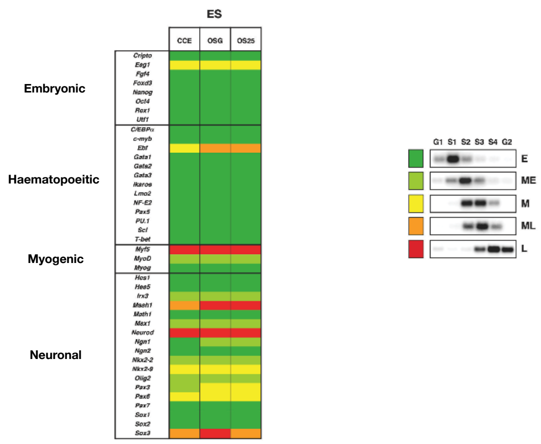
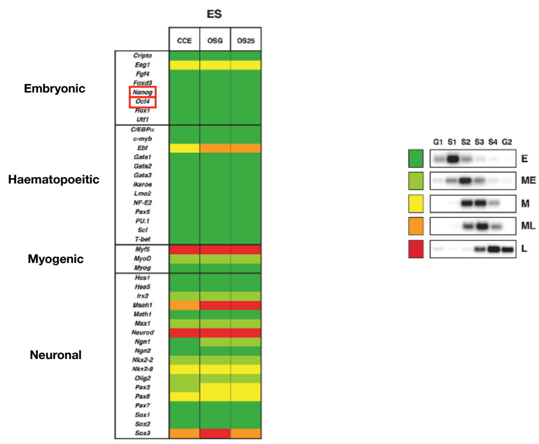
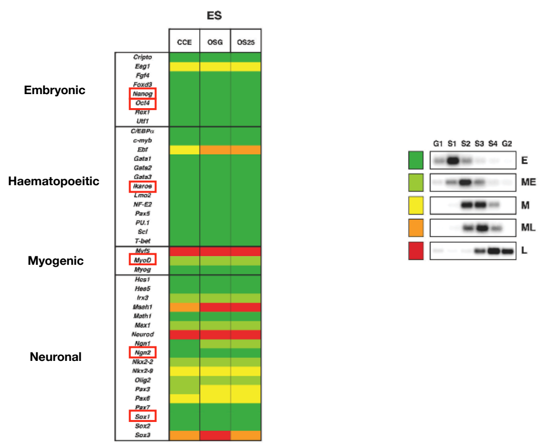
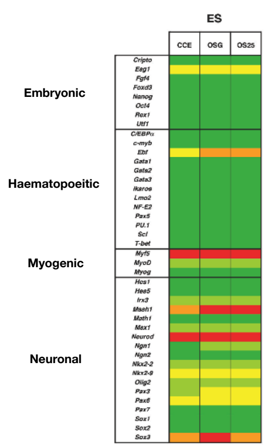


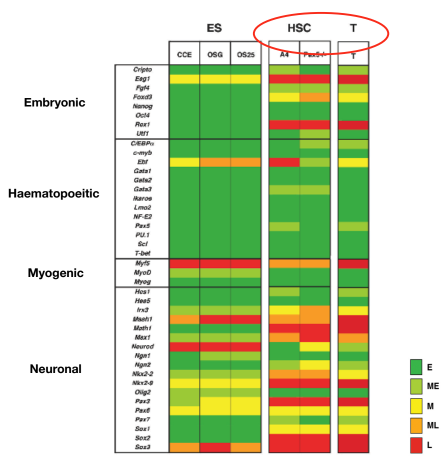




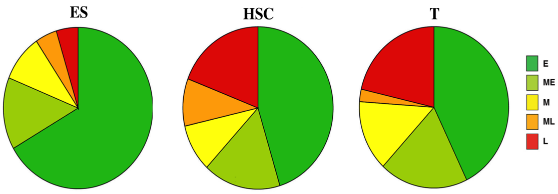
In ES cells

Broadly accessible chromatin Across lineage-specifying genes

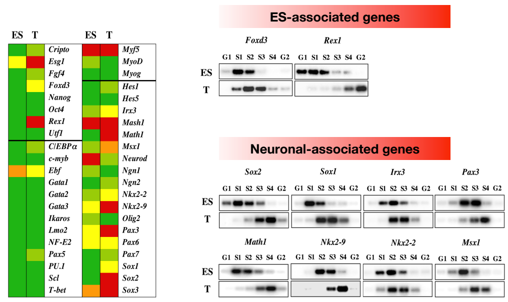




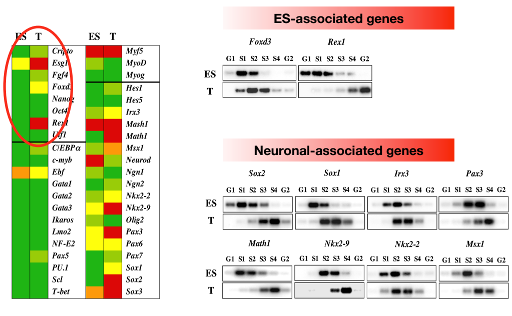
Replication timing can distinguish stem cells from more committed cells



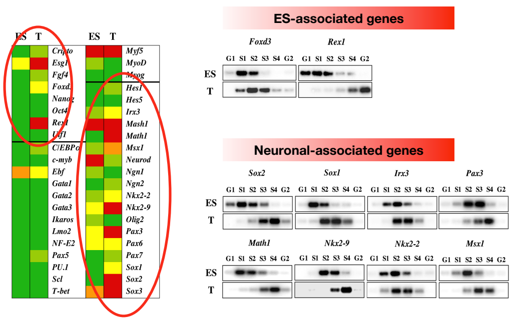
Delayed replication timing at developmental stage and lineage-inappropriate genes



Delayed replication timing at developmental stage and lineage-inappropriate genes



Delayed replication timing at developmental stage and lineage-inappropriate genes



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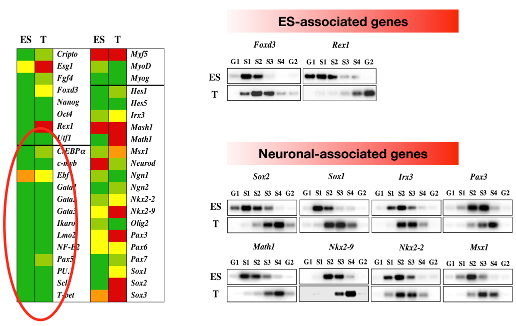
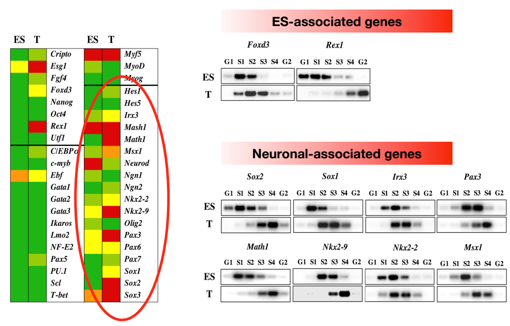
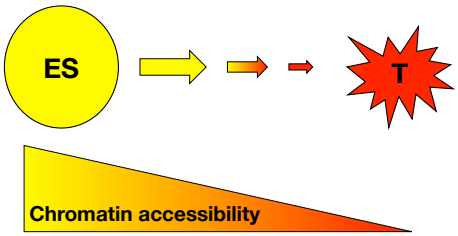


Delayed replication timing at developmental stage and lineage-inappropriate genes

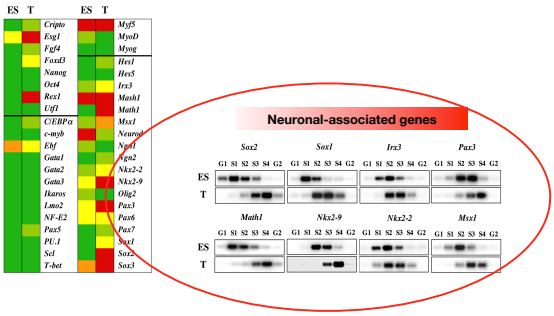


Epigenetic changes reflect differences in transcriptional 'competence' and lineage affiliation

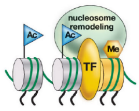
Loss of pluripotency & Chromatin accessibility

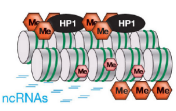


Several inactive neural-specifying genes replicate later in T cells than in ES cells



Chromatin structure & Histone modifications

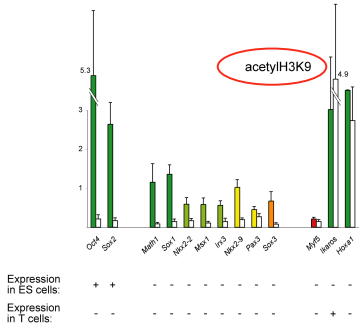




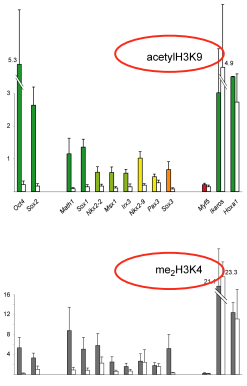
Accessible **Repressed**

acetylH3K9	me$_3$H3K27
me$_2$H3K4	me$_3$H3K9

Analysis of histone modifications characteristic of accessible or repressed chromatin



Inactive neuronal genes in ES cells are substantially enriched for active marks



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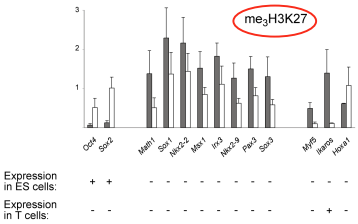
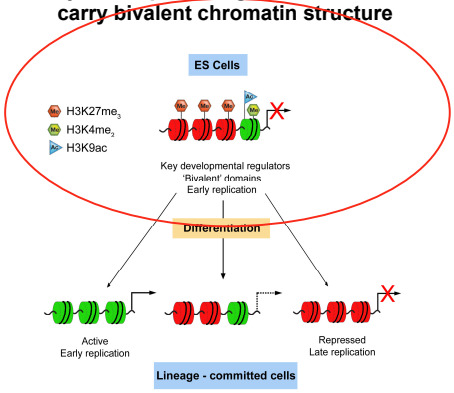


Key developmental genes in ES cells carry bivalent chromatin structure



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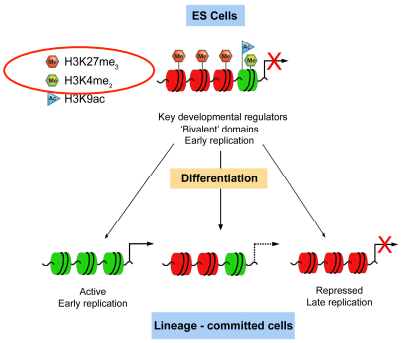

Representative Polycomb Group and Trithorax Group protein complexes in stem cells

*** Polycomb Group (PcG) proteins**

PRC2 complex
Repression of developmental genes in mES cells; together, **Suz12, Eed,** and **Ezh2** catalyze **H3K27 trimethylation**; essential for early embryogenesis and ES cell differentiation.
(Cao and Zhang, 2004; Faust et al., 1998; Pasini et al., 2004 and 2007; O'carroll et al., 2001)

PRC1 complex
Catalyzes **mono-ubiquitinylation of histone H2A** implicated in Pol II pausing in mES cells; **Ring1b** is essential for early embryogenesis and for proper maintenance of ES cells.
(de Napoles et al., 2004; Stock et al., 2007; van der Stoop et al., 2008; Voncken et al., 2003)

*** Trithorax Group (Trx) proteins**

MLL
MLL complex is a **H3K4 methyltransferase** whose activity counteracts the repressive effect of PcG proteins; essential for cell fate transitions in neuronal (Mll1) and hematopoietic (Mll5) lineages. *(Ayton et al., 2001; Lim et al., 2009; Madan et al., 2009)*

PRC2 and its core components

Early Ectoderm Development
Affects Ezh2 substrate specificity
Required for methylation

Enhancer of Zeste Homolog 2
Histone H3K27 methyltransferase

Suppressor of Zeste 12 protein homolog
Required for methylation

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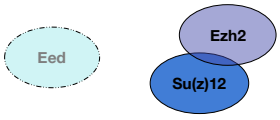
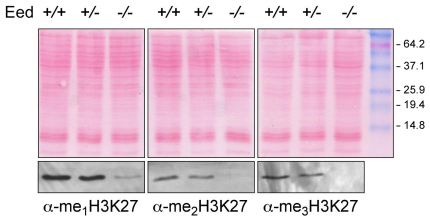


Suppressor of Zeste 12 protein homolog
Required for methylation

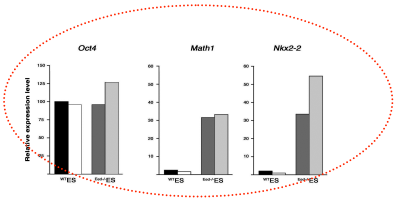
Global reduction of H3K27 methylation levels in Eed-deficient ES cells



PRC2-mediated repression of neuronal-associated genes in undifferentiated ES cells

	WT ES cells		Eed-/- ES cells	
	OS25	OSG	G8.1	B1.3
Oct4	100	96	96	127
Rex1	100	152	86	120
Sox2	100	115	46	66

	Embryo Head (E15)	WT ES cells		Eed-/- ES cells	
		OS25	OSG	G8.1	B1.3
Msx1	100	<1	<1	7	3
Pax3	100	<1	<1	10	3
Sox1	100	7	5	7	5
Sox3	100	13	3	9	7
Math1	100	2	2	32	33
Nkx2-2	100	2	1	33	55



In ES cells

key developmental genes are primed for activation yet held in check by PRC2-mediated repression

LETTERS

nature cell biology

Chromatin signatures of pluripotent cell lines

Véronique Azuara[1,2], Pascale Perry[1], Stephan Sauer[1], Mikhail Spivakov[1], Helle F. Jørgensen[1], Rosalind M. John[1,2], Mina Gouti[3,4], Miguel Casanova[1], Gary Warnes[5], Matthias Merkenschlager[1] and Amanda G. Fisher[1,2]

Cell

A Bivalent Chromatin Structure Marks Key Developmental Genes in Embryonic Stem Cells

Bradley E. Bernstein,[1,2,3,4,7] Tarjei S. Mikkelsen,[3,4] Xiaohui Xie,[5] Michael Kamal,[3] Dana J. Huebert,[1] James Cuff,[3] Ben Fry,[5] Alex Meissner,[3] Marius Wernig,[3] Kathrin Plath,[3] Rudolf Jaenisch,[3] Alexandre Wagschal,[6] Robert Feil,[6] Stuart L. Schreiber,[1,2] and Eric S. Lander[3,4]

Vol 441|18 May 2006|doi:10.1038/nature04733

nature

LETTERS

Polycomb complexes repress developmental regulators in murine embryonic stem cells

Laurie A. Boyer[1,*], Kathrin Plath[1,*], Julia Zeitlinger[1], Tobias Brambrink[1], Lea A. Medeiros[1,2], Tong Ihn Lee[1], Stuart S. Levine[1], Markus Wernig[1], Adriana Tajonar[1], Mridula K. Ray[1], George W. Bell[1], Arie P. Otte[3], Miguel Vidal[3], David K. Gifford[2], Richard A. Young[1,*] & Rudolf Jaenisch[1,2]

Cell

Control of Developmental Regulators by Polycomb in Human Embryonic Stem Cells

Tong Ihn Lee,[1,6] Richard G. Jenner,[1,6] Laurie A. Boyer,[1,6] Matthew G. Guenther,[1,6] Stuart S. Levine,[1,6] Rozita M. Kumar,[1] Brett Chevalier,[1] Sarah E. Johnstone,[1,4] Megan F. Cole,[1,4] Kyo-ichi Isono,[2] Haruhiko Koseki,[2] Takuya Fuchikami,[3] Kuniya Abe,[3] Heather L. Murray,[1] Jacob P. Zucker,[1] Bingbing Yuan,[1] George W. Bell,[1] Elizabeth Herbolsheimer,[1] Nancy M. Hannett,[1] Kaiming Sun,[1] Duncan T. Odom,[1] Anne P. Otte,[4] Thomas L. Volkert,[1] David P. Bartel,[1,5] Douglas A. Melton,[1] David K. Gifford,[1,*] Rudolf Jaenisch,[1,*] and Richard A. Young[1,6,*]

ES cells are ‘primed’ for future activation

LETTERS

nature cell biology

Ring1-mediated ubiquitination of H2A restrains poised RNA polymerase II at bivalent genes in mouse ES cells

Julie K. Stock[1,*], Sara Giadrossi[1,*], Miguel Casanova[1], Emily Brookes[1], Miguel Vidal[1], Haruhiko Koseki[2], Neil Brockdorff[3], Amanda G. Fisher[1,4] and Ana Pombo[1,4]

PRC1 and RNAP are functionally linked in ES cells to prime genes for future activation

LETTERS

nature cell biology

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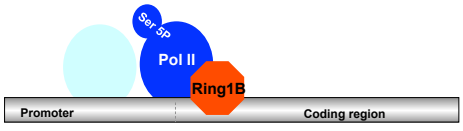

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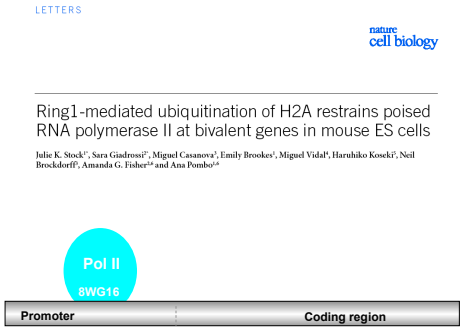

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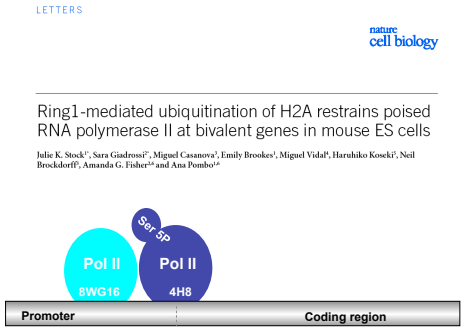

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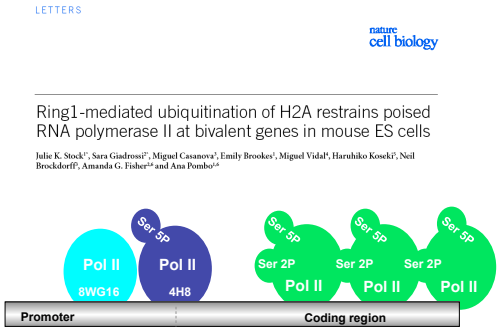
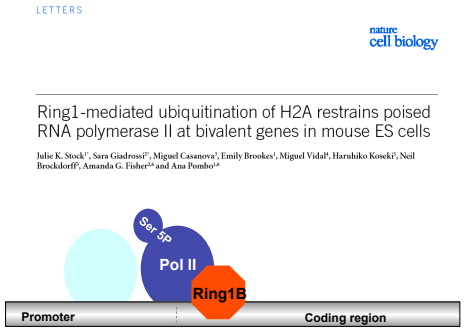


PRC1 (Ring1B) and RNAP are functionally linked in ES cells to prime genes for future activation



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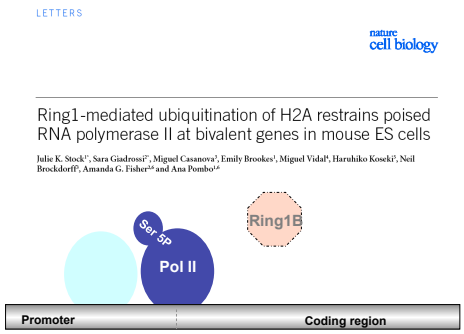

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LETTERS

nature cell biology

Ring1-mediated ubiquitination of H2A restrains poised RNA polymerase II at bivalent genes in mouse ES cells

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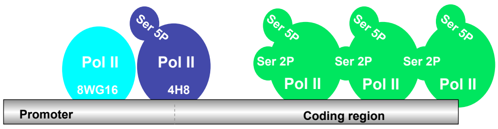
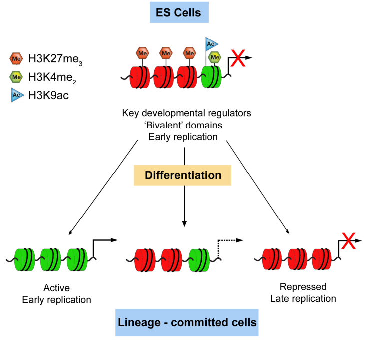


Key developmental genes in ES cells carry bivalent chromatin structure



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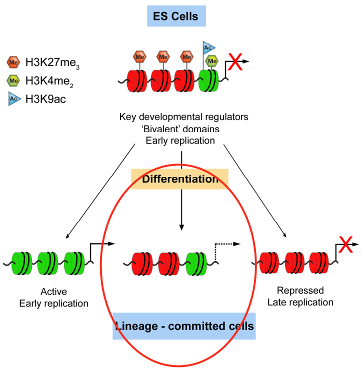

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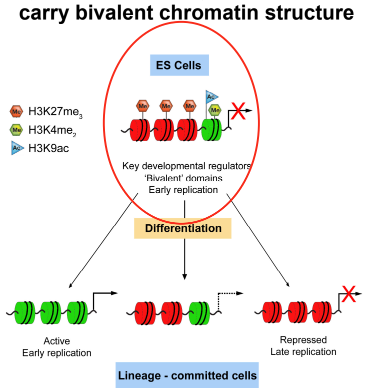
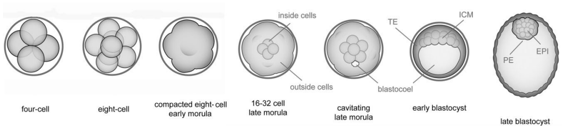
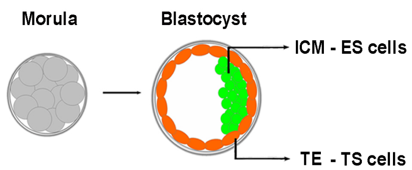


Balancing cell potency and specification in stem cells and in the early embryo

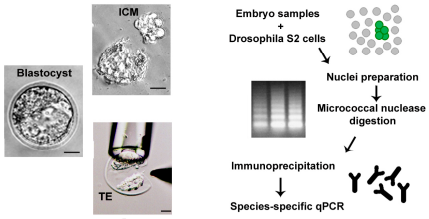


Analysis of bivalent chromatin signatures upon blastocyst formation

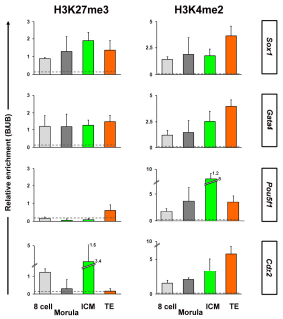


Alder O. *et al.*
Development (2010)

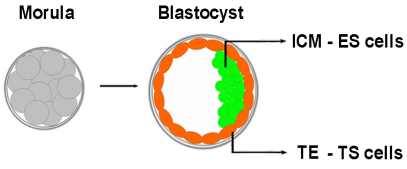
Analysis of bivalent chromatin signatures in ICM and TE cells *in vivo*



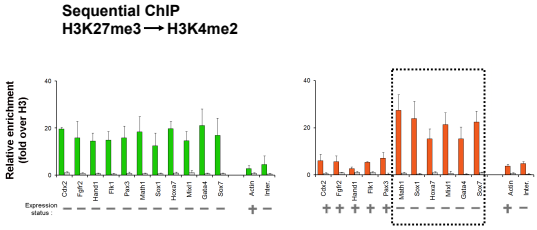
Bivalent histone marking operates *in vivo* at silent genes in ICM and TE cells



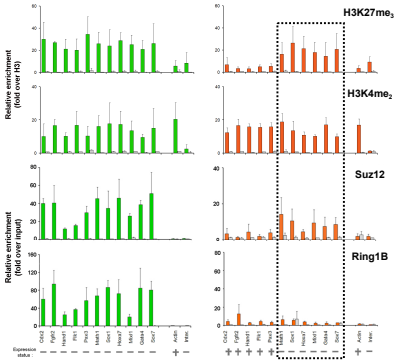
Analysis of bivalent chromatin signatures in ES and TS cells



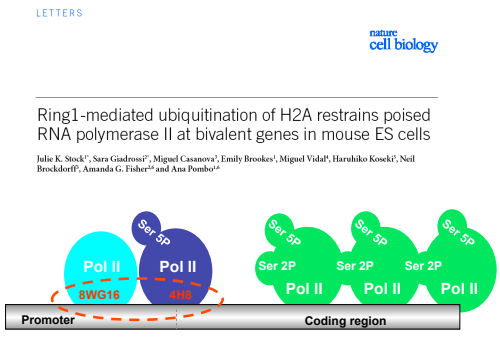
Analysis of bivalent chromatin signatures in ES and TS cells



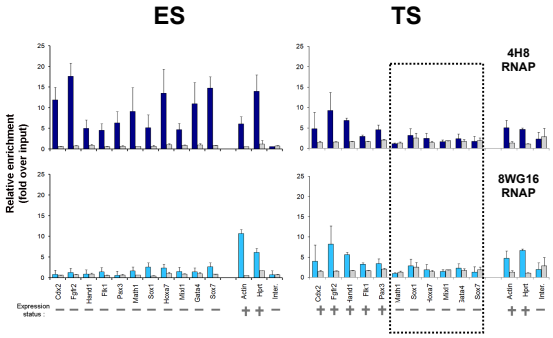
Differential recruitment of Ring1B at bivalent genes in ES and TS cells



Ring1B and RNAP are functionally linked in ES cells to prime genes for future activation

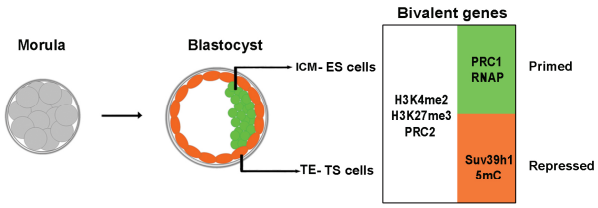


Loss of gene priming for transcription at bivalent genes in TS cells



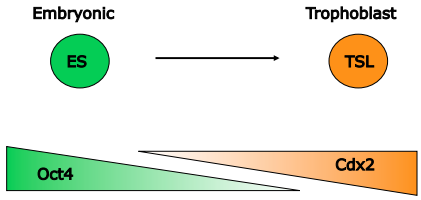
PRC1 and poised RNAP are not recruited to genes that retain bivalent signatures in TE-derived stem cells

PRC1 and Suv39h are differentially recruited at bivalent genes upon blastocyst formation

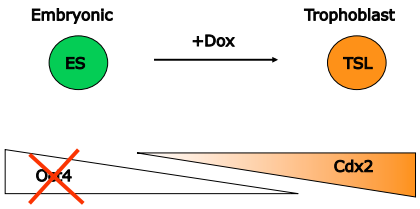


Alder O. *et al.*
Development (2010)

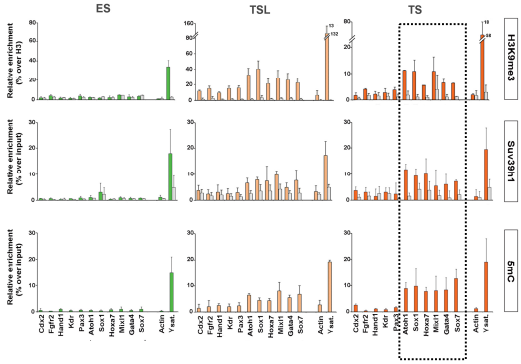
De-differentiation of ES cells into TS-like (TSL) cells



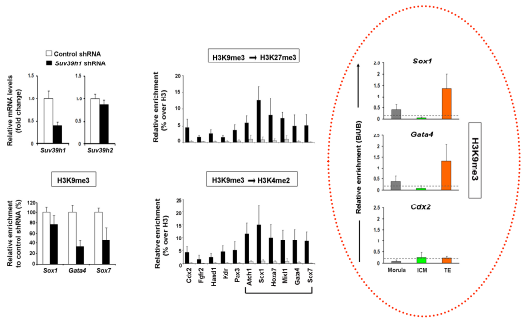
De-differentiation of ES cells into TS-like (TSL) cells



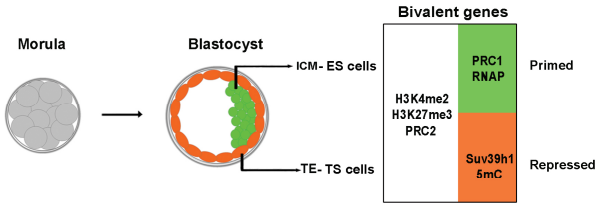
Bivalent genes are targeted by Suv39h1-mediated H3K9me3 upon trophoblast lineage commitment



Bivalent genes are targeted by Suv39h1-mediated H3K9me3 upon trophoblast lineage commitment



PRC1 and Suv39h are differentially recruited at bivalent genes upon blastocyst formation



Alder O. *et al.*
Development (2010)

Chromatin in ES cells differs from that in lineage-restricted cells

Chromatin modifying factors with known roles in stem cells and during mammalian development

*** Histone lysine methylation and demethylation**

G9a (H3K9 methyltransferase)
Heterochromatin formation; required for repression of key pluripotency genes during ES cell differentiation; null mice are embryonic letha.
(Epsztejn-Litman et al., 2008; Feldman et al., 2006; Tachibana et al., 2002).

Jmjd1a/Jmjd2c (H3K9 demethylases)
Maintenance of pluripotency; loss of function leads to inappropriate differentiation.
(Loh et al., 2007).

Rbp2 (H3K4me3 demethylase)
Repression of developmental regulators in ES cells; cell fate transitions.
(Lopez-Bigas et al., 2008; Pasini et al., 2008).

Jmjd3, Utx (H3K27me3 demethylases)
Resolution of bivalent domains in neuronal lineage; necessary for cellular differentiation and body axis patterning; cell fate transitions.
(Agger et al., 2007; Burgold et al., 2008; Hong et al., 2007; Lan et al., 2007; Lee et al., 2007; Sen et al., 2008; Xiang et al., 2007).

Chromatin modifying factors with known roles in stem cells and during mammalian development

*** Histone acetylation and deacetylation**

Tip60/p400 complex
Transcriptional activity; maintenance of ES cell identity
(Fazzio et al., 2008).

HDAC1 (histone deacetylase)
Transcriptional repression; developmental roles in early embryogenesis; deficiency leads to defects in organogenesis while gain of function confers a cancerous state.
(Ma and Schultz, 2008; Weichert et al., 2008).

*** ATP-dependent chromatin remodeling**

BAF250A BAF250B
Stem cell self-renewal and pluripotency; roles in early embryogenesis.
(Gao et al., 2008; Yan et al., 2008).

BRG1
catalytic subunit of mammalian SWI/SNF complex; depletion promotes loss of self-renewal and pluripotency in ES cells and induce differentiation; essential for proper development; implicated in tumorigenesis.
(Ho et al., 2009a; Ho et al., 2009b; Kidder et al., 2008; Roberts and Orkin, 2004).

Developmental Cell *10*, 105–116, January, 2006 ©2006 Elsevier Inc. DOI 10.1016/j.devcel.2005.10.017

Hyperdynamic Plasticity of Chromatin Proteins in Pluripotent Embryonic Stem Cells

Eran Meshorer,[1] Dhananjay Yellajoshula,[2] Eric George,[2] Peter J. Scambler,[3] David T. Brown,[2] and Tom Misteli[1,*]

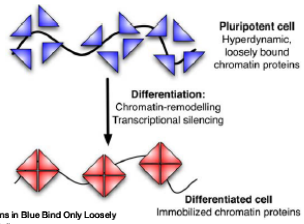


Figure 1. Chromatin-Associated Proteins in Blue Bind Only Loosely and Are Hyperdynamic in Pluripotent Cells
This loosely bound fraction of chromatin proteins plays a key role in the remodeling process during differentiation of pluripotent cells. Immobilization of these dynamic chromatin-associated proteins (red) could lead to higher-order silencing of portions of the genome during differentiation of pluripotent cells.

nature genetics

Large histone H3 lysine 9 dimethylated chromatin blocks distinguish differentiated from embryonic stem cells

Bo Wen[1,2], Hao Wu[1,3], Yoichi Shinkai[4], Rafael A Irizarry[1,3] & Andrew P Feinberg[1,2]

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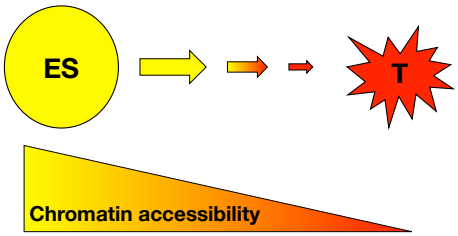
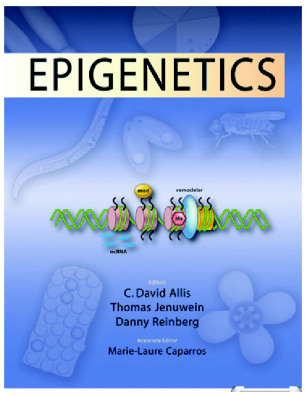
LETTERS

Genome-scale DNA methylation maps of pluripotent and differentiated cells

Alexander Meissner[1,2,3]*, Tarjei S. Mikkelsen[2,4]*, Hongcang Gu[2], Marius Wernig[1], Jacob Hanna[1], Andrey Sivachenko[2], Xiaolan Zhang[2], Bradley E. Bernstein[2,5,6], Chad Nusbaum[2], David B. Jaffe[2], Andreas Gnirke[2], Rudolf Jaenisch[1,7] & Eric S. Lander[1,2,7,8]

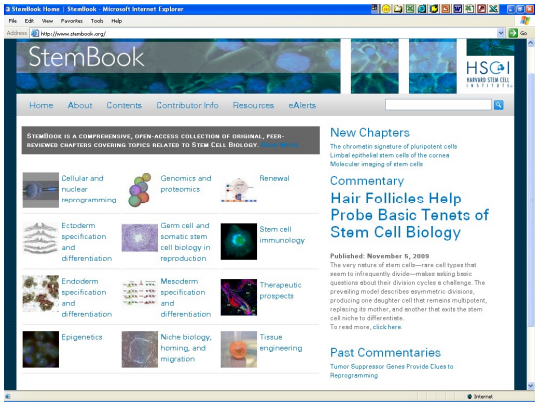
Loss of pluripotency & Chromatin accessibility





Cold Spring Harbor Laboratory Press

www.stembook.org



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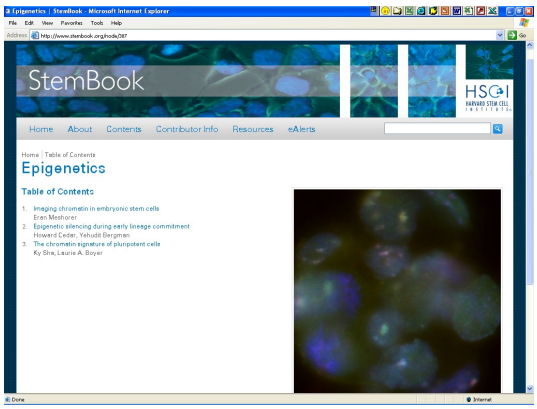

Margot, March 2011