Unravelling the molecular mechanisms that govern the maintenance of pluripotency in hESCs and mESCs

Anna García Serra - Degree in Biochemistry - Tutor: Mireia Duñach

Objective: a current *state-of-the-art* review

Pluripotency is defined as a dual property of self-renewal and differentiation potential that is progressively lost as lineage commitment and development occur. The maintenance of pluripotency is guaranteed by the sustainment of self-renewal and the suppression of differentiation processes (Figure 1). Pluripotency is not a unique static state. In fact, murine and human embryonic stem cells (mESCs and hESCS respectively) represent different pluripotent states. The molecular mechanisms which cooperate to maintain the undifferentiated state in both ESCs are described below.

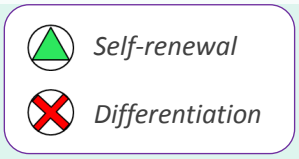

Figure 1. Schematic diagram of the two processes that are necessarily regulated to achieve the pluripotent state.

A Signaling pathways

Extrinsic signals can be propagated through intracellular signal transduction pathways. **Extracellular signals** contribute either to maintenance of pluripotency or the stimulation of differentiation. The extrinsic mechanisms that modulate stem-cell self-renewal in humans are different from those in mice. The **consensus factors** are shown in Figure 2.

C Epigenetic modifiers

The **epigenetic landscape** determines the transcriptional outcome of a cell. Epigenetic machinery displays regulatory mechanisms by which signaling cascades can directly regulate **histone modifications** and **chromatin modifying enzymes**. Pluripotency gene expression is activated while developmental genes are repressed, but poised.

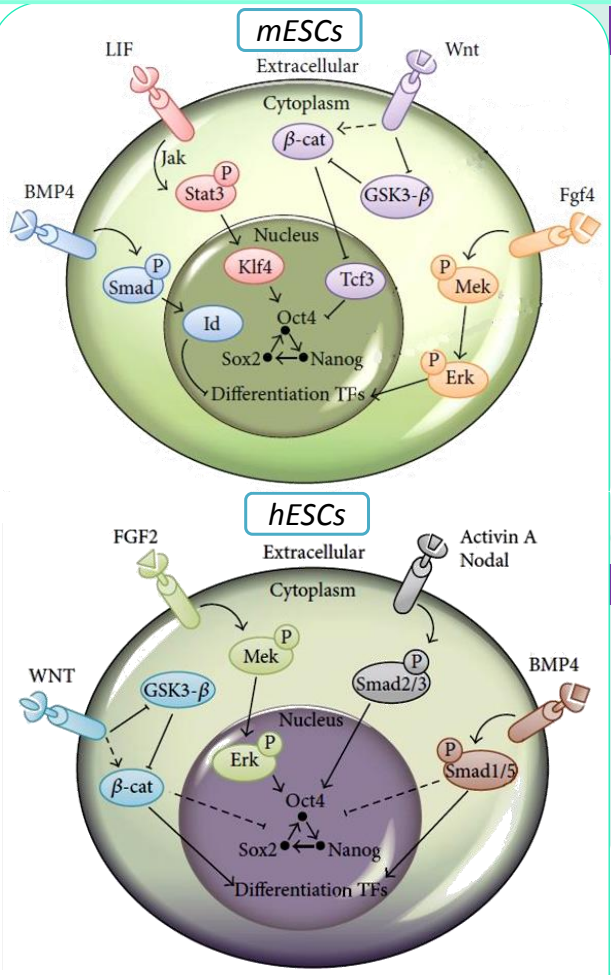

Figure 2. Representation of the differences in the pluripotent state regulation by extrinsic factors and their signaling pathways between mouse ESCs (mESCs, above) and human ESCs (hESCS below). Image modified from reference 4.

Transcriptional core B

Oct4, **Sox2** and **Nanog** are the three transcription factors in charge of specific gene expression for maintaining the pluripotency. This triumvirate is self-regulated by a **positive auto-regulatory loop** and integrates the signalling pathways with the expression of key pluripotent genes by a multiprotein complex based on Oct4-Sox2 heterodimer able to recruit Polymerase II.

MicroRNAs D

MicroRNAs prevent specific translation of their target mRNAs. They are essential **post-transcriptional regulators** as they contribute to pluripotency maintenance, proliferation and early development. **ESCs** express a small subset of **unique microRNAs** that belong to miR-371, miR-302, miR-17, miR-106, and let-7 families.

Conclusions and future perspectives

To determine pluripotency in ESCs multiple pieces interplay to form a complex and integrated functioning network. There is a **fine-tuned control** of the pluripotency machinery at many regulatory levels, where various players are involved. The **differences of pluripotency regulation between hESCs and mESCs** have to be highlighted, as well as the flexibility in the pluripotency governance factors in some cases as an evolutionary advantage. Further studies on pluripotent stem cells will be of interest for a better understanding of **developmental biology** and **cancer** regulation and eventually could be applied to new **regenerative medicine** technologies or generation of **patient-specific induced pluripotent stem cells**.

Main references:

1. De Los Angeles, A., Ferrari, F., Xi, R. et al. (2015). Hallmarks of pluripotency. *Nature*, *525*, 469–78.
2. Chambers, I., & Tomlinson, S. R. (2009). The transcriptional foundation of pluripotency. *Development (Cambridge, England)*, *136*, 2311–22.
3. Hackett, J. A., & Azim Surani, M. (2014). Regulatory principles of pluripotency: From the ground state up. *Cell Stem Cell*, *15*, 416–430.
4. Fagnocchi, L., Mazzoleni, S., & Zippo, A. (2016). Integration of Signaling Pathways with the Epigenetic Machinery in the Maintenance of Stem Cells. *Stem Cells International*, *2016*.