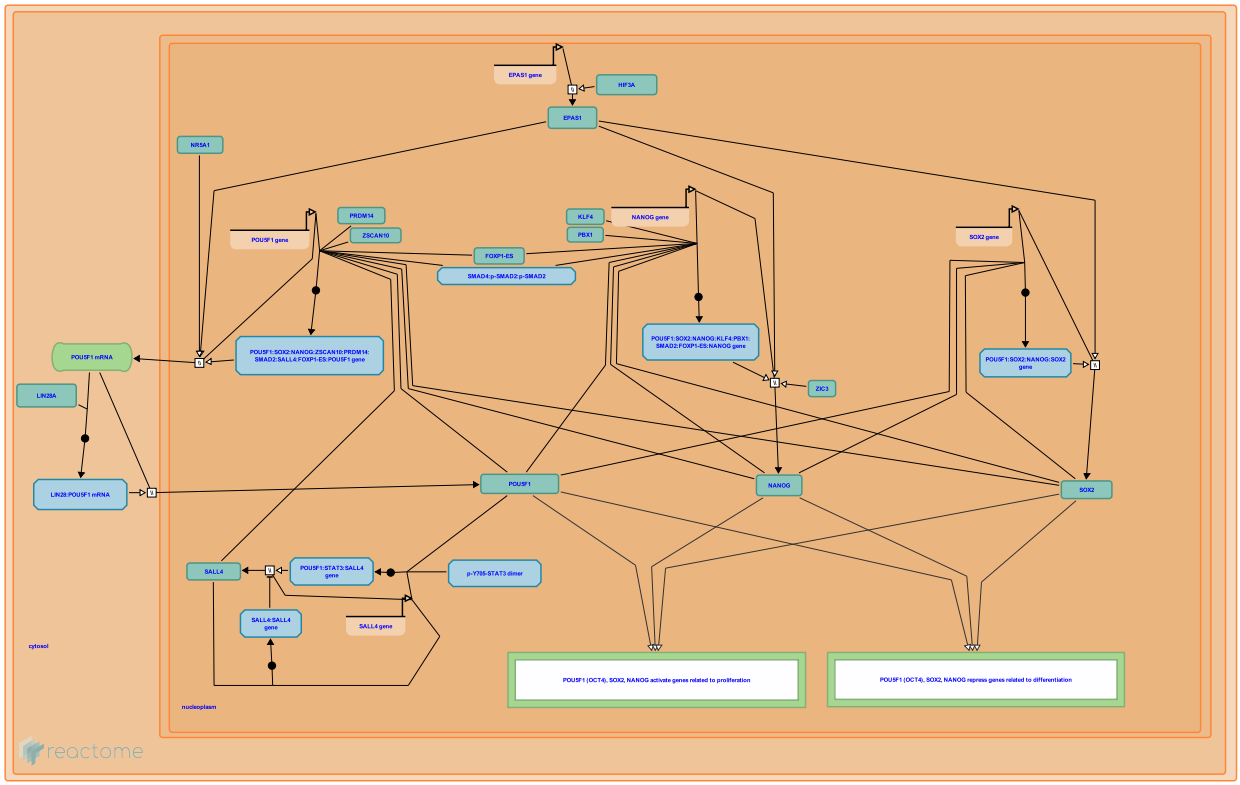
Transcriptional regulation of pluripotent stem cells



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07/03/2021

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.

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Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

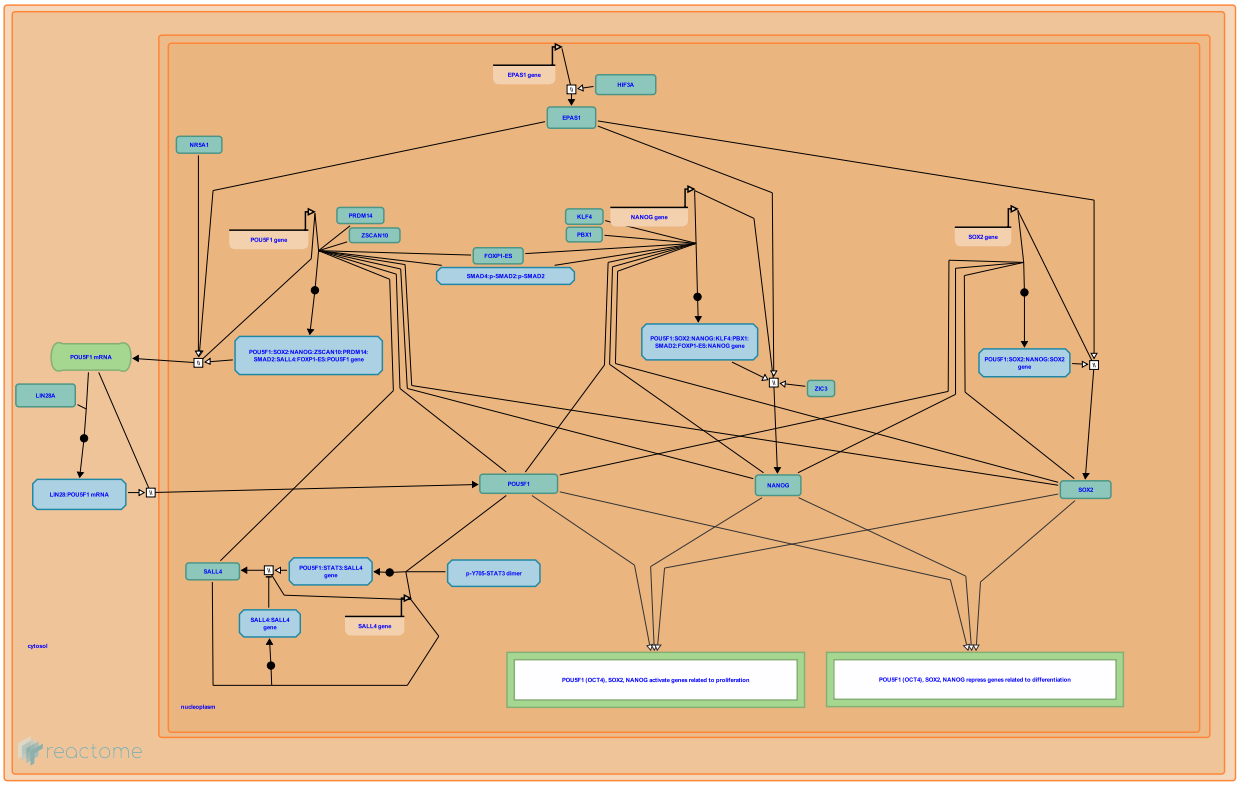
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Transcriptional regulation of pluripotent stem cells ↗

Stable identifier: R-HSA-452723

Compartments: cytosol, nucleoplasm



Pluripotent stem cells are undifferentiated cells posessing an abbreviated cell cycle (reviewed in Stein et al. 2012), a characteristic profile of gene expression (Rao et al. 2004, Kim et al. 2006, Player et al. 2006, Wang et al 2006 using mouse, International Stem Cell Initiative 2007, Assou et al. 2007, Assou et al. 2009, Ding et al. 2012 using mouse), and the ability to self-renew and generate all cell types of the body except extraembryonic lineages (Marti et al. 2013, reviewed in Romeo et al. 2012). They are a major cell type in the inner cell mass of the early embryo in vivo, and cells with the same properties, induced pluripotent stem cells, can be generated in vitro from differentiated adult cells by overexpression of a set of transcription factor genes (Takahashi and Yamanaka 2006, Takahashi et al. 2007, Yu et al. 2007, Jaenisch and Young 2008, Stein et al. 2012, reviewed in Dejosez and Zwaka 2012).

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

with cell differentiation (Boyer et al. 2005, Matoba et al. 2006, Babaie et al. 2007, Chavez et al. 2009, Forristal et al. 2010, Guenther 2011).

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

Sun, Y., Li, H., Liu, Y., Mattson, MP., Rao, MS., Zhan, M. (2008). Evolutionarily conserved transcriptional co-expression guiding embryonic stem cell differentiation. *PLoS One, 3*, e3406. ↗

Wang, J., Rao, S., Chu, J., Shen, X., Levasseur, DN., Theunissen, TW. et al. (2006). A protein interaction network for pluripotency of embryonic stem cells. *Nature, 444*, 364-8. ↗

Stein, GS., Stein, JL., van J Wijnen, A., Lian, JB., Montecino, M., Medina, R. et al. (2012). The architectural organization of human stem cell cycle regulatory machinery. *Curr. Pharm. Des., 18*, 1679-85. ↗

Reményi, A., Lins, K., Nissen, LJ., Reinbold, R., Schöler, HR., Wilmanns, M. (2003). Crystal structure of a POU/HMG/DNA ternary complex suggests differential assembly of Oct4 and Sox2 on two enhancers. *Genes Dev, 17*, 2048-59. ↗

Kim, CG., Kim, CG., Lee, JJ., Jung, DY., Jeon, J., Heo, HS. et al. (2006). Profiling of differentially expressed genes in human stem cells by cDNA microarray. *Mol Cells, 21*, 343-55. ↗

Editions

2010-11-12	Authored, Edited	May, B.
2014-01-23	Reviewed	Wang, J.

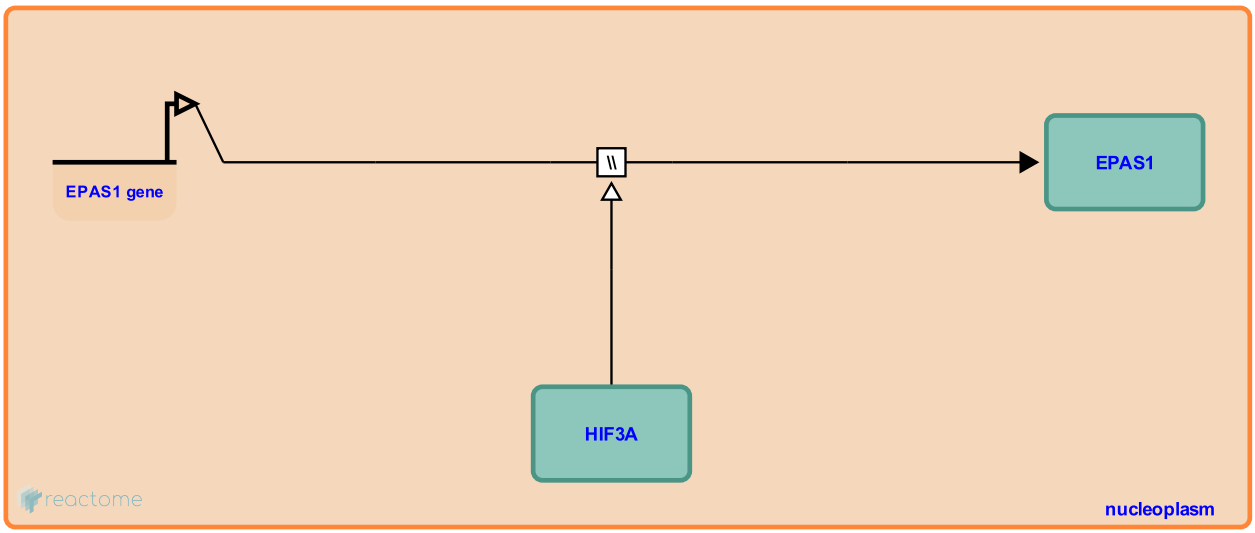
Expression of EPAS1 (HIF2A)

Location: Transcriptional regulation of pluripotent stem cells

Stable identifier: R-HSA-480301

Type: omitted

Compartments: nucleoplasm



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-dependient 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).

Literature references

Forristal, CE., Wright, KL., Hanley, NA., Oreffo, RO., Houghton, FD. (2010). Hypoxia inducible factors regulate pluripotency and proliferation in human embryonic stem cells cultured at reduced oxygen tensions. *Reproduction, 139* , 85-97.

Tian, H., McKnight, SL., Russell, DW. (1997). Endothelial PAS domain protein 1 (EPAS1), a transcription factor selectively expressed in endothelial cells. *Genes Dev, 11*, 72-82.

Editions

2010-11-12	Authored, Edited	May, B.
2014-01-23	Reviewed	Wang, J.

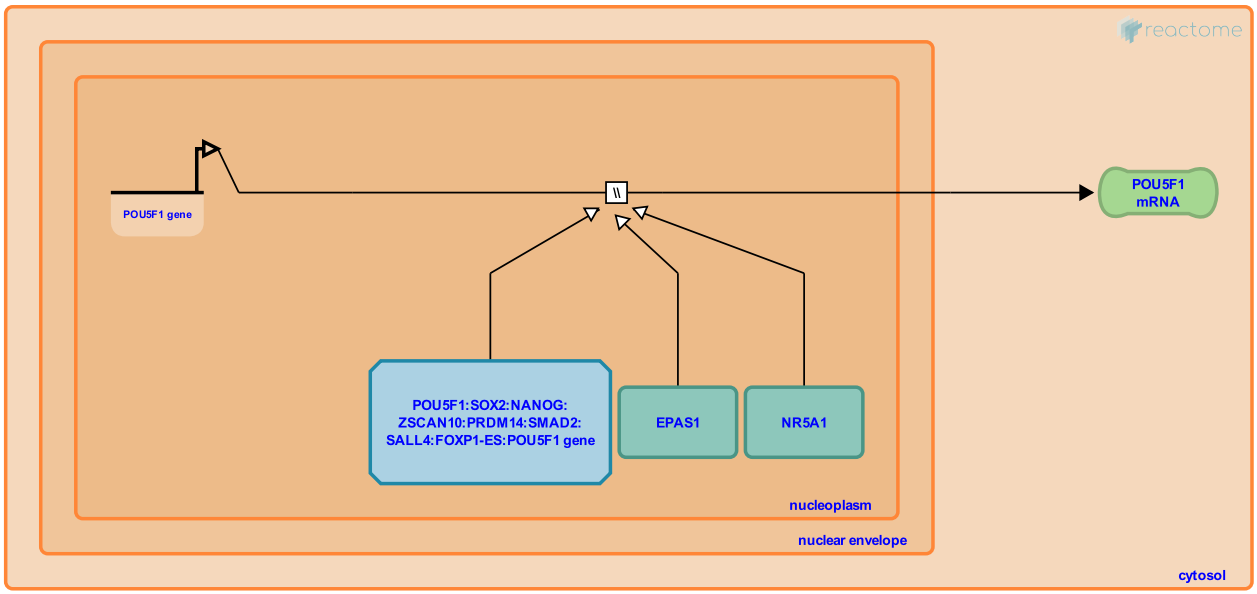
Transcription of POU5F1 (OCT4) ↗

Location: Transcriptional regulation of pluripotent stem cells

Stable identifier: R-HSA-452392

Type: omitted

Compartments: nucleoplasm, cytosol



The POU5F1 (OCT4) gene is transcribed to yield mRNA and the mRNA is translated to yield protein (Rao et al. 2004, Richards et al. 2004, Cauffman et al. 2005, Tai et al. 2005, Gerrard et al. 2005, Li et al. 2006, Adewumi et al. 2007,Assou etal. 2007). POU5F1 mRNA and protein are found in the cytoplasm of oocytes and cleavage-stage embryos (Cauffman et al. 2005). POU5F1 protein becomes nuclear during compaction, and protein and mRNA are present in inner cell mass and trophectoderm (Cauffman et al. 2005). Transcripts are also detectable in some differentiated tissues (Cauffman et al. 2005). POU5F1 is expressed in adult stem cells and cancers (Tai et al. 2005). POU5F1, SOX2, NANOG, SALL4, and SF-1(NR5A1) bind the promoter of the POU5F1 gene and enhance transcription (Matin et al. 2004, Chew et al. 2005, Boyer et al. 2005, Babaie et al. 2007, Greber et al. 2007, Wang et al. 2007, Yang et al. 2010, Chia et al. 2010). POU5F1 and SOX2 bind adjacent sites at the promoter and form a heterodimer on the DNA. SALL4 binds the promoter of the POU5F1 gene and activates transcription of POU5F1 (Yang et al. 2010). POU5F1 activates SALL4 expression thus forming a self-reinforcing loop. Activation-induced cytidine deaminase (AID) binds the methylated promoter of the POU5F1 gene, demethylates it, and enhances expression of POU5F1 (Bhutani et al. 2009). Hypoxia acts via HIF3A and EPAS1 (HIF2A) to enhance expression of POU5F1 (Forristal et al. 2010). LIN28 binds the POU5F1 mRNA and increases translation (Qiu et al. 2009).

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

Followed by: LIN28 binds POU5F1 (OCT4) mRNA

Literature references

Tai, MH., Chang, CC., Kiupel, M., Webster, JD., Olson, LK., Trosko, JE. (2005). Oct4 expression in adult human stem cells: evidence in support of the stem cell theory of carcinogenesis. *Carcinogenesis, 26*, 495-502. ↗

Rao, RR., Calhoun, JD., Qin, X., Rekaya, R., Clark, JK., Stice, SL. (2004). Comparative transcriptional profiling of two human embryonic stem cell lines. *Biotechnol Bioeng, 88*, 273-86. ↗

Chew, JL., Loh, YH., Zhang, W., Chen, X., Tam, WL., Yeap, LS. et al. (2005). Reciprocal transcriptional regulation of Pou5f1 and Sox2 via the Oct4/Sox2 complex in embryonic stem cells. *Mol Cell Biol, 25*, 6031-46. ↗

Matin, MM., Walsh, JR., Gokhale, PJ., Draper, JS., Bahrami, AR., Morton, I. et al. (2004). Specific knockdown of Oct4 and beta2-microglobulin expression by RNA interference in human embryonic stem cells and embryonic carcinoma cells. *Stem Cells, 22*, 659-68. ↗

Gerrard, L., Zhao, D., Clark, AJ., Cui, W. (2005). Stably transfected human embryonic stem cell clones express OCT4-specific green fluorescent protein and maintain self-renewal and pluripotency. *Stem Cells, 23*, 124-33. ↗

Editions

2010-11-12	Authored, Edited	May, B.
2014-01-23	Reviewed	Wang, J.

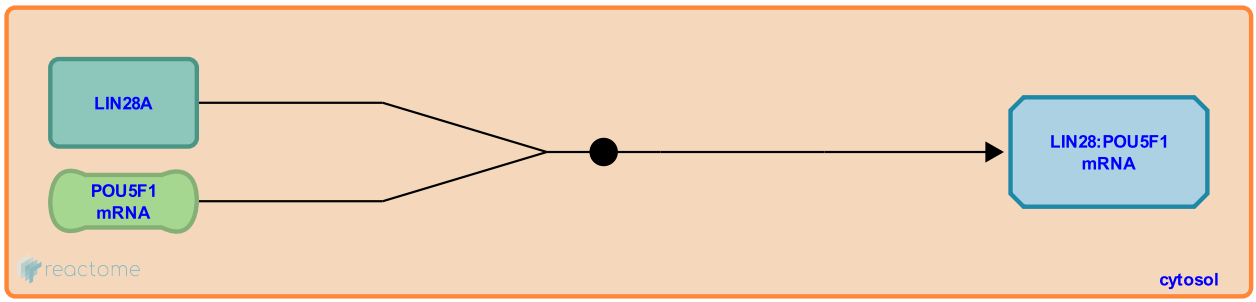
LIN28 binds POU5F1 (OCT4) mRNA ↗

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

Qiu, C., Ma, Y., Wang, J., Peng, S., Huang, Y. (2009). Lin28-mediated post-transcriptional regulation of Oct4 expression in human embryonic stem cells. *Nucleic Acids Res, 38*, 1240-8. ↗

Lei, XX., Xu, J., Ma, W., Qiao, C., Newman, MA., Hammond, SM. et al. (2012). Determinants of mRNA recognition and translation regulation by Lin28. *Nucleic Acids Res., 40*, 3574-84. ↗

Editions

2010-11-12	Authored, Edited	May, B.
2014-01-23	Reviewed	Wang, J.

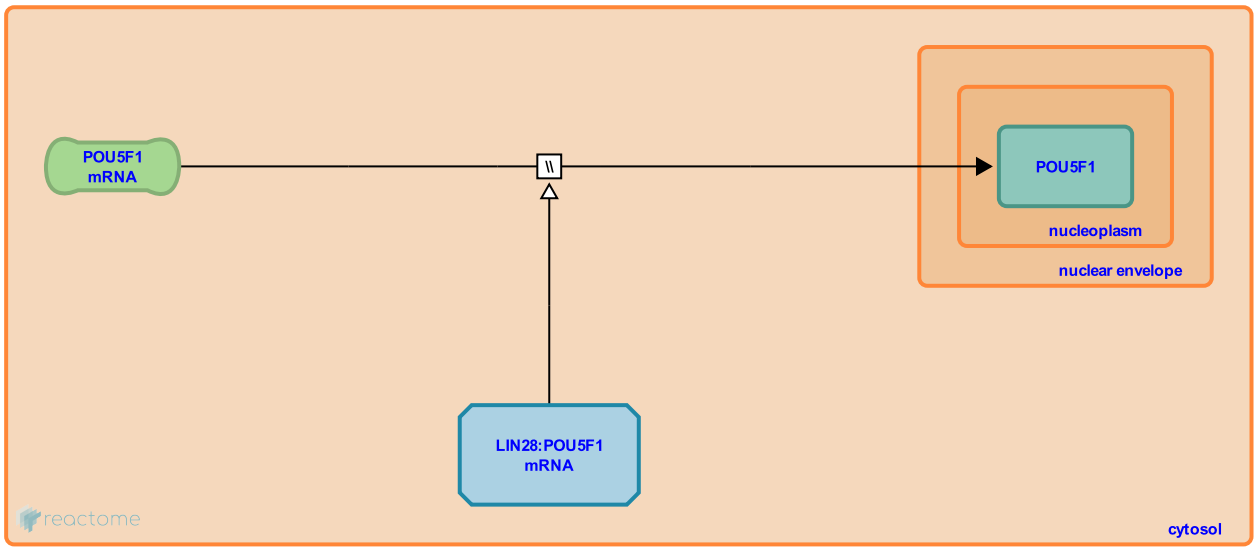
Translation of OCT4 mRNA ↗

Location: Transcriptional regulation of pluripotent stem cells

Stable identifier: R-HSA-2889036

Type: omitted

Compartments: cytosol, nucleoplasm



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

Qiu, C., Ma, Y., Wang, J., Peng, S., Huang, Y. (2009). Lin28-mediated post-transcriptional regulation of Oct4 expression in human embryonic stem cells. *Nucleic Acids Res, 38*, 1240-8. ↗

Lei, XX., Xu, J., Ma, W., Qiao, C., Newman, MA., Hammond, SM. et al. (2012). Determinants of mRNA recognition and translation regulation by Lin28. *Nucleic Acids Res., 40*, 3574-84. ↗

Editions

2012-12-30	Authored, Edited	May, B.
2014-01-23	Reviewed	Wang, J.

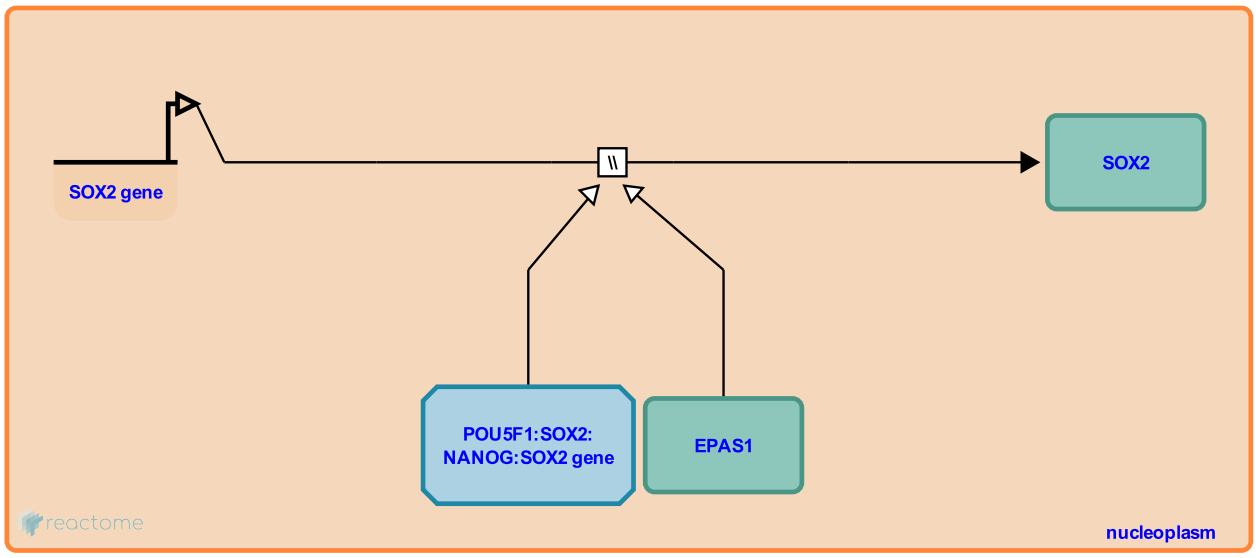
Expression of SOX2 ↗

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

Literature references

Rao, RR., Calhoun, JD., Qin, X., Rekaya, R., Clark, JK., Stice, SL. (2004). Comparative transcriptional profiling of two human embryonic stem cell lines. *Biotechnol Bioeng, 88*, 273-86. ↗

Takahashi, K., Tanabe, K., Ohnuki, M., Narita, M., Ichisaka, T., Tomoda, K. et al. (2007). Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell, 131*, 861-72. ↗

Chew, JL., Loh, YH., Zhang, W., Chen, X., Tam, WL., Yeap, LS. et al. (2005). Reciprocal transcriptional regulation of Pou5f1 and Sox2 via the Oct4/Sox2 complex in embryonic stem cells. *Mol Cell Biol, 25*, 6031-46. ↗

Richards, M., Tan, SP., Tan, JH., Chan, WK., Bongso, A. (2004). The transcriptome profile of human embryonic stem cells as defined by SAGE. *Stem Cells, 22*, 51-64. ↗

Babaie, Y., Herwig, R., Greber, B., Brink, TC., Wruck, W., Groth, D. et al. (2007). Analysis of Oct4-dependent transcriptional networks regulating self-renewal and pluripotency in human embryonic stem cells. *Stem Cells, 25*, 500-10. ↗

Editions

2010-11-12	Authored, Edited	May, B.
2014-01-23	Reviewed	Wang, J.

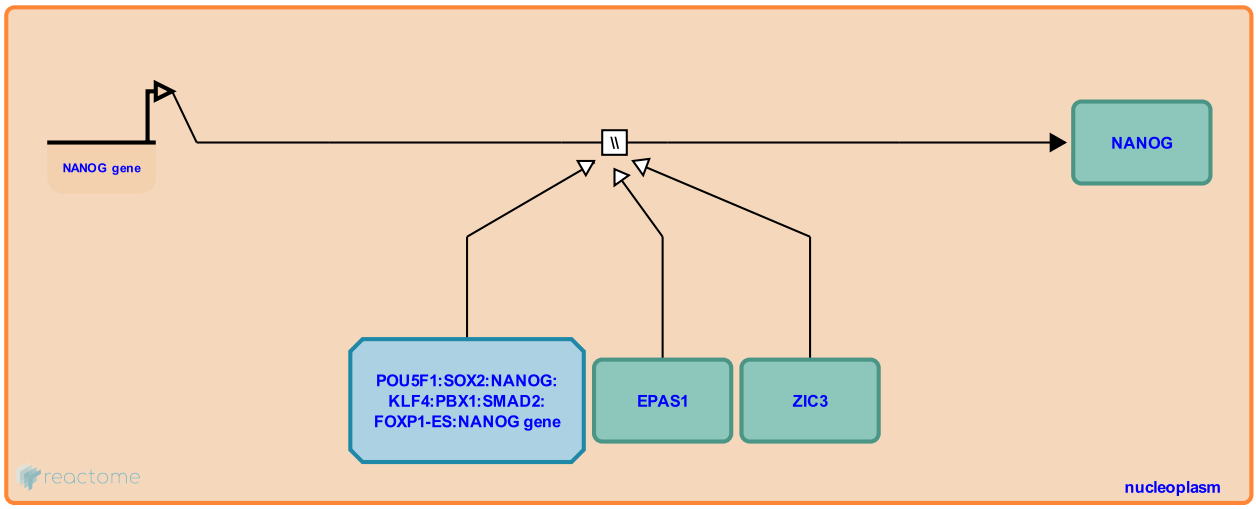
Expression of NANOG

Location: Transcriptional regulation of pluripotent stem cells

Stable identifier: R-HSA-452838

Type: omitted

Compartments: nucleoplasm



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 expreiments 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

Boyer, LA., Lee, TI., Cole, MF., Johnstone, SE., Levine, SS., Zucker, JP. et al. (2005). Core transcriptional regulatory circuitry in human embryonic stem cells. *Cell, 122*, 947-56.

Hart, AH., Hartley, L., Ibrahim, M., Robb, L. (2004). Identification, cloning and expression analysis of the pluripotency promoting Nanog genes in mouse and human. *Dev Dyn, 230*, 187-98.

Chambers, I., Colby, D., Robertson, M., Nichols, J., Lee, S., Tweedie, S. et al. (2003). Functional expression cloning of Nanog, a pluripotency sustaining factor in embryonic stem cells. *Cell, 113*, 643-55.

Rodda, DJ., Chew, JL., Lim, LH., Loh, YH., Wang, B., Ng, HH. et al. (2005). Transcriptional regulation of nanog by OCT4 and SOX2. *J Biol Chem, 280*, 24731-7. ↗

Hatano, SY., Tada, M., Kimura, H., Yamaguchi, S., Kono, T., Nakano, T. et al. (2005). Pluripotential competence of cells associated with Nanog activity. *Mech Dev, 122*, 67-79. ↗

Editions

2010-11-12	Authored, Edited	May, B.
2014-01-23	Reviewed	Wang, J.

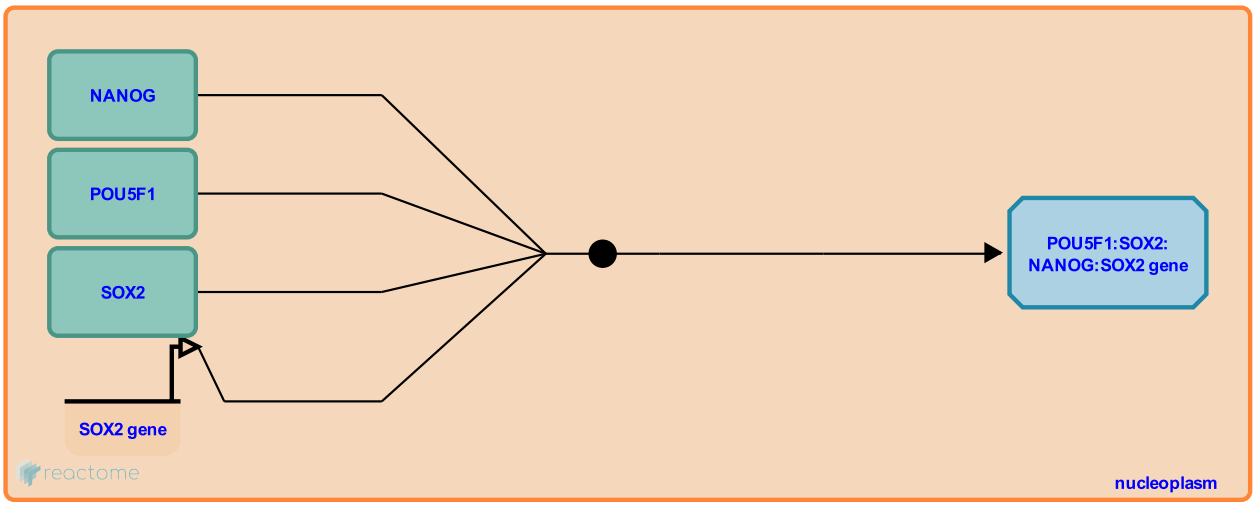
POU5F1 (OCT4), SOX2, NANOG bind the SOX2 promoter ↗

Location: Transcriptional regulation of pluripotent stem cells

Stable identifier: R-HSA-480685

Type: binding

Compartments: nucleoplasm



POU5F1 (OCT4), SOX2, and NANOG bind distinct sites in the promoter of the SOX2 gene (Boyer et al. 2005, Jin et al. 2007, Lister et al. 2009, Jung et al. 2010). 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 (Boyer et al. 2005, Chew et al. 2005, Rodda et al. 2005, Babaie et al. 2007, Jung et al. 2010, Goke et al. 2011).

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

Followed by: Expression of SOX2

Literature references

Boyer, LA., Lee, TI., Cole, MF., Johnstone, SE., Levine, SS., Zucker, JP. et al. (2005). Core transcriptional regulatory circuitry in human embryonic stem cells. *Cell, 122*, 947-56. ↗

Chew, JL., Loh, YH., Zhang, W., Chen, X., Tam, WL., Yeap, LS. et al. (2005). Reciprocal transcriptional regulation of Pou5f1 and Sox2 via the Oct4/Sox2 complex in embryonic stem cells. *Mol Cell Biol, 25*, 6031-46. ↗

Rodda, DJ., Chew, JL., Lim, LH., Loh, YH., Wang, B., Ng, HH. et al. (2005). Transcriptional regulation of nanog by OCT4 and SOX2. *J Biol Chem, 280*, 24731-7. ↗

Babaie, Y., Herwig, R., Greber, B., Brink, TC., Wruck, W., Groth, D. et al. (2007). Analysis of Oct4-dependent transcriptional networks regulating self-renewal and pluripotency in human embryonic stem cells. *Stem Cells, 25*, 500-10. ↗

Göke, J., Jung, M., Behrens, S., Chavez, L., O'Keeffe, S., Timmermann, B. et al. (2011). Combinatorial binding in human and mouse embryonic stem cells identifies conserved enhancers active in early embryonic development. *PLoS Comput. Biol., 7*, e1002304. ↗

Editions

2010-11-12	Authored, Edited	May, B.
2014-01-23	Reviewed	Wang, J.

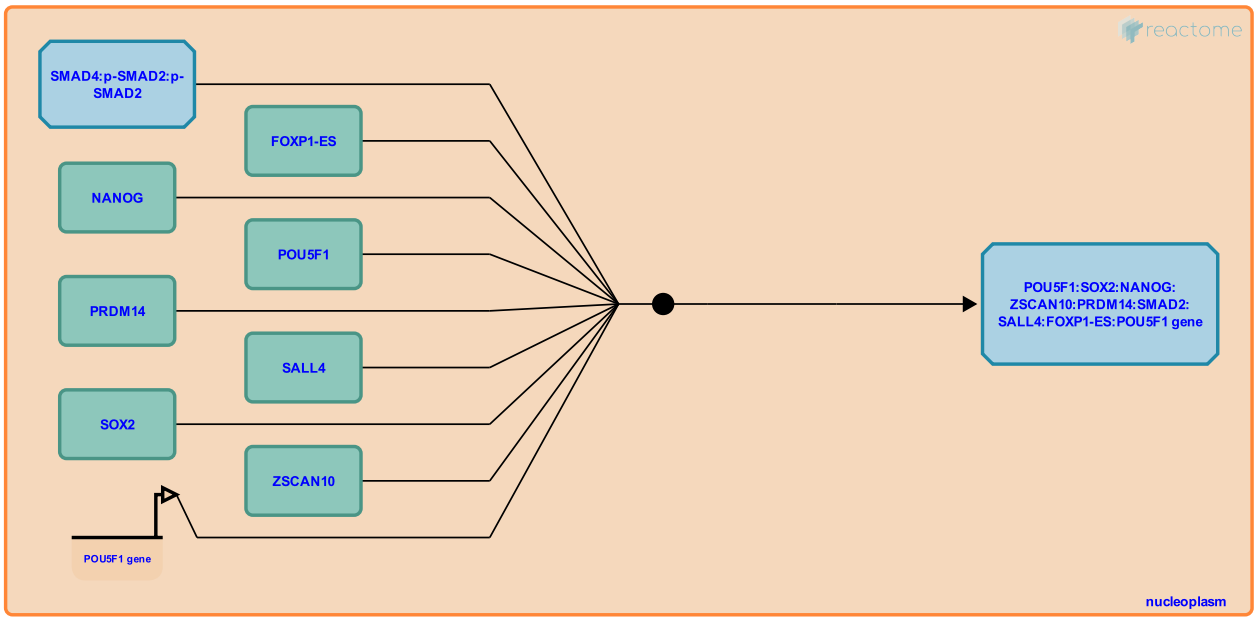
POU5F1 (OCT4), SOX2, NANOG, ZSCAN10, PRDM14, SMAD2, FOXP1-ES bind the POU5F1 (OCT4) promoter ↗

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

Boyer, LA., Lee, TI., Cole, MF., Johnstone, SE., Levine, SS., Zucker, JP. et al. (2005). Core transcriptional regulatory circuitry in human embryonic stem cells. *Cell, 122*, 947-56. ↗

Chew, JL., Loh, YH., Zhang, W., Chen, X., Tam, WL., Yeap, LS. et al. (2005). Reciprocal transcriptional regulation of Pou5f1 and Sox2 via the Oct4/Sox2 complex in embryonic stem cells. *Mol Cell Biol, 25*, 6031-46. ↗

Jung, M., Peterson, H., Chavez, L., Kahlem, P., Lehrach, H., Vilo, J. et al. (2010). A data integration approach to mapping OCT4 gene regulatory networks operative in embryonic stem cells and embryonal carcinoma cells. *PLoS One , 5*, e10709. ↗

Chia, NY., Chan, YS., Feng, B., Lu, X., Orlov, YL., Moreau, D. et al. (2010). A genome-wide RNAi screen reveals determinants of human embryonic stem cell identity. *Nature, 468*, 316-20. ↗

Brown, S., Teo, A., Pauklin, S., Hannan, N., Cho, CH., Lim, B. et al. (2011). Activin/Nodal signaling controls divergent transcriptional networks in human embryonic stem cells and in endoderm progenitors. *Stem Cells, 29*, 1176-85. ↗

Editions

2010-11-12	Authored, Edited	May, B.
2014-01-23	Reviewed	Wang, J.

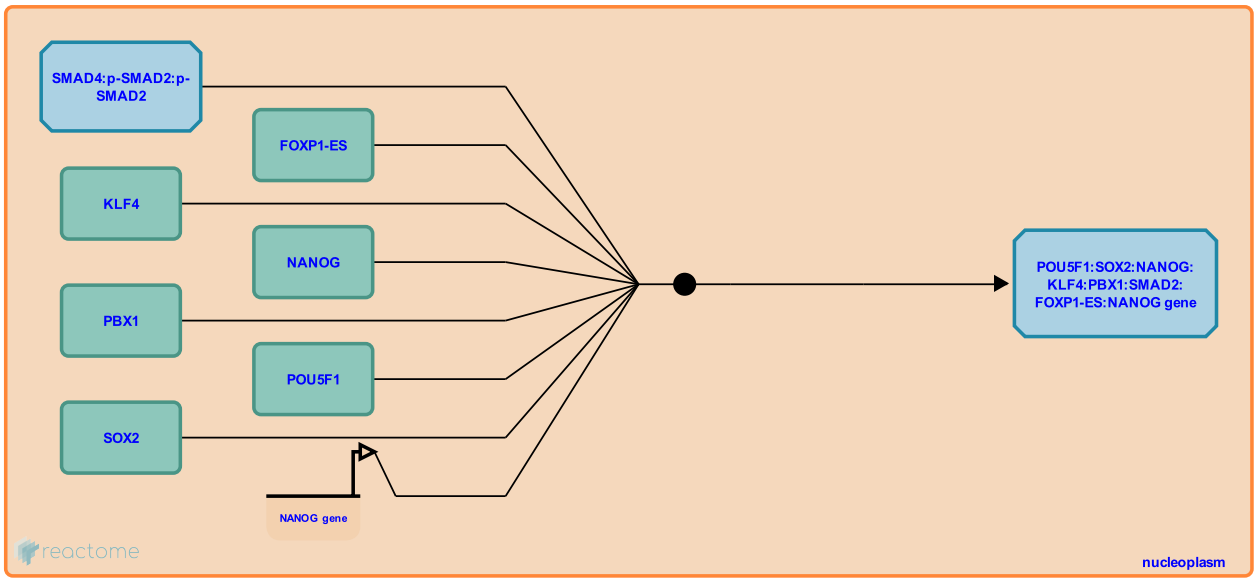
POU5F1 (OCT4), SOX2, NANOG, KLF4, PBX1, SMAD2 bind the NANOG promoter ↗

Location: Transcriptional regulation of pluripotent stem cells

Stable identifier: R-HSA-480204

Type: binding

Compartments: nucleoplasm



KLF4, PBX1, POU5F1 (OCT4), SOX2, and NANOG bind the promoter of the NANOG gene and enhance expression of NANOG (Rodda et al. 2005, Boyer et al. 2005, Babaie et al. 2007, Jin et al. 2007, Chan et al. 2009, Vallier et al. 2009, Jung et al. 2011). In mouse Nanog has been shown to repress its own expression (Fidalgo et al. 2012, Navarro et al. 2012). ZIC3, a NANOG target, also positively regulates NANOG expression, possibly by binding the NANOG promoter and activating transcription (Lim et al. 2007). Activin/Nodal signaling regulates NANOG via SMAD2 and SMAD3 (Brown et al. 2011)

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

Followed by: Expression of NANOG

Literature references

Chan, KK., Zhang, J., Chia, NY., Chan, YS., Sim, HS., Tan, KS. et al. (2009). KLF4 and PBX1 directly regulate NANOG expression in human embryonic stem cells. *Stem Cells, 27*, 2114-25. ↗

Babaie, Y., Herwig, R., Greber, B., Brink, TC., Wruck, W., Groth, D. et al. (2007). Analysis of Oct4-dependent transcriptional networks regulating self-renewal and pluripotency in human embryonic stem cells. *Stem Cells, 25*, 500-10. ↗

Boyer, LA., Lee, TI., Cole, MF., Johnstone, SE., Levine, SS., Zucker, JP. et al. (2005). Core transcriptional regulatory circuitry in human embryonic stem cells. *Cell, 122*, 947-56. ↗

Brown, S., Teo, A., Pauklin, S., Hannan, N., Cho, CH., Lim, B. et al. (2011). Activin/Nodal signaling controls divergent transcriptional networks in human embryonic stem cells and in endoderm progenitors. *Stem Cells, 29*, 1176-85. ↗

Jung, M., Peterson, H., Chavez, L., Kahlem, P., Lehrach, H., Vilo, J. et al. (2010). A data integration approach to mapping OCT4 gene regulatory networks operative in embryonic stem cells and embryonal carcinoma cells. *PLoS One , 5*, e10709. ↗

Editions

2010-11-12	Authored, Edited	May, B.
2014-01-23	Reviewed	Wang, J.

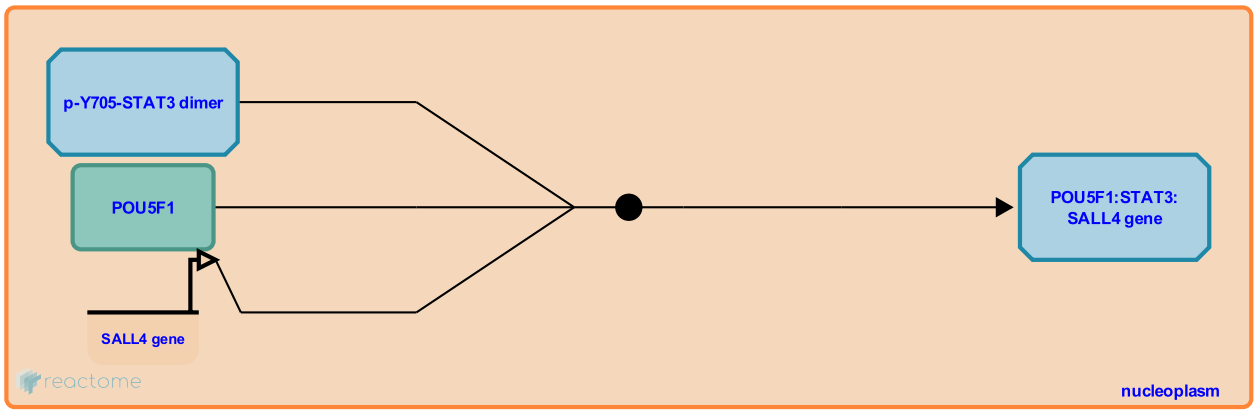
POU5F1 (OCT4), STAT3 bind the SALL4 promoter ↗

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

Yang, J., Gao, C., Chai, L., Ma, Y. (2010). A novel SALL4/OCT4 transcriptional feedback network for pluripotency of embryonic stem cells. *PLoS One, 5*, e10766. ↗

Tantin, D., Gemberling, M., Callister, C., Fairbrother, WG. (2008). High-throughput biochemical analysis of in vivo location data reveals novel distinct classes of POU5F1(Oct4)/DNA complexes. *Genome Res, 18*, 631-9. ↗

Bard, JD., Gelebart, P., Amin, HM., Young, LC., Ma, Y., Lai, R. (2009). Signal transducer and activator of transcription 3 is a transcriptional factor regulating the gene expression of SALL4. *FASEB J, 23*, 1405-14. ↗

Babaie, Y., Herwig, R., Greber, B., Brink, TC., Wruck, W., Groth, D. et al. (2007). Analysis of Oct4-dependent transcriptional networks regulating self-renewal and pluripotency in human embryonic stem cells. *Stem Cells, 25*, 500-10. ↗

Humphrey, RK., Beattie, GM., Lopez, AD., Bucay, N., King, CC., Firpo, MT. et al. (2004). Maintenance of pluripotency in human embryonic stem cells is STAT3 independent. *Stem Cells, 22*, 522-30. ↗

Editions

2013-01-02	Authored, Edited	May, B.
2014-01-23	Reviewed	Wang, J.

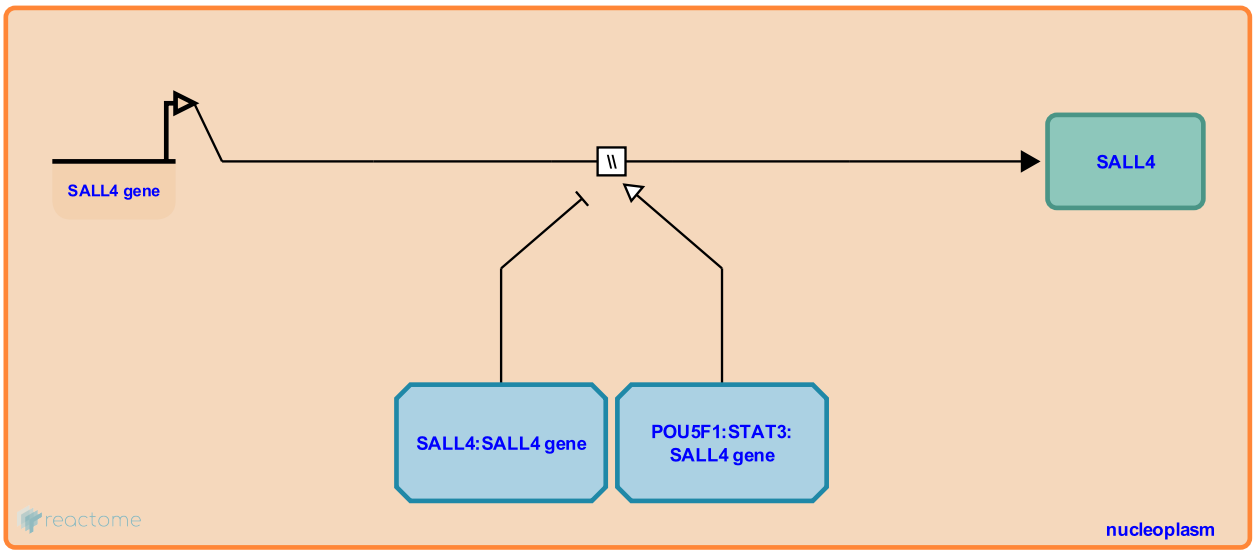
Expression of SALL4

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

Li, SS., Liu, YH., Tseng, CN., Chung, TL., Lee, TY., Singh, S. (2006). Characterization and gene expression profiling of five new human embryonic stem cell lines derived in Taiwan. *Stem Cells Dev, 15*, 532-55.

Cauffman, G., De Rycke, M., Sermon, K., Liebaers, I., Van de Velde, H. (2009). Markers that define stemness in ESC are unable to identify the totipotent cells in human preimplantation embryos. *Hum Reprod, 24*, 63-70.

Shih, YR., Kuo, TK., Yang, AH., Lee, OK., Lee, CH. (2009). Isolation and characterization of stem cells from the human parathyroid gland. *Cell Prolif, 42*, 461-70.

Yang, J., Gao, C., Chai, L., Ma, Y. (2010). A novel SALL4/OCT4 transcriptional feedback network for pluripotency of embryonic stem cells. *PLoS One, 5*, e10766.

Bard, JD., Gelebart, P., Amin, HM., Young, LC., Ma, Y., Lai, R. (2009). Signal transducer and activator of transcription 3 is a transcriptional factor regulating the gene expression of SALL4. *FASEB J, 23*, 1405-14.

Editions

2010-11-12	Authored, Edited	May, B.
2014-01-23	Reviewed	Wang, J.

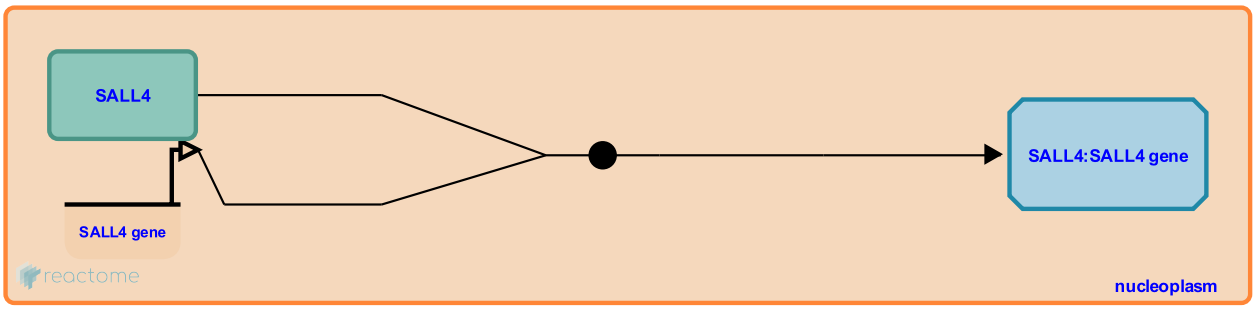
SALL4 binds the SALL4 promoter ↗

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

Yang, J., Gao, C., Chai, L., Ma, Y. (2010). A novel SALL4/OCT4 transcriptional feedback network for pluripotency of embryonic stem cells. *PLoS One, 5*, e10766. ↗

Editions

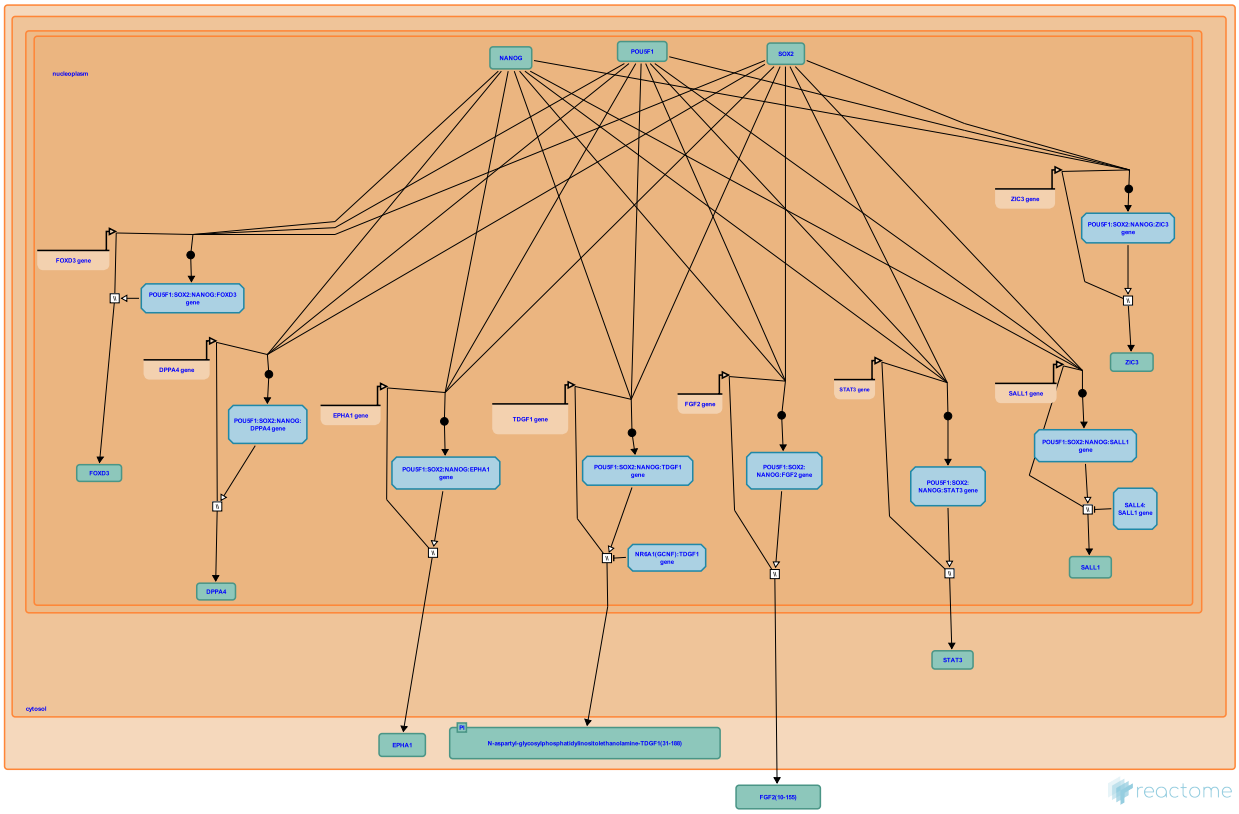
2013-01-03	Authored, Edited	May, B.
2014-01-23	Reviewed	Wang, J.

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).

Literature references

Jung, M., Peterson, H., Chavez, L., Kahlem, P., Lehrach, H., Vilo, J. et al. (2010). A data integration approach to mapping OCT4 gene regulatory networks operative in embryonic stem cells and embryonal carcinoma cells. *PLoS One , 5*, e10709. ↗

Assou, S., Le Carrour, T., Tondeur, S., Ström, S., Gabelle, A., Marty, S. et al. (2007). A meta-analysis of human embryonic stem cells transcriptome integrated into a web-based expression atlas. *Stem Cells, 25*, 961-73. ↗

Babaie, Y., Herwig, R., Greber, B., Brink, TC., Wruck, W., Groth, D. et al. (2007). Analysis of Oct4-dependent transcriptional networks regulating self-renewal and pluripotency in human embryonic stem cells. *Stem Cells, 25*, 500-10. ↗

Player, A., Wang, Y., Bhattacharya, B., Rao, M., Puri, RK., Kawasaki, ES. (2006). Comparisons between transcriptional regulation and RNA expression in human embryonic stem cell lines. *Stem Cells Dev, 15*, 315-23. ↗

Boyer, LA., Lee, TI., Cole, MF., Johnstone, SE., Levine, SS., Zucker, JP. et al. (2005). Core transcriptional regulatory circuitry in human embryonic stem cells. *Cell, 122*, 947-56. ↗

Editions

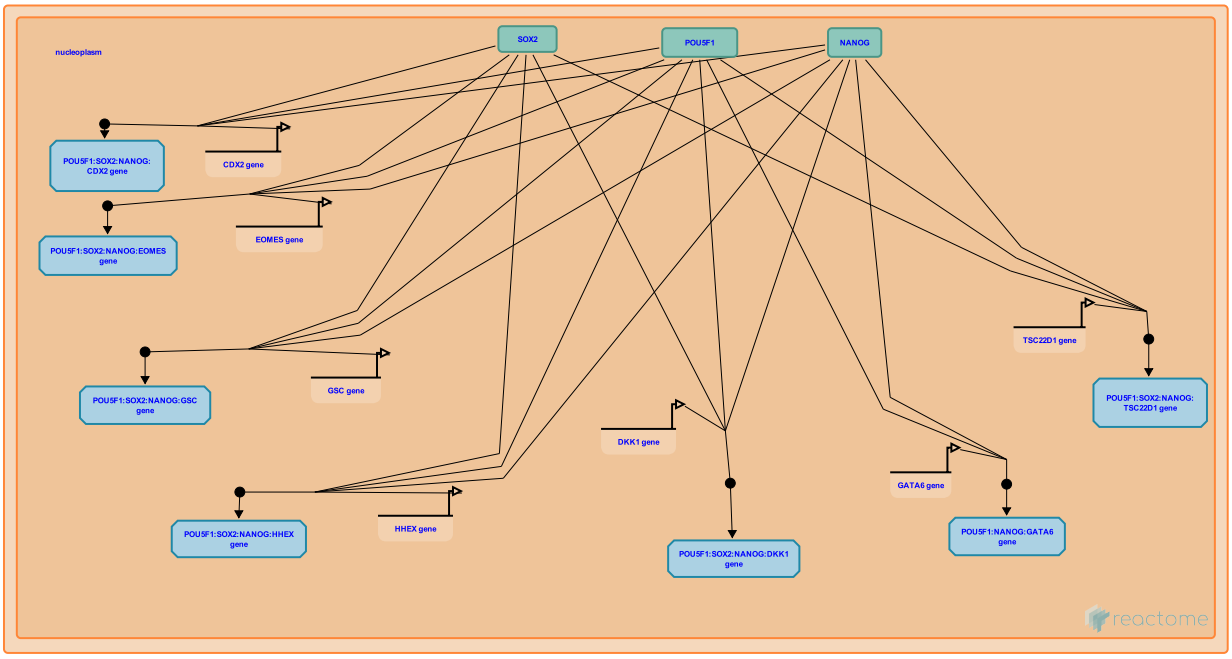
2013-01-01	Authored, Edited	May, B.
2014-01-23	Reviewed	Wang, J.

POU5F1 (OCT4), SOX2, 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).

Literature references

Jung, M., Peterson, H., Chavez, L., Kahlem, P., Lehrach, H., Vilo, J. et al. (2010). A data integration approach to mapping OCT4 gene regulatory networks operative in embryonic stem cells and embryonal carcinoma cells. *PLoS One , 5*, e10709. ↗

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Boyer, LA., Lee, TI., Cole, MF., Johnstone, SE., Levine, SS., Zucker, JP. et al. (2005). Core transcriptional regulatory circuitry in human embryonic stem cells. *Cell, 122*, 947-56. ↗

Editions

2013-01-01	Authored, Edited	May, B.
2014-01-23	Reviewed	Wang, J.

Table of Contents