Transcriptional regulation of pluripotent stem cells

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16/09/2019
Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 70

This document contains 3 pathways and 12 reactions (see Table of Contents)

Pluripotency is maintained by a self-reinforcing loop of transcription factors (Boyer et al. 2005, Rao et al. 2006, Matoba et al. 2006, Player et al. 2006, Babaie et al. 2007, Sun et al. 2008, Assou et al. 2009, reviewed in Kashyap et al. 2009, reviewed in Dejosez and Zwaka 2012). In vivo, initiation of pluripotency may depend on maternal factors transmitted through the oocyte (Assou et al. 2009) and on DNA demethylation in the zygote (recently reviewed in Seisenberger et al. 2013) and hypoxia experienced by the blastocyst in the reproductive tract before implantation (Forristal et al. 2010, reviewed in Mohyeldin et al. 2010). In vitro, induced pluripotency may initiate with demethylation and activation of the promoters of POU5F1 (OCT4) and NANOG (Bhutani et al. 2010). Hypoxia also significantly enhances conversion to pluripotent stem cells (Yoshida et al. 2009). POU5F1 and NANOG, together with SOX2, encode central factors in pluripotency and activate their own transcription (Boyer et al. 2005, Babaie et al. 2007, Yu et al. 2007, Takahashi et al. 2007). The autoactivation loop maintains expression of POU5F1, NANOG, and SOX2 at high levels in stem cells and, in turn, complexes containing various combinations of these factors (Remenyi et al. 2003, Lam et al. 2012) activate the expression of a group of genes whose products are associated with rapid cell proliferation and repress the expression of a group of genes whose products are associated

Comparisons between human and mouse embryonic stem cells must be made with caution and for this reason inferences from mouse have been used sparingly in this module. Human ESCs more closely resemble mouse epiblast stem cells in having inactivated X chromosomes, flattened morphology, and intolerance to passaging as single cells (Hanna et al. 2010). Molecularly, human ESCs differ from mouse ESCs in being maintained by FGF and Activin/Nodal/TGFbeta signaling rather than by LIF and canonical Wnt signaling (Greber et al. 2010, reviewed in Katoh 2011). In human ESCs POU5F1 binds and directly activates the FGF2 gene, however Pou5f1 does not activate Fgf2 in mouse ESCs (reviewed in De Los Angeles et al. 2012). Differences in expression patterns of KLF2, KLF4, KLF5, ESRRB, FOXD3, SOCS3, LIN28, NODAL were observed between human and mouse ESCs (Cai et al. 2010) as were differences in expression of EOMES, ARNT and several other genes (Ginis et al. 2004).

**Literature references**


**Editions**

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The EPAS1 (HIF2A) gene is transcribed to yield mRNA and the mRNA is translated to yield protein. EPAS1 is expressed in most adult tissues, but not in peripheral blood leukocytes (Tian et al. 1997). Normoxia causes constitutive oxygen-dependent hydroxylation of EPAS1 on asparagine and proline residues, resulting in degradation of EPAS1 via ubiquitinylation. Hypoxia therefore inhibits degradation of EPAS1 and also causes an increase in EPAS1 expression via HIF3A in embryonic stem cells, which experience hypoxic conditions in the reproductive tract prior to implantation (Forristal et al. 2010).

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</table>
Transcription of POU5F1 (OCT4)

Location: Transcriptional regulation of pluripotent stem cells

Stable identifier: R-HSA-452392

Type: omitted

Compartments: nucleoplasm, cytosol

![Diagram of POU5F1 transcription](https://www.reactome.org)


Preceded by: POU5F1 (OCT4), SOX2, NANO2, ZSCAN10, PRDM14, SMAD2, FOXP1-ES bind the POU5F1 (OCT4) promoter

Followed by: LIN28 binds POU5F1 (OCT4) mRNA

Literature references


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LIN28 binds POU5F1 (OCT4) mRNA

**Location:** Transcriptional regulation of pluripotent stem cells

**Stable identifier:** R-HSA-500366

**Type:** binding

**Compartments:** cytosol

LIN28 binds the R2 region of the POU5F1 (OCT4) mRNA and increases translation of a luciferase reporter mRNA containing the binding site (Qiu et al. 2009, Lei et al. 2012). Reduction of LIN28 levels in embryonic stem cells causes a reduction in POU5F1 protein (Qiu et al. 2009).

**Preceded by:** Transcription of POU5F1 (OCT4)

**Followed by:** Translation of OCT4 mRNA

**Literature references**


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The POU5F1 (OCT4) mRNA is translated to yield protein. LIN28 bound to the mRNA appears to enhance translation (Qiu et al. 2009, Lei et al. 2012).

**Preceded by:** LIN28 binds POU5F1 (OCT4) mRNA

**Followed by:** POU5F1 (OCT4), STAT3 bind the SALL4 promoter, POU5F1 (OCT4), SOX2, NANOG, KLF4, PBX1, SMAD2 bind the NANOG promoter, POU5F1 (OCT4), SOX2, NANOG bind the SOX2 promoter, POU5F1 (OCT4), SOX2, NANOG, ZSCAN10, PRDM14, SMAD2, FOXP1-ES bind the POU5F1 (OCT4) promoter

**Literature references**


Expression of SOX2

Location: Transcriptional regulation of pluripotent stem cells

Stable identifier: R-HSA-452894

Type: omitted

Compartments: nucleoplasm

The SOX2 gene is transcribed to yield mRNA and the mRNA is translated to yield protein (Rao et al. 2004, Richards et al. 2004). SOX2 protein is expressed in the cytoplasm of oocytes and day-2 cleavage-stage embryos and in the nuclei of all cells of the inner cell mass of blastocysts (Cauffman et al. 2009). POU5F1 (OCT4), SOX2, and NANOG bind the promoter of the SOX2 gene and enhance transcription (Chew et al. 2005, Boyer et al. 2005, Babaie et al. 2007, Assou et al. 2007, Greber et al. 2007). POU5F1 and SOX2 bind adjacent sites at the promoter and form a heterodimer on the DNA (Boyer et al. 2005). Hypoxia acts via HIF3A and EPAS1 (HIF2A) to activate expression of SOX2 (Forristal et al. 2010).

Preceded by: POU5F1 (OCT4), SOX2, NANOG bind the SOX2 promoter

Followed by: POU5F1 (OCT4), SOX2, NANOG, KLF4, PBX1, SMAD2 bind the NANOG promoter, POU5F1 (OCT4), SOX2, NANOG, ZSCAN10, PRDM14, SMAD2, FOXP1-ES bind the POU5F1 (OCT4) promoter, POU5F1 (OCT4), SOX2, NANOG bind the SOX2 promoter

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The NANOG gene is transcribed to yield mRNA and the mRNA is translated to yield protein (Chambers et al. 2003, Hart et al. 2004, Hatano et al. 2005, Hyslop et al. 2005, Li et al. 2006). NANOG protein is not detected in oocytes or early cleavage-stage embryos, but is seen later in some but not all nuclei of the inner cell mass of blastocysts (Cauffman et al. 2009). KLF4, PBX1, POU5F1 (OCT4), SOX2, NANOG, and SMAD2 bind the promoter of the NANOG gene and enhance transcription (Boyer et al. 2005, Rodda et al. 2005, Kuroda et al. 2005, Babaie et al. 2007, Assou et al. 2007, Greber et al. 2007, Vallier et al. 2009, Brown et al. 2011). Activation-induced cytidine deaminase (AID) binds the methylated NANOG promoter and demethylates it (Bhutani et al. 2009). Hypoxia acts via HIF3A and EPAS1 (HIF2A) to enhance expression of NANOG (Forristal et al. 2010). In mouse Nanog negatively regulates its own expression and this may account for the heterogeneous expression observed in cells of the inner cell mass (Fidalgo et al. 2012, Navarro et al. 2012). In human embryonic stem cells NANOG has been observed to be expressed monoallelically in the early pre-implantation embryo then expression becomes biallelic (Miyanari and Torres-Padilla 2012), however this is controversial because experiments in mouse embryonic stem cells have shown biallelic expression (Faddah et al. 2013, Filipczyk et al. 2013). POU5F1 and SOX2 bind adjacent sites at the promoter and form a heterodimer on the DNA. In mice KLF4 interacts with POU5F1 and SOX2.

**Preceded by:** POU5F1 (OCT4), SOX2, NANOG, KLF4, PBX1, SMAD2 bind the NANOG promoter

**Followed by:** POU5F1 (OCT4), SOX2, NANOG, KLF4, PBX1, SMAD2 bind the NANOG promoter, POU5F1 (OCT4), SOX2, NANOG, ZSCAN10, PRDM14, SMAD2, FOXP1-ES bind the POU5F1 (OCT4) promoter, POU5F1 (OCT4), SOX2, NANOG bind the SOX2 promoter

**Literature references**


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POU5F1 (OCT4), SOX2, NANOG bind the SOX2 promoter

**Location:** Transcriptional regulation of pluripotent stem cells

**Stable identifier:** R-HSA-480685

**Type:** binding

**Compartments:** nucleoplasm


**Preceded by:** Expression of NANOG, Expression of SOX2, Translation of OCT4 mRNA

**Followed by:** Expression of SOX2

**Literature references**


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POU5F1 (OCT4), SOX2, NANOG, ZSCAN10, PRDM14, SMAD2, FOXP1-ES bind the POU5F1 (OCT4) promoter

**Location:** Transcriptional regulation of pluripotent stem cells

**Stable identifier:** R-HSA-1112609

**Type:** binding

**Compartments:** nucleoplasm

POU5F1 (OCT4), SOX2, and NANOG bind distinct sites in the promoter of the POU5F1 gene (Boyer et al. 2005, Chew et al. 2005, Rodda et al. 2005, Jin et al. 2007, Lister et al. 2009, Jung et al. 2010, Goke et al. 2011). The set of target genes of POU5F1, SOX2, and NANOG includes POU5F1, SOX2, and NANOG themselves, thus their expression is a component of an autoregulatory loop. Activin/Nodal signaling also regulates POU5F1 transcription via SMAD2 and SMAD3 (Brown et al. 2011). PRDM14 binds the POU5F1 promoter and regulates transcription (Chia et al. 2010).

**Preceded by:** Expression of NANOG, Expression of SOX2, Translation of OCT4 mRNA

**Followed by:** Transcription of POU5F1 (OCT4)

**Literature references**


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POU5F1 (OCT4), SOX2, NANOG, KLF4, PBX1, SMAD2 bind the NANOG promoter

Location: Transcriptional regulation of pluripotent stem cells

Stable identifier: R-HSA-480204

Type: binding

Compartments: nucleoplasm


Preceded by: Expression of NANOG, Expression of SOX2, Translation of OCT4 mRNA

Followed by: Expression of NANOG

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POU5F1 (OCT4), STAT3 bind the SALL4 promoter

**Location:** Transcriptional regulation of pluripotent stem cells

**Stable identifier:** R-HSA-2895778

**Type:** binding

**Compartments:** nucleoplasm

POU5F1 (OCT4) and STAT3 bind the promoter of the SALL4 gene and activate its transcription (Babaie et al. 2007, Tantin et al. 2008, Bard et al. 2009, Yang et al. 2010). SALL4, in turn, positively regulates POU5F1 expression (Yang et al. 2010). In mouse STAT3 is activated by Leukemia Inhibitory Factor (LIF), however LIF in humans does not have the same activity in promoting stem cell maintenance (Humphrey et al. 2004).

**Preceded by:** Translation of OCT4 mRNA

**Followed by:** Expression of SALL4

**Literature references**


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### Expression of SALL4

**Location:** Transcriptional regulation of pluripotent stem cells

**Stable identifier:** R-HSA-480520

**Type:** omitted

**Compartments:** nucleoplasm

The SALL4 gene is transcribed to yield mRNA and the mRNA is translated to yield protein. SALL4 protein is expressed weakly in the nuclei and cytoplasm of oocytes and day-2 cleavage-stage embryos and is expressed strongly in nuclei of blastocysts (Cauffman et al. 2009) and in induced pluripotent stem cells (Nishino et al. 2010). POU5F1 (OCT4) and STAT3 bind the promoter of the SALL4 gene and enhance transcription (Yang et al. 2010, Bard et al. 2009). SALL4 activates expression of POU5F1, thus forming a self-reinforcing loop (Yang et al. 2010). SALL4 binds the promoter of the SALL4 gene and represses transcription, thus forming a negative autoregulatory loop (Yang et al. 2010). As inferred from mouse the shorter isoform of SALL4, SALL4B is more effective at maintaining pluripotency (Rao et al. 2010).

**Preceded by:** POU5F1 (OCT4), STAT3 bind the SALL4 promoter, SALL4 binds the SALL4 promoter

**Followed by:** SALL4 binds the SALL4 promoter

**Literature references**


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SALL4 binds the SALL4 promoter

Location: Transcriptional regulation of pluripotent stem cells

Stable identifier: R-HSA-2972968

Type: binding

Compartments: nucleoplasm

SALL4 binds the promoter of the SALL4 gene and represses its own expression (Yang et al. 2010).

Preceded by: Expression of SALL4

Followed by: Expression of SALL4

Literature references


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POU5F1 (OCT4), SOX2, NANOG activate genes related to proliferation

Location: Transcriptional regulation of pluripotent stem cells

Stable identifier: R-HSA-2892247

Compartments: nucleoplasm, cytosol, endosome membrane, extracellular region, plasma membrane

POU5F1 (OCT4), SOX2, and NANOG bind elements in the promoters of target genes. The target genes of each transcription factor overlap extensively: POU5F1, SOX2, and NANOG co-occupy at least 353 genes (Boyer et al. 2005). About half of POU5F1 targets also bind SOX2 and about 90% of these also bind NANOG (Boyer et al. 2005). Upon binding the transcription factors activate expression of one subset of target genes and repress another subset (Kim et al. 2006, Matoba et al. 2006, Player et al. 2006, Babaie et al. 2007). The targets listed in this module are those that have been described as composing activated genes in the core transcriptional network of pluripotent stem cells (Assou et al. 2007, Chavez et al. 2009, Jung et al. 2010). Inferences from mouse to human have been made with caution because of significant differences between the two species (Ginis et al. 2004).

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POU5F1 (OCT4), SOX2, and NANOG repress genes related to differentiation

**Location:** Transcriptional regulation of pluripotent stem cells

**Stable identifier:** R-HSA-2892245

**Compartments:** nucleoplasm, cytosol, extracellular region, plasma membrane

POU5F1 (OCT4), SOX2, and NANOG bind elements in the promoters of target genes. The target genes of each transcription factor overlap extensively: POU5F1, SOX2, and NANOG co-occupy at least 353 genes (Boyer et al. 2005). About half of POU5F1 targets also bind SOX2 and about 90% of these also bind NANOG (Boyer et al. 2005). Upon binding the transcription factors activate expression of one subset of target genes in the core transcriptional network of pluripotent stem cells and repress another subset (Kim et al. 2006, Matoba et al. 2006, Player et al. 2006, Assou et al. 2007, Babaie et al. 2007, Chavez et al. 2009, Jung et al. 2010). The target genes listed in this module are the repressed genes. Caution must be used when making inferences about human stem cells from mouse stem cells because of significant differences between the two species (Ginis et al. 2004).

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