may have an impact on iPSCs differentiation potential, inducing that cell type of origin may bias the differentiation potential into the cell lineage of origin.

Nevertheless, cell memory can be erased by continued passaging, which leads to molecularly and functionally indistinguishable iPSCs and indicates that reprogramming process is gradual.

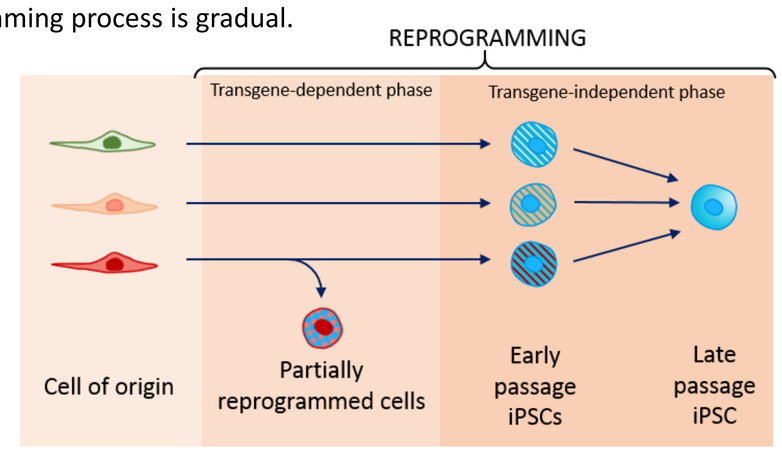

Figure 3. iPSCs derived from different somatic cell types retain a transient cell memory at early-passage, which affects to the differentiation potential of iPSCs. However, continuous passaging leads to the loss of this memory. Late-passage iPSCs are molecularly and functionally indistinguishable.

IMMUNOGENICITY

Mouse iPSCs

Table 1. Summary of mouse iPSCs (miPSCs) immunogenicity data reported in three studies. Finding immune response of autologous iPSC-derived cell transplants was unexpected. Nevertheless, more recent reports support the immune privilege of iPSC-derived cells and their safety.

Syngeneic cells injected	Zhao *et al*. (2011)	Araki *et al*. (2013)	Guha *et al*. (2013)
Undifferentiated miPSCs	Immune rejection	Immune rejection	No immune rejection
Undifferentiated mESCs	No immune rejection	Immune rejection	No immune rejection
In vivo differentiated miPSCs	-	No immune rejection	-
In vitro differentiated miPSCs	-	Immune rejection	No immune rejection

Mouse NT-ESCs

NT-ESCs are mismatched mitochondria, which cause alloantigenicity and make an immune rejection possible. Mouse NT-ESCs (NT-mESCs) with allogenic mitochondria and nucleus-identical to the recipient mouse may trigger an immune response when transplanted to the mouse, impairing the survival of NT-mESCs graft. The immune response caused is adaptive, directed against mitochondrial content and amenable for tolerance induction.

CONCLUSIONS

NT-ESCs are more faithfully reprogrammed than iPSCs, although iPSCs from late passages present less cell memory than early passages' ones and are molecularly and functionally indistinguishable.

Regarding to immunogenicity, the possibility of autologous iPSC-derived cell transplant immune response is still a topic of debate. About NT-ESCs, mismatched mitochondria cause immune adaptive response.

Further research will assess functionality –especially of NT-ESCs– and immunogenicity of pluripotent cells.

REFERENCES

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