Pluripotency of Embryonic Stem Cells – Role of Wnt pathway

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Introduction

Embryonic Stem Cells (ESC) are pluripotent Stem Cells derived from the pre or peri-implantation embryo, where pluripotency is the ability of a cell to give rise to all cells of the embryo. Human ESC (hESC) show several differences with respect to mouse ESC (mESC). However, it is unknown whether hESC and mESC correspond to distinct stages of development or they simply show evolutionary differences. The canonical Wnt pathway is one of the main pathways involved in pluripotency, and seems to show different roles in mouse and human ESCs. The main aim of this field is to use ESCs to replace dysfunctional or absent cells in human diseases.

Aims

The aim of this Review is to understand the mechanisms involved in maintenance of pluripotency state in hESC and mESC:

- Identify molecular networks involved in pluripotency maintenance
- Identify transcription factors essential for ESC state
- Analyze the importance of the Wnt pathway in Pluripotency

Methodology

Search for papers in PubMed and PMC. Key words used for the research: Pluripotency, ESC, Wnt, GSK3, β-catenin and TCF3.
Search in: Lanza, R.P. (2009). *Essentials of stem cell biology.* San Diego, CA: Academic Press.

Maintenance of pluripotency

The maintenance of ESC-like state is controlled by extrinsic factors, intrinsic signaling pathways and transcriptional regulating factors. These signaling pathways regulate the core set of transcription factors formed by Oct4, Sox2 and Nanog[1].

In mESC

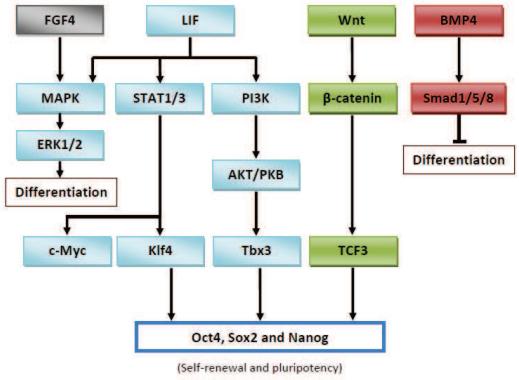

Figure 1. Main pathways involved in pluripotency maintenance of mESCs.

In hESC

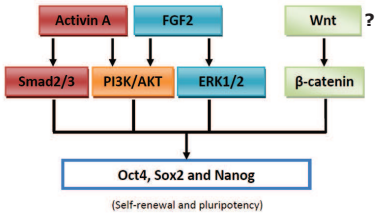

Figure 2. Main pathways involved in pluripotency maintenance of hESCs.

There are also other factors that can influence the pluripotent state of ESCs:

✓Chromatin regulators: silence genes involved in lineage commitment (Epigenetic)[1].
✓ miRNAs: control translation and stability of target mRNAs[1].

Canonical Wnt pathway

In mESC

Wnt/β-catenin pathway is known to participate in pluripotency maintenance through the inactivation of TCF3-mediated repression of pluripotency, and it seems to occur in a manner that does not require β-catenin's transcriptional activity[2].
It has recently been reported that, during self-renewal, this low transcriptional activity of β-catenin is due to its association with the membrane in complexes with Oct4 and E-cadherin[2]. Moreover, β-catenin's transcriptional activity increases during differentiation, coinciding with the disassembly of the complex[2].

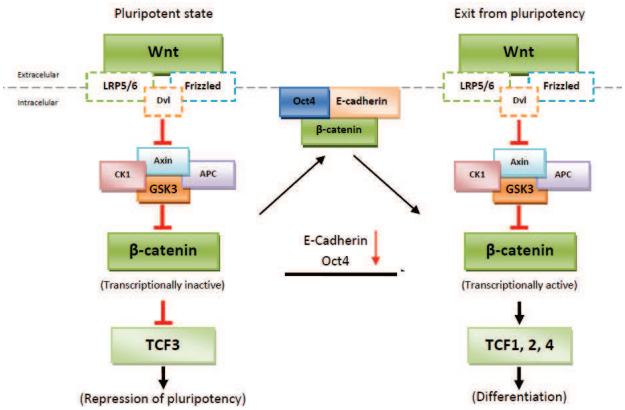

Figure 3. Mechanisms involved in Wnt signaling in mESCs.

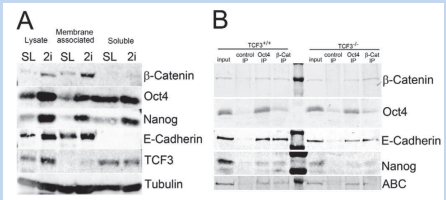

Figure 4. β-catenin/Oct4 complex associated with membranes in pluripotent mESCs. **A)** E14TgA cells grown in either serum+LIF or 2i for at least two passages prior to lysis and ConA fractionation. **B)** Oct4- and β-catenin-containing complexes immunoprecipitated from membrane associated protein extracts of *Tcf3-null (Tcf3−/−)* and their wild-type parental *(Tcf3+/+) mESC cells* were maintained in 2i media for at least two passages prior to lysis. (Faunes et al., 2013).

In hESC

Recent studies reported that Wnt/β-catenin signaling is inactive during self-renewal in hESC, but active during differentiation. Thus, Wnt/β-catenin pathway seem to be repressed during pluripotency. Two possibilities for this repression are Oct4[3] and GSK3[4].

Conclusions

The mechanisms involved in the maintenance of ESC state in mice and humans are highly complex and most of their functions still remain unknown. Wnt has been seen to have an important implication in ESC state, but some results seem controversial and it is not clear which its exact role is.
Due to the importance of the potential applications of ESCs, it is crucial to continue the research in this field in order to achieve a better understanding in the subject of study.

References:
1. Young, R. A. (2012). Control of Embryonic Stem Cell State. *Cell* 144, 940–954. **2. Faunes, F. *et al.* (2013).** A membrane-associated β-catenin/Oct4 complex correlates with ground-state pluripotency in mouse embryonic stem cells. *Development* 140, 1171–83. **3. Davidson, K. C. *et al.* (2012).** Wnt/β-catenin signaling promotes differentiation, not self-renewal, of human embryonic stem cells and is repressed by Oct4. *Proc. Natl. Acad. Sci. U. S. A.* 109, 4485–90. **4. Singh, A. M. *et al.* (2012).** Reconciling the different roles of Gsk3β in "naive" and "primed" pluripotent stem cells. *Cell Cycle* 11, 2991–2996.