SIGNALING PATHWAYS REGULATING PLURIPOTENCY OF STEM CELLS

Naive stem cells

Mouse ES cells (mESCs)

Mouse iPS cells (miPSCs)

LIF (mESCs, miPSC) → LIFR → JAK → STAT3 (Jak-STAT signaling pathway) → DNA → Klf4 → DNA → Sox2

LIFR → Grb2 → Mek (MAPK signaling pathway) → Erk1/2 (+p) → c-Myc

LIFR → PI3K → Akt → Tbx3 (DNA) → DNA → Nanog

Activin / Nodal (mESCs) → ACVRII → SMAD2/3 → Proliferation

Erk1/2 → DUSP9

SMAD4 (TGFβ signaling pathway) → SMADs → ID (DNA)

BMP4 (mESCs, miPSC) → BMPRII → SMADs; BMPRII ⊣ Erk1/2, p38

Wnt (mESCs) → Frizzled → Dvl (Wnt signaling pathway) ⊣ GSK-3β (+p) — Axin, APC — β-catenin → TCF1 (DNA) → Wnt target genes

β-catenin → TCF3 ⊣ Esrrb → Pluripotency-associated genes

Core transcriptional network: Sox2, Nanog, Oct4 (DNA) → Self-renewal

	Totipotency	Pluripotency	Multipotency	Unipotency	
(In vitro)		**iPS cells**			
(In vivo)	Zygote → Blastocyst	→ Epiblast	→ Somatic stem cells		→ Functional differentiated cells
(In vitro)		→ **EpiS cells**			→ Differentiated somatic cells
		ES cells →	*In vitro*-derived somatic stem cells		→ Differentiated somatic cells
				Primodal germ cells	→ Sperm and oocytes

Primed stem cells

Human ES cells (hESCs)

Human iPS cells (hiPSCs)

Mouse EpiS cells (mEpiSCs)

BMP4 (hESCs, hiPSC, mEpiSCs) → BMPRII → SMADs (SMAD4) → DNA

Activin / Nodal (hESCs, hiPSC, mEpiSCs) → ACVRII → SMAD2/3 (TGFβ signaling pathway, SMAD4) → DNA

FGF2 (hESCs, hiPSC, mEpiSCs) → FGFR → Ras → Raf (+p) → Mek (+p) → Erk1/2 (MAPK signaling pathway) → DNA

IGF (hESCs) → IGF-IR → PI3K → Akt (PI3K-Akt signaling pathway)

Wnt (hESCs) → Frizzled → Dvl (Wnt signaling pathway) ⊣ GSK-3β (+p) — Axin, APC — β-catenin → DNA; +p → c-Myc

Core transcriptional network: Sox2, Nanog, Oct4 (DNA) → Self-renewal

OCT4, SOX2, and NANOG target genes in human and/or mouse ES cells

Key pluripotency genes: Oct4, Sox2, Nanog

ES cell transcription factors: Stat3, Hesx1, Zic3, Esrrb

ES cell signaling: Tcf3, Fgf2, Lefty2, Skil

Epigenetic regulators: Smarcad1, Myst3, Setdb1, Jarid2

Inhibitor of neurogenesis: Rest

Telomere-associated protein: Rif1

Pluripotency maintenance (DNA) ⊣ PcG

Ectoderm development: Pax6, Meis1, Hoxb1, Lhx5, Otx1, Neurog1

Mesoderm development: Hand1, Dlx5, Myf5, Onecut1

Endoderm development: Isl1, Atbf1

Extra-embryonic development: Esx1l

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