Nac1 Coordinates a Sub-netowrk of Pluripotency Factors to Regulate Embryonic Stem Cell Differentiation

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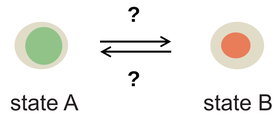
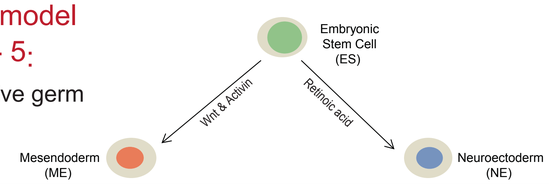
Primary Research Focus:



Discovering the mechanisms which control cell states[1] and their transitions

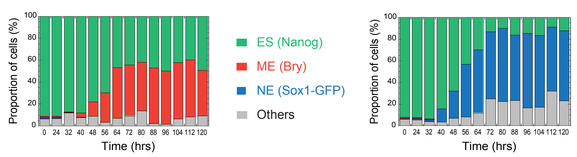
Embryonic stem cells (ESC) model system to study cell states[2 - 5]:

ESC differentiation into the alternative germ layer precursors - Mesendoderm and Neuroectoderm.

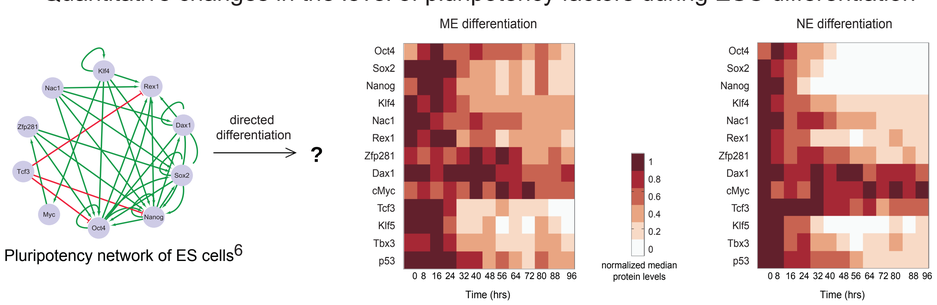


1. Reorganization of ESC TFs network during differentiation:

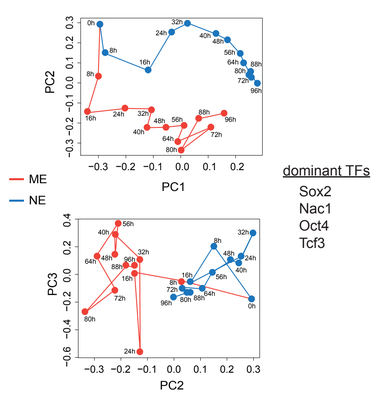
Efficient differentiation of ESCs into ME or NE



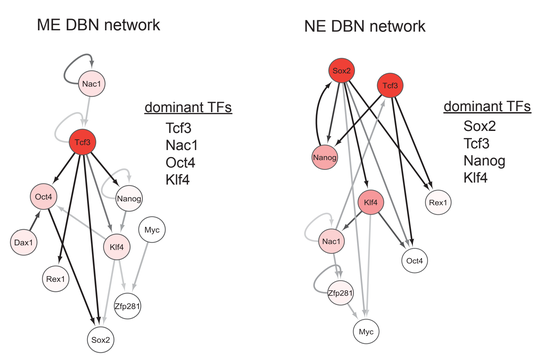
Quantitative changes in the level of pluripotency factors during ESC differentiation



Principal component analysis (PCA)



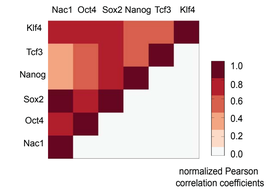
Dynamic Bayesian network (DBN) analysis



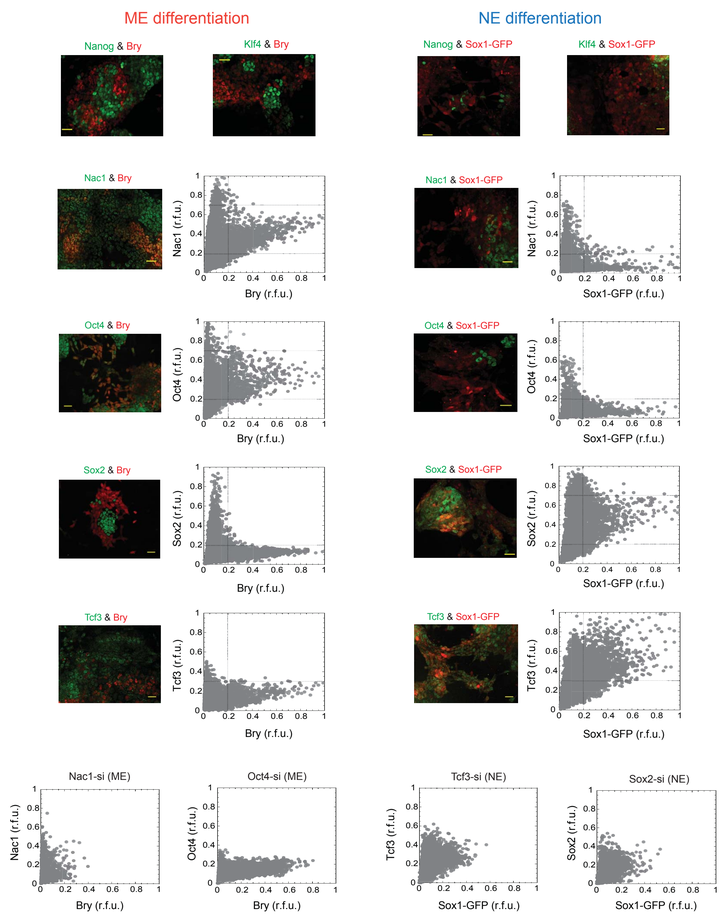
Nodes: white (< = 0.5), red gradient (0.5 - 1) and red (1)
Edges: off-white (0.25), gray scale (0.25 - 0.5) and black (> 0.5)

2. Key pluripotency TFs also regulate ESCs fate choice

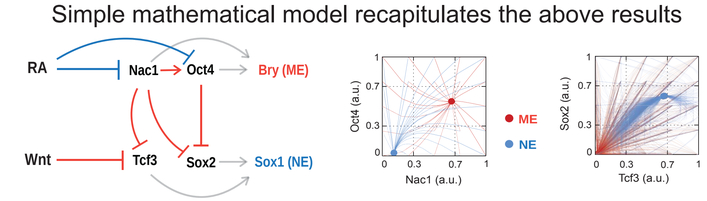
Key TFs, identified by PCA & DBN, protein correlations in ES cells



Distinct requirement of key TFs for the ME or NE choice



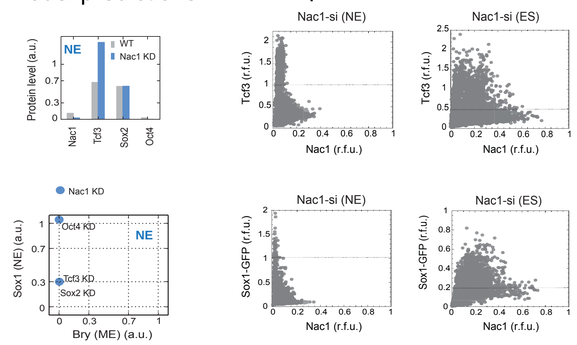
Simple mathematical model recapitulates the above results



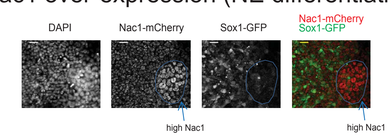
3. Nac1 controls the key TFs sub-network

Model predictions

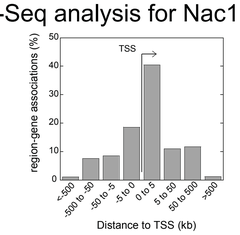
Experimental verification



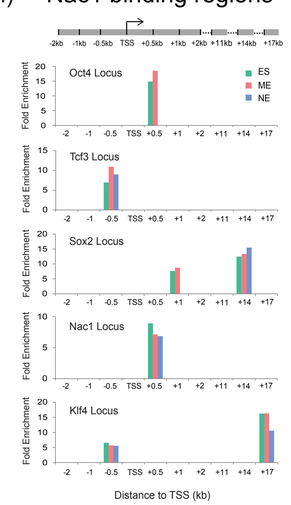
Nac1 over-expression (NE differentiation)



ChIP-Seq analysis for Nac1 binding



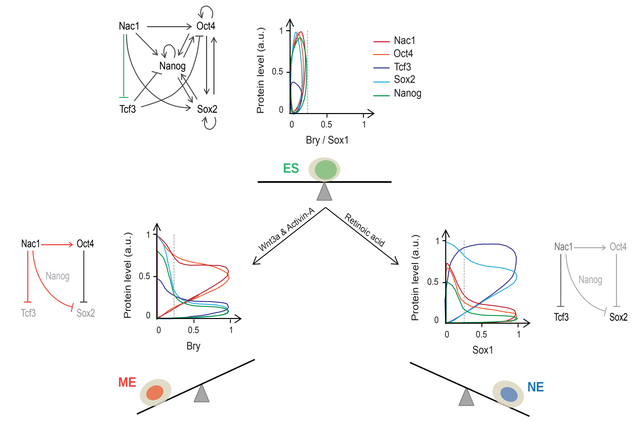
Nac1 binding regions



Nac1 binding motifs

de novo motif	CcGCCcCC	CCCCcCcC	CCcCCCcC
% of targets	79	77	43
p value	$8.3\ e^{-261}$	$4.0\ e^{-240}$	$4.3\ e^{-173}$

Summary of ES, ME and NE cell states regulation by the key TFs



Conclusion and perspectives:

1. A sub-network of pluripotency TFs consisting of Nac1, Oct4, Tcf3, and Sox2 promotes ESC differentiation.
2. Nac1 controls the sub-network to promote ME and repress NE fate selection.
3. Quantitatively constrained Nac1 and Oct4 favor the ME, and Tcf3 and Sox2 favor the NE, fate choice.
4. Similar mechanisms among shared TFs may govern cell-fate decisions during development and in disease states such as cancer.

References:

1. Graf T & Enver T. Nature 462, 587-594 (2009). 2. Young RA. Cell 144, 940-954 (2011). 3. Ying QL. et.al. Nature 453, 519-523 (2008). 4. Silva J & Smith A. Cell 132, 532-536 (2008). 5. Takahashi K & Yamanaka S. Cell 126, 663-676 (2006). 6. Kim J. et.al. Cell 132, 1049-1061 (2008).

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