4.Dst

2.3.1.Signalübertragunswege oder die Molekulare Grundlage der Selbsterneuerung von (embryonalen) Stammzellen

2.3.1.1. LIF Signalübertragung

2.3.1.2. Bmp2/4 // Tgf-ß Signalübertragung

2.3.1.3. FGF Signalübertragung

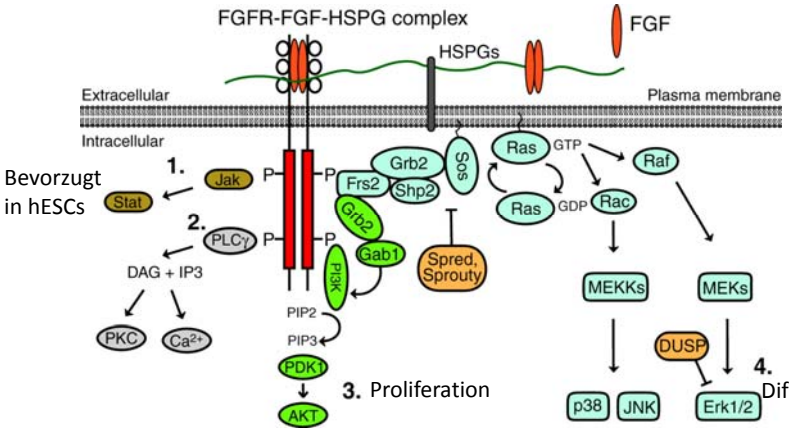
2.3.1.4. Wnt Signalübertragung

2.3.2. Unterschiede zwischen Mensch und Maus

2.3.3. Naive - poised - primed states der ESCs

2.3.1.3. FGF Signalübertragung

FGF signaling in stem cells

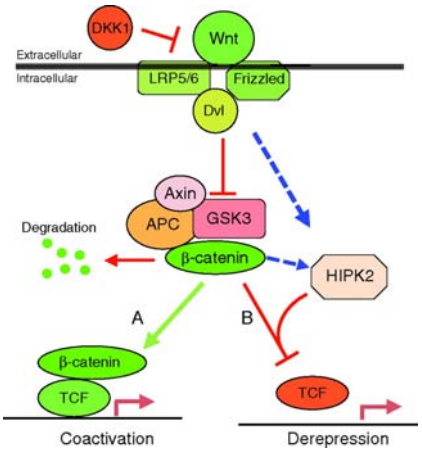


HSPG, Heparan sulphate Proteoglycans
PKC, Protein Kinase C
PI3K, Phosphoinositid-3-Kinasen

http://dev.biologists.org/content/137/20/3351

2.3.1.4. Wnt Signalübertragung

Wnt – ß Catenin – Signaling in ESCs



Siehe auch:
Maintaining embryonic stem cell pluripotency with Wnt signaling by Sergei Y. Sokol
Development 2011 138: 4341-4350;
doi: 10.1242/dev.066209

CR, Corepressor
TCF3, Transcription factor 3, auch T-cell factor 3

2.3.1.4. Wnt Signalübertragung

Wnt – ß Catenin – Signaling in ESCs - einfaches Aktivierungsmodell

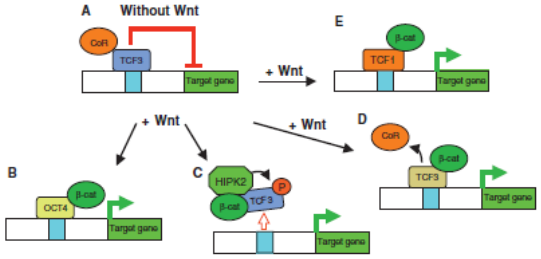


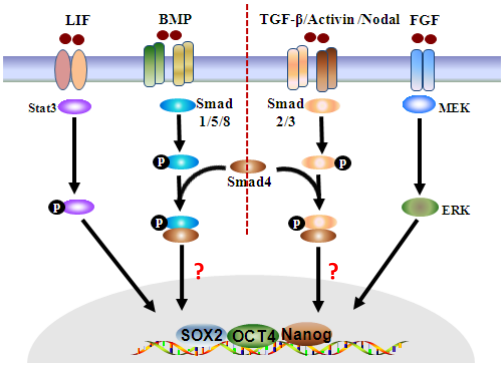
Fig. 4. Models for how Wnt signaling maintains pluripotency in ES cells. (**A**) In the absence of Wnt signaling, β-catenin (βcat) is degraded, and TCF3 in complex with transcriptional co-repressors (CoR) constitutively represses Wnt target genes. (**B-E**) Upon Wnt pathway activation, several alternative models leading to pluripotency are possible: (B) stabilized β-catenin associates with OCT4 to activate OCT4-dependent transcription; (C) HIPK2 is activated by Wnt signaling, associates with β-catenin and phosphorylates TCF3; this phosphorylation results in the removal of TCF3 from target promoters, leading to transcriptional derepression; (D) stabilized β-catenin associates with TCF3, causing the removal of the co-repressors resulting in target derepression (this model predicts that TCF3 is still bound to the promoter but no longer represses its gene targets); and (E) the TCF switch model, in which TCF3 repressor is replaced by TCF1 activator, leading to target activation and pluripotency. OCT4, octamer-binding transcription factor 4.

Siehe auch:
Maintaining embryonic stem cell pluripotency
with Wnt signaling by Sergei Y. Sokol
Development 2011 138: 4341-4350;
doi: 10.1242/dev.066209

Zusammenfassung der Unterschiede zwischen mESCs und hESCs

Maus:
mESCs

+ LIF (~ FGF2)



Mensch:
hESCs

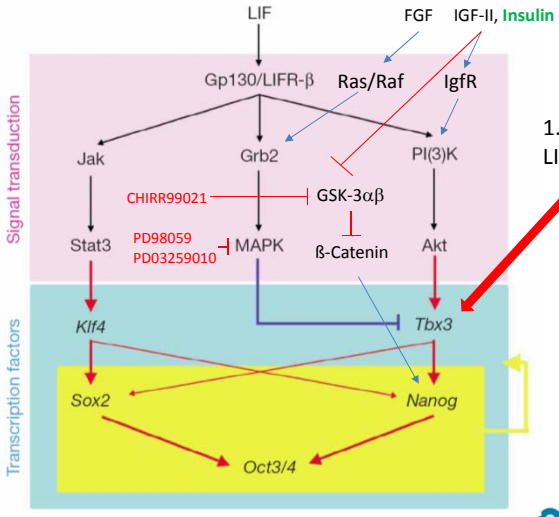
+ FGF2

ICM-like cells primitive Ectoderm-like cells

Ground state (naive state) → poised state → primed state

A parallel circuit of LIF signalling pathways maintains pluripotency of mouse ES cells (and hESCs)

Hitoshi Niwa[1,2,3], Kazuya Ogawa[1], Daisuke Shimosato[1,2] & Kenjiro Adachi[1]
nature Vol 460|2 July 2009|doi:10.1038/nature08113



1. Bindeglied zwischen LIF und Oct4 … aber nur indirekt

2009 publiziert;
erste Hinweise bereits 1981

Grb2 … growth factor receptor binding protein 2
Jak … Janus activated kinase
Stat … Signal transducer and activator of transcription
PI3K … Phosphoinositid-3-Kinasen Phoshpatydyl inositol
Klf4 … Krüppel-like factor 4
Tbx3 … T-box factor 3
Akt … Protein kinase B (PKB)

2i-Inhibitoren

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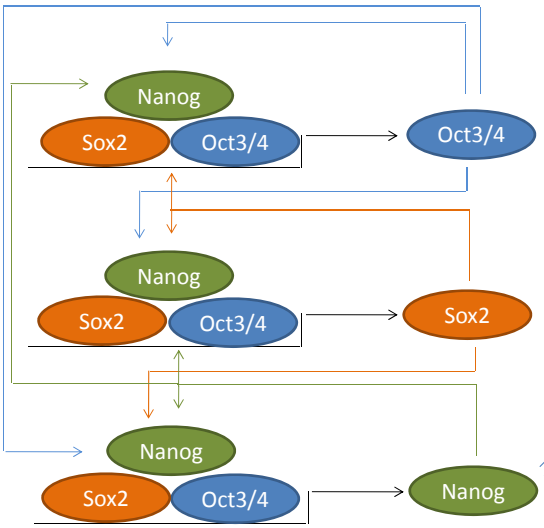
Das Netzwerk der „trinity factors“ zur Erhaltung der Pluripotenz



Netzwerk von Differenzierungs-faktoren z.B.: Brachyury, Tgfß, Bmps, Smads, Wnts, ß-Catenin Tcfs, Lefs

LEF1, Lymphoid Enhancer Binding Factor 1

Oct4	Hans Schöller und Austin Smith 1998 (1991 von Japan. Gruppen entdeckt)
Sox2	Hitoshi Niva und Hans Schöller 2003 (1994 hSox2 und 1999 mSox2)
Nanog	Austin Smith und Hans Schöller 2003

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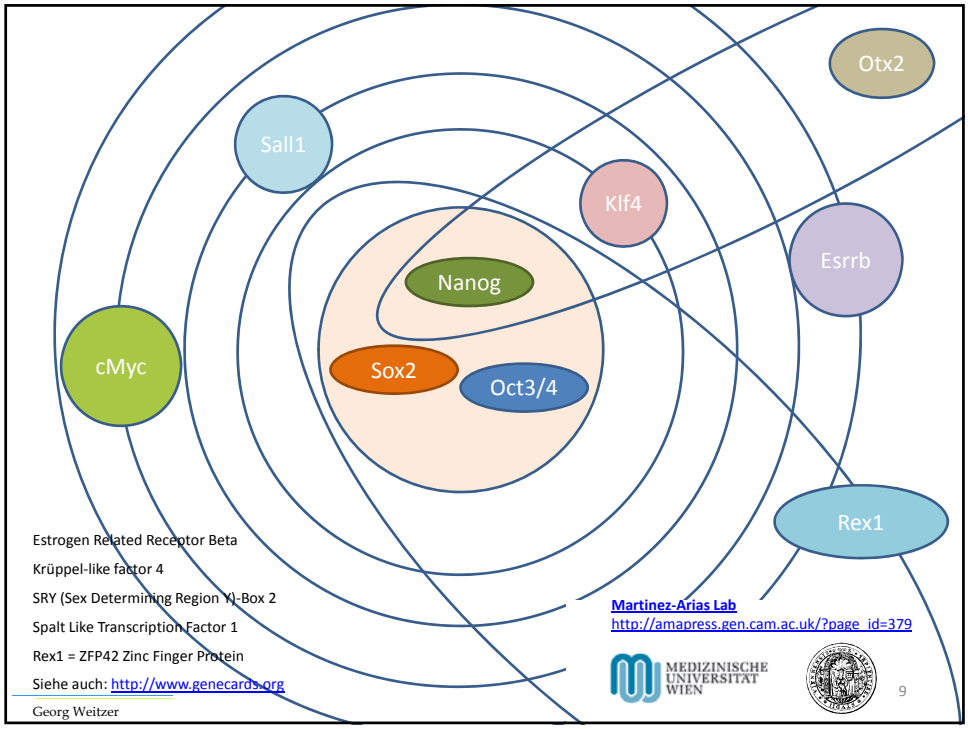


Estrogen Related Receptor Beta
Krüppel-like factor 4
SRY (Sex Determining Region Y)-Box 2
Spalt Like Transcription Factor 1
Rex1 = ZFP42 Zinc Finger Protein
Siehe auch: http://www.genecards.org

Martinez-Arias Lab
http://amapress.gen.cam.ac.uk/?page_id=379

2.3.2. Unterschiede zwischen murinen und humanen embryonalen Stammzellen

mESCs:		hESC:
LIF (STAT3)		FGF2 (MEK) + STAT3
Bmp2/4		TGFß / Activin / Nodal,
		Noggin (a Bmp and TGFß antagonist),
	gemeinsam:	
Wnt (ß-Catenin)		Wnt (ß-Catenin)
Insulin		Insulin

Warum dieser Unterschied?

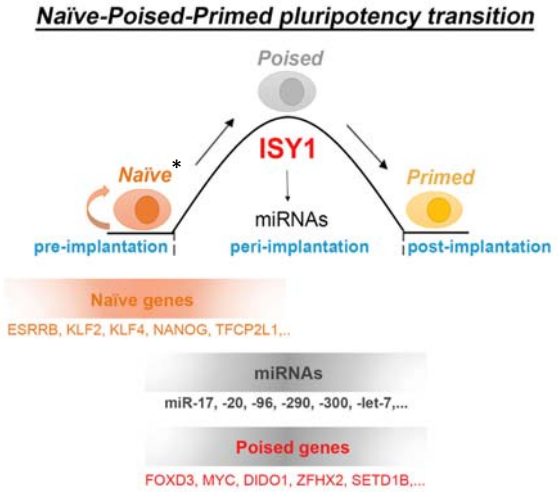
Weil zwei verschiedene Spezies, die entwicklungsgeschichtlich zu weit weg sind?

Sind ESC, durch die Isolierungsmethode bedingte Artefakte?

Es haben doch alle Stammzellen die gleiche „stemness“ oder „ trinity“ Transkriptions-faktoren Gene als Ziel-Gene dieser Signalübertragungswege.

Könnten unterschiedliche Entwicklungsstadien sein.

2.3.3. Naive - poised - primed states der ESCs



*Tabula rasa versus richly set table (abgeschabte Schreibtafel; metaphorisch leergefegter Tisch versus reich gedeckter Tisch)

Pre-mRNA-splicing factor ISY1 homolog

Siehe: Cell Stem Cell. 2018 Jun 1;22(6):851-864.e5. doi: 10.1016/j.stem.2018.04.021. Epub 2018 May 24.

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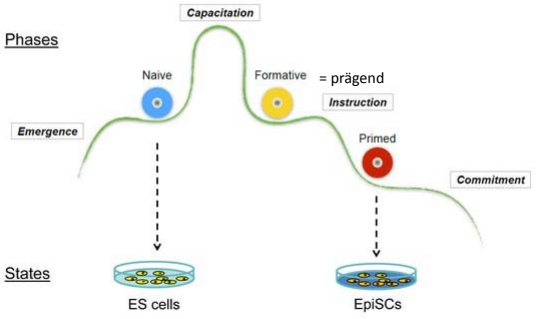
Landscape of Pluripotency

(from Austin Smith 2018)

Poised = schwebend



z.B.: Oct4 Gene has 2 enhanchers, one active in naive mESCs and the other in primed mESCs.
(Choi et al., Stem Cell Report 2016)

Naive Pluripotent Stem Cells Derived Directly from Isolated Cells of the Human Inner Cell Mass (Guo et al., Stem Cell Report 2016)

„Tankyrase = Poly-ADP-ribosyltransferase drives hESCs into the primed state" (siehe http://www.uniprot.org/uniprot/O95271)

Tankyrase inhibition *with XAV939* promotes a stable human naïve pluripotent state with improved functionality (Zimmerlin et al., Development 2016)

→ **3i + LIF für hESC ausreichend**

Was ist eine embryonale Stammzelle?

Der Blickwinkel ist entscheiden:

Siehe Geozentrischens versus Heliozentrisches Weltbild:

See also https://www.youtube.com/watch?v=waexG16WZrE