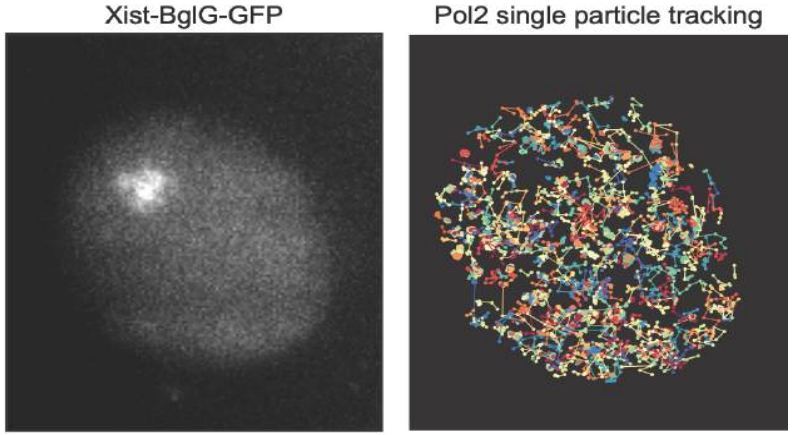
CHAIRE ÉPIGÉNÉTIQUE ET MÉMOIRE CELLULAIRE

Année 2024-2025 :

Nouvelles conaissances sur les mécanismes épigénétiques :
l'inactivation du chromosome X et d'autres exemples d'expression monoallélique



Cours III, 26 mai 2025

Évolution de l'inactivation du chromosome X et dynamique développementale

Steve Quake: 2nd Lecture
"Understanding the Mysteris of the Cell: How do Mutations arise in our Bodies?
Lundi 26 mai, 17.00-18.00

COURS 2025

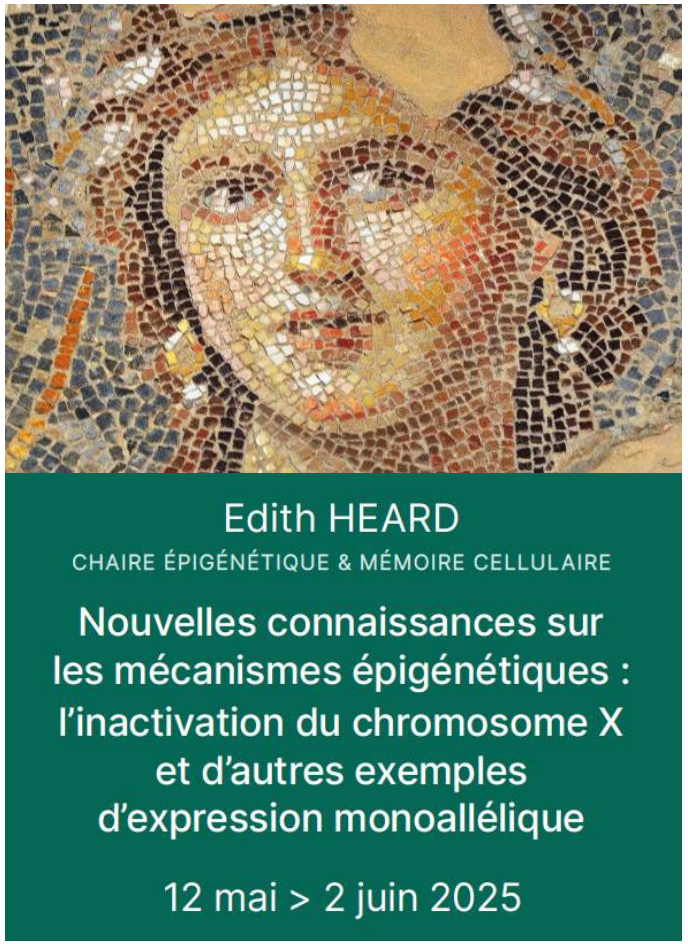
12 mai 2025
Découverte de l’inactivation du chromosome X (lyonisation)

19 mai 2025
La génétique et l’épigénétique de l’inactivation du chromosome X et d’autres exemples d’expression monoallélique

26 mai 2025
Évolution de l’inactivation du chromosome X et dynamique développementale

2 juin 2025
Implications de l’inactivation du chromosome X pour la biologie féminine

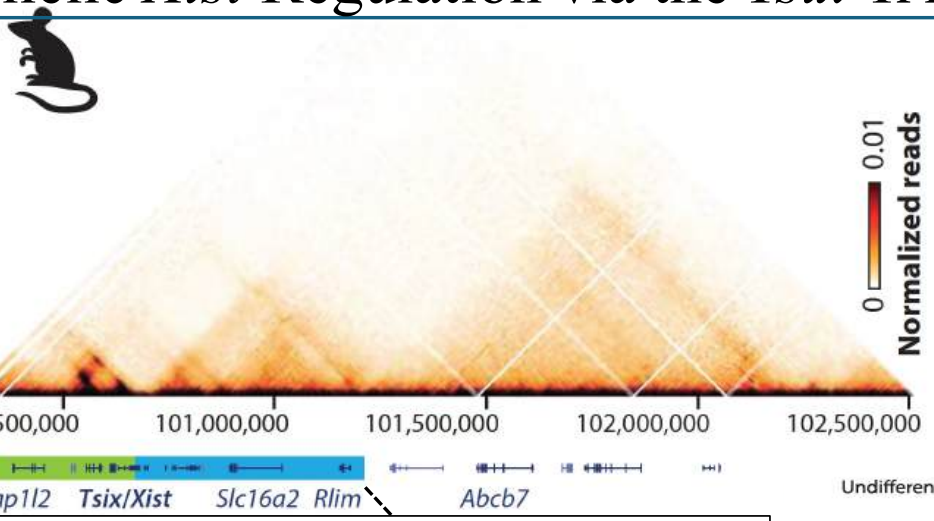
10-11 juin 2025 Colloque



SUMMARY of COURS 2

- Notion that the Xic not only has to trigger XCI in *cis*, but also enable XX cells to:
  Sense their X-chromosome number and trigger XCI if there is >1 X
  Count the number of X's relative to autosomes to ensure one X stays active per diploid autosome set
  Choose which X wil stay active (and/or which X will be silenced)
- Quest for the the X-inactivation centre (Xic): the region on the X that is both *necessary* and *sufficient* for initiation of X inactivation.
- Serendipitous discovery of *Xist* non-coding RNA within candidate XIC region in humans and mice (and other eutherians) and demonstration that its deletion prevents XCI *in cis* in mice.
- Discovery that multicopy *Xist* transgenes can trigger XCI in *cis* in mice and ESCs. However single copy Transgenes even up to 460kb in length cannot recapitulate full Xic function during random XCI in ESCs or in mice **=> search for missing sequences**
- Discovery of Topologically Associating Domains (TADs) and implications for *Xist's* developmental and monoallelic regulation, as well as for gene regulation in general.
- Demonstration that Xist RNA can induce gene silencing during defined differentiation time windows and definition of the essential regions for its different functions (cis-silencing, chromosome coating, recruitment of chromatin factors etc). *More next week*
- Current understanding of the Xic and *Xist* regulation.

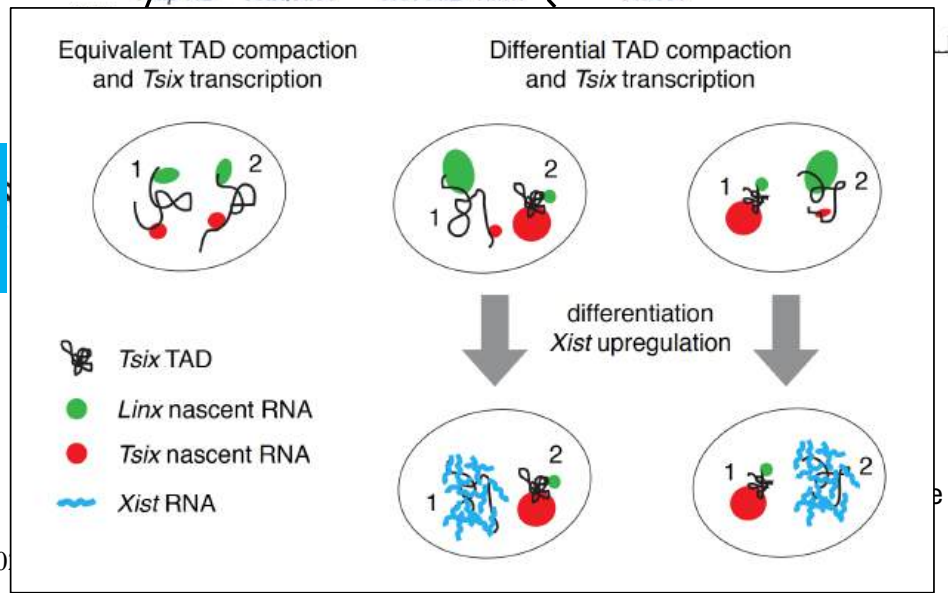
The Organisation of the X-inactivation Centre into TADs may help to ensure accurate monoallelic *Xist* Regulation via the *Tsix* TAD in the mouse?

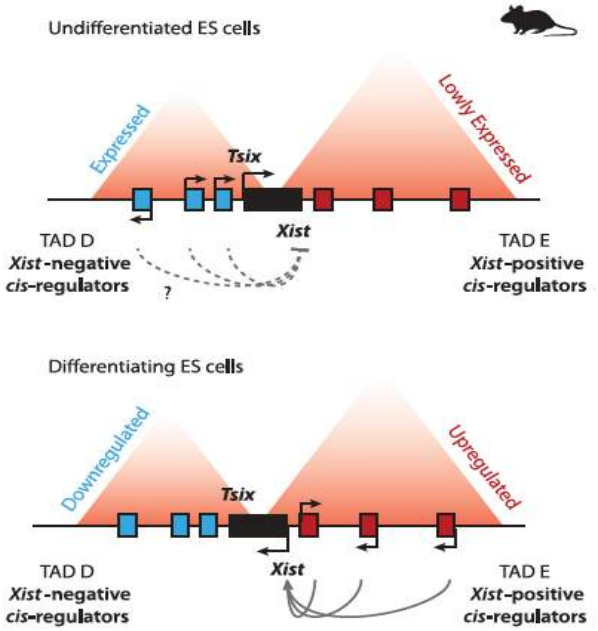


Adapted from Galupa and Heard, Annu. Rev. Genet. 2018. 52:535–66

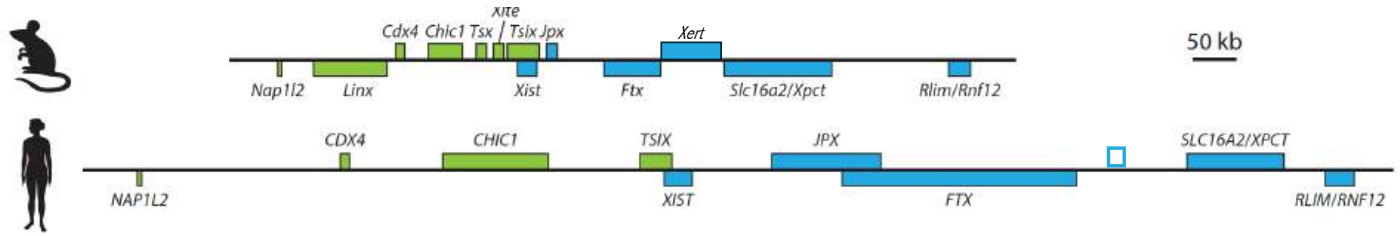
Predictive Polymer Modelling Reveals Coupled Fluctuations in Chromosome Conformation and Transcription.
Giorgetti et al, Cell 2014

Luca Giorgetti



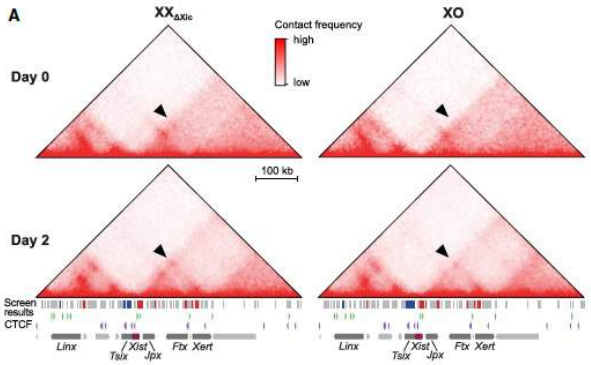


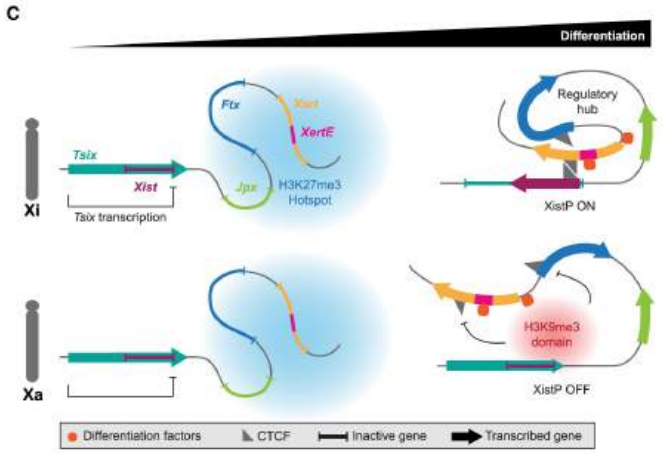
Further definition of specific *cis* and *trans* regulators: the 5*'Xist* TAD



Edda Schulz
MPI for Molecular Genetics, Berlin

- In the mouse Xic, promoter-proximal elements control female-specific *Xist* expression in a binary fashion
- Some long-range repressors control *Xist* even across the TAD boundary eg *Linx* promoter(Galupa et al, 2020)
- Long-range enhancer elements regulate developmental timing of *Xist* upregulation
- Several distal enhancers are associated with a previously unannotated lncRNA, Xert
- *Xert* is upregulated concomitantly with Xist and activates Xist in *cis*
- *Xert* lncRNA does not seem to be conserved in humans but an enhancer similarly bound by SMAD2/3 may be present





Article

Distal and proximal *cis*-regulatory elements sense X chromosome dosage and developmental state at the *Xist* locus

Rutger A.F. Gjaltema,[1,7] Till Schwämmle,[1,7] Pauline Kautz,[1] Michael Robson,[2,3] Robert Schöpflin,[2,4,5] Liat Ravid Lustig,[1] Lennart Brandenburg,[1] Ilona Dunkel,[2] Carolina Vechiatto,[1] Evgenia Ntini,[2] Verena Mutzel,[1] Vera Schmiedel,[1] Annalisa Marsico,[6] Stefan Mundlos,[2,4] and Edda G. Schulz[1,8,*]

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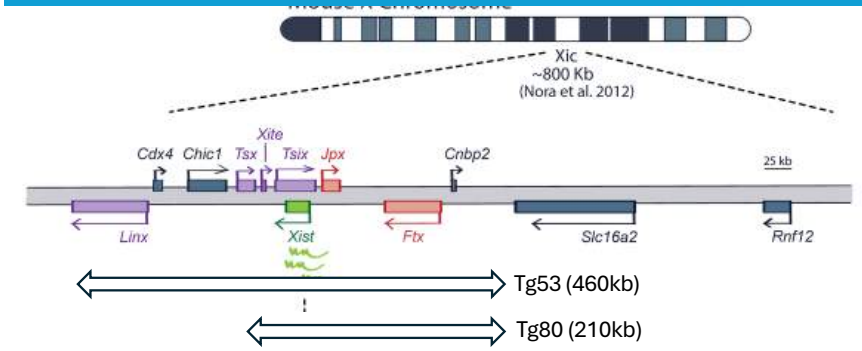
Chromatin Folding into TADs Partitions the Xic and *Xist's* regulatory landscape

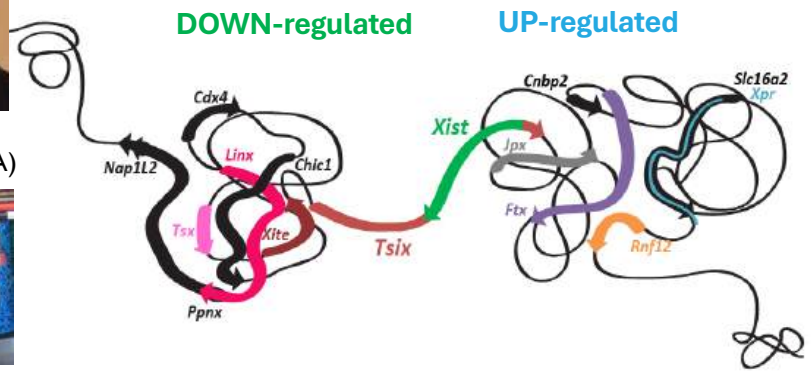
The Xic is partitioned into 2 TADs spanning ~800kb Containing *Xist's* complex regulatory landscape

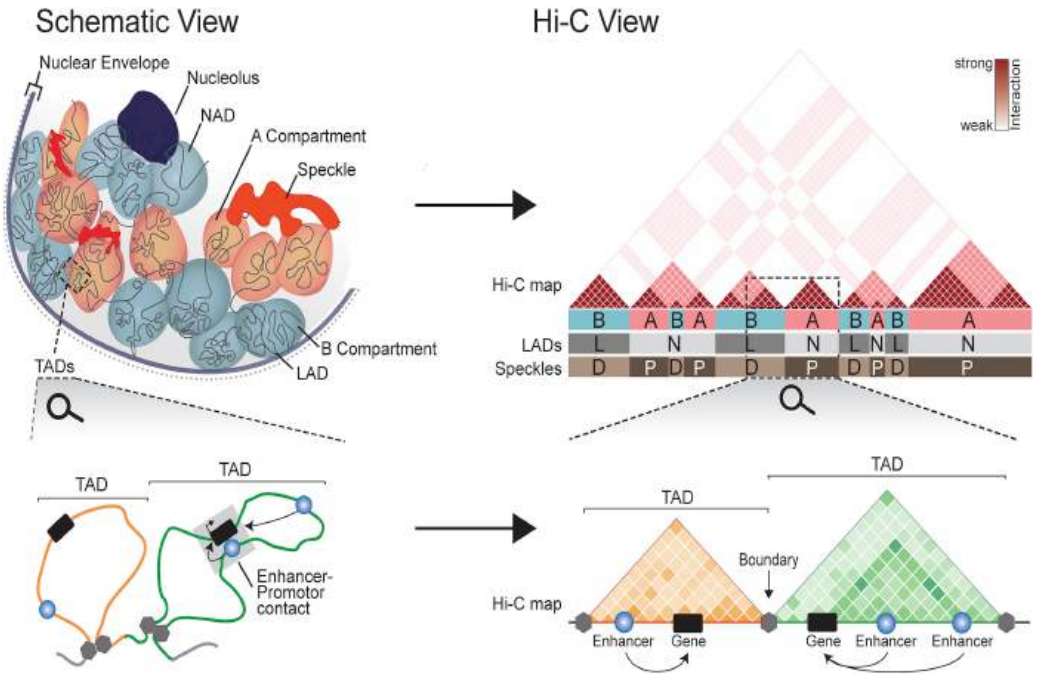
In general, TADs may help Define the Operational Limits of Regulatory Landscapes



Job Dekker
(UMass, USA)

Elphege Nora





Molecular Cell 2019 741110-1122DOI: (10.1016/j.molcel.2019.05.032)

Nora et al "Spatial partitioning of the regulatory landscape of the X-inactivation centre". Nature, 2012

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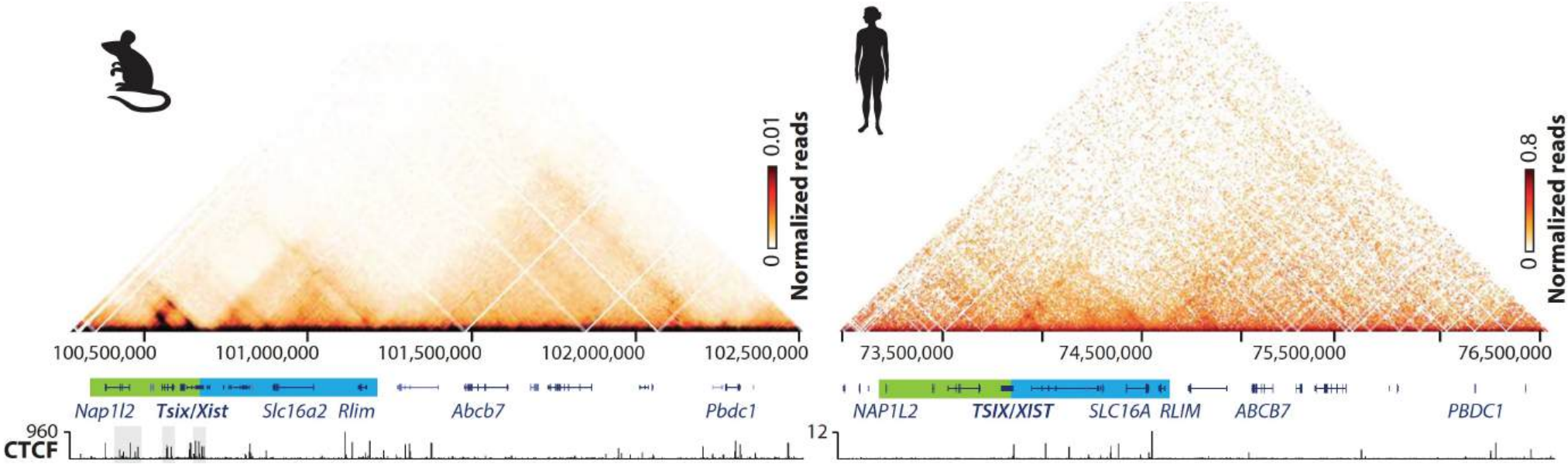
How conserved is the X-inactivation Centre and *Xist* Regulation?



In the murine Xic region, the *Xist* promoter and the *Tsix* promoter are organised into two separate TADs within which direct regulators of *Xist*, and *Tsix* are located, respectively.

In the human XIC region, the *XIST* promoter is also within a **TAD** spanning similar loci as the mouse, but *TSIX* is not well conserved and the extent or role of a corresponding **TAD**, downstream of XIST, is not so clear.

Galupa and Heard, Annu. Rev. Genet.
2018. 52:535–66

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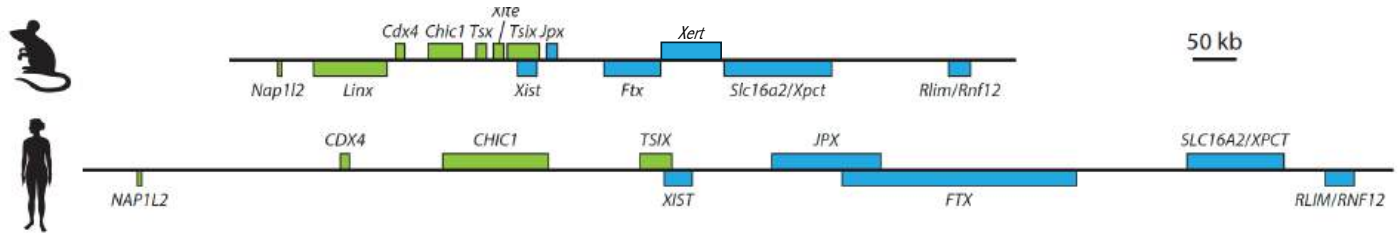
Current understanding of the mouse Xic and *Xist* Regulation during random XCI



Adapted from Galupa and Heard, Annu. Rev. Genet. 2018. 52:535–66

Table 2 Loci within the *Tsix* TAD and their involvement in XCI

Locus	Coding potential	KO phenotype in mice	Mechanism of action in XCI	Additional observations
Tsix	Noncoding	XCI-related lethality (108, 118)	Repressive role on *Xist* through *Tsix* transcription across its promoter (113, 133, 134, 143, 166, 187, 191)	*Tsix* lncRNA seems to be dispensable for *Xist* regulation (167, 177, 191)
Xite	Noncoding	Unknown	Deletion in female ESCs leads to preferential *Xist* upregulation in *cis* (142)	Reported to be an enhancer of *Tsix* (188) but unclear whether it can influence *Xist* independently of *Tsix*
Tsx	Protein coding (44, 54) and noncoding (2)	Subfertility and neurological alterations (2)	*Tsix* and *Xist* expression are slightly affected in KO ESCs but no skewing observed (2)	Testis-specific expression (2, 54)
Chic1	Protein coding	Unknown	Unknown; harbors a structural element involved in the folding of the *Tsix* TAD (77)	Expressed in ESCs and in brain (179)
Cdx4	Protein coding	No significant phenotype (104)	Never implicated in XCI	Homeobox protein
Linx	Noncoding (lncRNA)	Unknown	Unknown; levels of expression correlated with those of *Tsix* and with the compaction of the *Tsix* TAD (77, 138)	Expression restricted to the inner cell mass, absent from extraembryonic tissues (138)
Ppnx	Protein coding	Unknown	Never implicated in XCI	Testis-specific expression (44); also reported in ESCs, but it shares exons with *Linx*
Nap1l2	Protein coding	Lethality associated with neural tube defects in embryo chimaeras (163)	Never implicated in XCI	Brain-specific expression (164)

Table 1 Loci within the *Xist* TAD and their involvement in XCI

Locus	Coding potential	KO phenotype in mice	Mechanism of action in XCI	Additional observations
Xist	Noncoding (lncRNA)	Female-specific lethality (119)	The key lncRNA for XCI; coats the X-chromosome in *cis* and triggers gene silencing, chromatin remodeling, and structural reorganization of the X chromosome	Xist RNA is essential to trigger XCI and becomes dispensable once the inactive state is maintained by epigenetic mechanisms (209)
Jpx	Noncoding (lncRNA)	Unknown	Some studies describe the Jpx lncRNA as a *trans*-activator of *Xist* (199); this would be achieved by evicting CTCF from the *Xist* locus (192). A recent study reported no *trans*-activity for *Jpx* but rather a *cis*-effect on *Xist* (9)	
Ftx	Noncoding (lncRNA)	Viable mice, no apparent XCI-related phenotype (183)	Transcription of *Ftx* is required for *Xist* activation and establishment of XCI during differentiation of female ESCs (71), but its RNA products are not required. KO in early differentiated male ESCs leads to reduced *Xist* upregulation (43)	Hosts microRNAs in its introns (43), which do not seem involved in *Xist* regulation (71)
Cnbp2	Protein coding	Unknown	Never implicated in XCI	Zinc-finger protein (44)
Xpr	Within Xpct	Unknown	Mediates X-chromosome pairing during early differentiation (4)	X-chromosome pairing, through *Xpr* or *Tsix*/*Xite*, is dispensable for XCI (9, 128)
Xpct	Protein coding	Unknown	Never implicated in XCI	Transmembrane transporter (106)
Rnf12	Protein coding	Female-specific lethality (178)	Rnf12 ubiquitin ligase targets Rex1 for degradation, thereby triggering and sustaining *Xist* activation (in *trans*) (8, 9, 80, 96)	$Rnf12^{+/\Delta p}$ mice are viable (178) and some $Rnf12^{+/-}$ cells undergo XCI (96), implying the involvement of other *Xist* activators during random XCI (128)

Abbreviations: ESCs, embryonic stem cells; KO, knockout; lncRNA, long noncoding RNA; TAD, topologically associating domain; XCI, X-chromosome inactivation.

E. Heard, May 26th, 2025

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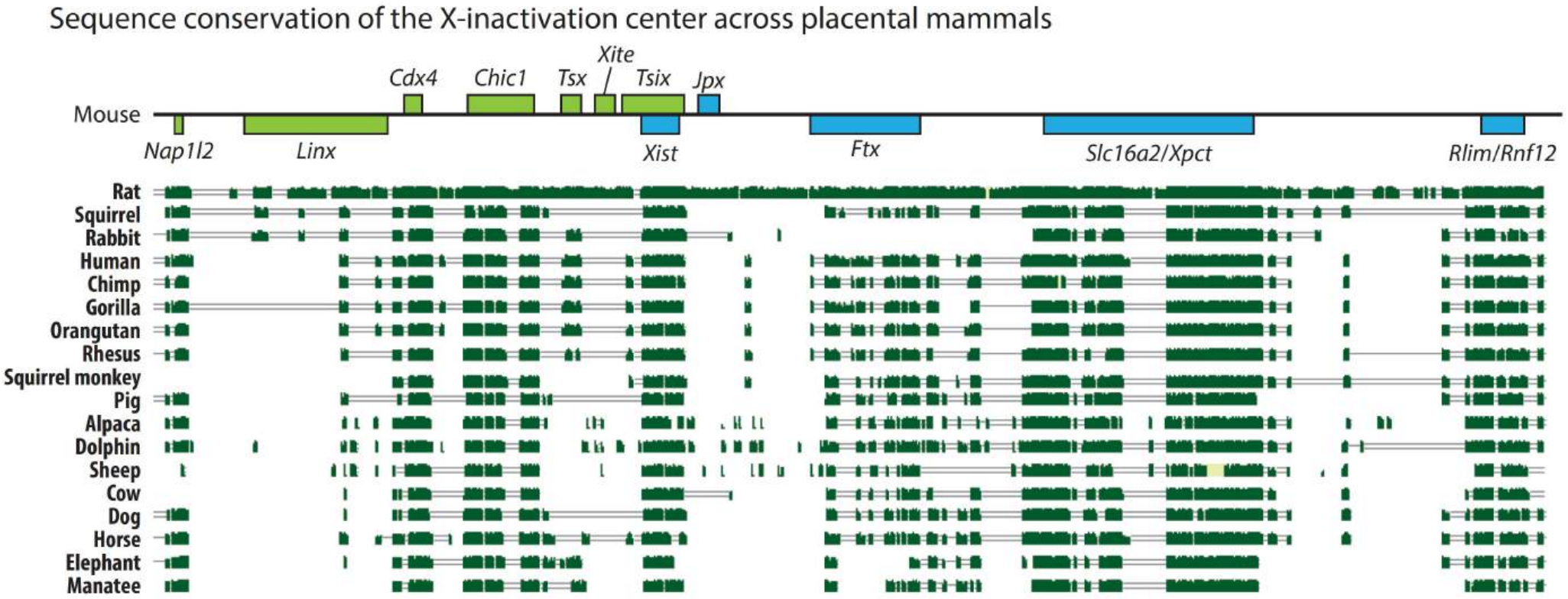
What is the Evolutionary Conservation of the Xic region across Eutherian mammals?



Galupa and Heard, Annu. Rev. Genet. 2018. 52:535–66

E. Heard, May 26th, 2025

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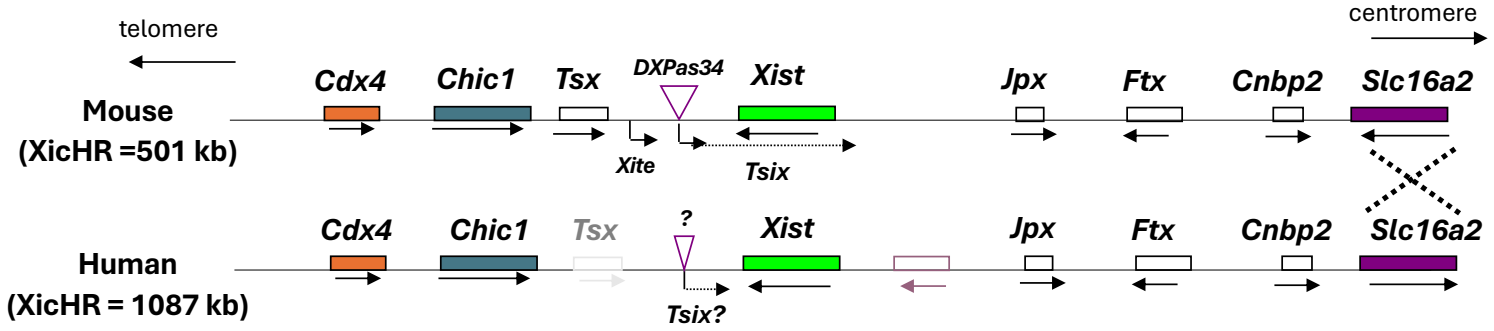
Conservation of the Xic and evolution of *Xist* ?

Laurent Duret
LBBE, Lyon, France

Phil Avner
Pasteur Institute
Paris, France



The *Xist* RNA Gene Evolved in Eutherians by Pseudogenization of a Protein-Coding Gene

Laurent Duret,[1]* Corinne Chureau,[2] Sylvie Samain,[3] Jean Weissenbach,[3] Philip Avner[2]

- *Xist* evolved only in eutherians (pseudogenisation of the protein coding *Lnx* gene)
- Two exons of Lnx3 are homologous to Xist (probability of this happening by chance is very low (5×10^{-5})
- In marsupials : there is no *Xist* gene, and the Xic region is broken up (in particular the *Xist* upstream region)

How is marsupial XCI controlled? Another locus?

Carry over of meiotic sex chromosome inactivation (SEE LATER)

Chureau et al, 2002; Duret et al, 2006; Hore et al, 2007; Davidow et al, 2007 ; Zakharova et al, 2007; Elisaphenko et al., 2008

Conservation of the Xic and evolution of alternative strategies

James Turner
The Francis Crick Institute
London, UK

Rsx is a metatherian RNA with *Xist*-like properties in X-chromosome inactivation

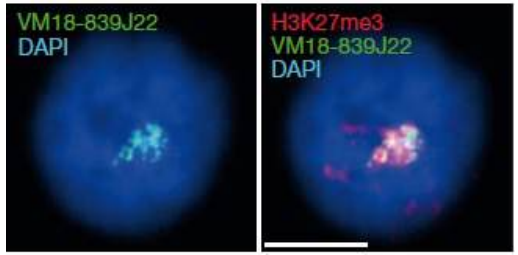
Jennifer Grant[1], Shantha K. Mahadevaiah[1], Pavel Khil[2], Mahesh N. Sangrithi[1], I
John R. McCarrey[4], John L. VandeBerg[5], Marilyn B. Renfree[6], Willie Taylor[1], Gi
Mike J. Gilchrist[1] & James M. A. Turner[1]

Grant et al (2012) Nature 487, 254-258

Article

A single-cell transcriptome atlas of marsupial embryogenesis and X inactivation

Mahadevaiah et al (2020) Nature 586, 612-634



- Rsx is a non-coding RNA with no homology to Xist but potentially similar role
- The origin of Rsx is unknown
- The syntenic region in eutheria is flanked by *HPRT* and FAM122B and contains the placenta-specific gene *PLAC1*
- An antisense to *Rsx* – *Xsr* – has also been identified and may play a role in its monoalleic control.

- Non-coding RNAs such as Xist, Rsx (and their antisense RNAs) may be easier to evolve for rapidly needed "dosage compensation strategies) than proteins
- Such ncRNAs are often driven by retransposon – see COURS 2016)
- Easy to regulate dynamically in development
- Could be useful "triggers" or modulators for epigenetic processes

(More about Marsupials later)

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The Epigenetics of X-Chromosome Inactivation

E. Heard, May 26th, 2025

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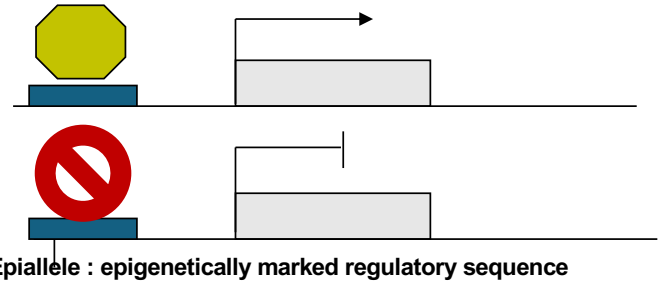
The Epigenetics of X-Chromosome Inactivation

- The two X chromosome can be genetically identical
- Yet one of them will have its genes “turned off” and this state will be maintained through tens to hundreds of mitotic cell divisions
- X inactivation is therefore a classic example of epigenetic regulation, monoallelic gene expression and heterochromatin formation on a chromosome-wide scale.

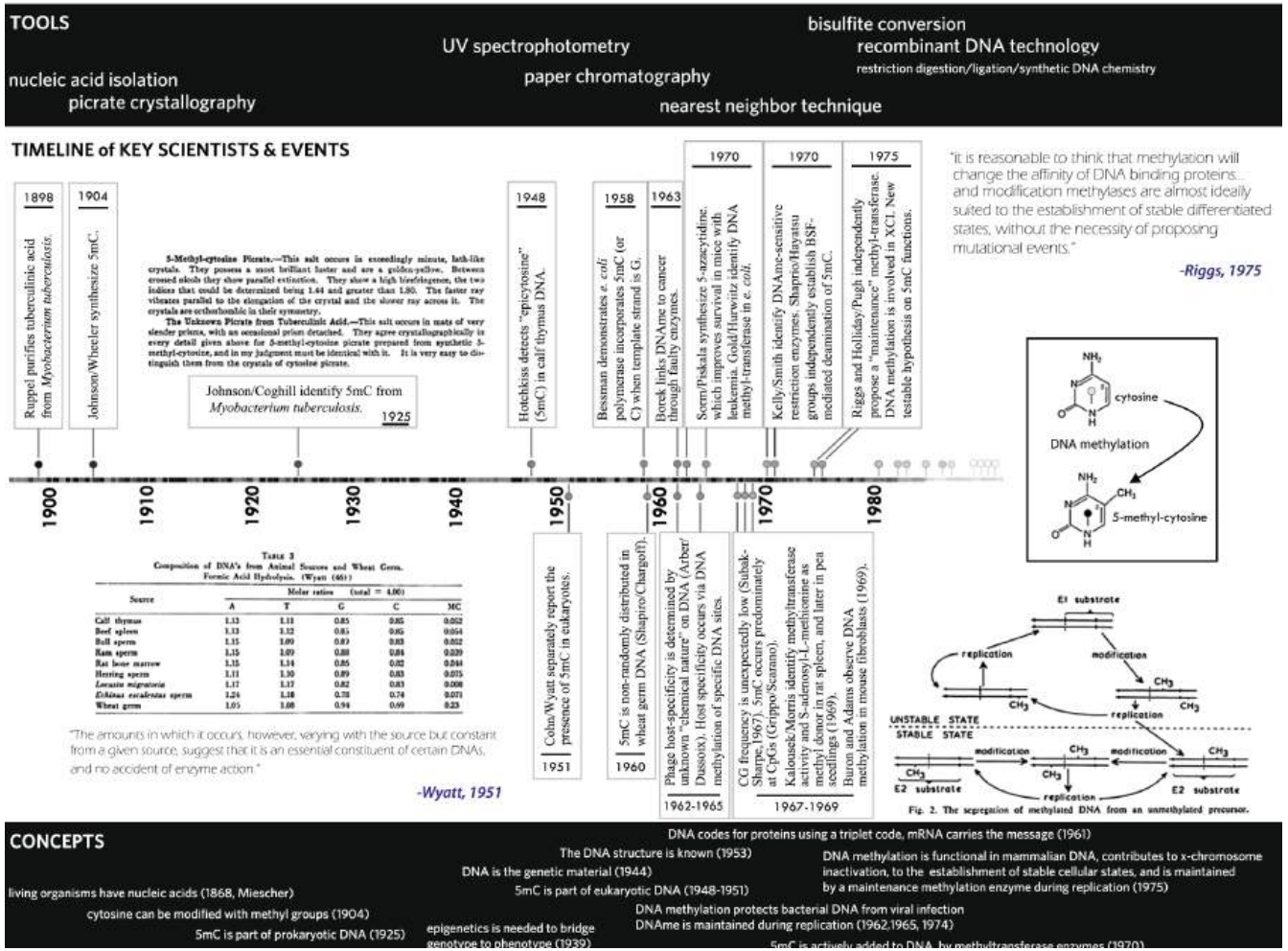


What are the epigenetic mechanisms that ensure the propragation of inactivity through cell divisions as well as in non-dividing cells?

DNA Methylation was the first ”EPIGENETIC MARK” proposed to account for spreading and maintenance of XCI

Riggs, A. D. 1975. X inactivation, differentiation and DNA methylation. Cytogellet. Cell Gellet. 14:9-25

DNA Methylation: its discovery, its proposed role in epigenetic memory and XCI



Tomkins, Discovering DNA Methylation the History and Future of the Writing on DNA
Journal of the History of Biology (2022) 55:865–887; doi.org/10.1007/s10739-022-09691-8

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(Re-)Définition de l'épigénétique (Holliday – Riggs)

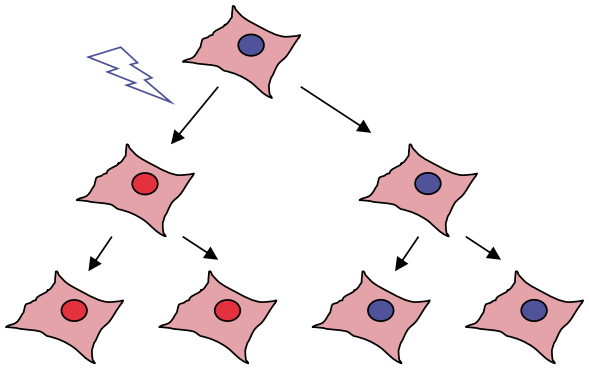
L'étude des changements d'expression des gènes transmissibles au travers des divisions cellulaires (voire des générations), sans changement de la séquence de l'ADN

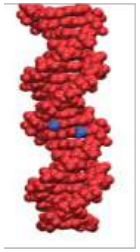
Epigénétique et Mémoire Cellulaire

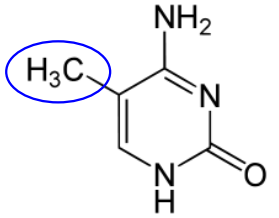
Russo, V.E.A., R.A. Martienssen & A.D. Riggs Eds. 1996.
Cold Spring Harbor Laboratory Press.

Robin Holliday (1935-2014)

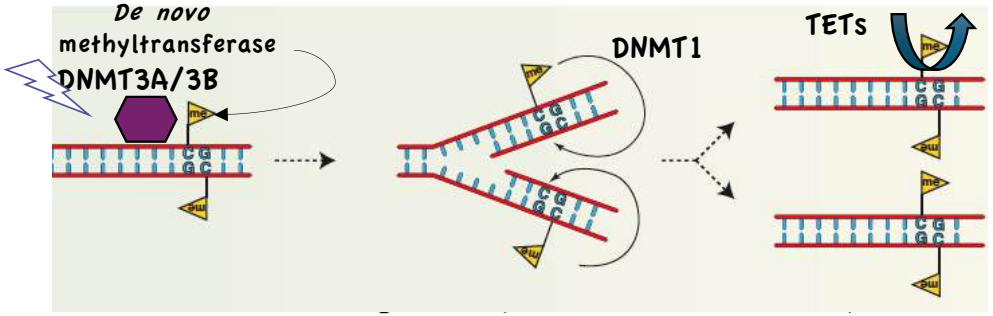
Art Riggs (born 1939)

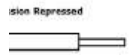


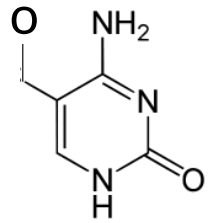




Faithful transmission of DNA methylation patterns from one cell to its daughters...
May be less faithful than DNA sequence replication ...







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E. Heard, 2016

ART RIGGS – one of the fathers of modern Epigenetics

Arthur D. Riggs
1939–2022

THE ORIGINS OF THE MODERN DEFINITION OF EPIGENETICS

The maintenance methylase model 1975

X inactivation, differentiation, and DNA methylation

A.D. RIGGS

City of Hope National Medical Center, Duarte, Calif.

A model based on DNA methylation is proposed to explain the initiation and maintenance of mammalian X inactivation and certain aspects of other permanent events in eukaryotic cell differentiation. A key feature of the model is the proposal of sequence-specific DNA methylases that methylate unmethylated sites with great difficulty but easily methylate half-methylated sites. Although such enzymes have not yet been detected in eukaryotes, they are known in bacteria. An argument is presented, based on recent data on DNA-binding proteins, that DNA methylation should affect the binding of regulatory proteins. In support of the model, short reviews are included covering both mammalian X inactivation and bacterial restriction and modification enzymes.

Cytogenetics and Cell Genetics. 2003;99(1-4):17-24. doi:10.1159/000071569

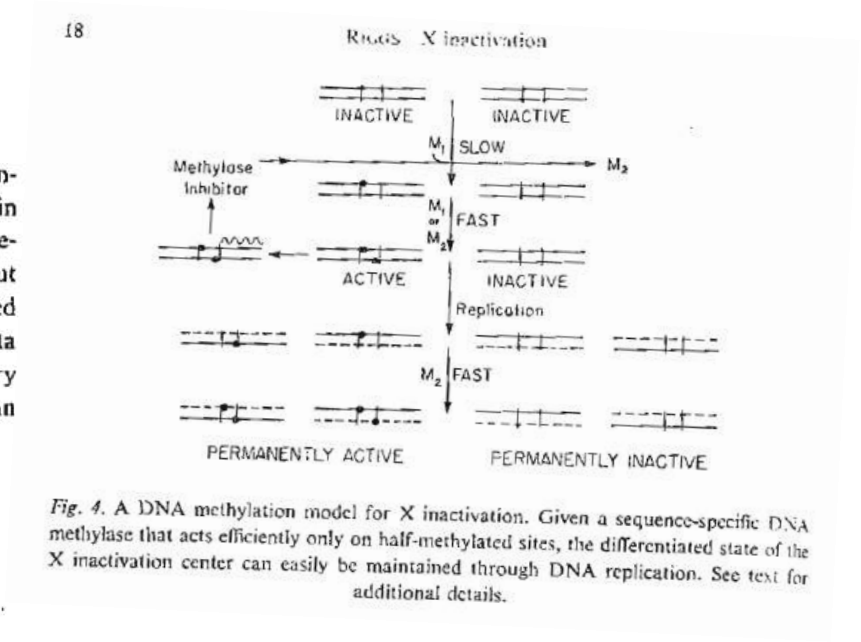

Fig. 4. A DNA methylation model for X inactivation. Given a sequence-specific DNA methylase that acts efficiently only on half-methylated sites, the differentiated state of the X inactivation center can easily be maintained through DNA replication. See text for additional details.

The "way station" model for the spread of X inactivation 1983
(in Gartler and Riggs, ARG 1983)

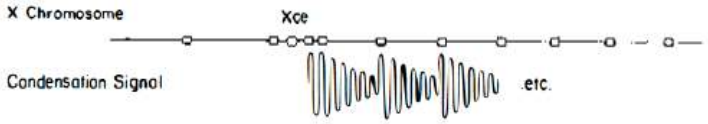

Figure 4 **A "way station" model for the spreading of X-chromosome inactivation. The squares represent X-chromosome-specific DNA sites that function, by interacting with specific proteins, to stabilize and thereby enhance the spreading of the condensed and inactive state. The amplitude of the oscillating line represents the strength of the condensation signal, which at the molecular level depends on the stability of cooperative protein-protein and protein-DNA interactions.**

E. Heard, May 26th, 2025

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ART RIGGS – one of the fathers of modern Epigenetics

Arthur D. Riggs
1939–2022

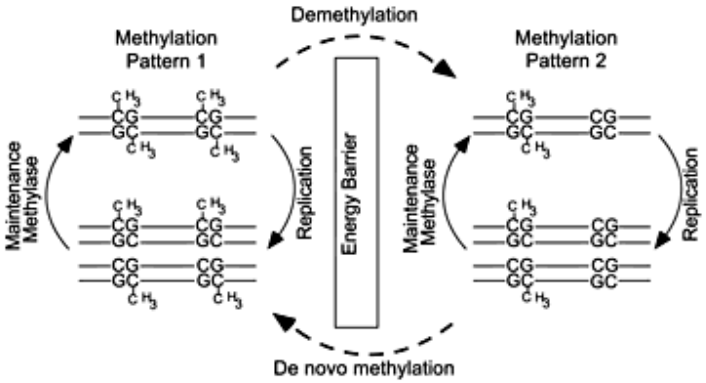
THE ORIGINS OF THE MODERN DEFINITION OF EPIGENETICS

The maintenance methylase model 1975

- In the 1970s, Riggs played a key role in launching the field of modern epigenetics. Inspired by his earlier studies on the Lac
- repressor in bacteria, Riggs had become fascinated with DNA modifications, recognizing that these modifications may interfere with protein–DNA interactions, perhaps best exemplified by the bacterial restriction and modification systems. In a landmark conceptual paper published in 1975.
- Riggs proposed that in mammals, patterns of DNA methylation, which exist chiefly in the form of 5-methylcytosines at CpG dinucleotide sequences, can be faithfully copied during DNA replication by a DNA methyltransferase (DNMT1). This enzyme maintains fully methylated CpG sites by acting preferentially on hemi-methylated intermediates arising shortly after DNA replication.
- He also proposed that DNA methylation sites could control gene expression by interfering with the binding of regulatory proteins and could be involved in X-chromosome inactivation.

The "way station" model for the spread of X inactivation 1983
(in Gartler and Riggs, ARG 1983)

- Therefore, the heritability of DNA methylation provides a mechanism for maintaining epigenetic states during cell divisions.
- All these predictions turned out to be correct.
- A conceptually similar proposal for DNA methylation maintenance during replication was developed independently by Holliday and Pugh and published in that same year.



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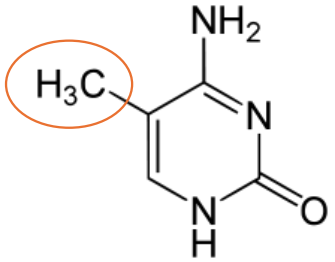
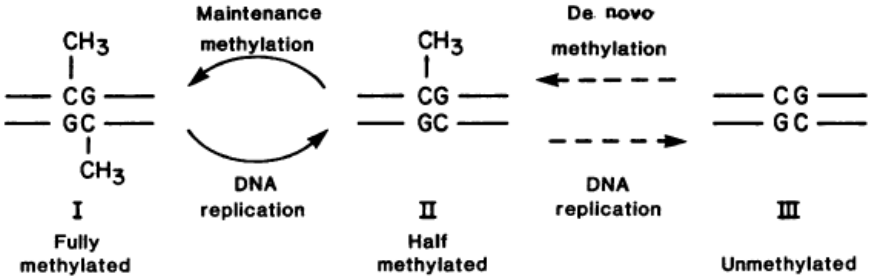
1530

A role for DNA Methylation in X inactivation

First proposed by Riggs, 1975, Cytogenet. Cell Genet. 14, 9-25





Proc. Natl. Acad. Sci. USA
Vol. 79, pp. 5357–5361, September 1982
Genetics

CpG islands of X-linked genes are hypermethylated on the inactive X chromosome
Unlike their counterparts on the active X

Evidence for DNA modification in the maintenance of X-chromosome inactivation of adult mouse tissues

(Searle's translocation/DNA-mediated cell transformation/hypoxanthine phosphoribosyltransferase)

V. M. Chapman*, P. G. Kratzer*, L. D. Siracusa*, B. A. Quarantillo*, R. Evans†, and R. M. Liskay†

Proc. Natl. Acad. Sci. USA
Vol. 81, pp. 1759–1763, March 1984
Genetics

Differential methylation of hypoxanthine phosphoribosyltransferase genes on active and inactive human X chromosomes

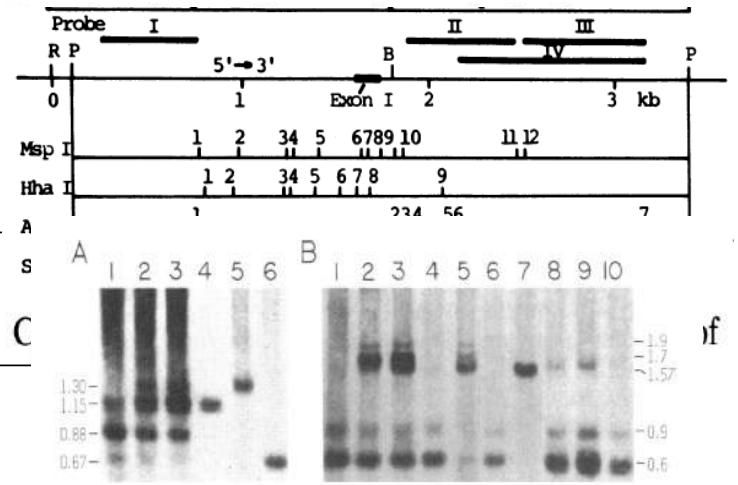
(X inactivation/5-azacytidine/mouse–human hybrid cell/Southern blotting)

Pauline H. Yen*†, Pragna Patel‡, A. Craig Chinault‡, T. Mohandas*†, and Larry J. Shapiro*†§

Methylation of the hypoxanthine phosphoribosyltransferase locus on the human X chromosome: Implications for X-chromosome inactivation

(dosage compensation/"housekeeping" genes/5-azacytidine/X-chromosome reactivation/mouse–human hybrids)

Stanley F. Wolf*, Douglas J. Jolly†, Keith D. Lunnen*, Theodore Friedmann†, and Barbara R. Migeon*



The Epigenetics of X-Chromosome Inactivation

Reactivation of an Inactive Human X Chromosome: Evidence for X Inactivation by DNA Methylation

Abstract. *A mouse-human somatic cell hybrid clone, deficient in hypoxanthine-guanine phosphoribosyltransferase (HPRT) and containing a structurally normal inactive human X chromosome, was isolated. The hybrid cells were treated with 5-azacytidine and tested for the reactivation and expression of human X-linked genes. The frequency of HPRT-positive clones after 5-azacytidine treatment was 1000-fold greater than that observed in untreated hybrid cells. Fourteen independent HPRT-positive clones were isolated and analyzed for the expression of human X markers. Isoelectric focusing showed that the HPRT expressed in these clones is human. One of the 14 clones expressed human glucose-6-phosphate dehydrogenase and another expressed human phosphoglycerate kinase. Since 5-azacytidine treatment results in hypomethylation of DNA, DNA methylation may be a mechanism of human X chromosome inactivation.*

Treatment and concentration	Frequency of HPRT-positive clones (per 10^5 cells)						
	37-26R-D			A9		37-26R-A	
	I	II	Relative plating efficiency (%)	I	II	I	II
Control	0.1	0	100	0	0	0	0
Cytidine (10 μM)	0.1	0	136	0	0	0	0
6-Azacytidine (10 μM)	0						
6-Azacytidine (2 μM)		0	80				
5-Azacytidine (10 μM)	28.3			0	0	0	0
5-Azacytidine (5 μM)	74.5						
5-Azacytidine (2 μM)		117.4	63		0		0
5-Azacytidine (2 μM) + cytidine (10 μM)		0	61				
5-Azacytidine (2 μM) + cytidine (20 μM)		0.4	63				
Arabinosylcytosine (2 μM)		0	5				
5-Bromodeoxyuridine (10 μM)		0	45				

- DNA methylation is clearly involved in maintenance of X inactivation b*ut* there was no clear mechanism of action on the Xi: DNA binding proteins? Chromatin accessibility?
- Replication timing?
- Furthermore CpG island DNA methylation does not seem to be conserved in marsupials!
- And DNA methylation on the Xi appears to be a relatively late event during mouse development…

5-azacytidine treatment on cultured human/hamster hybrid cells with an inactive X chromosome revealed that **X-linked genes (Hprt) could be reactivated by inhibiting DNA methylation maintenance.**

The Epigenetics of X-Chromosome Inactivation

Cell, Vol. 48, 39–46, January 16, 1987, Copyright © 1987 by Cell Press

Methylation of the *Hprt* Gene on the Inactive X Occurs after Chromosome Inactivation

Leslie F. Lock,*† Nobuo Takagi,‡ and Gail R. Martin*

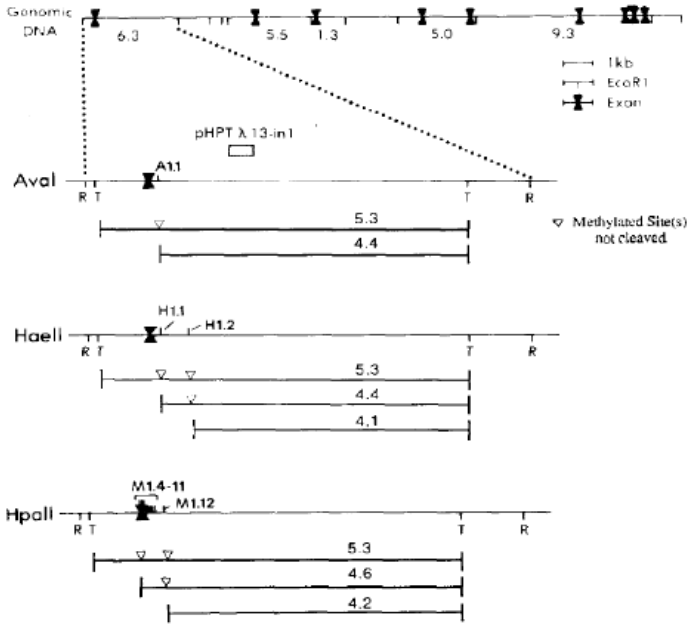
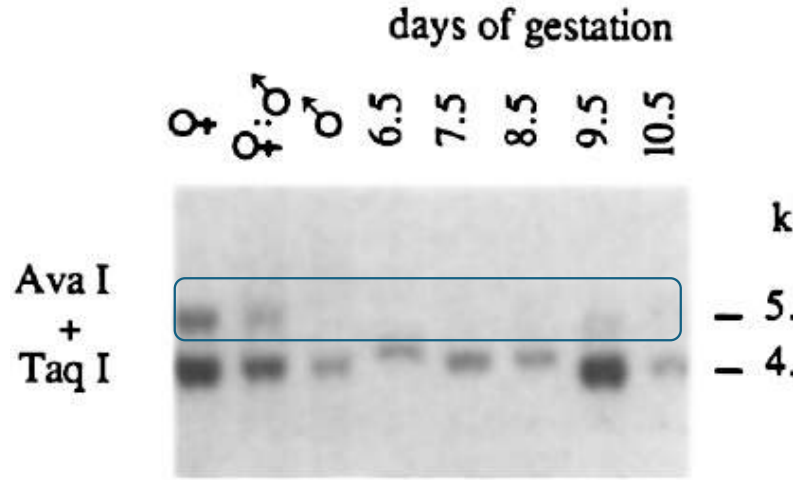


Figure 1. Map of the Mouse *Hprt* Gene Showing the Location of Restriction Sites in and near the First Intron That Are Methylated on X^i and Unmethylated on X^a

The *Hprt* gene has nine exons that are contained within almost 40 kb of genomic DNA. Its structure, including the placement of exons and a map of EcoRI restriction sites, is shown (from Melton et al., 1984). Below, expanded maps show the locations of the AvaI (A1.1), HaeII, (H1.1, H1.2), and HpaII (MspI) (M1.4-11, M1.12) sites in the EcoRI (R) fragment containing the first exon; the only restriction endonuclease sites depicted are those that have been shown to be differentially methylated on the X^i and X^a (Lock et al., 1986). Beneath each of these maps are depicted the restriction fragments detected in Southern blots of female genomic DNA digested with AvaI, HaeII, or HpaII in combination with TaqI (T) and hybridized to the pHPTλ13-in1 (intron 1) probe. The location in the expanded map of the genomic DNA sequence represented by this probe is indicated by the stippled box. For each restriction fragment, the location of a differentially methylated site that has not been cleaved is marked by an open triangle.



- And DNA methylation on the Xi appears to be a relatively late event during mouse development…

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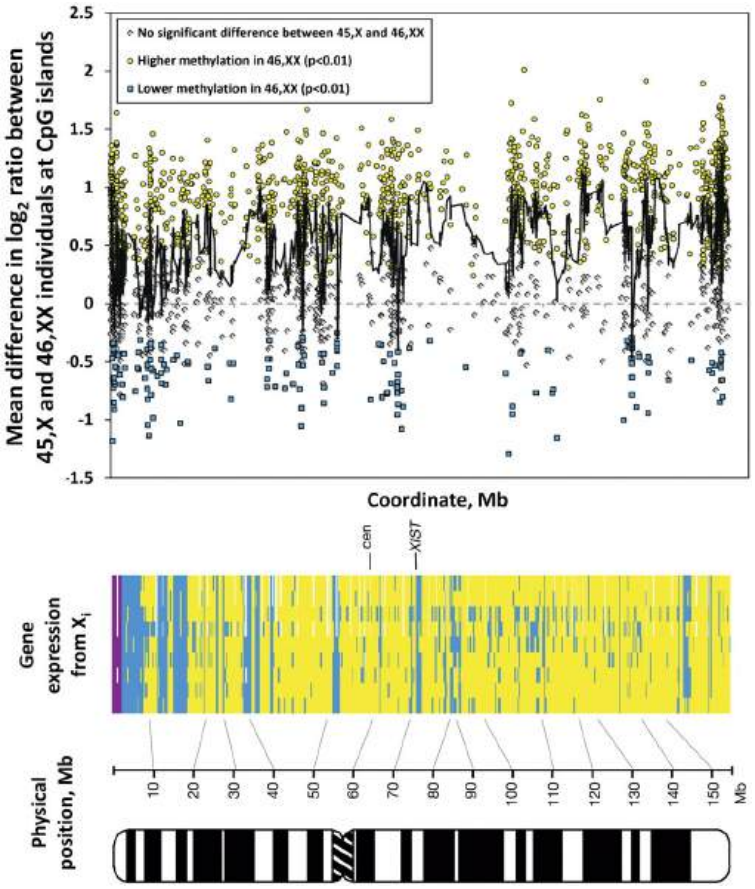
X-Chromosome wide DNA methylation status

X inactivation results in highly variable changes in methylation of CpG islands that correlate with the location of genes escaping X inactivation.



Sharp A J et al. Genome Res. 2011;21:1592-1600

How exactly 5mC can regulate gene expression when present at promoters remains unclear, but classically it is thought to recruit methyl-binding domain-containing factors, which would execute its repressive function.

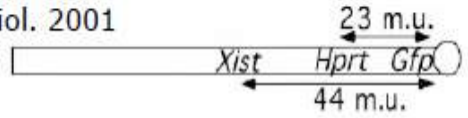
Alternatively, CpG methylation within binding motifs seems to change the binding affinity of multiple TFs.

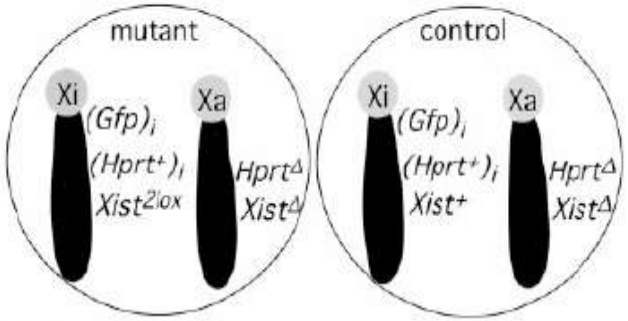
A whole range of other chromatin marks are also associated with transcriptional silencing.
These include not only repressive histone modifications (e.g. H4K20me1, H3K9me3, H3K27me3) but also histone variants that replace canonical histones (e.g. macroH2A).

Synergy of Multiple Epigenetic Mechanisms to maintain the Xi

Synergy between Xist RNA, DNA methylation Histone hypoacetylation, Polycomb - in maintaining the Inactive state

Csankovszki et al, J. Cell Biol. 2001
Zhang et al, Cell 2007





Evaluating **reactivation** of the inactive state :
- GFP - fluorescence
- Hprt - HAT resistance
- Synchronous replication

Xist KO:
lose Xist RNA coating => loss of macroH2A , HRK27me3

5-azadC or *Dnmt1 KO* :
Lose DNA methylation

Trichostatin A, (TSA, inhibitor of HDACs):
Re-acetylation of X chromosome

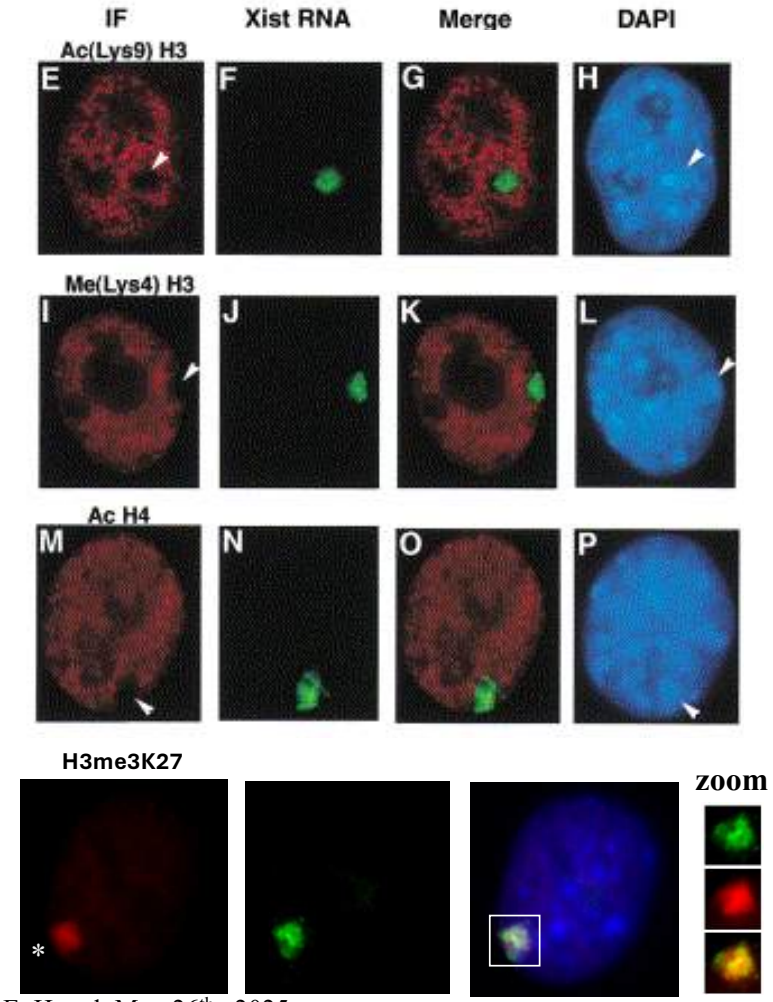
Reactivation frequences using GFP ($1/10^4$) transgenesis		
Xist KO	-> 2 X	*primary and immortalised cells*
Treatment TSA	-> no effect	
Treatment 5-azadC	-> 20 X	
Treatment 5-azadC + TSA	-> 30 X	
Dnmt1 KO	-> 1500 X	
Xist and *Dnmt1* KOs	-> 3000 X	

Spontaneous reactivation of Hprt ($1/10^9$)		
Xist KO	-> 160 X	*Immortalised cells*
5-azadC	-> 60 X	
Xist KO + 5-azadC	-> 10 000 X	

Synergy between different marks maintains the inactive state

Csankovski et al, 2001
Zhang et al, 2007

Xist RNA coating is followed by numerous chromatin changes on the X during ES cell differentiation



E. Heard, May 26th, 2025

COURS 2013, 2015

➡ Exclusion of euchromatic marks from the Xist RNA-coated chromosome

➡ Enrichment for H3K27me3, H3K9me2, H4K20me1, macroH2A
Polycomb complexes PRC2, PRC1

➡ Chromatin modifications on the X(i) are Xist RNA dependent initially
– some become Xist-independent eg H4Ac

Heard 2001, Chaumeil et al, 2002
Plath et al 2003, Silva et al 2003

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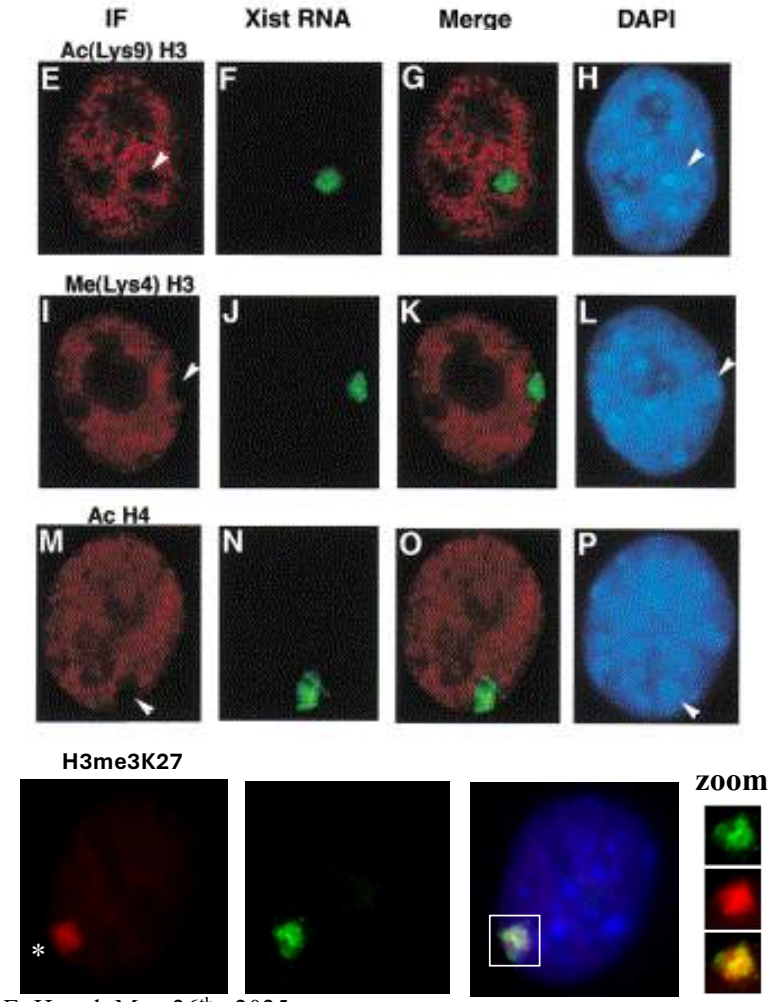
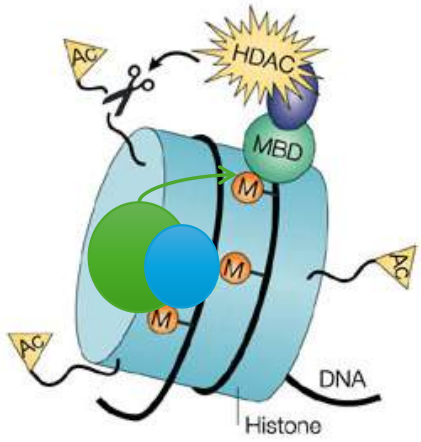
Xist RNA coating is followed by numerous chromatin changes on the X



E. Heard, May 26th, 2025

COURS 2013, 2015



Histone 'readers' and 'writers' of the Xi ?

So far, PRC2/H3K27me3/PRC1/H2Aub Polycomb group complexes can write certain marks (eg H3K27me3 by PRC2) (eg H2AK119ub by PRC1) that can be "read" by others
(Cbx7 in PRC1 can bind H3K27me3)
Jarid2 in PRC2 can bind H2AK119Ub)

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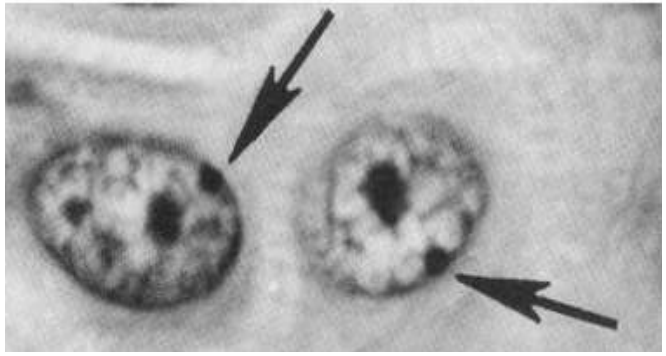
X inactivation: a classic example of facultative heterochromatin and a paradigm for epigenetic control

- Transcriptionally inert
- Compact chromatin
- Unusual 3D organisation
- Particular nuclear localisation
- Silent nuclear compartment
- Depletion of active chromatin marks
  (H3K4me3, H3K9ac, H4ac, H3K27ac)
- Enriched for repressive histone marks
  (H3K9me2, H3K27me3, H2AK119Ub)

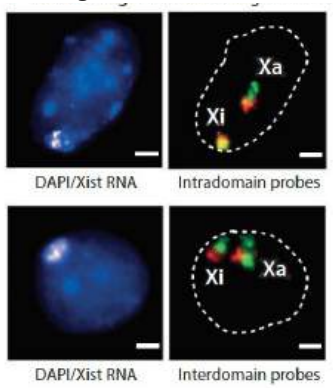
1. **How is facultative heterochromatin established?**
2. **How does chromosome organisation influence gene activity on the X?**

Also see COURS 2013, 2015, 2018

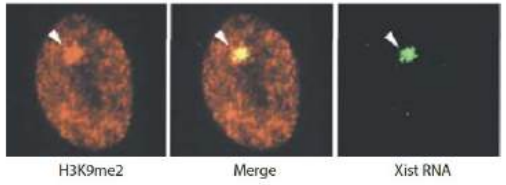
Bertram et Barr, 1949



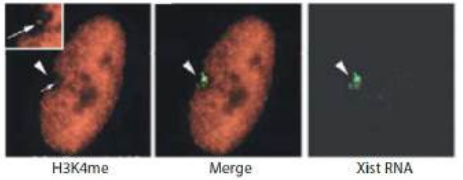
Giorgetti et al, 2001

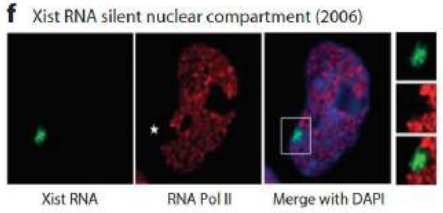


Boggs et al, 2001

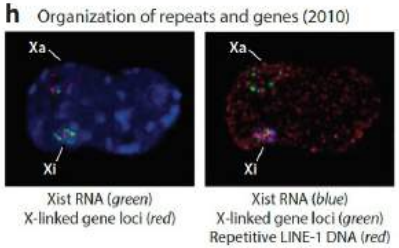


Heard et al, 2001





Chameil et al, 2002



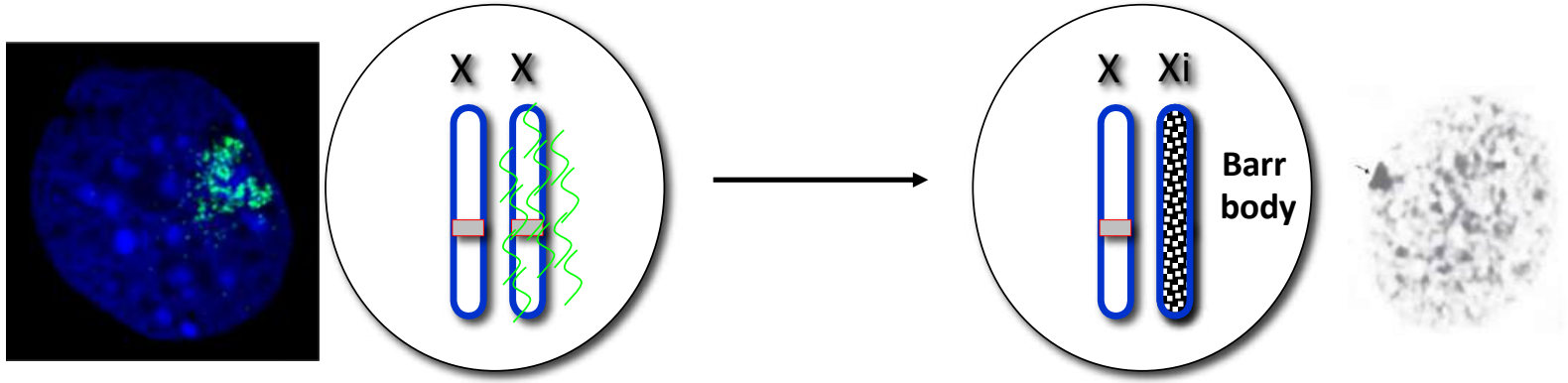
Chow et al, 2010

From Galupa and Heard, ARG 2018

Xist RNA is the trigger for X-Chromosome Inactivation in *cis*

Differential treatment of the two X chromosomes in the same nucleus

This means that technologies that can distinguish the two X chromosomes have to be used!

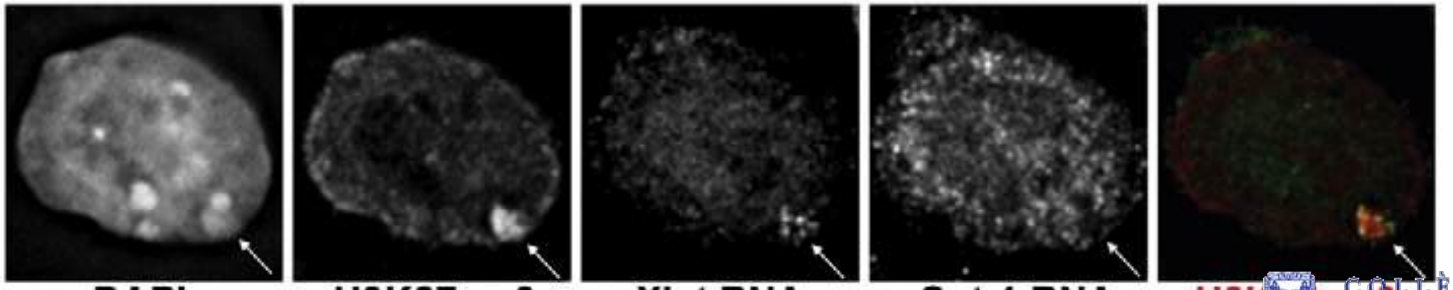


Xist RNA triggers X inactivation

A multitasking RNA: gene silencing, chromatin changes, chromosome reorganisation

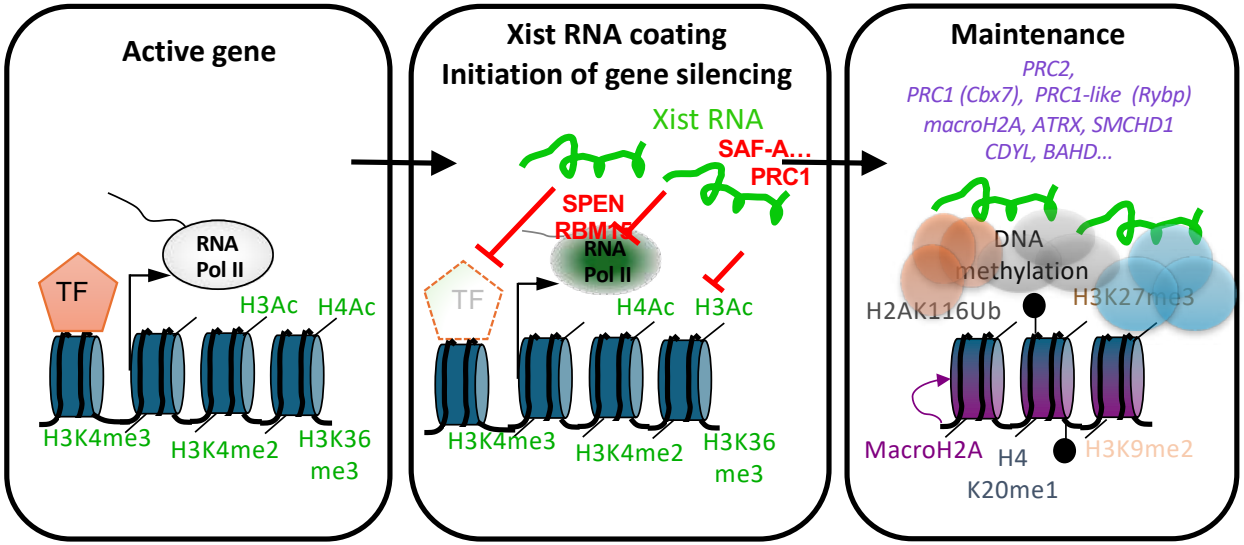
Maintenance (Epigenetics)

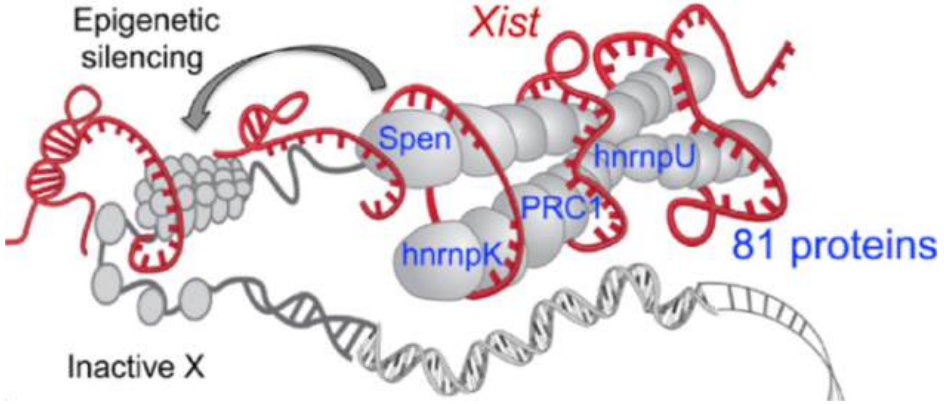
Chromatin status , chromosome structure nuclear organisation, asynchronous replication



Xist RNA is the trigger for gene silencing *and* epigenetic marking of the Xi

(Last week COURS 2)





Xist RNA recruits key **factors** involved in gene silencing and induces chromatin changes that stably propagate the inactive state

Chu et al, Cell 2015
McHugh et al, Nature 2015
Chen et al Science 2016
Minajigi et al, Science 2015
Moindrot et al, Cell Rep. 2015
Monfort et al, Cell Rep. 2015

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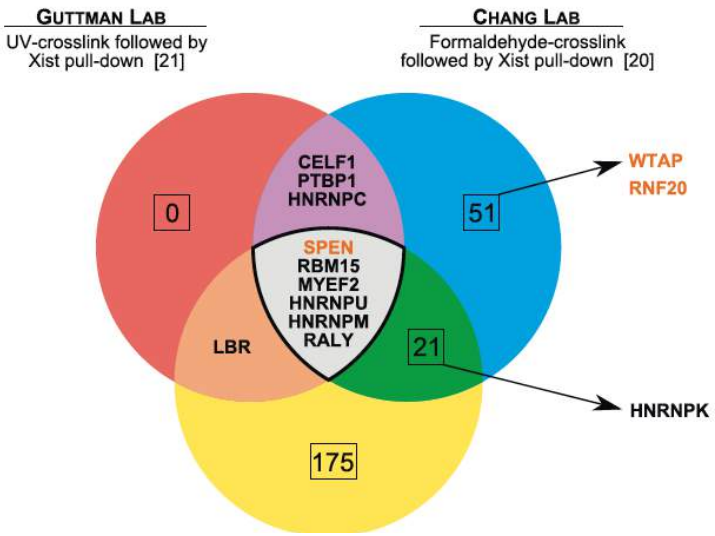
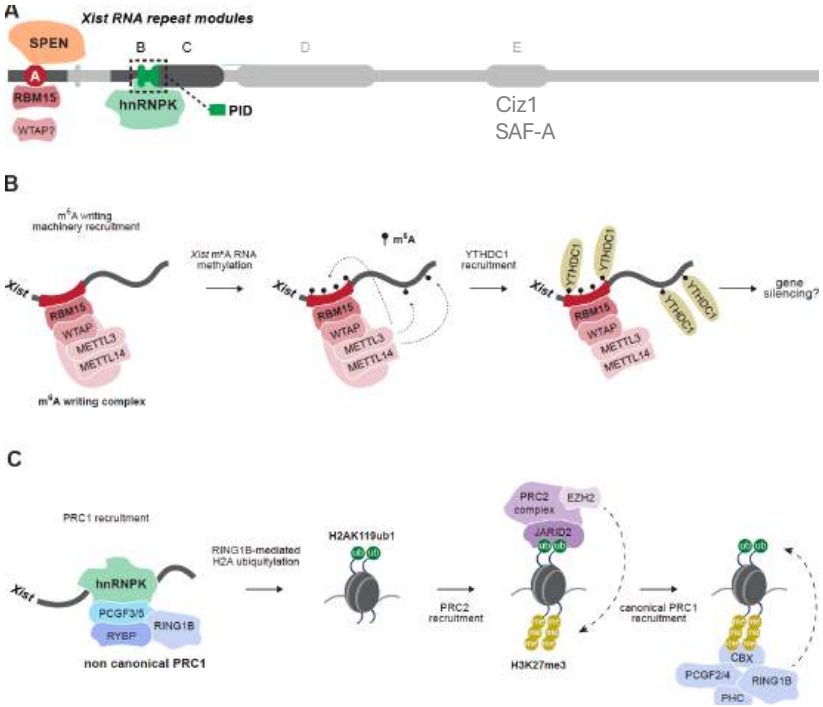
Xist is a multi-tasking RNA that recruits gene silencing & maintenance factors





SPEN / SHARP : 3,664 a.a. protein Implicated in RNA-directed transcriptional regulation in the context of hormone responsive nuclear receptor pathways

Spen´s SPOC domain interacts with the ubiquitous transcriptional co-repressors, SMRT/NCOR2 and NCOR1 and recruits histone deacetylases, including HDAC3.

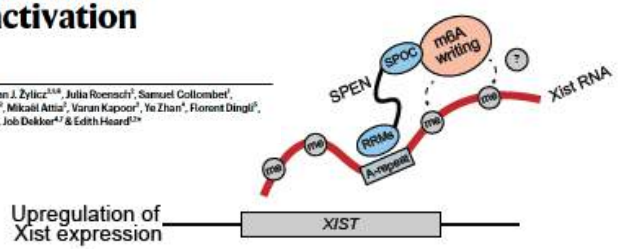
SPEN is Recruited by Xist RNA and brings with it Transcriptional and Epigenetic Regulators

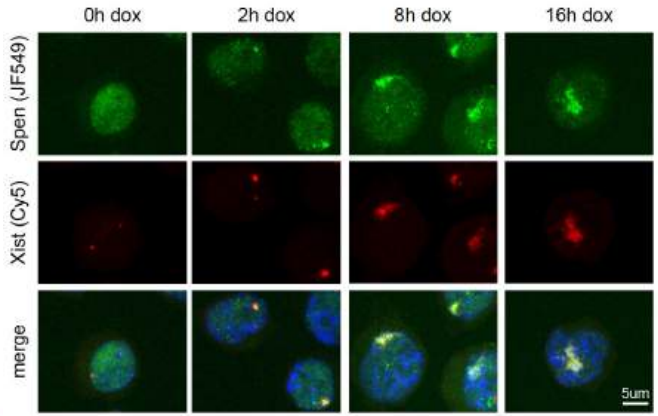
SPEN integrates transcriptional and epigenetic control of X-inactivation

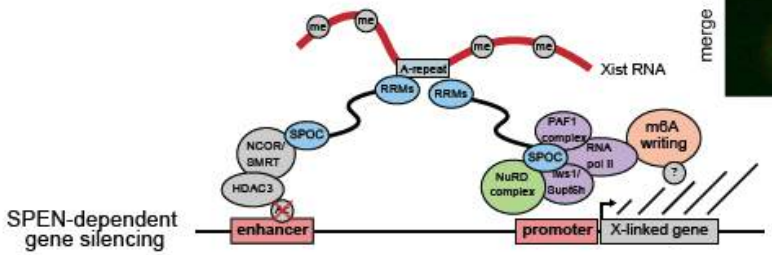
https://doi.org/10.1038/s41586-020-1974-9
Received: 4 June 2019
Accepted: 10 January 2020

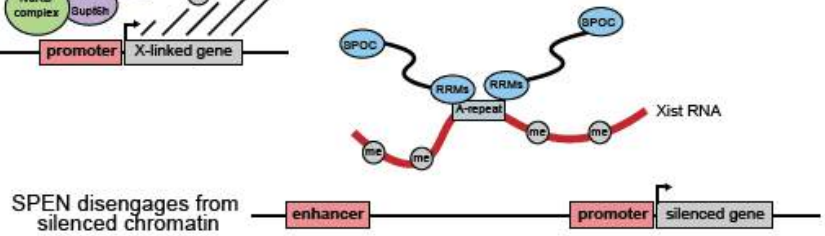
François Dossin[1], Inês Pinheiro[1,9], Jan J. Żylicz[2,3,9], Julia Roensch[1], Samuel Collombet[1], Agnès Le Saux[4], Tomasz Cholmicki[5], Mikaël Attia[1], Varun Kapoor[6], Ye Zhan[6], Florent Dingli[5], Damarys Loew[5], Thomas Mercher[4], Job Dekker[4,7] & Edith Heard[1,8]*

Francois Dossin









SPEN is an essential regulator of gene silencing in X inactivation

Xist RNA recruits SPEN through its RNA binding motifs

Through its SPOC domain, SPEN interacts with transcriptionally active promoters and enhancers

SPEN disengages from chromatin as soon as gene silencing occurs

SPEN remains associated with Xist RNA even after XCI is established

Dossin et al, Nature (2020) « SPEN integrates transcriptional and epigenetic control of X-inactivation »

SPEN integrates transcriptional and epigenetic control of XCI

SPEN integrates transcriptional and epigenetic control of X-inactivation

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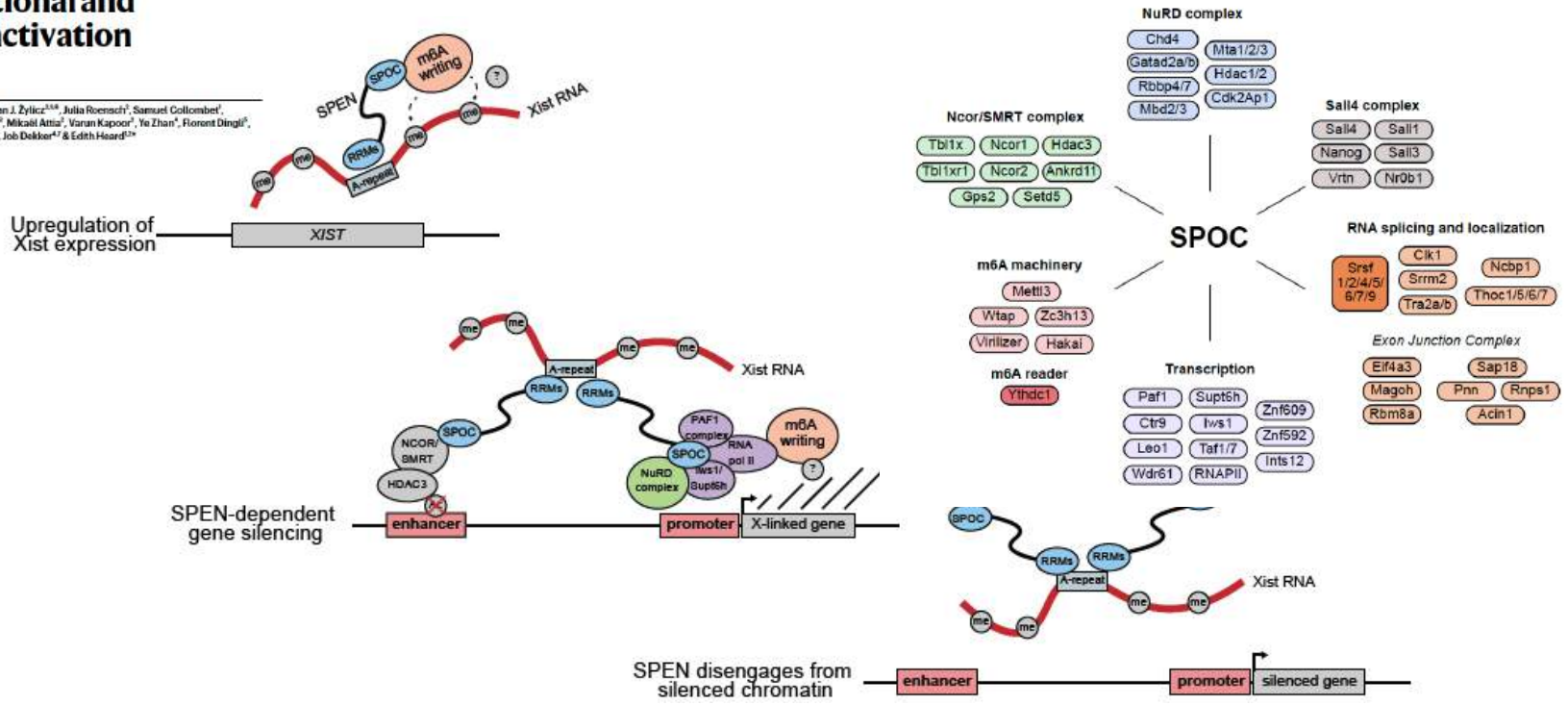
Francois Dossin



SPEN is an essential regulator of gene silencing in X inactivation

The SPOC domain of SPEN acts as a platform for recruitment of multiple protein complexes including SMRT/NCoR/HDAC3 (cf Oswald et al, 2016; Zylicz et al, 2019)
the NuRD complex, the m6A machinery and RNA PolII machinery

Dossin et al, Nature (2020) « SPEN integrates transcriptional and epigenetic control of X-inactivation »

X inactivation: a classic example of facultative heterochromatin and a paradigm for epigenetic control

- Transcriptionally inert
- Compact chromatin
- Unusual 3D organisation
- Particular nuclear localisation
- Silent nuclear compartment
- Depletion of active chromatin marks
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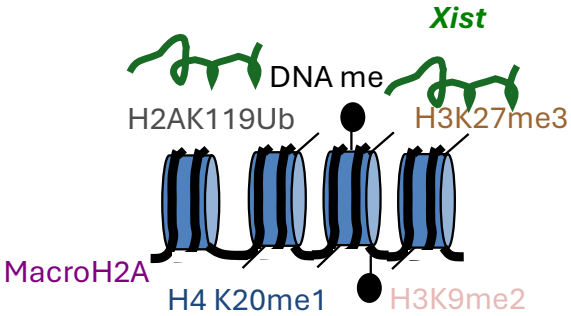
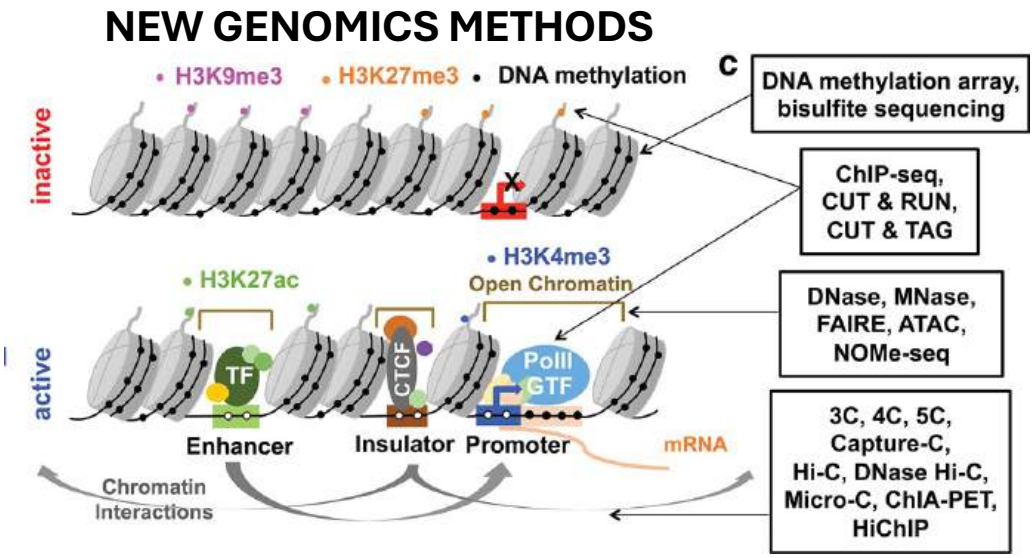
- Enriched for repressive histone marks
  (H3K9me2, H3K27me3, H2AK119Ub)

1. **How is facultative heterochromatin established?**
2. **How does chromosome organisation influence gene activity on the X?**





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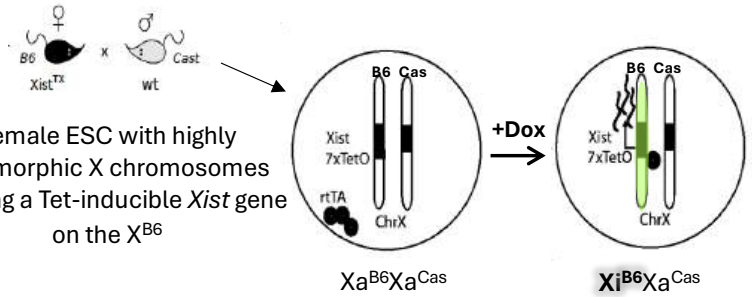
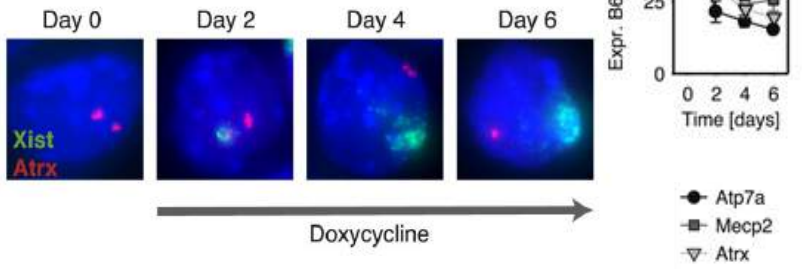
Kinetics of Epigenetic marks during X inactivation *in vitro*

Mouse embryonic stem cells (mESCs) with inducible, non-random
X-chromosome inactivation uncoupled from differentiation



- Gene silencing similar to in vivo kinetics
- Rapid loss of euchromatic marks after Xist coating
- Gain of early heterochromatin marks

(but not later heterochromatic marks such as H3K9me2 and DNA methylation)

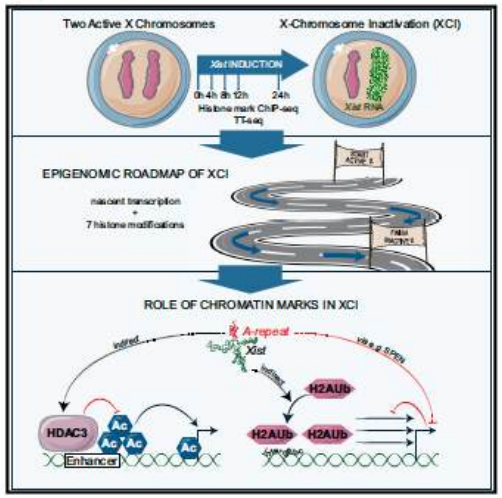


Schulz et al, Cell Stem Cell 2014

E. Heard, May 26th, 2025

The Implication of Early Chromatin Changes in X Chromosome Inactivation

Graphical Abstract



Authors

Jan Jakub Żylicz, Aurélie Bousard, Kristina Žumer, ..., Damarys Loew, Patrick Cramer, Edith Heard

Correspondence

edith.heard@curie.fr

In Brief

Żylicz et al. provide a detailed characterization of the earliest stages of X chromosome inactivation, tracing chromatin modification dynamics and uncovering the key role of chromatin changes in initiation of gene silencing.

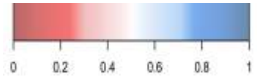
Highlights

- An epigenomic roadmap for initiation of X chromosome inactivation (XCI)
- Histone deacetylation and H2A ubiquitination are among the earliest XCI events
- HDAC3-mediated histone deacetylation is required for efficient XCI
- PcG marks are first deposited intergenically and spread when gene silencing occurs

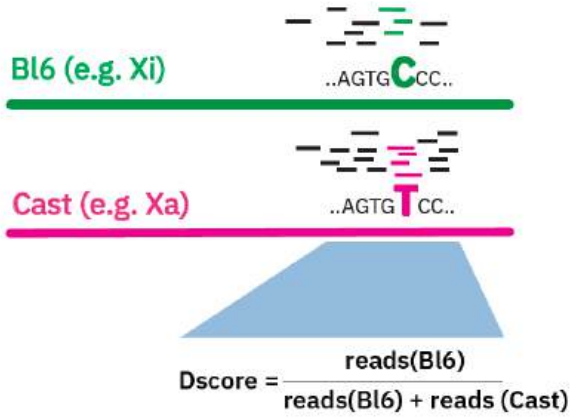
Jan Zylicz

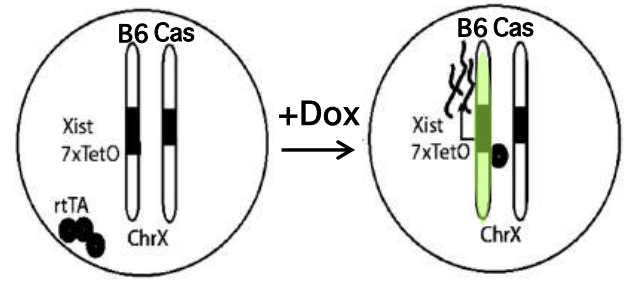
Aurelie Bousard

The Implication of Early Chromatin Changes in X Inactivation



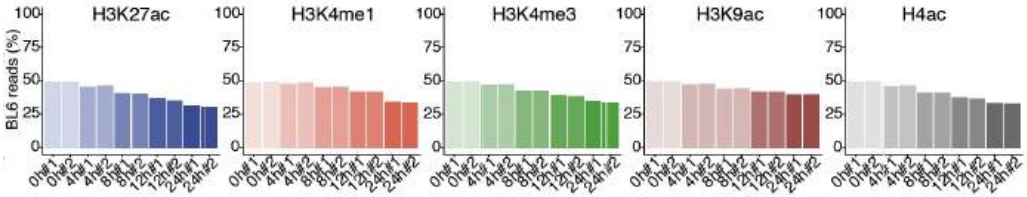
d-score

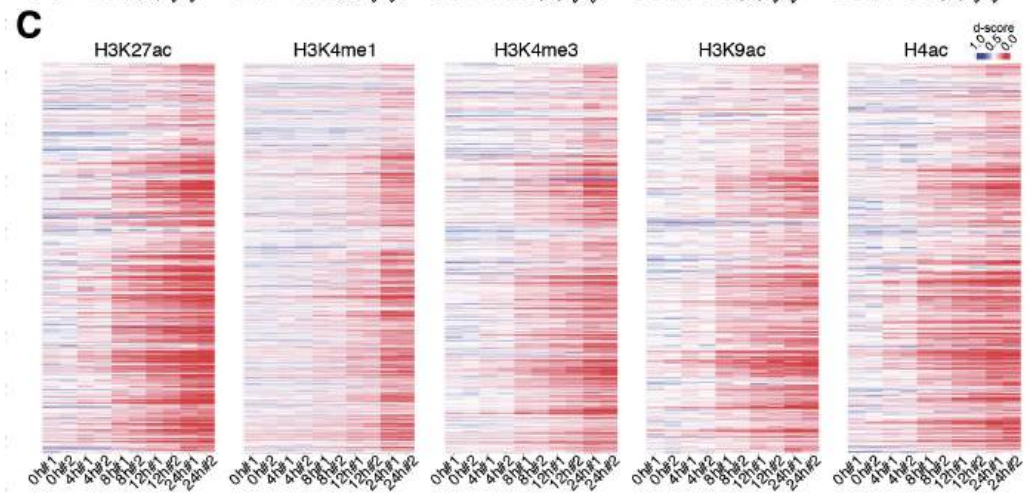




$Xa^{B6}Xa^{Cas}$ $Xi^{B6}Xa^{Cas}$

Native ChIPseq
At 0, 4h, 8h, 12h and 24h





Active Promoters:
H3K4me3, H3K27ac, H3K9ac, H4ac

Active Enhancers: H3K4me1 and H3K27ac

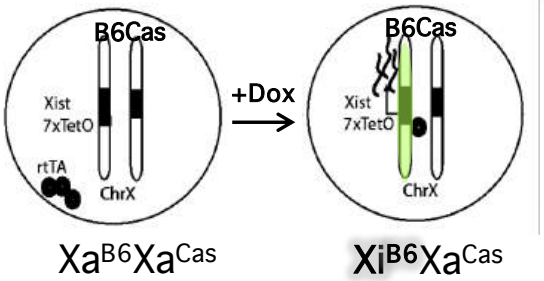
Polycomb repressive marks: H2AK119Ub and H3K27me3

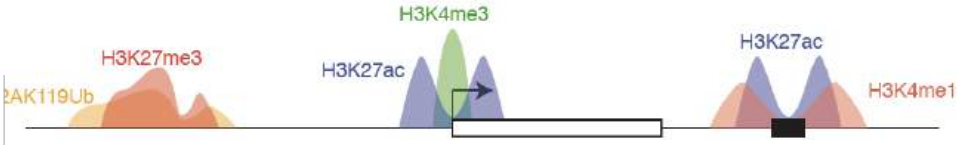
5 time-points x 8 samples x 2 biological replicates

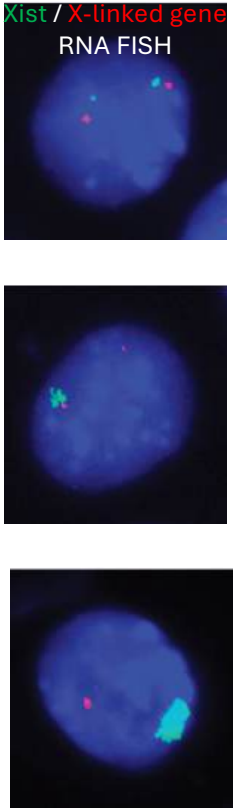
= 80 libraries

Zylicz, Bousard et al, Cell 2019

The Implication of Early Chromatin Changes in X Inactivation



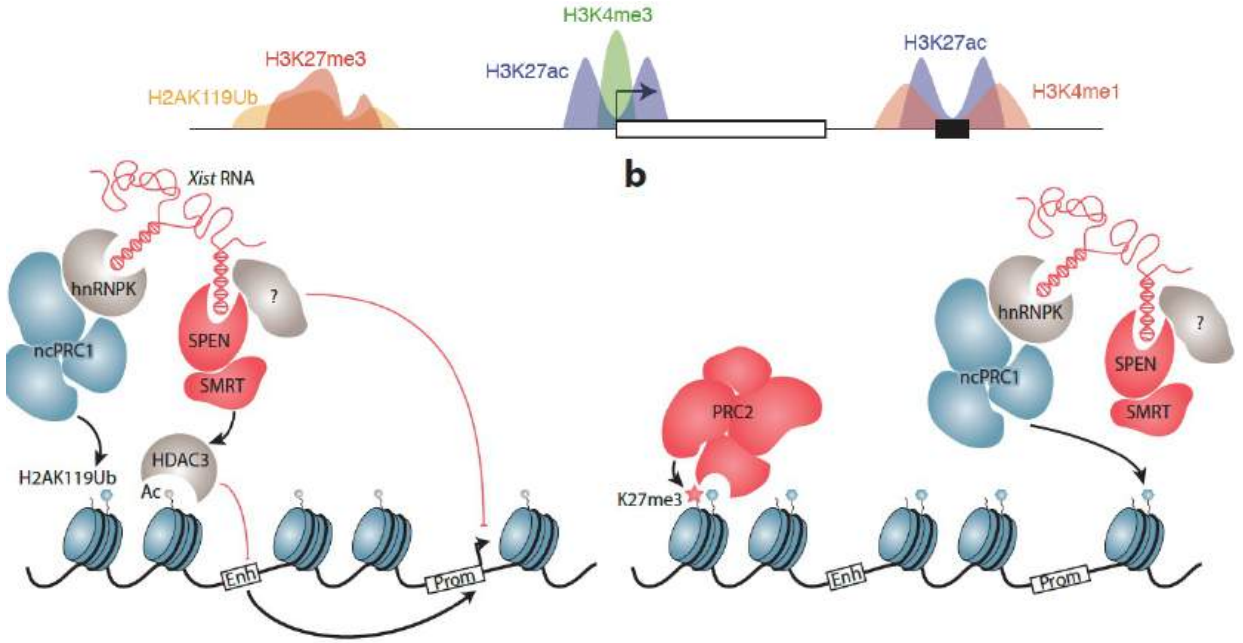




- Histone deacetylatic
- HDAC3 is required for efficient XCI of most, but not all X-linked genes
- PRC1-mediated H2AK119Ub precedes H3K27me3 (PRC2) on the Xist RNA-coated X
- Both Polycomb marks accumulate initially at intergenic regions, then spread to genic regions but only after gene silencing has occurred

Zylicz, Bousard
Bousard et all, E

The Implication of Polycomb Complexes in X Inactivation

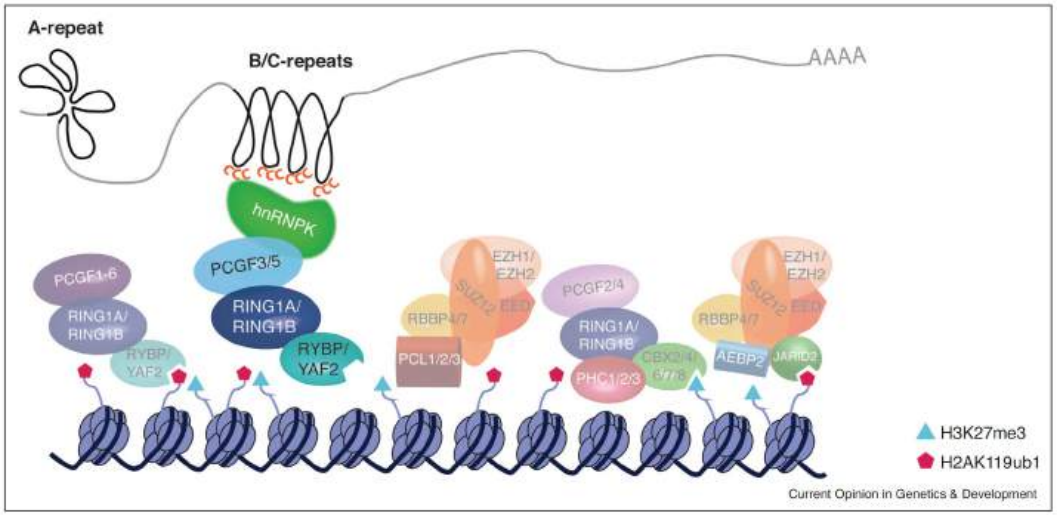


From Zylicz and Heard,
Ann Rev Biochem 2020∂

- Histone deacetylation via HDAC3 is a very early event in XCI
- HDAC3 is required for efficient XCI of most, but not all X-linked genes
- PRC1-mediated H2AK119Ub precedes H3K27me3 (PRC2) on the Xist RNA-coated X
- Both Polycomb marks accumulate initially at intergenic regions, then spread to genic regions but only after gene silencing has occurred
- During Initiation of XCI PRC1 precedes PRC2; during maintenance both PRC1 and PRC2 are required
- Different genes may have different requirements for PRC1, PRC2 or both…

Zylicz, Bousard et al, Cell 2019
Bousard et al EMBO Reports 2019

Multiple Polycomb Combinations at Different Stages of Life May Contribute to the Silent State of the Inactive X Chromosome



- Expression of Xist RNA promotes enrichment of multiple subtypes of Polycomb complexes on the inactive X chromosome.
- This is mediated by the direct interaction between the Xist B/C-repeat region of the RNA and a nuclear matrix protein, hnRNPK, which specifically engages PCGF3/5-PRC1 complexes.
- Downstream of initial PCGF3/5-PRC1 catalytic activity, self-reinforcing loops of recruitment acting through recognition mechanisms involving all non-canonical PRC1 complexes (via RYBP binding H2AK119ub1), PRC2 (via JARID2 binding H2AK119ub1) and canonical PRC1 (via CBX binding H3K27me3 deposited by PRC2)
- Once established – different genes on the inactive X have different Polycomb dependencies (for ex. in early extra-embryonic tissues) (Masui, Corbel et al, 2023 –next week)

Publication	Model(s)	Xist sequence for Polycomb recruitment	Effect on gene silencing	Identification of hnRNPK	Effect of hnRNPK KD
da Rocha *et al.*, 2014 [52]	XY mESCs with Xist transgene targeted to the *Hprt* locus	XN region: F-repeat, B-repeat and C-repeat regions (3.8kb)	No defect in gene silencing by RNA-FISH after four days of ΔXN Xist induction and similar to WT in cell survival assay (five days)	n/a	n/a
Chu *et al.*, 2015 [47]	XY mESCs with autosomal Xist transgene	n/a	n/a	Xist ChIRP-MS in mESCs	Reduced H3K27me3/ H2AK119ub1 enrichment and gene silencing after four days of Xist induction
Almeida *et al.*, 2017 [57••]	XY mESCs with autosomal Xist transgene	XN region: F-repeat, B-repeat and C-repeat regions (3.8kb)	Defect after three days of Xist induction in *Pcgf3/5* knockout mESCs compared to *Pcgf5* knockout	n/a	n/a
Pintacuda *et al.*, 2017 [58••]	XY mESCs with autosomal Xist transgene	B-repeat + partial C-repeat (0.6kb)	Defect after three days of ΔB/C Xist induction	Quantitative MS comparison of binding to *in vitro* transcribed A versus B/C repeat sequences	Reduced H2AK119ub1 enrichment after one day of Xist induction
Colognori *et al.*, 2019 [59•]	Tetraploid MEFs and XX mESCs	B-repeat only (0.3kb)	No defect in ΔB/C MEFs, major defect after fourteen days of ΔB/C mESC differentiation	LC-MS/MS of aptamer-tagged B-repeat RNA, EMSA confirming interaction *in vitro*	Loss of Xi enrichment in MEFs after two days (H2AK119ub1) or six days (H3K27me3) of RNAi
Bousard *et al.*, 2019 [60]	XY mESCs with inducible Xist	B-repeat + total C-repeat (2kb)	Little defect after two days of ΔB/C Xist induction with differentiation	ChIRP-MS comparison of full length versus ΔB/C Xist RNA	n/a
Nesterova *et al.*, 2019 [46•]	XX mESCs with inducible Xist	B-repeat + partial C-repeat (1.1kb)	Moderate defect after one day of ΔB/C Xist induction in mESCs or six days of ΔB/C Xist induction with differentiation	n/a	n/a
Schertzer *et al.*, 2019 [70••]	Trophoblast stem cells (imprinted XCI)	n/a	n/a	n/a	Reduced enrichment of H3K27me3 on ChrX and other lncRNA-imprinted regions

mESC= mouse embryonic stem cells; MEF= mouse embryonic fibroblasts; MS=mass spectometry; ChIRP-MS= comprehensive identification of RNA-binding proteins by MS; LC= liquid chromatography; EMSA= electrophoretic mobility assay

mESC, mouse embryonic stem cells; MEF, mouse embryonic fibroblasts; MS, mass spectrometry; ChIRP-MS, comprehensive identification of RNA-binding proteins by MS; LC, liquid chromatography; EMSA, electrophoretic mobility shift assay.

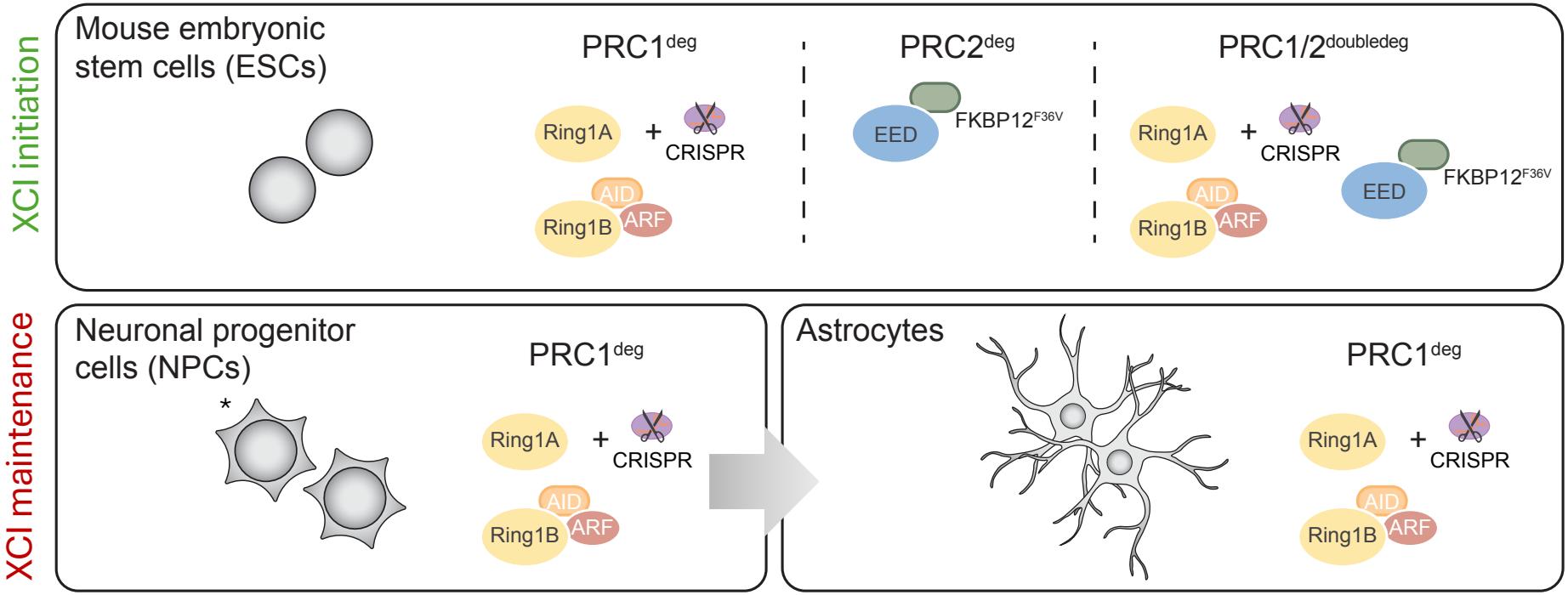
Almeida et al (2020) Curr. Op. Gen.Dev
https://doi.org/10.1016/j.gde.2020.02.023

Dissecting the roles of Polycomb complexes during X-chromosome inactivation (XCI)

Knock out of PRC1 or PRC2 in vivo (NEXT WEEK)

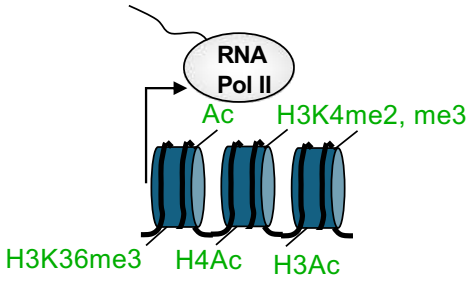
Polycomb complex degrons in F1 hybrid Xist-inducible mouse embryonic stem cells, neuronal progenitor cells + astrocytes (ongoing work in Heard lab):

- Dox-inducible upregulation of *Xist* in ESCs or random XCI by cellular differentiation
- Remove PRC1 and PRC2 acutely and reversibly via targeted proteasomal degradation

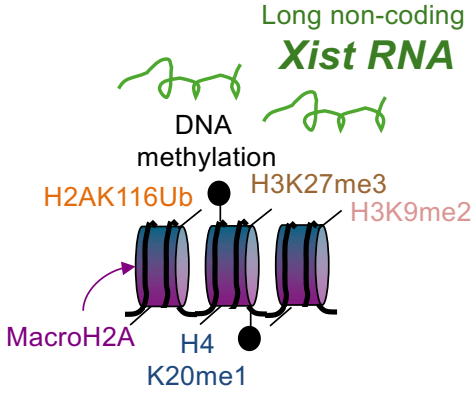


Chromatin Characteristics of the inactive X Chromosome

Identical (or almost) DNA sequences
Opposite gene activity states
Heritable through cell divisions



Active X chromatin



Inactive X chromatin

Chromatin proteins and histone modifications:

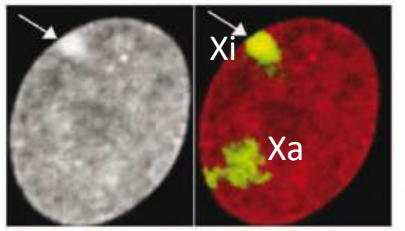
PRC1 and PRC2 complexes play roles in early maintainence of XCI

DNA methylation

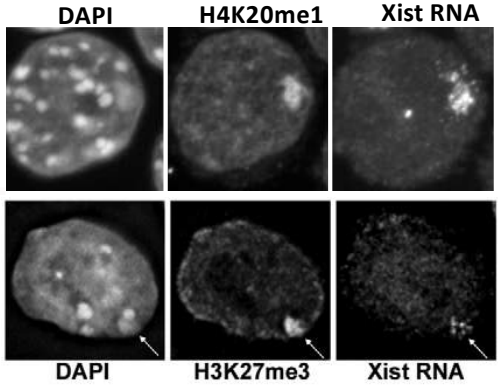
Plays a role in maintenance of the stable inactive state

Asynchronous replication timing?

Chromosome architecture?



Teller et al, Nucleus, 2013

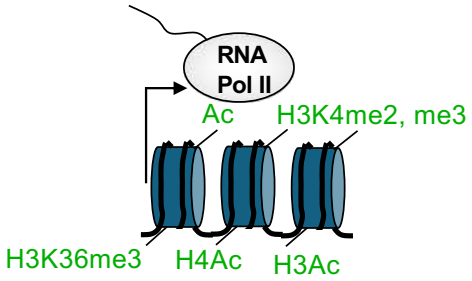


Xi-associated proteins:

SPEN
SAF-A
macroH2A
PRC2
PRC1
ATRX
SMCHD1
CDYL

Chromatin and 3D Organisation of the Inactive X Chromosome

Identical (or almost) DNA sequences
Opposite gene activity states
Heritable through cell divisions



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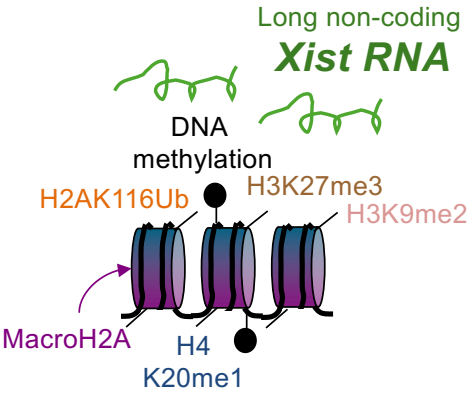

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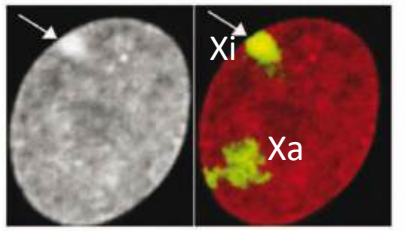
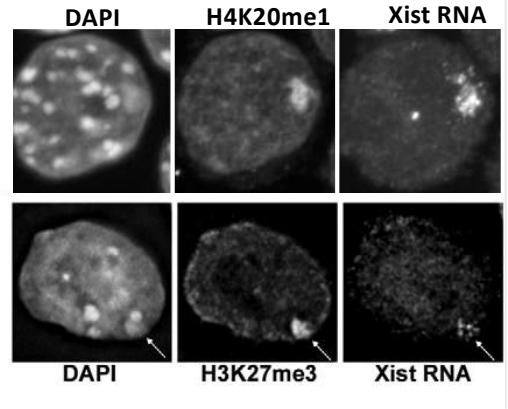
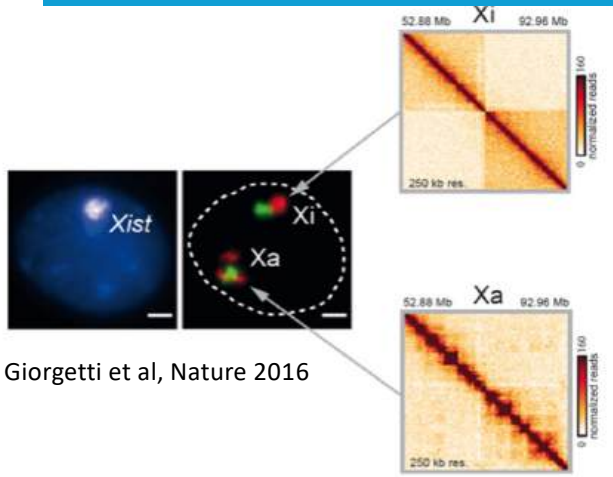


Teller et al, Nucleus, 2013

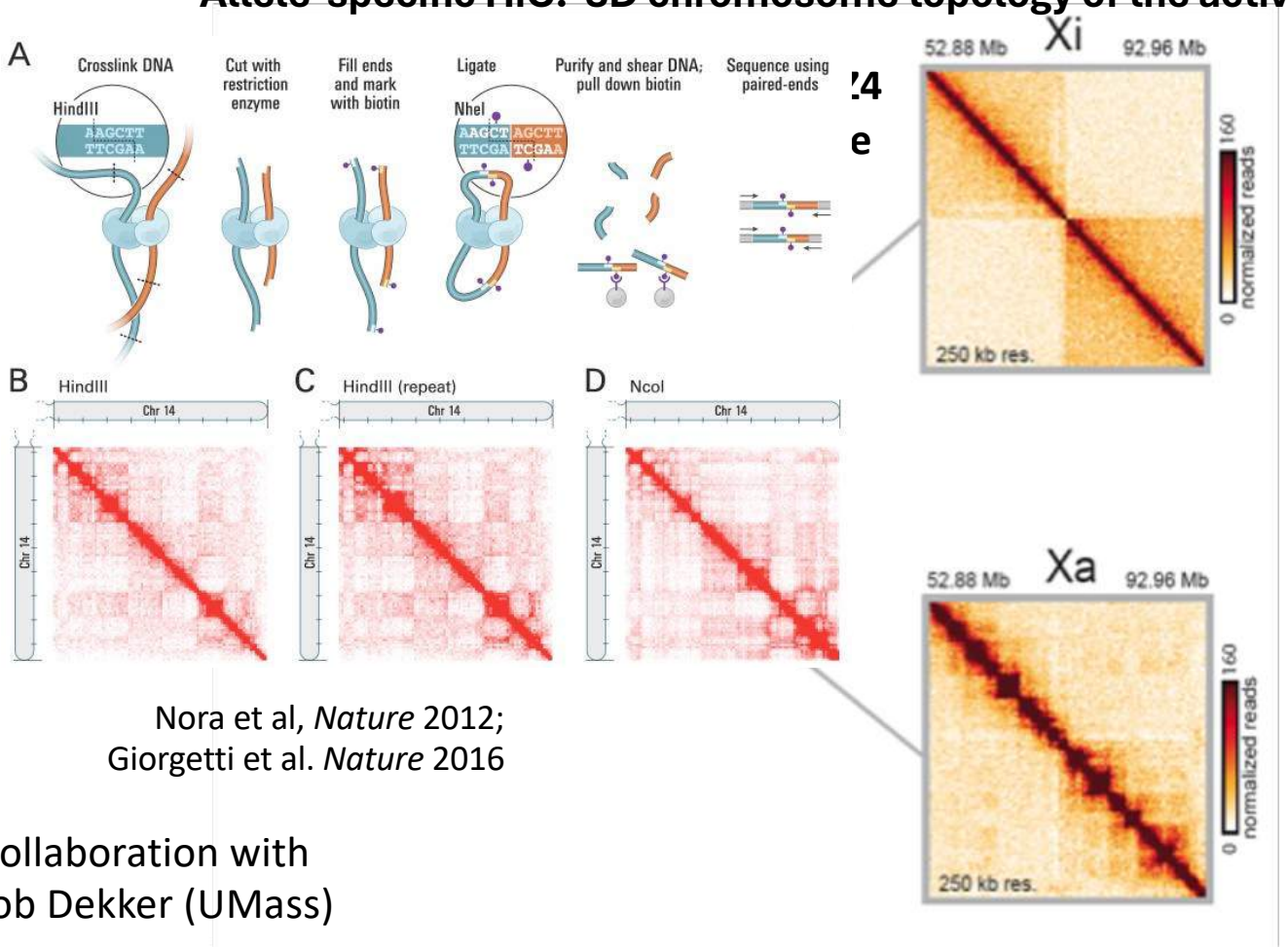




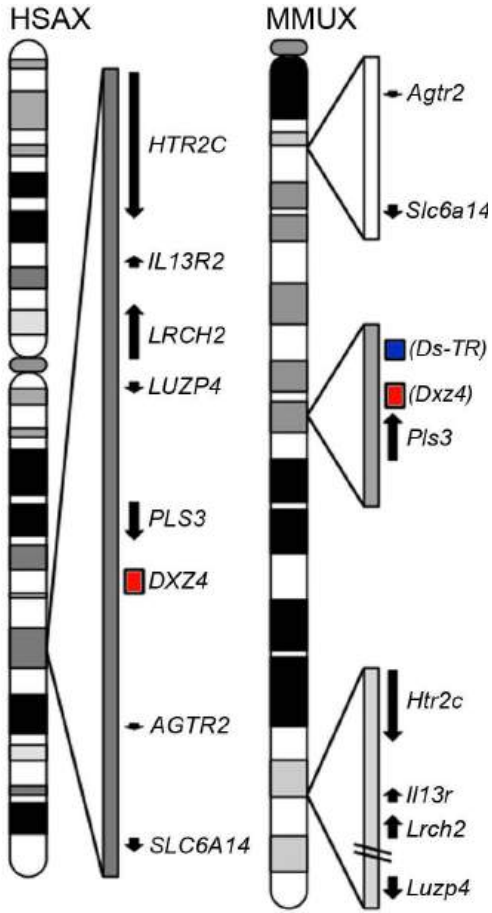
Giorgetti et al, Nature 2016

Inactive X-Chromosome 3D Organisation

Allele-specific HiC: 3D chromosome topology of the active and inactive X chromosomes



Nora et al, *Nature* 2012;
Giorgetti et al. *Nature* 2016



Collaboration with
Job Dekker (UMass)

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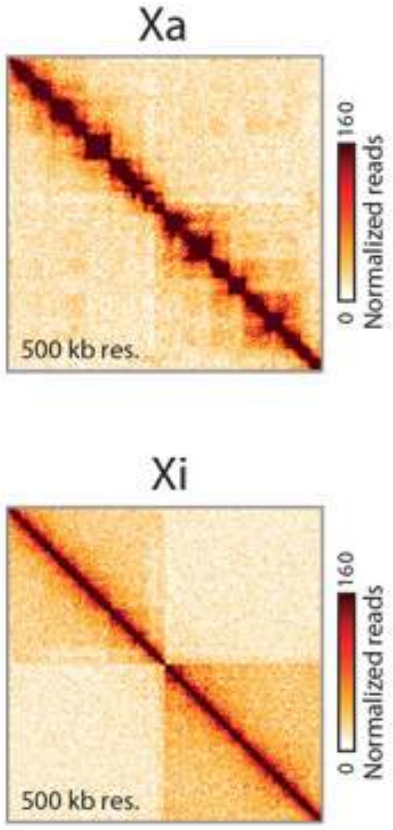
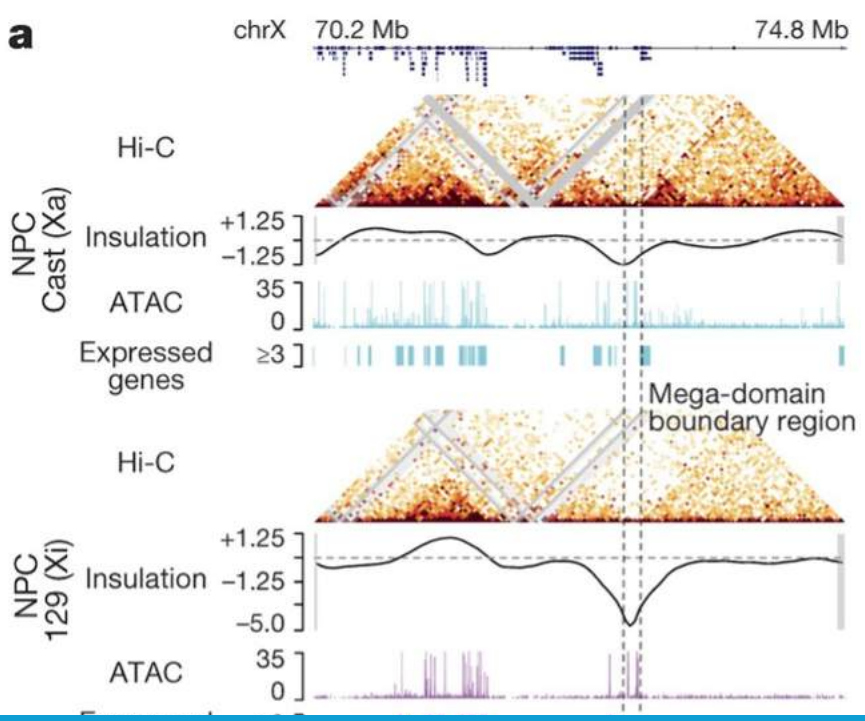
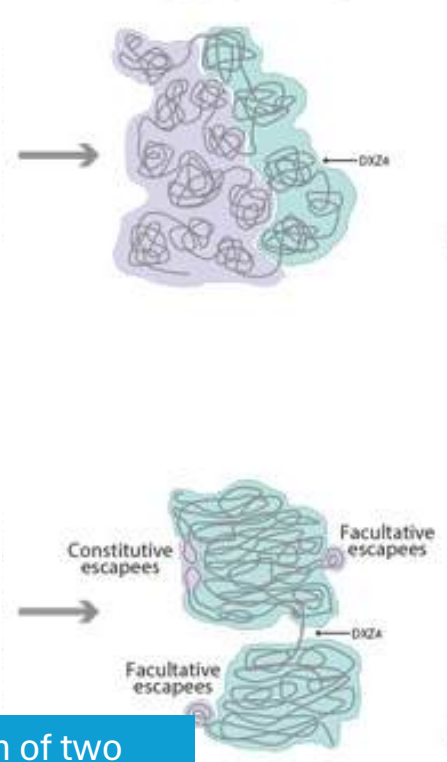
Inactive X-Chromosome 3D Organisation



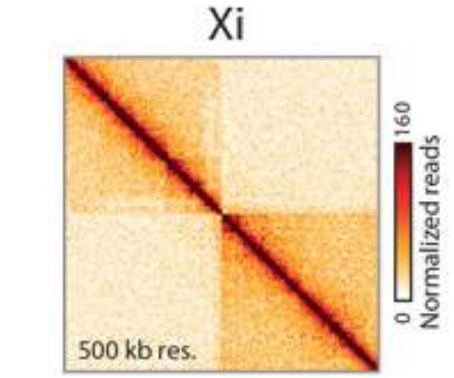


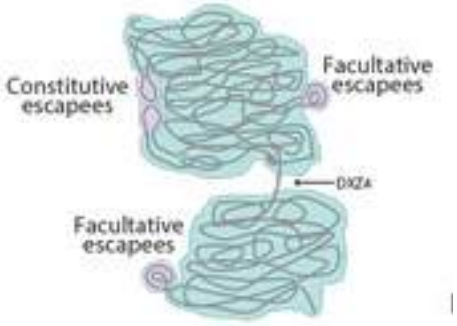


Giorgetti et al. *Nature* 2016

- The inactive X is “unstructured” except for the formation of two megadomains, spearated by DXZ4 macrosatelllite
- Plus a few TAD-like domains that correspond to genes escaping XCI: are these a cause or consequence of escape?
- The CTCF-enriched DXZ4 macrosatellite does NOT influence XCI but it does influence frequency of escape (NEXT WEEK)

Inactive X-Chromosome 3D Organisation





The non-canonical SMC protein SmcHD1 antagonises TAD formation and compartmentalisation on the inactive X chromosome

Michal R. Gdula[1], Tatyana B. Nesterova[1], Greta Pintacuda[1], Jonathan Godwin[1], Ye Zhan[2], Hakan Ozadam[2], Michael McClellan[3], Daniella Moralli[4], Felix Krueger[5], Catherine M. Green[4], Skirmantas Kriaucionis[3], Edith Heard[7], Job Dekker[2] & Neil Brockdorff[1]

- Non-canonical SMC family protein, SMCHD1 is essential for the maintenance of XCI (Gendrel et al 2012)
- It localizes to the Xi and may be involved in the hypermethylation of CpG islands, SMCHD1 contributes to the formation of H3K9me3 blocks on the Xi, which may also stabilize gene repression
- SMCHD1 may collaborate with Polycomb Repressive Complex 1 (PRC1) to reorganize the 3D structure of the inactive X chromosome (Xi) – eliminating compartments?

Smchd1-Dependent and -Independent Pathways Determine Developmental Dynamics of CpG Island Methylation on the Inactive X Chromosome

Anne-Valerie Gendrel,[1,7,8] Anwyn Apedaile,[3,8] Heather Coker,[1] Ausma Termanis,[4] Ilona Zvetkova,[3,9] Jonathan Godwin,[1] Y. Amy Tang,[3,10] Derek Huntley,[5] Giovanni Montana,[6] Steven Taylor,[2] Eleni Giannoulatou,[2] Edith Heard,[7] Irina Stancheva,[4] and Neil Brockdorff[1,*]

Article
Cell Reports

Smchd1 Targeting to the Inactive X Is Dependent on the *Xist*-HnrnpK-PRC1 Pathway

Authors
Natasha Jansz, Tatyana Nesterova, Andrew Keniry, ..., Neil Brockdorff, James M. Murphy, Marnie E. Blewitt

SMCHD1 Merges Chromosome Compartments and Assists Formation of Super-Structures on the Inactive X

Chen-Yu Wang,[1,2,3] Teddy Jégu,[1,2,3] Hsueh-Ping Chu,[1,2,3] Hyun Jung Oh,[1,2,3] and Jeannie T. Lee[1,2,3,4,*]

Gdula et al, Nat. Comm (2019) doi.org/10.1038/s41467-018-07907-2

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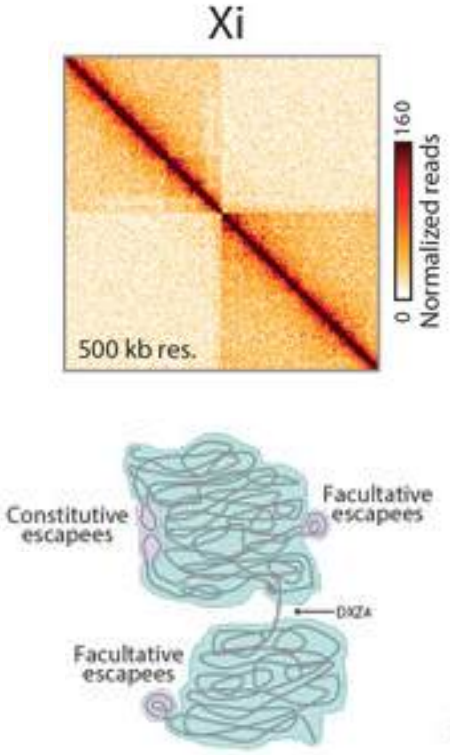
Inactive X-Chromosome 3D Organisation



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- Non-canonical SMC family protein, SmcHD1 is a key factor in defining the unique chromosome architecture of the Xi.
- Specifically, allelic mapping of the transcriptome and epigenome in SmcHD1 mutant cells reveals the appearance of submegabase domains defined by gene activation, CpG hypermethylation and depletion of Polycomb-mediated H3K27me3.

Tra

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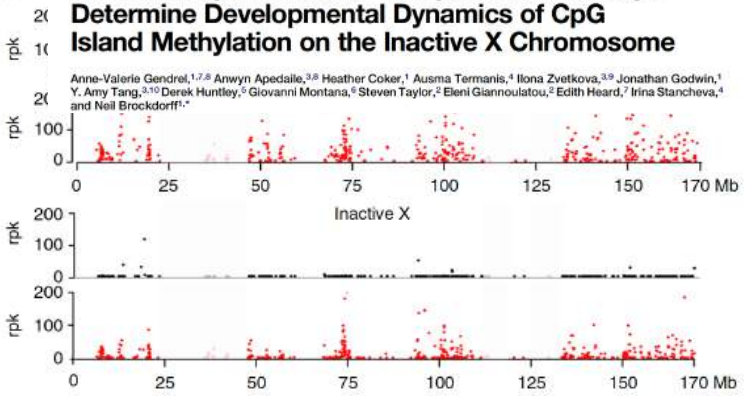
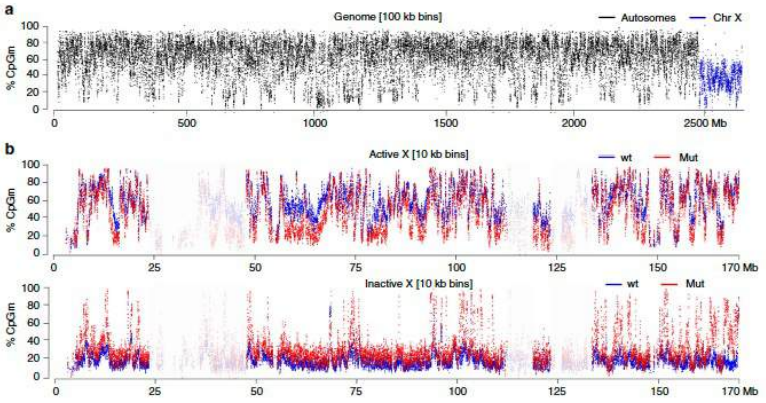


DNA Methylomes



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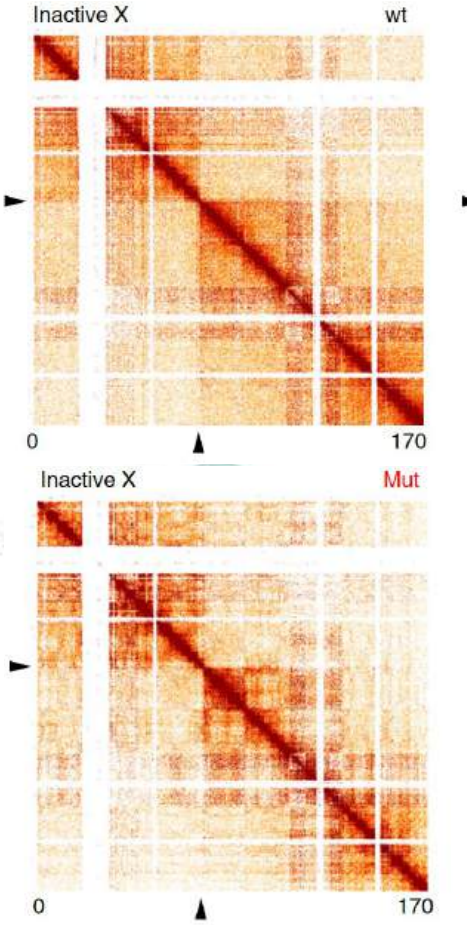

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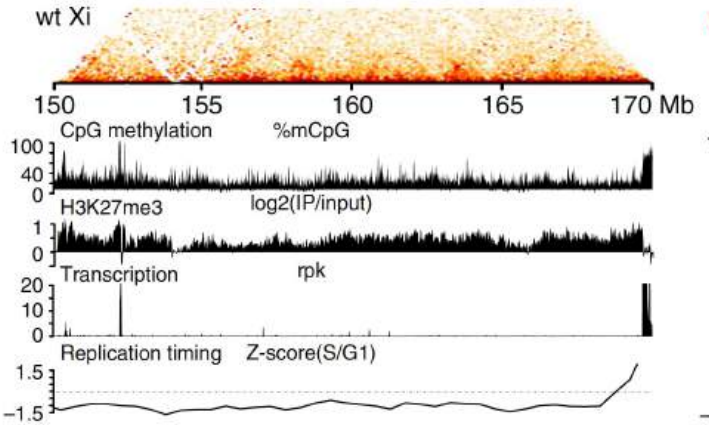
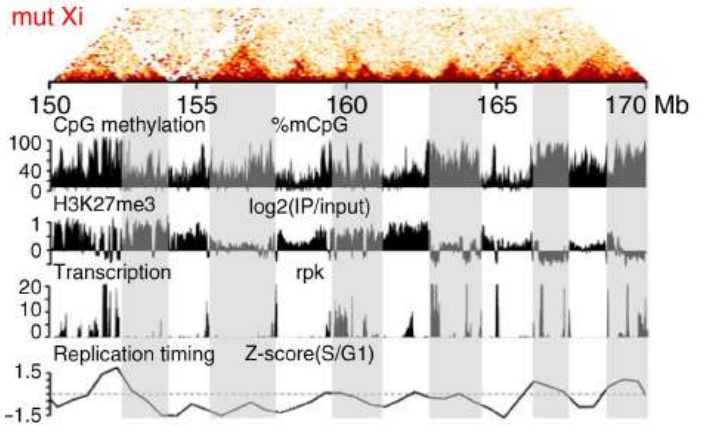
- Specifically, allelic mapping of the transcriptome and epigenome in SmcHD1 mutant cells reveals the appearance of submegabase domains defined by gene activation, CpG hypermethylation and depletion of Polycomb-mediated H3K27me3.
- These domains, which correlate with sites of SmcHD1 enrichment on Xi in wild-type cells, additionally adopt features of active X chromosome higher-order chromosome architecture, including A/B compartments and partial restoration of TAD boundaries.
- Xi chromosome architecture changes also occurred following SmcHD1 knockout in a somatic cell model, but in this case, independent of Xi gene derepression.





Gdula et al, Nat. Comm (2019) doi.org/10.1038/s41467-018-07907-2

COLLÈGE DE FRANCE 1530

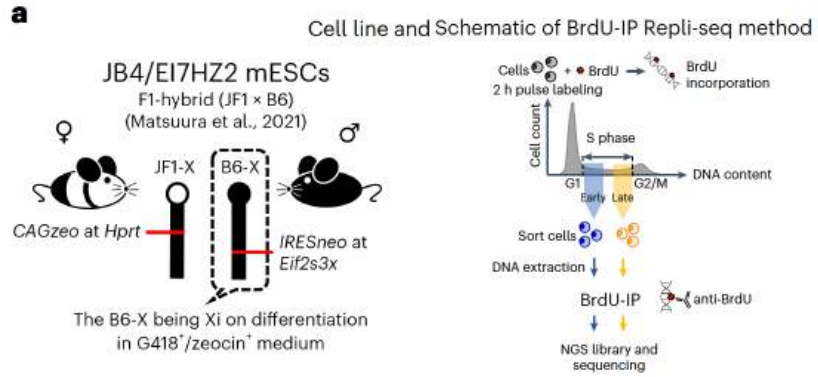
Inactive X-Chromosome DNA Replication

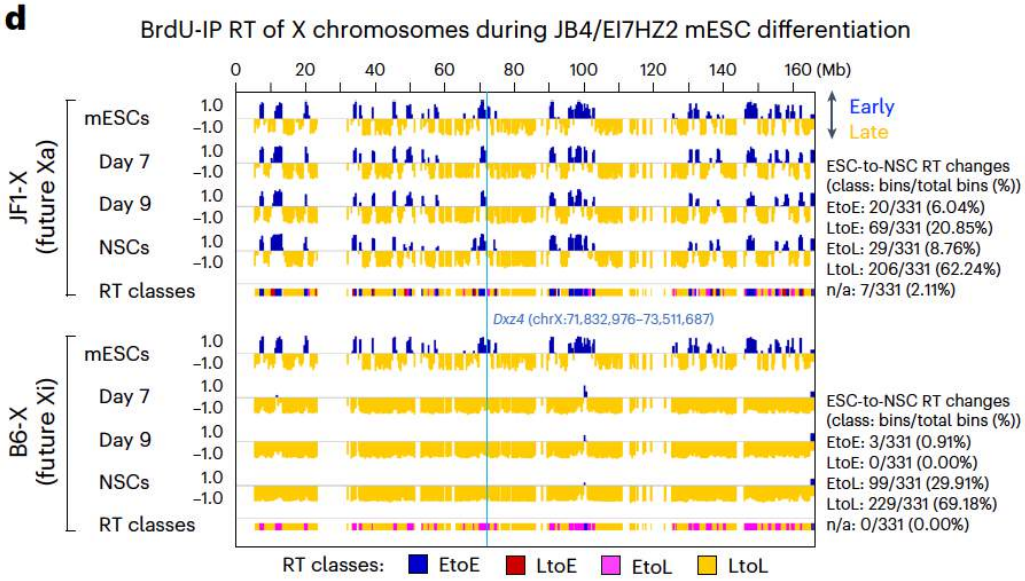
Replication dynamics identifies the folding principles of the inactive X chromosome

Received: 20 September 2022
Accepted: 28 June 2023

Rawin Poonperm[1], Saya Ichihara[2,5], Hisashi Miura[1], Akie Tanigawa[1], Koji Nagao[3], Chikashi Obuse[3], Takashi Sado[2,4] & Ichiro Hiratani[1]

- Chromosome-wide late replication is an enigmatic hallmark of the inactive X chromosome (Xi). How it is established and what it represents remains obscure.
- By single-cell DNA replication sequencing, we show that the entire Xi is reorganized to replicate rapidly and uniformly in late S-phase during X-chromosome inactivation (XCI), reflecting its relatively uniform structure revealed by Chromosome Conformation Capture.
- Despite this uniformity, only a subset of the Xi became earlier replicating in SmcHD1-mutant cells.





 Poonperm et al, NSMB (2023) https://doi.org/10.1038/s41594-023-01052-1

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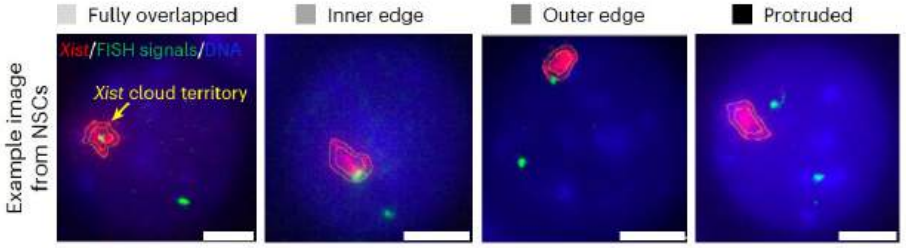

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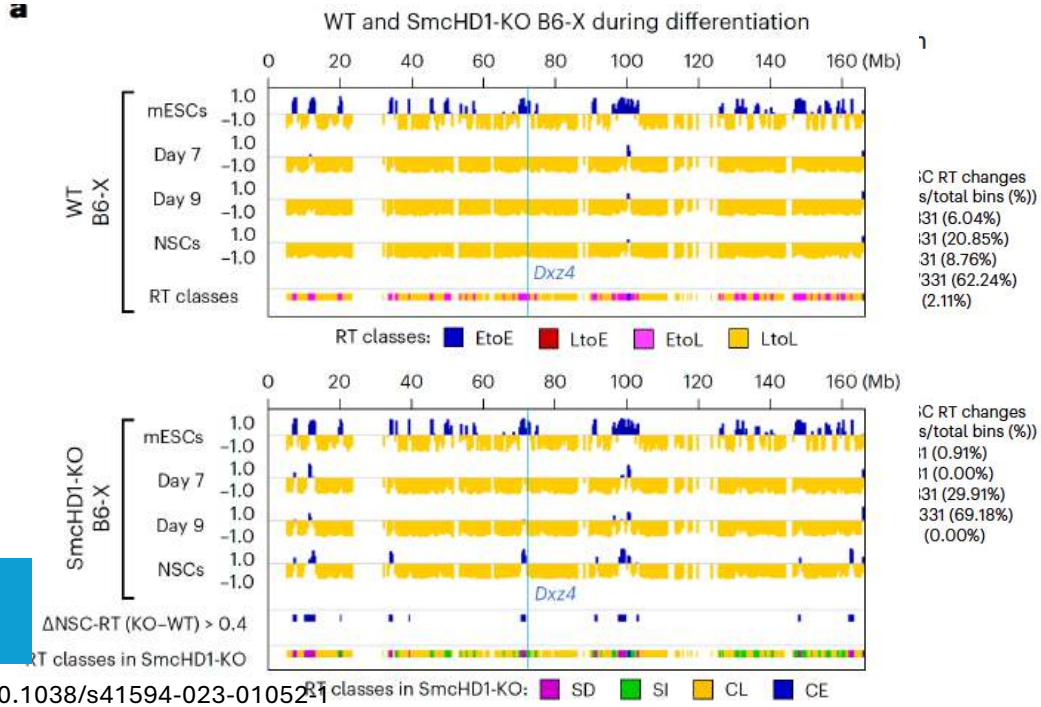
- Despite this uniformity, only a subset of the Xi became earlier replicating in SmcHD1-mutant cells.
- In the mutant, these domains protruded out of the Xi core, contacted each other and became transcriptionally reactivated. 4C-seq suggested that they constituted the outermost layer of the Xi even before XCI and were rich in escape genes.
- This default positioning may form the basis for their inherent heterochromatin instability in cells lacking the Xi-binding protein SmcHD1 or exhibiting XCI escape.
- These observations underscore the importance of 3D genome organization for heterochromatin stability and gene regulation.



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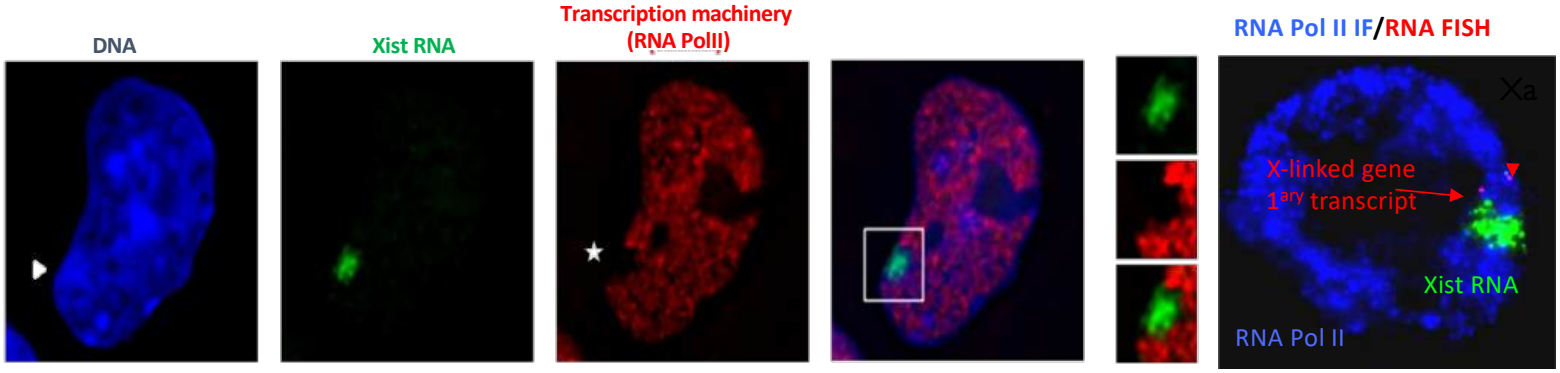
Xist RNA forms a Nuclear Compartment depleted of Transcription



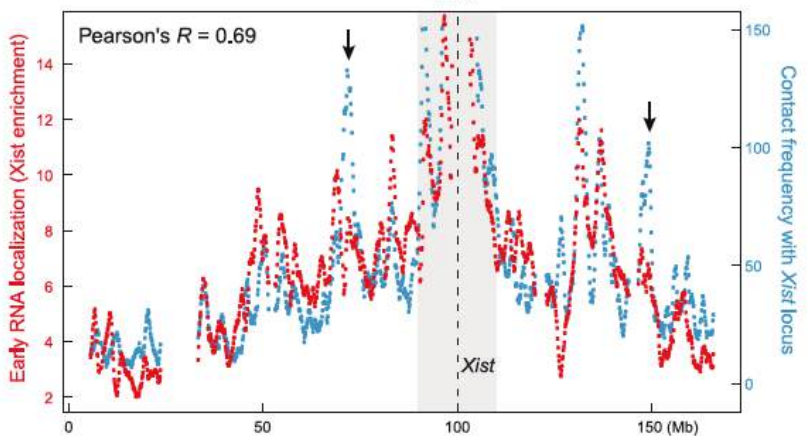
Xist RNA forms a silent "compartment" that is depleted for RNA PolII and transcription factors

Genes are positioned at the edge of the compartment but move into the Xist RNA domain as they are silenced.

Genes that escape XCI remain external to the Xist domain…

The Xist lncRNA Exploits Three-Dimensional Genome Architecture to Spread Across the X Chromosome

Jesse M. Engreitz,[1,2] Amy Pandya-Jones,[3] Patrick McDonel,[1] Alexander Shishkin,[1] Klara Sirokman,[1] Christine Surka,[1] Sabah Kadri,[1] Jeffrey Xing,[1] Alon Goren,[1] Eric S. Lander,[1,4,5*] Kathrin Plath,[3*] Mitchell Guttman[3*†]



Okamoto et al, Science 2004
Chaumeil et al, Genes Dev. 2006
Chow et al, Cell 2010

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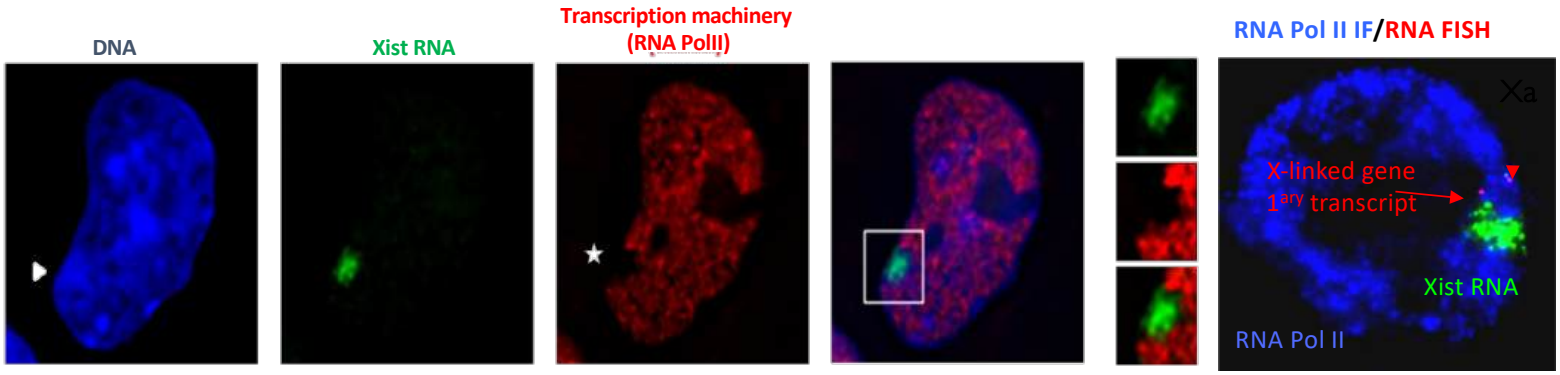

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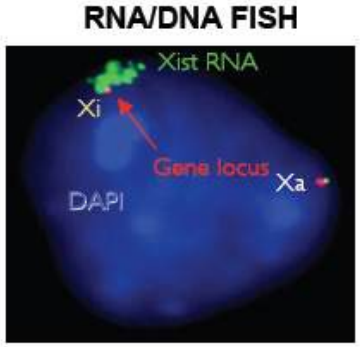
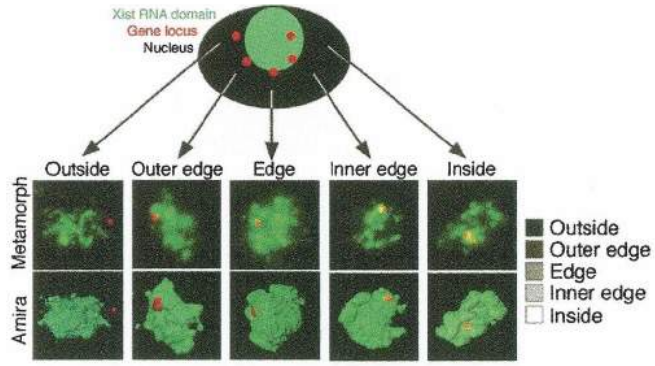




Does this RNA polymerase II depletion from the inactive X chromosome territory represent a physical compartmentalization?

Okamoto et al, Science 2004
Chaumeil et al, Genes Dev. 2006
Chow et al, Cell 2010

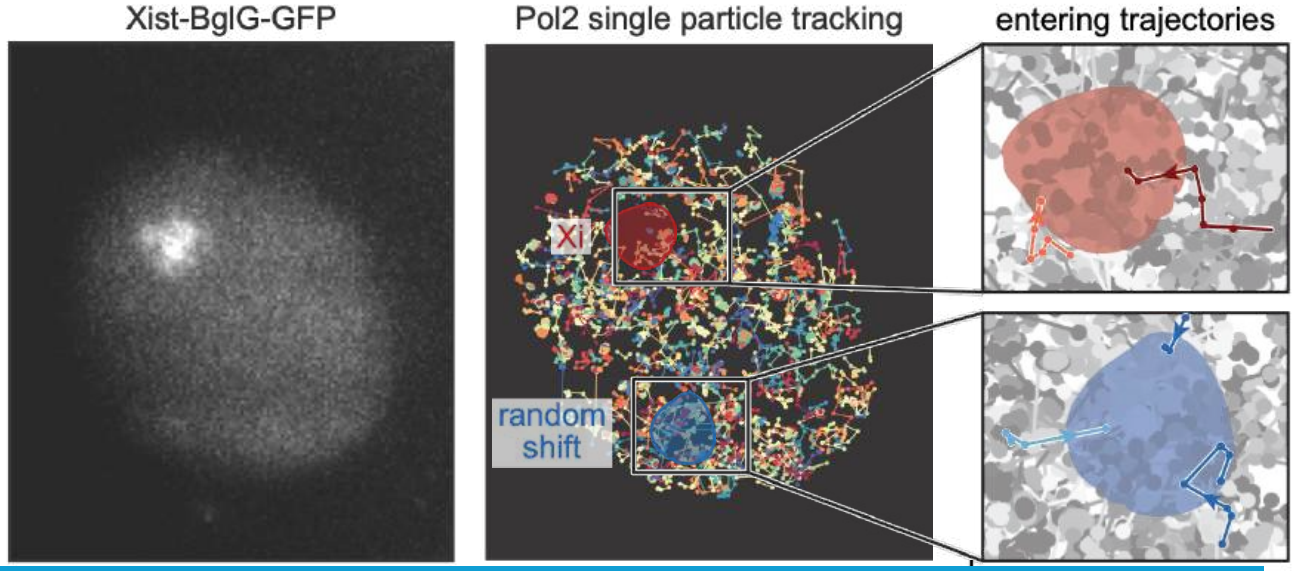
Does Xist RNA lead to RNA PolII physical exclusion/ phase separation?

SPT-PALM: single particle tracking

Xist-BGL-GFP imaging and RNAPII RPB1 and RPB3 single particle tracking

(5.477ms between frames, 1ms exposure, 3 min tracking) in the same cell.

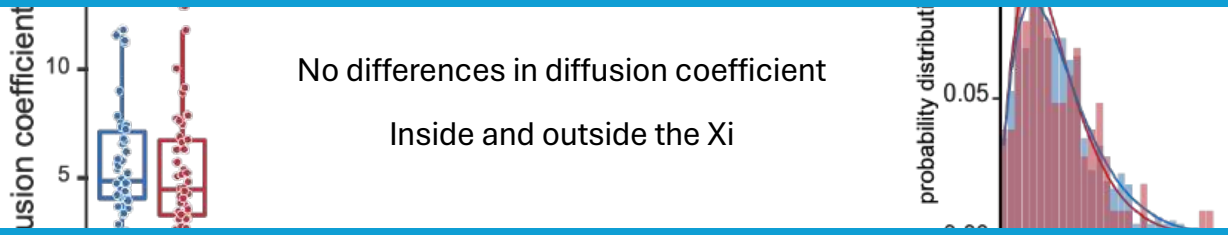
Each trajectory is shown with a random color.



Samuel Collombet

Collaboration with Darzaq/Tjian lab

No "barrier" effect on Xist-coated X chromosome preventing RNA PolII diffusion during initiation of XCI



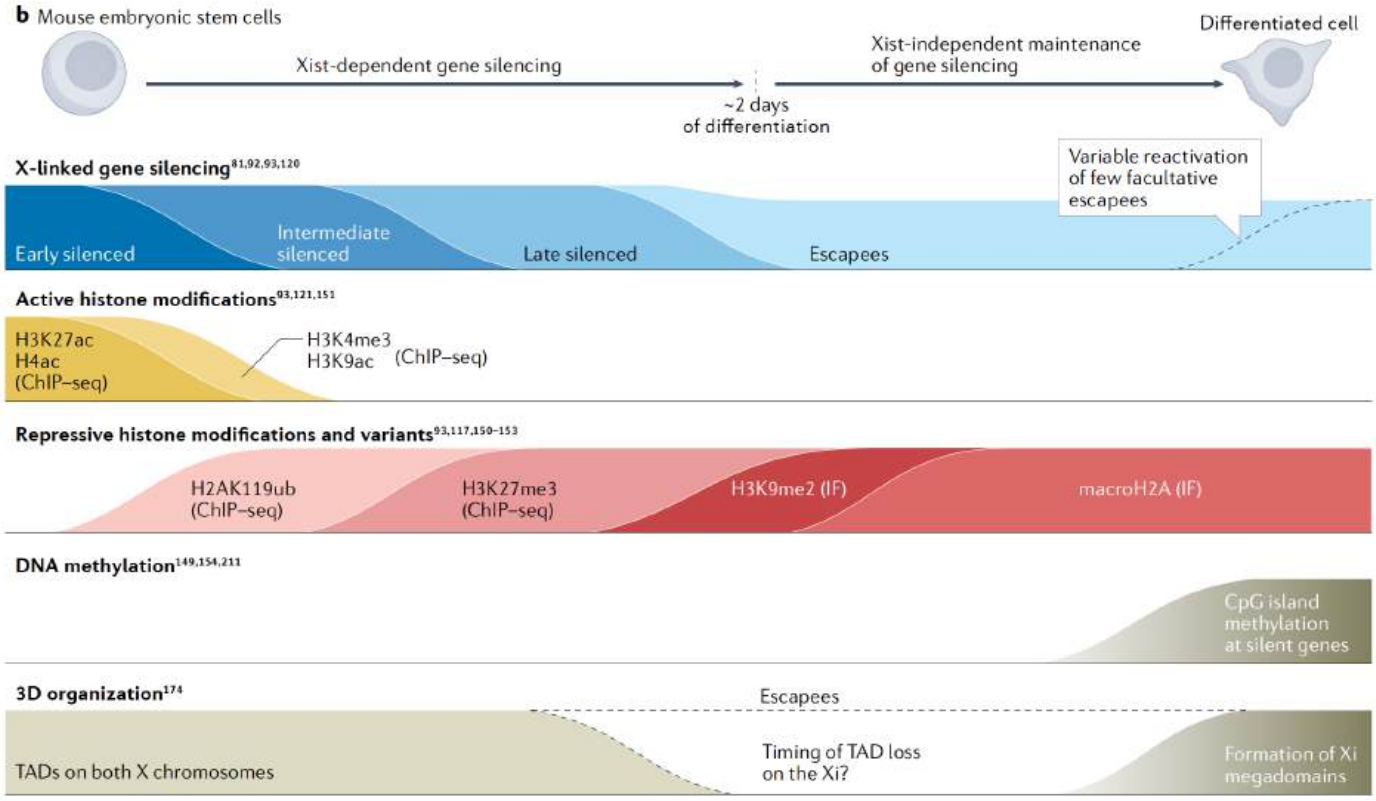
No differences in diffusion coefficient

Inside and outside the Xi

Early "exclusion" of RNA PolII during initiation of XCI is presumably due to the factors that Xist RNA recruits to silence genes

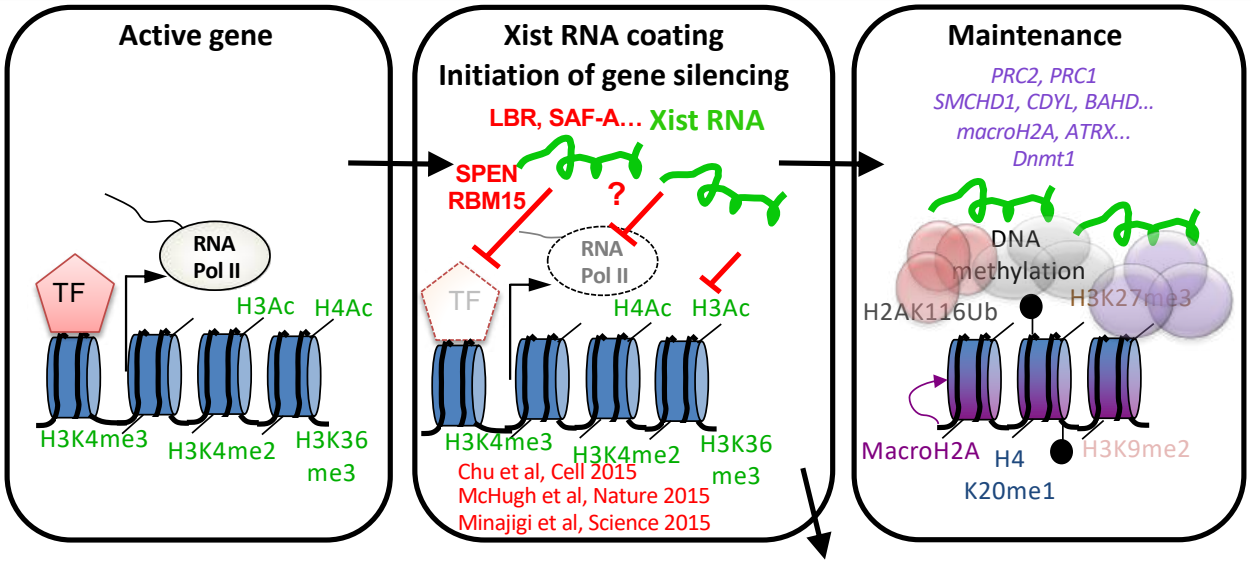
X inactivation: a classic example of facultative heterochromatin and a paradigm for epigenetic control

Kinetics of Random XCI in Embryonic Stem Cells

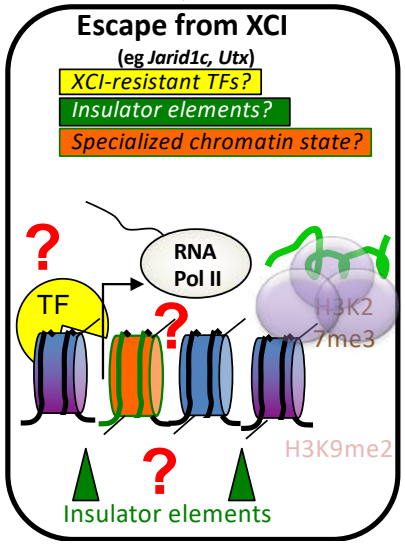


Review by Loda, Collombet and Heard, 2022

Silencing and Escape from X-chromosome inactivation

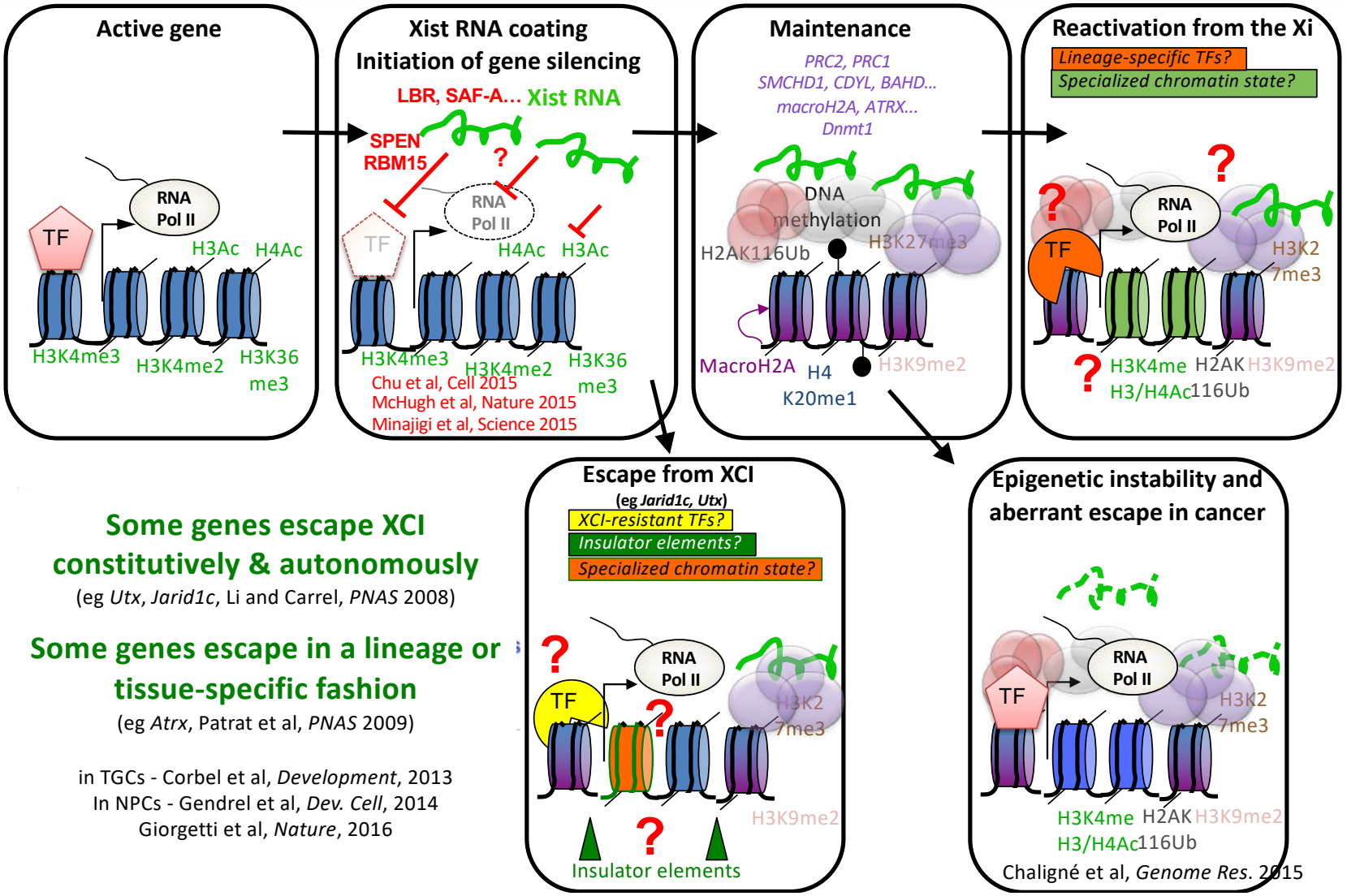


Some genes escape XCI constitutively & autonomously
(eg *Jarid1c*, Li and Carrel, *PNAS* 2008)



Reviewed in:
Gendrel and Heard, *Ann. Rev. Dev. Biol*. 2014
Galupa and Heard, *Curr. Op. Gen. Dev*. 2015

Silencing and Escape from X-chromosome inactivation



Chaligné et al, *Genome Res.* 2015

Some genes escape XCI constitutively & autonomously

(eg *Utx*, *Jarid1c*, Li and Carrel, *PNAS* 2008)

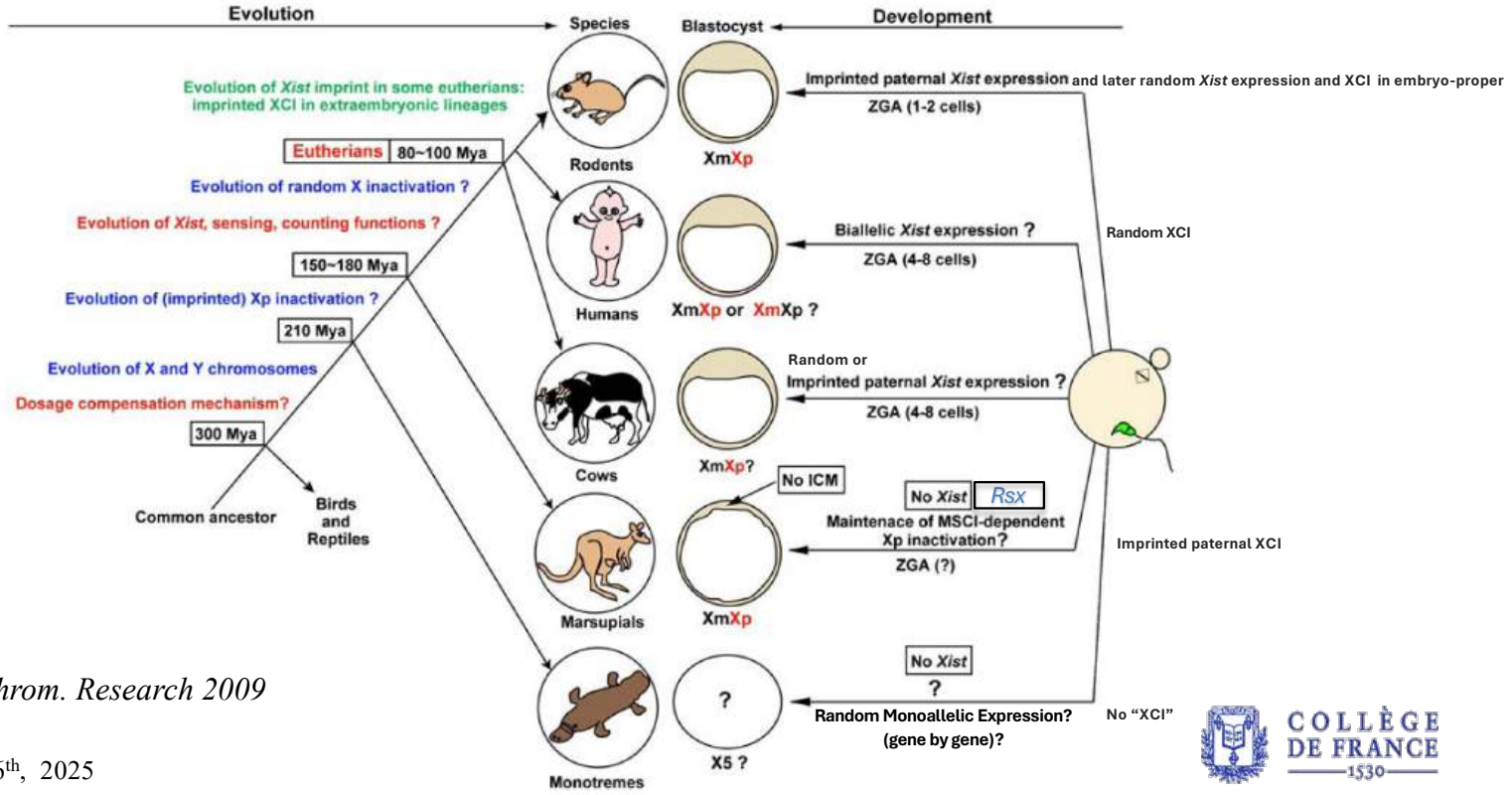
Some genes escape in a lineage or tissue-specific fashion

(eg *Atrx*, Patrat et al, *PNAS* 2009)

in TGCs - Corbel et al, *Development*, 2013
In NPCs - Gendrel et al, *Dev. Cell*, 2014
Giorgetti et al, *Nature*, 2016

NEXT WEEK: Developmental and Evolutionary Dynamics of XCI

Different mammals have chosen different strategies of paternally imprinted X inactivation and/or random X inactivation



From Okamoto and Heard, Chrom. Research 2009

E. Heard, May 26th, 2025

COLLÈGE DE FRANCE 1530

COURS 2025

12 mai 2025
Découverte de l’inactivation du chromosome X (lyonisation)

19 mai 2025
La génétique et l’épigénétique de l’inactivation du chromosome X et d’autres exemples d’expression monoallélique

26 mai 2025
Évolution de l’inactivation du chromosome X et dynamique développementale

2 juin 2025
Implications de l’inactivation du chromosome X pour la biologie féminine

10-11 juin 2025 Colloque