Genes involved in pluripotency and somatic reprogramming

Andrea Abbad Gómez

Degree in Biomedical Sciences| Faculty of Biosciences | Autonomous University of Barcelona

INTRODUCTION

Somatic reprogramming provides a new way of approaching regenerative and transplantational medicine. This technique erases and remodels epigenetic marks acquired throughout differentiation in order to reverse this state and generate undifferentiated and pluripotent stem cells. Pluripotency is the cellular state that gives a cell the potential of giving rise to any cell type of the three germ layers. Somatic reprogramming can be achieved by two techniques, principally: somatic cell nuclear transfer and induction of pluripotency. In order to understand those procedures it is needed to comprehend the genes and pathways involved in the establishment and maintenance of pluripotency.

METHODS

Data displayed in this poster has been obtained from original research papers and reviews using the searching engine Pubmed. The search was based in key words such as *gene, pluripotency, ES cell, somatic reprogramming* and specific gene names. Those articles bibliography was used to enlarge the search.

GENES AND PATHWAYS INVOLVED IN PLURIPOTENCY

Transcriptional core

Nanog:

- Its mRNA is expressed in pluripotent cells, both murine and human, and at much lower levels in adult tissues.
- Without Nanog embryos can not generate the epiblast layer of the ICM.
- Nanog deficient ESCs lose pluripotency entering into an extraembryonic endoderm lineage.

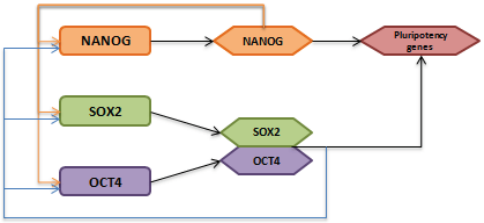


Figure 1. Diagram showing the interaction between the transcriptional core elements.

Squared boxes correspond to gene promoters and hexagonal boxes represent regulators.

Oct4 and Sox2:

- Their regulation in ESCs depends on a binding site for a composite sox-oct element.
- Both can bind to a composite sox-oct element located inside Nanog's proximal promoter.
- Some teams suggest that Sox2 is not essential in the Oct4-Nanog activation.

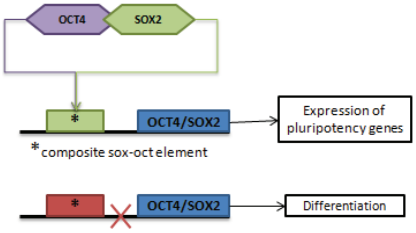
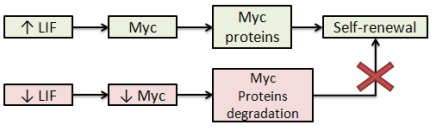


Figure 2. Sox2 and Oct4 have a composite sox-oct element as an enhancer to which both transcription factor can bin, allowing the expression of pluripotency genes.

Myc

- Although it is not essential in early development it becomes important in further stages.
- Myc presence, along with blocking proteins degradation, decreases LIF dependence.
- Myc represses primitive endoderm differentiation by inhibiting Gata6, with the help of Myc-dependant miRNAs.

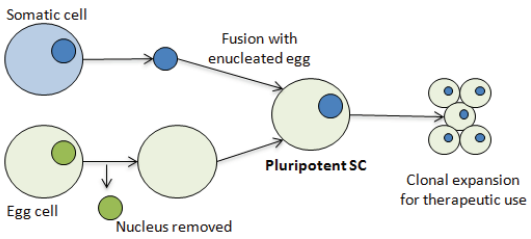


LIF pathway

- LIF was one of the first pluripotency factors described.
- MEF layers produce LIF, which has been used to culture without cell layers.
- LIF needs serum to maintain self-renewal or the cell will enter neural differentiation. BMP has been found to inhibit this differentiation and allow serum-free conditions.
- Human naive SCs are LIF and STAT3 dependant.

TECHNIQUES FOR SOMATIC REPROGRAMMING

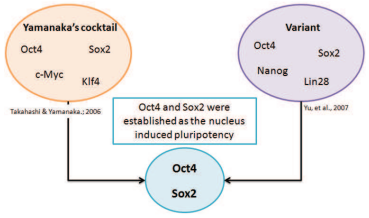
Somatic cell nuclear transfer



- It has been successfully used for generating mouse, lamb, pig, cattle, monkey embryos.
- In 2013 this technique was performed using human dermal fibroblasts of fetal origin.
- In 2014 SCNT went a step further by using adult fibroblasts.
- Ethical issues: it implies destroying an egg cell.

Induced pluripotency (iPS cells)

- iPS are generated from adult cells by introducing a specific set of pluripotency-associated genes that allow reprogramming.



- Nanog might not be needed because Klf4 seems to activate it through p53 repression.
- c-Myc is an oncogene and has to be excluded in order to translate the procedure into human therapy.

CONCLUSIONS

- Genes and pathways involved in pluripotency are well known but not the networks that interconnect them.
- LIF represents a good example of in which direction pluripotency research should go.
- SCNT is a real option due to the last discoveries in which adult cells have been used, but there are some ethical issues involved.
- iPS cells are an excellent alternative but some problems have to be solved, such as avoiding oncogenes use.

REFERENCES

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Takahashi, K. & Yamanaka, S., 2006. Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors. Cell, Volume 126, pp. 663-676.