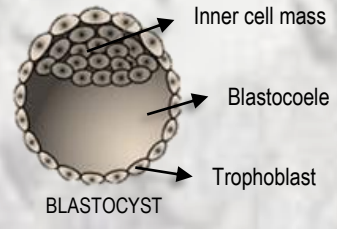
ACTIVITY AND REGULATION OF PLURIPOTENCY GENES IMPLICATED IN THE EMBRYONIC STEM CELLS FORMATION

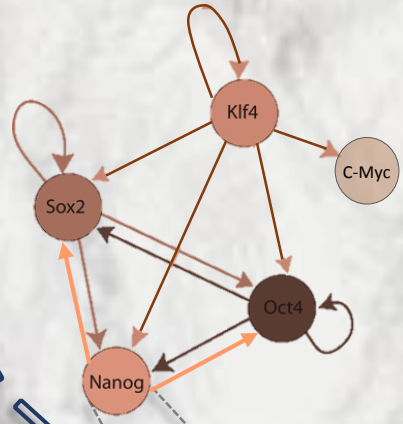
Estefania Carrillo, Facultat de Biociències, Universitat Autònoma de Barcelona

What are the hESCs?

The human embryonic stem cells (hESCs) are cells that have been developed at embryonic stages. Specifically, the hESCs are derived from inner cell mass of blastocyst, prior to its implantation within the uterus. So, hESCs are characterized by self-renewal and the capacity for differentiation. They also are PLURIPOTENT cells, that is, they are undifferentiated cells which remain inside inner cell mass and from which three embryonic layers are derived, contributing to the tissue generation.



INTRINSEC GENETIC DETERMINANTS



Oct4 is expressed in totipotent embryonic cells and germ cells. While totipotent cells differentiate in order to form somatic and/or extraembryonic tissues, Oct4 expression decreases.

Sox2 is found in embryonic neural stem cells as well as in all adult neural stem cells, where expression persists until cell differentiates. Also it is involved in the maintenance of neural stem cell properties, including proliferation/survival, self-renewal and neurogenesis.

Klf4 is essential for the maintenance of embryonic stem cell self-renewal. Depending on the promoter and/or other transcription factors contribution, it can achieve an activating or a suppressing function.

C-Myc belongs to the proto-oncogenes family. C-Myc binds, regulates and is implicated in the histone methylation patterns of genes involved in chromatin remodeling, differentiation and pluripotency. Thus, it interacts with the transcription factors Oct4, Sox2 and Klf4.

Nanog is a homodomain protein that directs the hESCs differentiation and is absent in differentiated cells. During cell differentiation, *Nanog* expression diminishes.

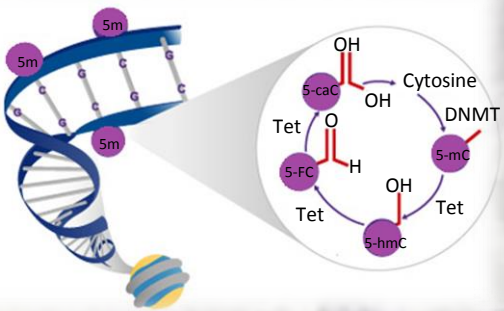
DNA METHYLATION

Maintenance of methylation: **Dnmt1**, **Dnmt3a** and **Dnmt3b**

Oxidation: **Tet** enzymes

Gene silencing

Gene activation



EXTRINSIC FACTORS

TGF-β is abundantly expressed in the endometrium and its action is associated with cell proliferation, diferentiation, apoptosis and tissue remodeling.

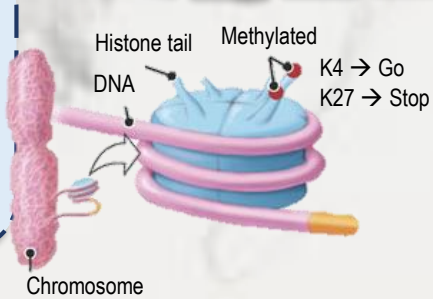
At the blastocyst stage, activin receptors (**ActRs**) are expressed. In particular, ActRIIA is expressed in the trophectoderm and ActRIIB is expressed in the trophectoderm and in the inner cell mass.

EPIGENETICS

HISTONE POSTTRANSLATIONAL MODIFICATIONS

Among modifications, acetylation, lysine and arginine methylation, serine and threonine phosphorylation, lysine ubiquitylation and sumoylation, and lysine ADP-ribosylation are highlighted.
Additionally, lysine acetylation is highly regulated by the opposite action of two enzyme families: the histone acetyltransferases (**HATs**) and the histone deacetylases (**HDACs**).

A histone modification distinctive feature is the "**bivalent domains**" hypothesis, where chromatin activation is giving by trimethylation of lysine 4 of histone 3 (**H3K4me3**). The inactivation is mediated by the trimehylation of lysine of histone H3 (**H3K27me3**). Both marks are observed mostly in promoters of hESCs genes and rarely in differentiated cells.



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