CHAIRE ÉPIGÉNÉTIQUE ET MÉMOIRE CELLULAIRE

Edith Heard

Année 2012-2013 :
"Épigénétique, développement et hérédité"

18 Février, 2013

Cours III
"L'inactivation du chromosome X chez les mammifères,
un exemple de mémoire mitotique"

Séminaire
Joost Gribnau
"X-Chromosome Inactivation Mechanisms"

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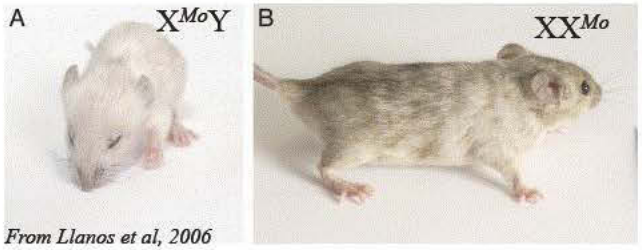
The Discovery of X-Chromosome Inactivation

Mary Lyon

"The (Mottled heterozygous) females were variegated…(but) I found one in which the original animal of this particular mutant was a mottled male, which was odd because males have got only one X chromosome. [] Then it occurred to me that he had a mutation that had occurred in him, when he was just an embryo, when he was just a few cells, and that gave rise to one progeny group of cells with a mutant X chromosome and another group of cells with the unmutated, normal X chromosome. So this original mutant male was a mosaic of two types of cells, some with the mutated X chromosome and others with the normal X chromosome.[]

So then, it occurred to me that if that explanation of him having two types of cells applied to his pattern, could it not also apply to the pattern of his daughters? His daughters could have two types of cells, one with the mutant gene active and one with the normal gene active."

Interview of M. Lyon by J. Gitschier, 2010, PloS Genet.



From Llanos et al, 2006

- Female mice carrying X-linked mutations such as *Mottled* or *Tabby* show coat colour variegation
- Male mutant mice show severe phenotypes and no coat colour variegation

Lyon, M. F. (1961), Gene Action in the X-chromosome of the Mouse (Mus musculus L.) Nature. 190 (4773): 372-3.

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The Discovery of X-Chromosome Inactivation

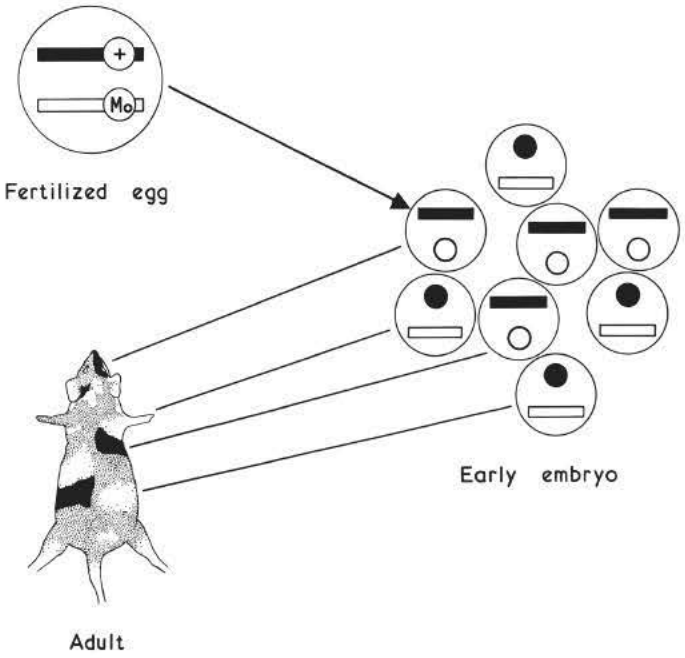
Mary Lyon

The hypothesis formulated by Mary Lyon in 1961 was that:

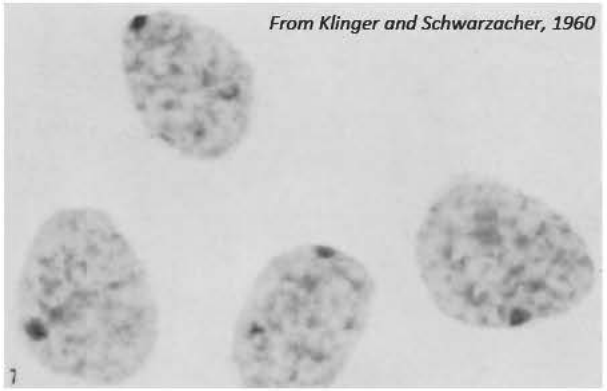
(1) the heteropyknotic X chromosome was genetically inactivated
(2) that it could be either paternal or maternal in origin in different cells of the same animal,
(3) that the inactivation occurred <u>early in embryonic development,</u> and once established was stably maintained

Also, XO mice are normal fertile females => female mice needs only one X chromosome to develop normally (Welshons and Russell, 1959)

Adapted from Mary Lyon, Henry Stewart Talks



Sex-chromatin in female mammals is seen in the mouse, rat, opossum, and man. Ohno et al, 1959, 1960, 1961.



Barr and Bertram, 1949, *Nature*.
Ohno et al, 1959, *Exp Cell Res*.

Lyon, M. F. (1961), Gene Action in the X-chromosome of the Mouse (Mus musculus L.) Nature. 190 (4773): 372-3.

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The Discovery of X-Chromosome Inactivation

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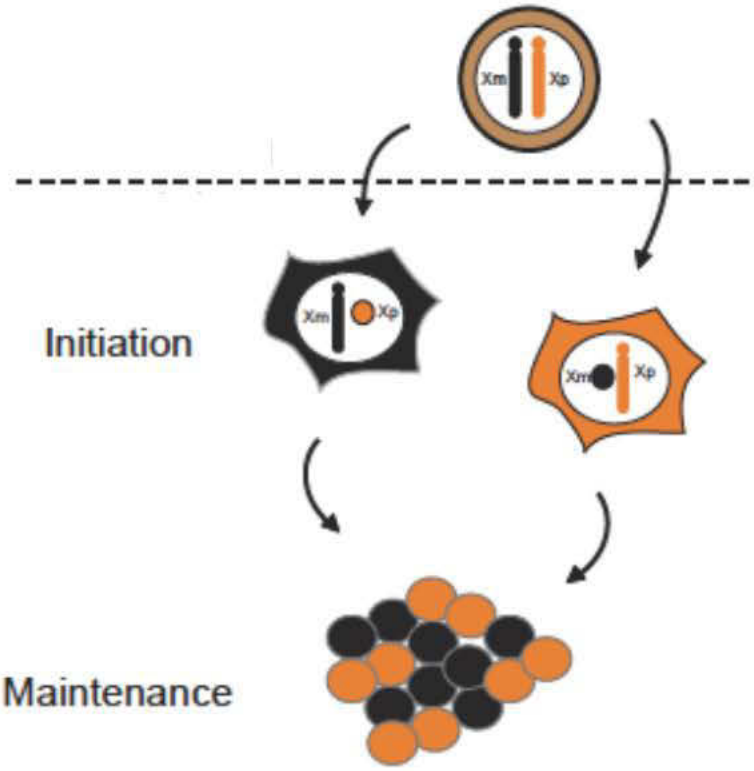

Lyon, M. F. (1961), Gene Action
(Mus musculus L.) Nature. 190 (

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The Discovery of X-Chromosome Inactivation

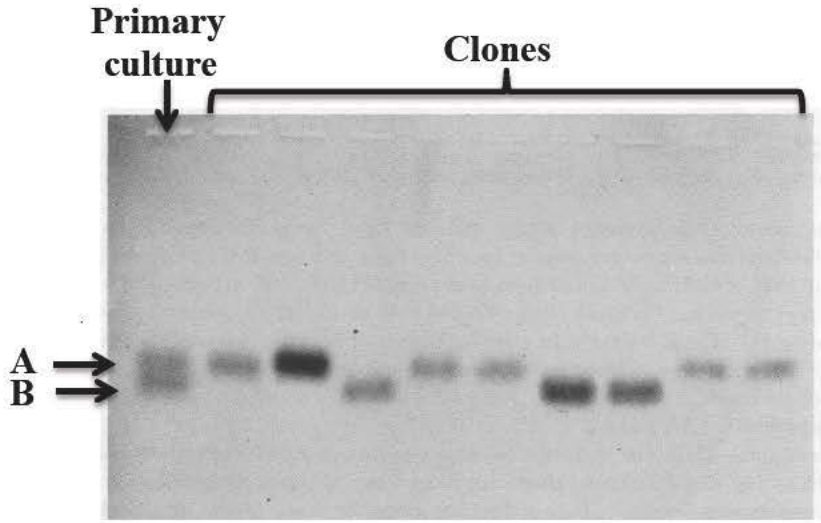
*DEMONSTRATION OF TWO POPULATIONS OF CELLS IN THE HUMAN FEMALE HETEROZYGOUS FOR GLUCOSE-6-PHOSPHATE DEHYDROGENASE VARIANTS**

Davidson et al, 1963, PNAS.

Males can have a fast migrating G-6-PD band (A) or a slow one (B).
Females can have A, B, or both A and B.

If the "Lyon Hypothesis" applies, the female who is heterozygous for the two electrophoretic variants should also be a mosaic: some of her cells producing A type G-6-PD, some the B type, but none producing both. The appearance of two distinct populations of cells in the female heterozygous (for) G-6-PD variants is direct evidence in favor of the "Lyon Hypothesis."

As far as the locus for G-6-PD is concerned, in each single cell only one X chromosome is functional. However, these data do not imply that one entire X chromosome is inactivated.

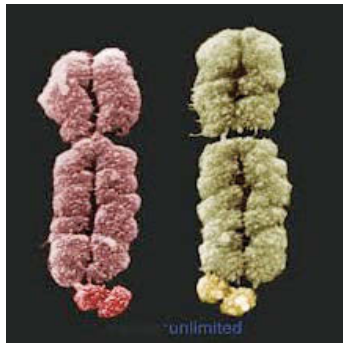


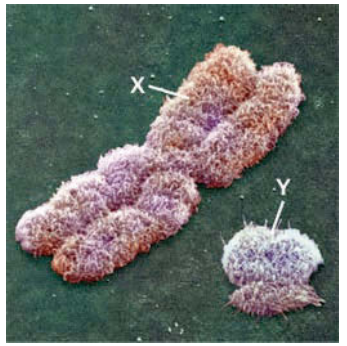
Electropheoresis patterns of G-6-PD enzyme from sonicates of cultured cells
Primary skin culture of Mrs. De. and 9 clones derived from this culture

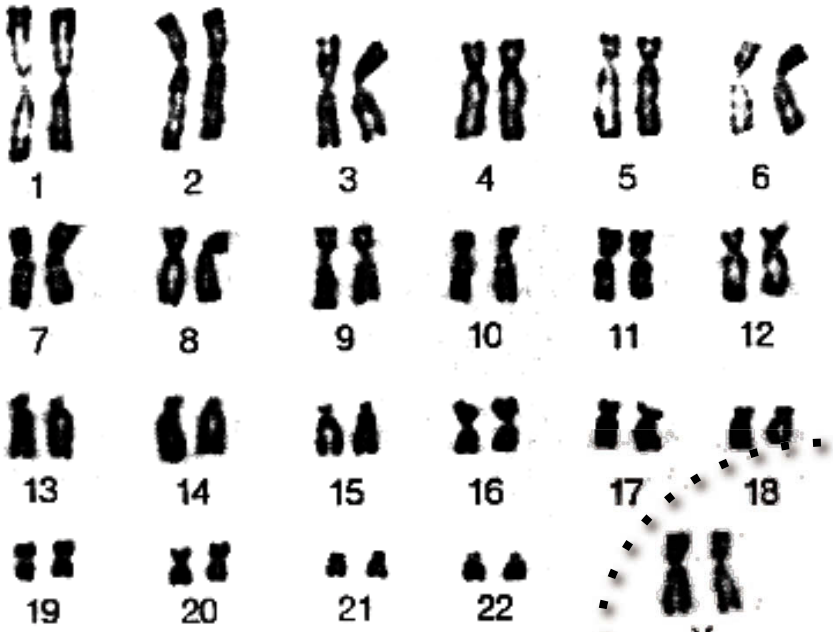
X inactivation enables Dosage Compensation in mammals

H. J. Muller first proposed the concept of dosage compensation as a result of his studies on the expression of X-linked genes in Drosophila.

Muller, et al. (1931) Effects of dosage changes of sex-linked genes, and the compensatory effects of the gene differences between male and female. Anat. Rec. (Abst.) 5 1 : 1 1 0.







X chromosome : 1300 genes
Y chromosome : ~200 genes

X inactivation compensates for the gene dosage imbalance between XX females and XY males

Open Questions:

For which genes did X inactivation evolve?

How important is dosage compensation at different developmental stages, or in different tissues?

XCI is an essential process (early lethality)

Implications of X inactivation for X-linked Diseases

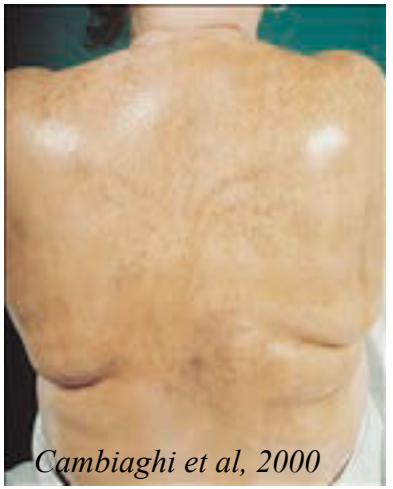
In 1875, Darwin described a disorder that appeared in each generation of one family's male members, affecting some but sparing others: "...small and weak incisor teeth ... very little hair on the body ... excessive dryness of the skin .... Though the daughters in the ... family were never affected, they transmit the tendency to their sons; and no case has occurred of a son transmitting it to his sons."

Anhidrotic ectodermal dysplasia (EDA)

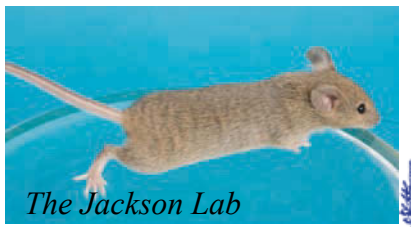
• X-linked disorder in which males are severely affected, have no sweat glands whatsoever, few teeth, little hair, and other malformations

• Females can also be affected, but the effects are much milder: for example, they have patches of skin with or without sweat glands, owing to random X inactivation and cellular mosaicism.

• The EDA gene encodes the Ectodysplasin-A(EDA-A) protein which regulates ectodermal appendage formation. It's murine homolog is the Tabby locus.



Cambiaghi et al, 2000

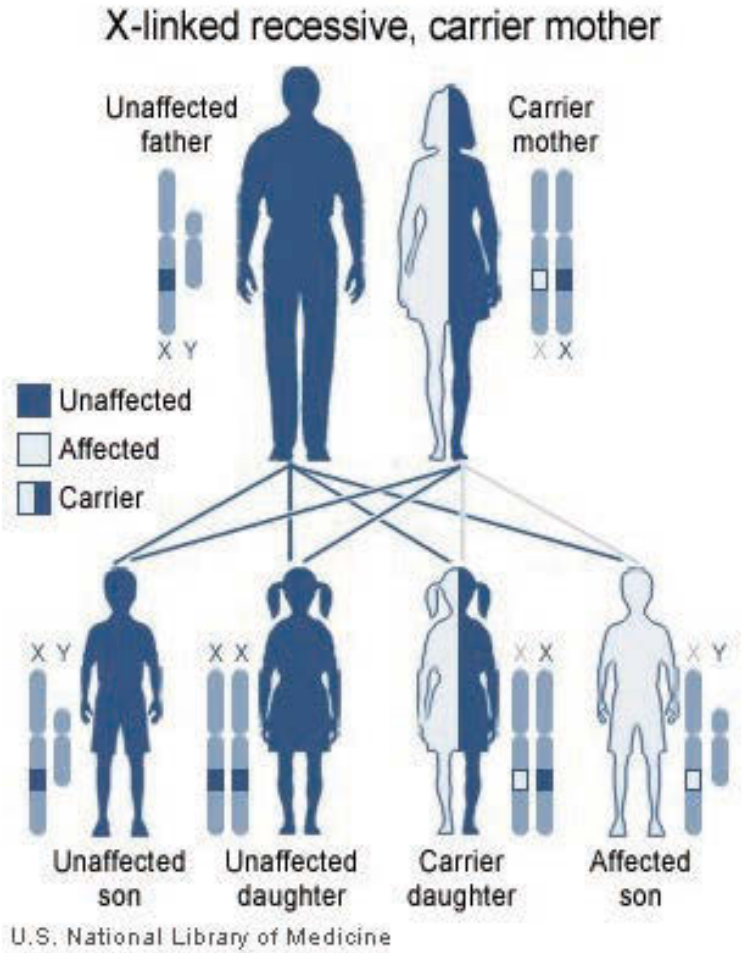


The Jackson Lab

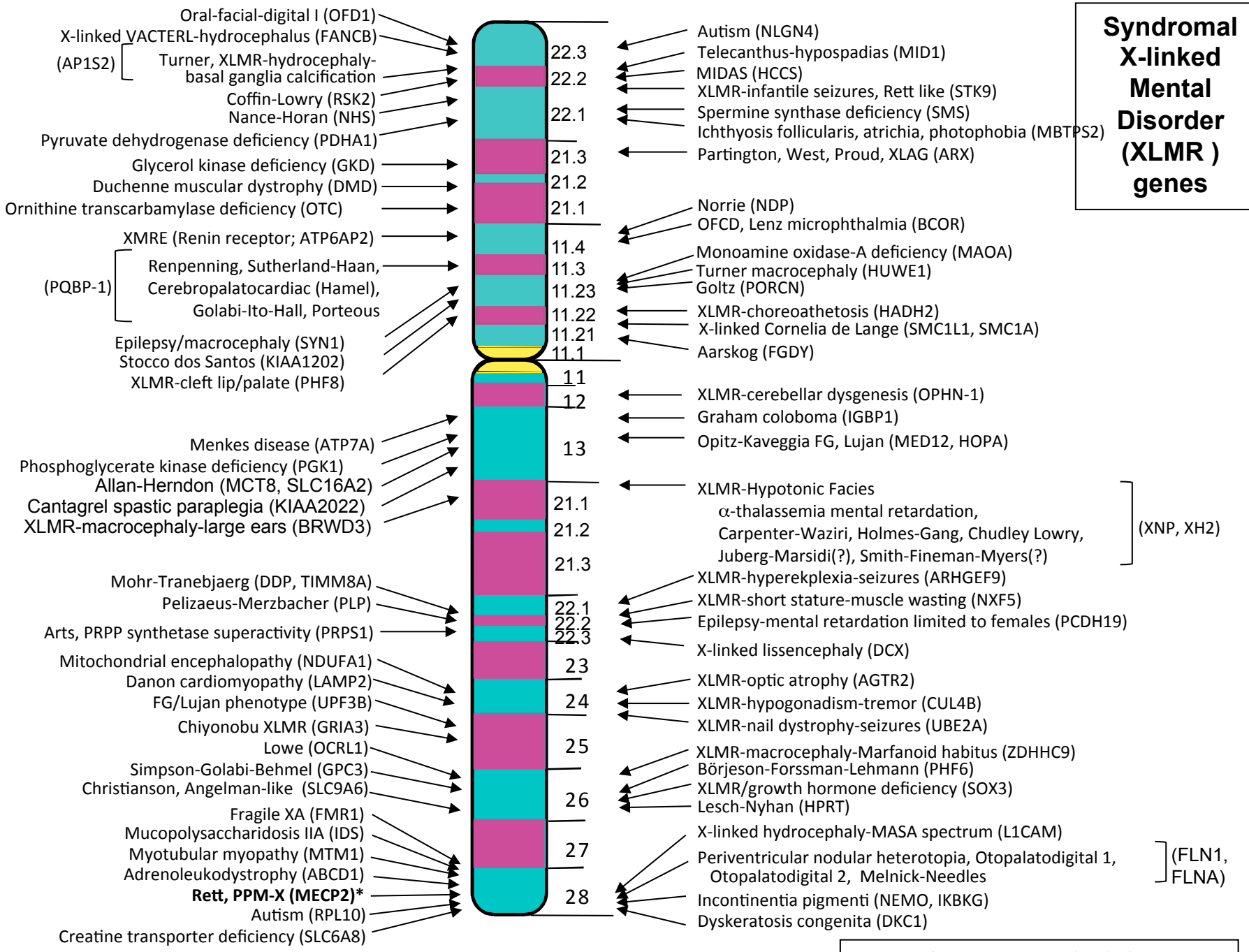
Implications of X inactivation for X-linked Diseases

Severe phenotypes or lethality in males
Variable and sometimes *no* phenotypes in females

Eg Haemophilia, muscular dystrophy, autism, Rett syndrome …



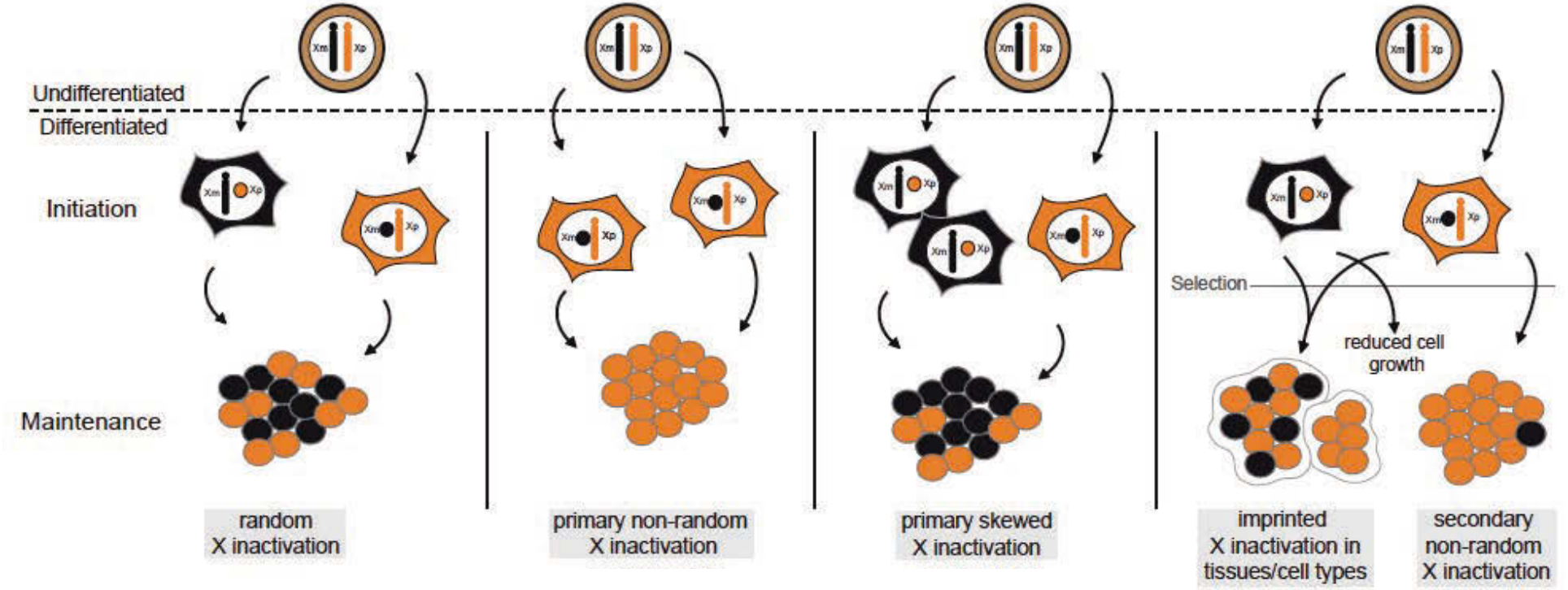
Syndromal X-linked Mental Disorder (XLMR) genes



*XLMR-hypotonia-recurrent infections (MECP2 dup)

Greenwood Genetic Center, updated July 2009

X INACTIVATION IS NOT ALWAYS RANDOM



From Gendrel and Heard, 2011

Effects of skewed XCI?

No phenotype whatsoever (mutation on Xi)

Severe phenotype, as in mutant male (mutation on Xa)

Causes?

Skewing in the initial choice of X to inactivate – either by chance, or due to genetic differences

Selection <u>against</u> cells expressing mutant allele

Selection <u>for</u> cells that happen to express the mutant allele (eg against cells expressing another upstream mutant allele)

Some genes escape from X inactivation

Non-Inactivation of an X-Chromosome Locus in Man

Abstract. *Cloned fibroblasts from women heterozygous for X-linked ichthyosis (steroid sulfatase deficiency) were examined to see whether or not this locus is subject to X-inactivation. Of 103 clones examined, all had normal levels of steroid sulfatase activity. Two of the women studied were also heterozygous for glucose-6-phosphate dehydrogenase deficiency. This allowed the demonstration that both X chromosomes were represented as the active X in various clones and that selection did not account for these findings. Thus, the steroid sulfatase locus, like the* **Xg**^{a} *locus to which it is linked, appears to escape X-inactivation in man.*

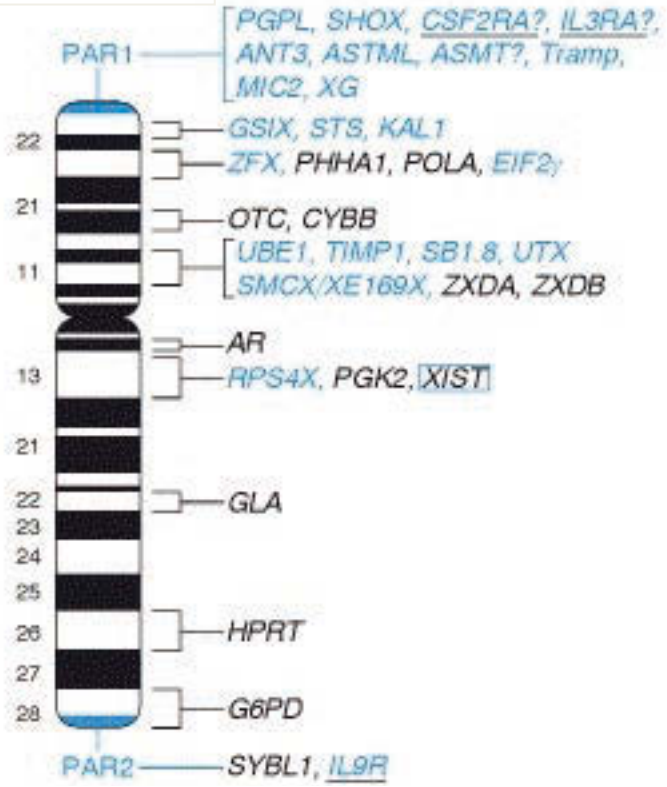
Shapiro, Mohandas, Weiss and Romeo, Science, 204, 1224-1226

Some genes escape from X inactivation

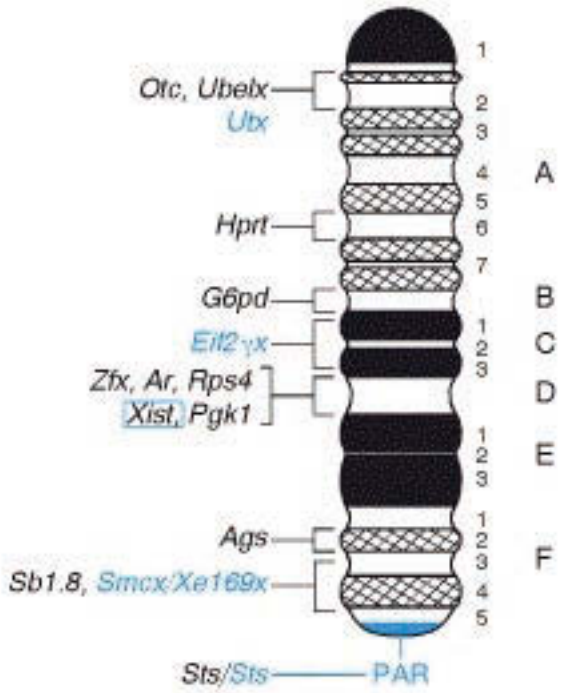
Expression of a double dose in females is important for some genes (XO : Turner's syndrome)

Expression of a double dose in females is not essential in mice (no XO phenotype)

Human X



Mouse X

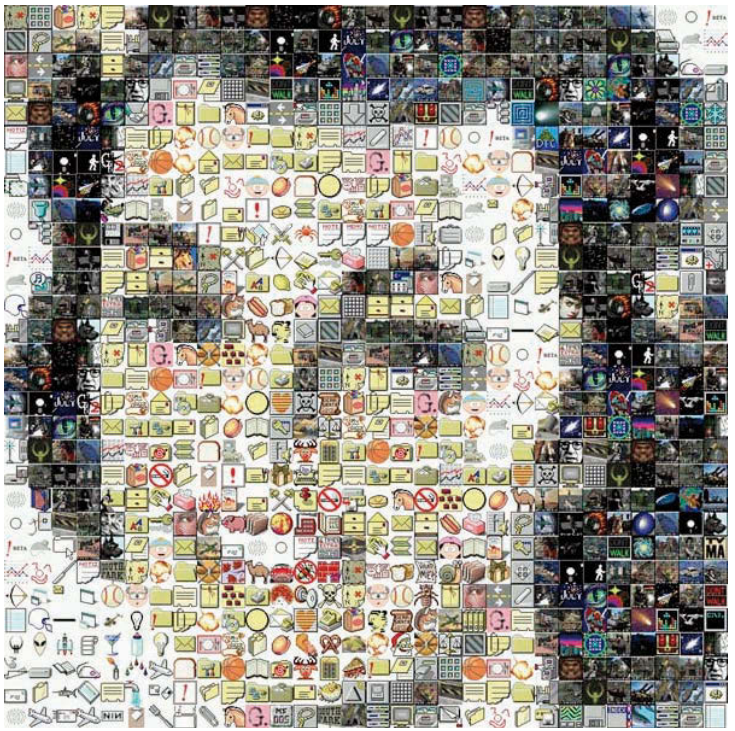


- Some genes apparently <u>have</u> to escape, others may escape due to 'leaky' or inefficient silencing
- Different tissues/ lineages in the mouse show different degrees of escape (eg Corbel et al, 2013)
- Some genes show lineage-specific escape from X inactivation (eg *Atrx*, Patrat et al, 2009)

Up to 25% of X-linked genes may escape from X inactivation in humans

X-inactivation profile reveals extensive variability in X-linked gene expression in females

Carrel and Willard (2005) *Nature* 434, 400-404



- 15% of human X-linked genes escape inactivation to some degree
- An additional 10% genes show variable patterns of inactivation between individuals

This suggests a remarkable and previously unsuspected degree of expression heterogeneity among females.

Eg female twins usually differ far more than male twins – presumably due to their mosaicism and the variable expression of their X-linked genes .

Huntington Willard: "*genetically speaking, if you've met one man, you've met them all. We are, I hate to say it, predictable. You can't say that about women. Men and women are farther apart than we ever knew. It's not Mars or Venus. It's Mars or Venus, Pluto, Jupiter and who knows what other planets.*"

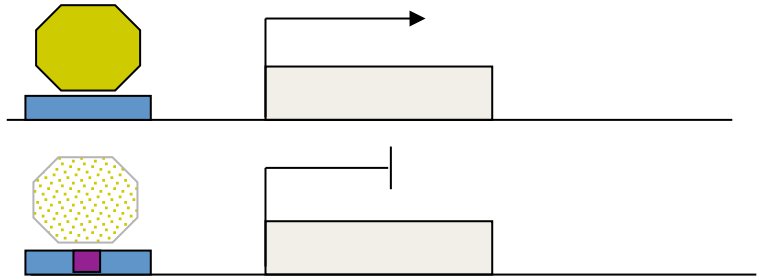
Mechanisms underlying X inactivation?

The two X chromosome can be genetically identical

And yet one of them will be shut down and this state will be maintained through hundreds of mitotic cell divisions

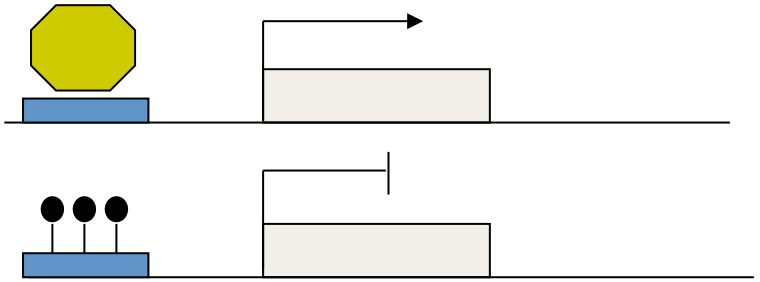
X inactivation is therefore a classic example of epigenetic regulation, monoallelic gene expression and heterochromatin formation on a chromosome-wide scale

Genetic



Allelic variation : Polymorphic regulatory sequences

Epigenetic



Epiallele : epigenetically marked regulatory sequence

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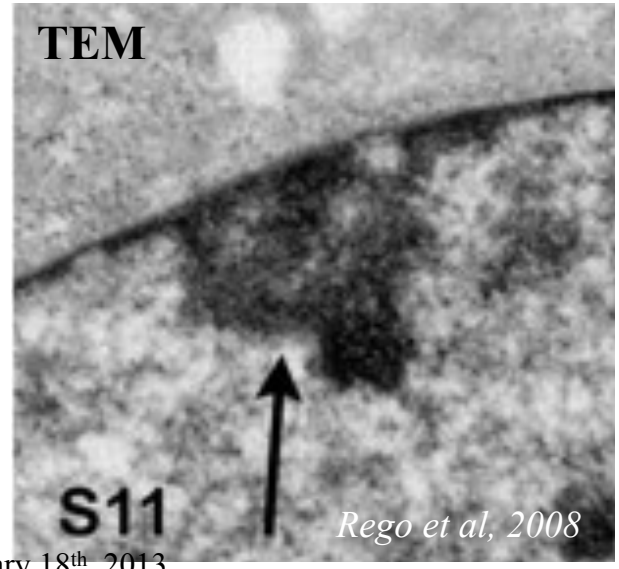
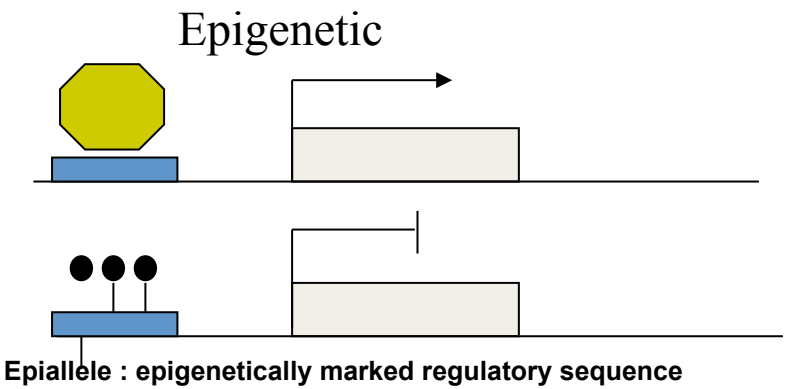




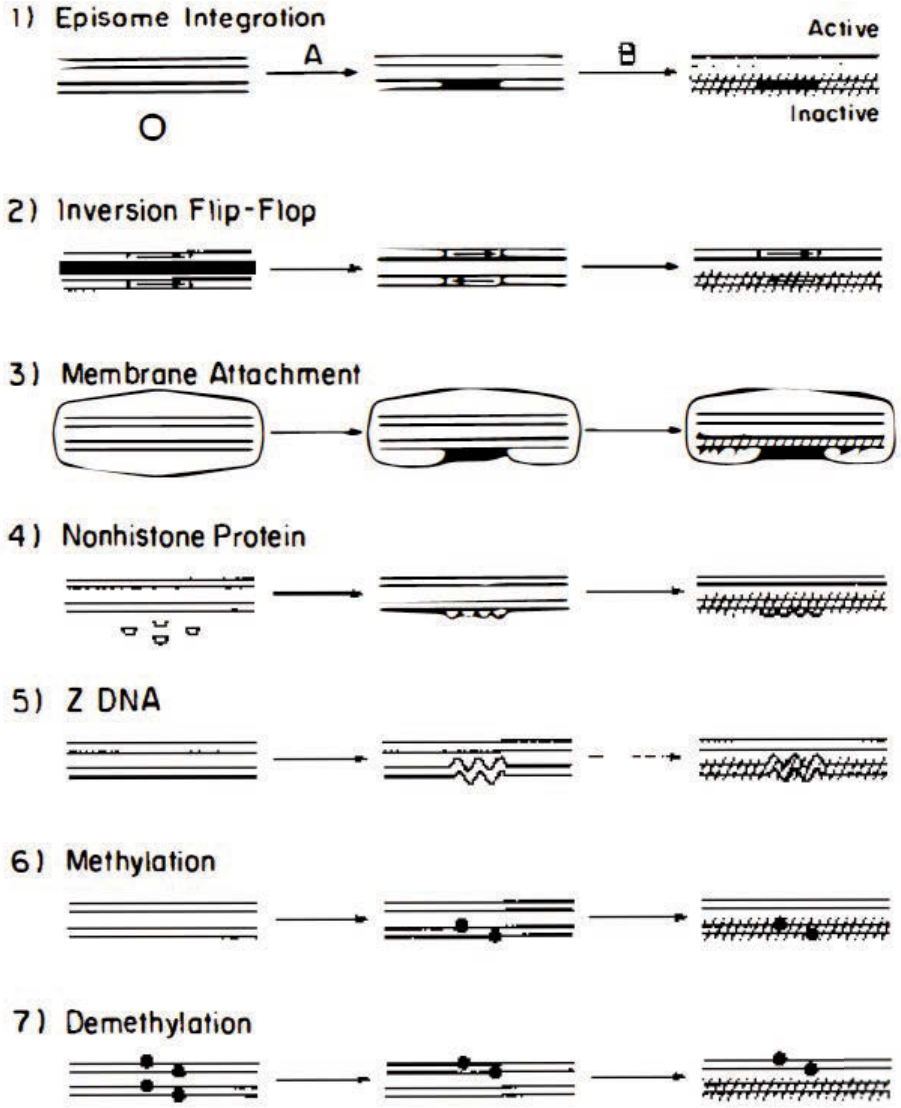
Mechanisms underlying X inactivation?

Early models for Initiation, Spreading and Maintenance

Gartler and Riggs (1983) Ann. Rev. Genet. 1983. 17:155-90

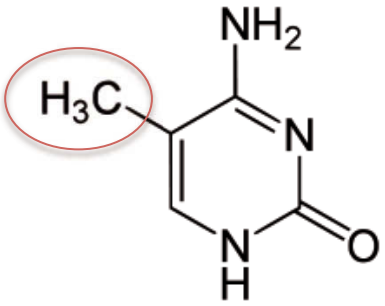
Models for X-chromosome inactivation. Two steps are shown for each model. The models differ mainly with respect to step A, which is the initiation step.
Step B is the event that follows the initial event and results in the observable spreading of condensation and genetic inactivity to cover most genes on the X chromosome.

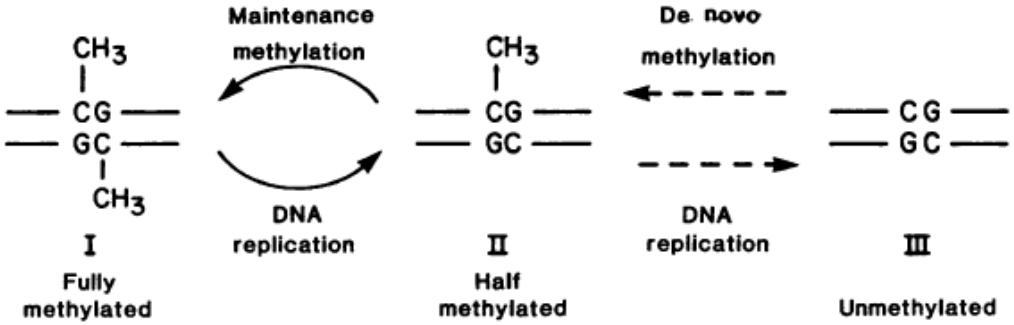
Inactivation of one X chromosome is also accompanied by a switch from early **to late replication** (Grumbach *et al.,* 1963; Taylor, 1960; Yoshida *et al.,* 1993).



A role for DNA Methylation in X inactivation

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





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

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*

In vivo footprint and methylation analysis by PCR-aided genomic sequencing: comparison of active and inactive X chromosomal DNA at the CpG island and promoter of human PGK-1

Pfeifer et al (1990) Genes Dev. 4, 1277-1287

CpG Island Promoter Region Methylation Patterns of the Inactive-X-Chromosome Hypoxanthine Phosphoribosyltransferase (*Hprt*) Gene

JONG-GWANG PARK AND VERNE M. CHAPMAN*

A role for DNA Methylation in X inactivation

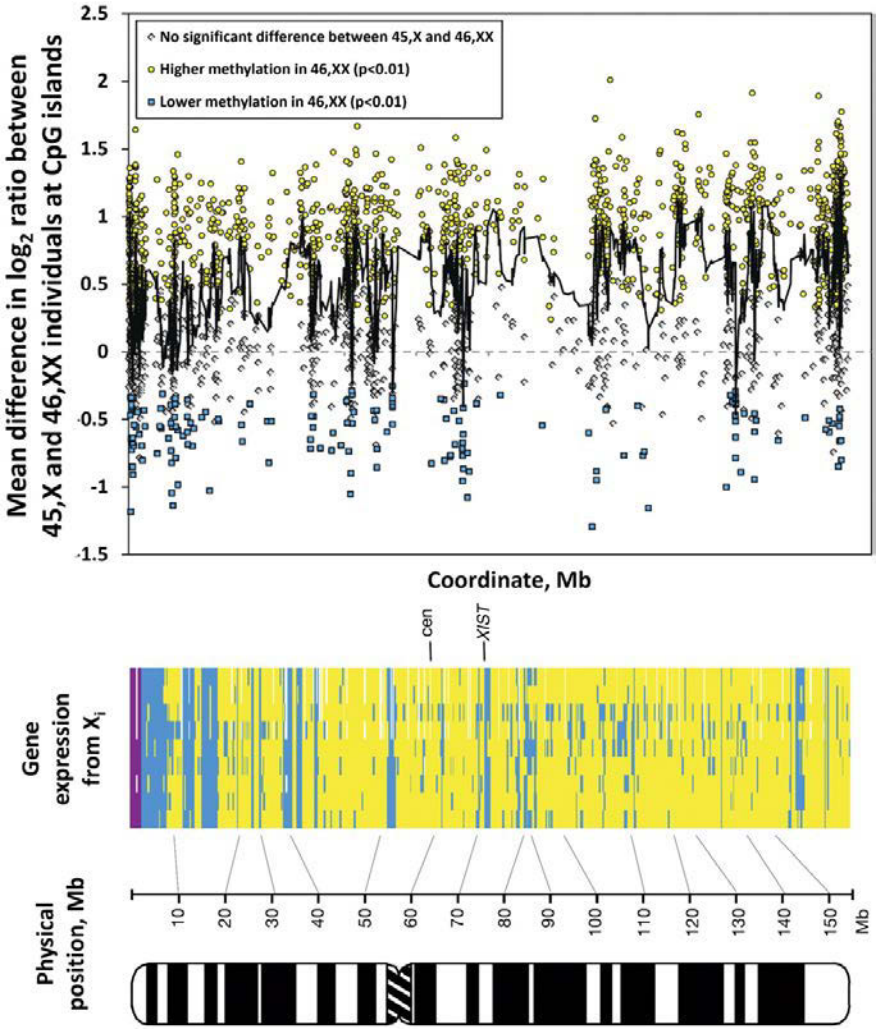
5-azacytidine treatment on cultured human/hamster hybrid cells with an inactive X chromosome revealed that X-linked genes could be reactivated by inhibiting DNA methylation maintenance

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

Hybrid clone	Human X markers				Human X constitution		
	G6PD	PGK	HPRT	STS	X	der(X)*	der(11)†
37-26	+	+	+	+	+	+	−
37-26R-D	−	−	−	+	+	−	−
37-26R-A	−	−	−	−	−	−	−
37-26R-D-1a	−	+	+	+			
37-26R-D-1b	−	−	+	+			
37-26R-D-1d	−	−	+	+			
37-26R-D-2a	−	−	+	+			
37-26R-D-2b	−	−	+	+			
37-26R-D-2c	−	−	+	+			
37-26R-D-1c/4	+	−	+	+	+	−	−
37-26R-D-1c/11 (HAT)	+	−	+	+			
37-26R-D-1c/11 (MEM)	+	−	+	+			
37-26R-D-1c-1	+	−	+	+			
37-26R-D-1c-2	+	−	+	+			
37-26R-D-1c-3	+	−	+	+			
37-26R-D-1c-4	+	−	+	+			
37-26R-D-1c-5	+	−	+	+			

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

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A role for DNA Methylation in X inactivation

DNA methylation clearly involved in maintenance of X inactivation

- *but* no obvious mechanism of action on the Xi
  (DNA binding proteins? Chromatin accessibility?)

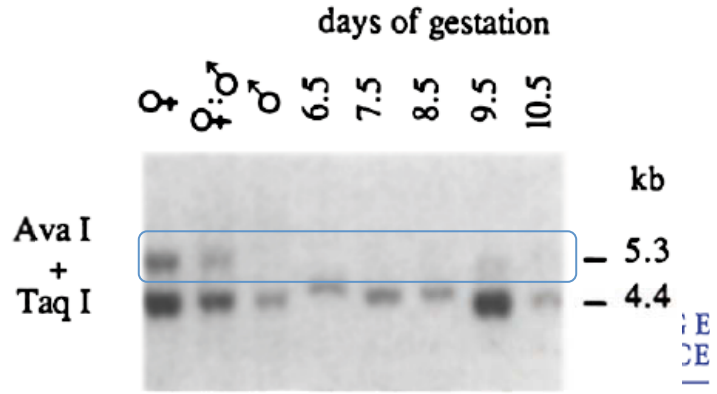
- CpG island DNA methylation does not seem to be conserved in marsupials

- DNA methylation on the Xi appears to be a relatively late event during mouse development (although this can vary we now know, see Gendrel et al. 2012)

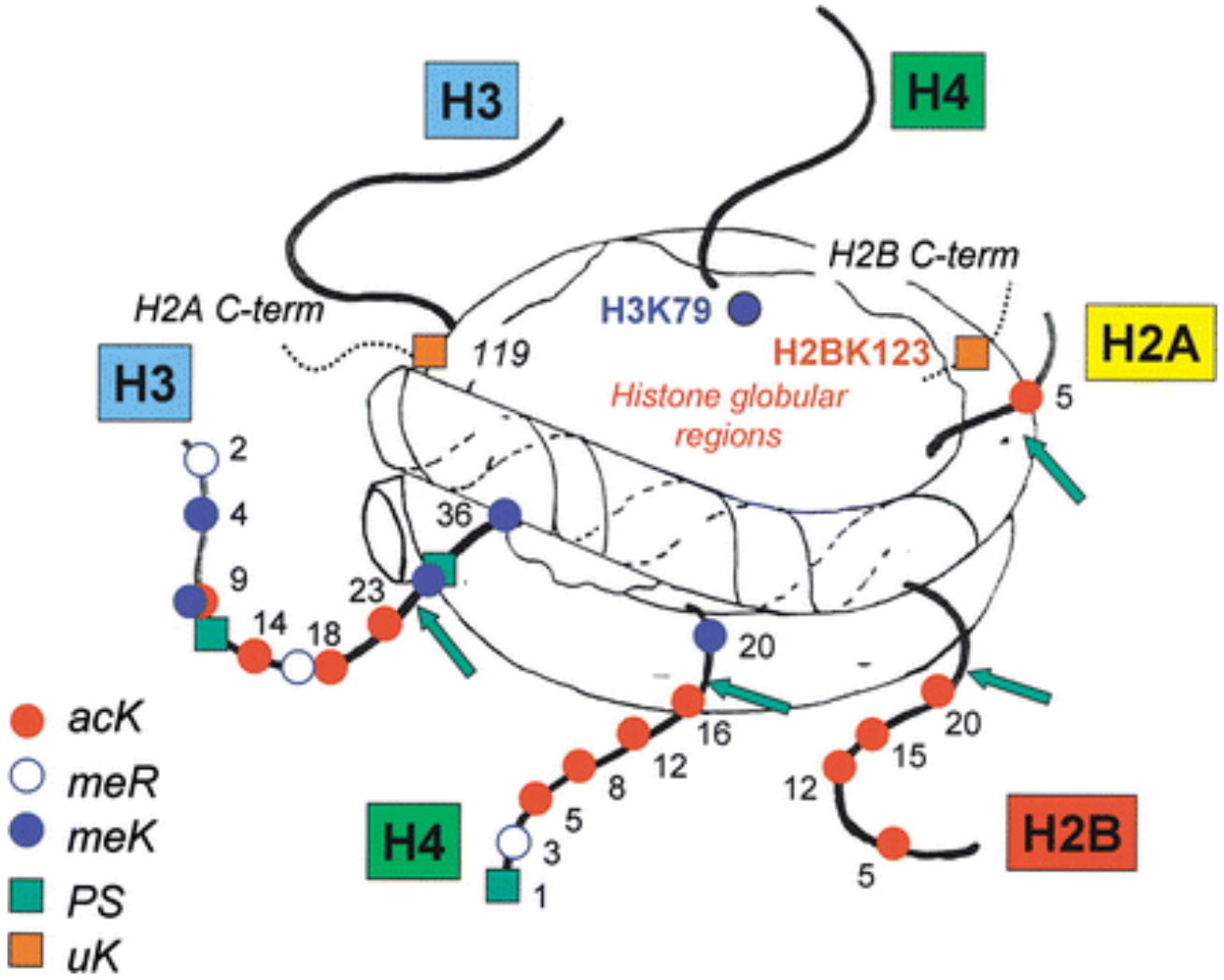
Cell, Vol. 48, 39–46, January 16, 1987, Copyright © 1987 by Cell Press

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

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



A role for Histone Modifications on the Xi?

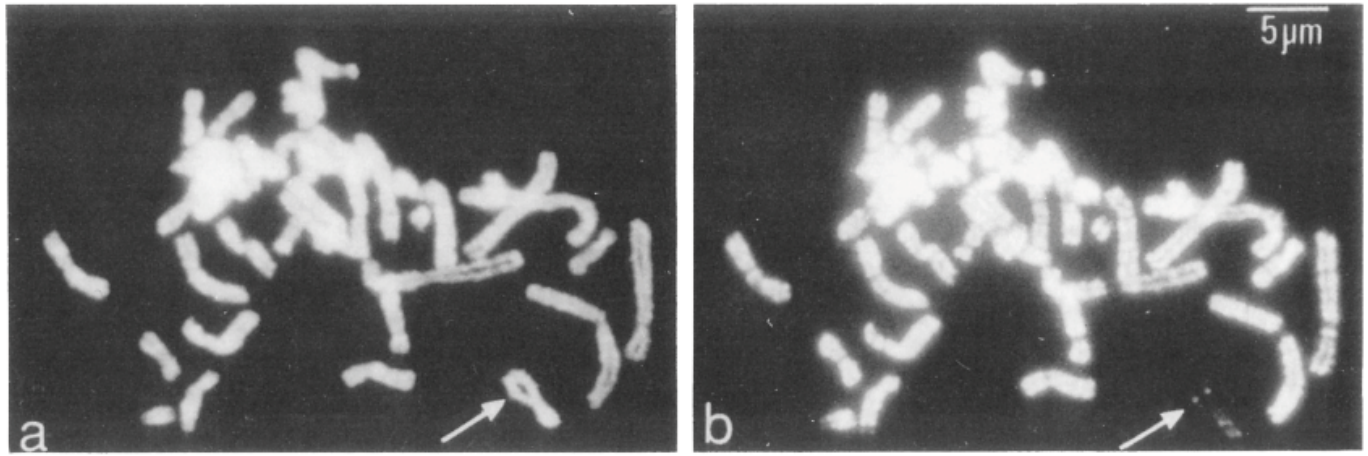


A role for Histone Modifications on the Xi?

Cell, Vol. 74, 281–289, July 30, 1993, Copyright © 1993 by Cell Press

The Inactive X Chromosome in Female Mammals Is Distinguished by a Lack of Histone H4 Acetylation, a Cytogenetic Marker for Gene Expression

Peter Jeppesen* and Bryan M. Turner†

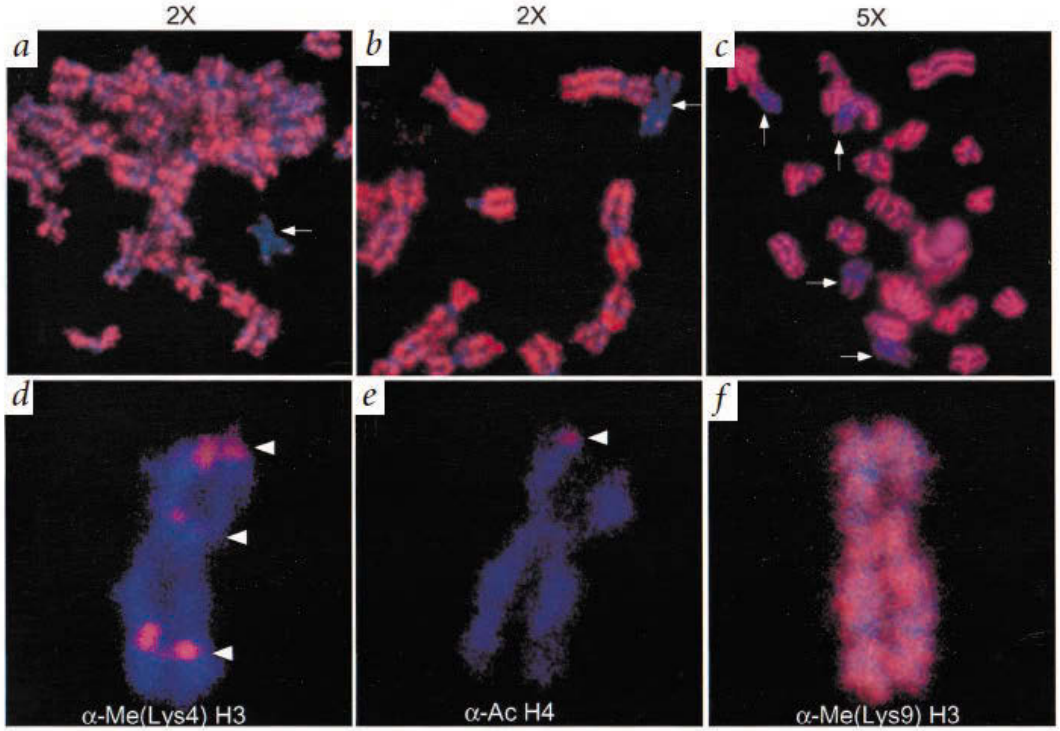


fluorescent staining with Hoechst 33258 (a) and immunofluorescent labeling (FITC) of acetylated histone H4 (Lys-12) using antiserum R5/12 (b). The Xi chromosome (arrows) shows three bands of acetylation (b).

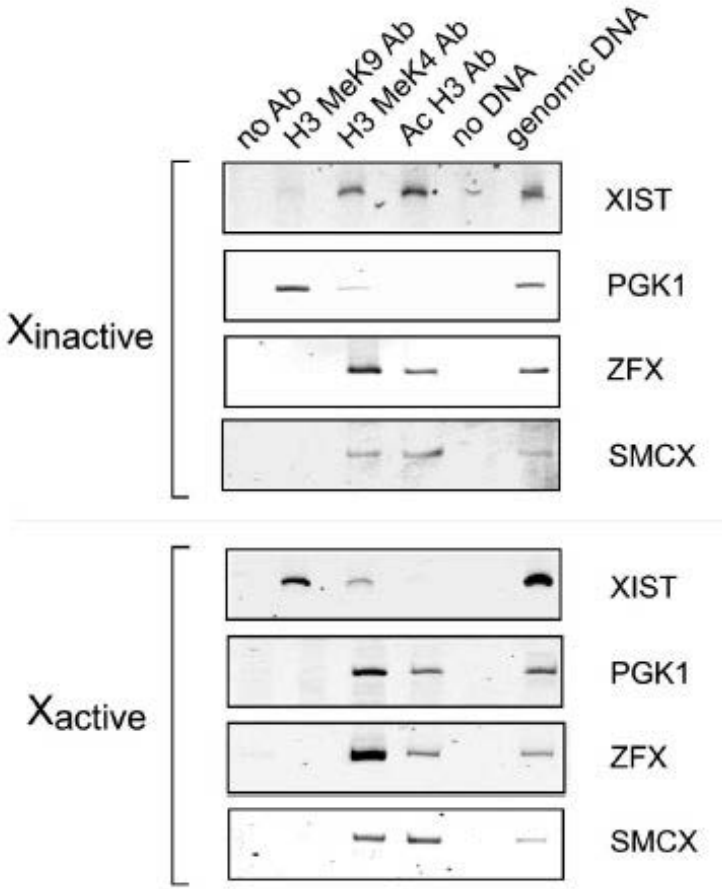
A role for Histone Modifications on the Xi?

Differentially methylated forms of histone H3 show unique association patterns with inactive human X chromosomes Boggs et al. (2002) Nat. Genet.30, 73-78.

Immunofluorescence staining of metaphase spreads



Chromatin Immunoprecipitation (ChIP) at promoters of X-linked genes



The inactive X is depleted in H4 Acetylation and H3K4 methylation, enriched for H3K9me2 (Boggs et al, 2002; Heard et al, 2002) and H3K27me3 (Silva et al, 2003; Plath et al, 2003)

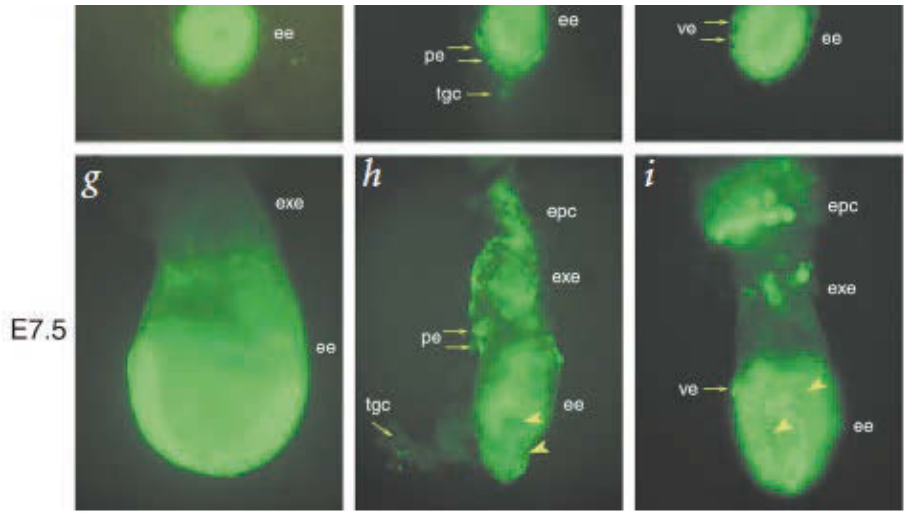
A role for Polycomb Group proteins on the Xi?

Imprinted X inactivation maintained by a mouse *Polycomb* group gene
Wang et al (2001) Nat. Genet. 28: 371-375.

Female embryos carrying a GFP transgene on their paternal X normally show silencing of the GFP in the extraembryonic tissues. In Polycomb (*Eed*) mutant embryos, GFP reactivation is observed in some extraembryonic cells – but only at later stages of development.

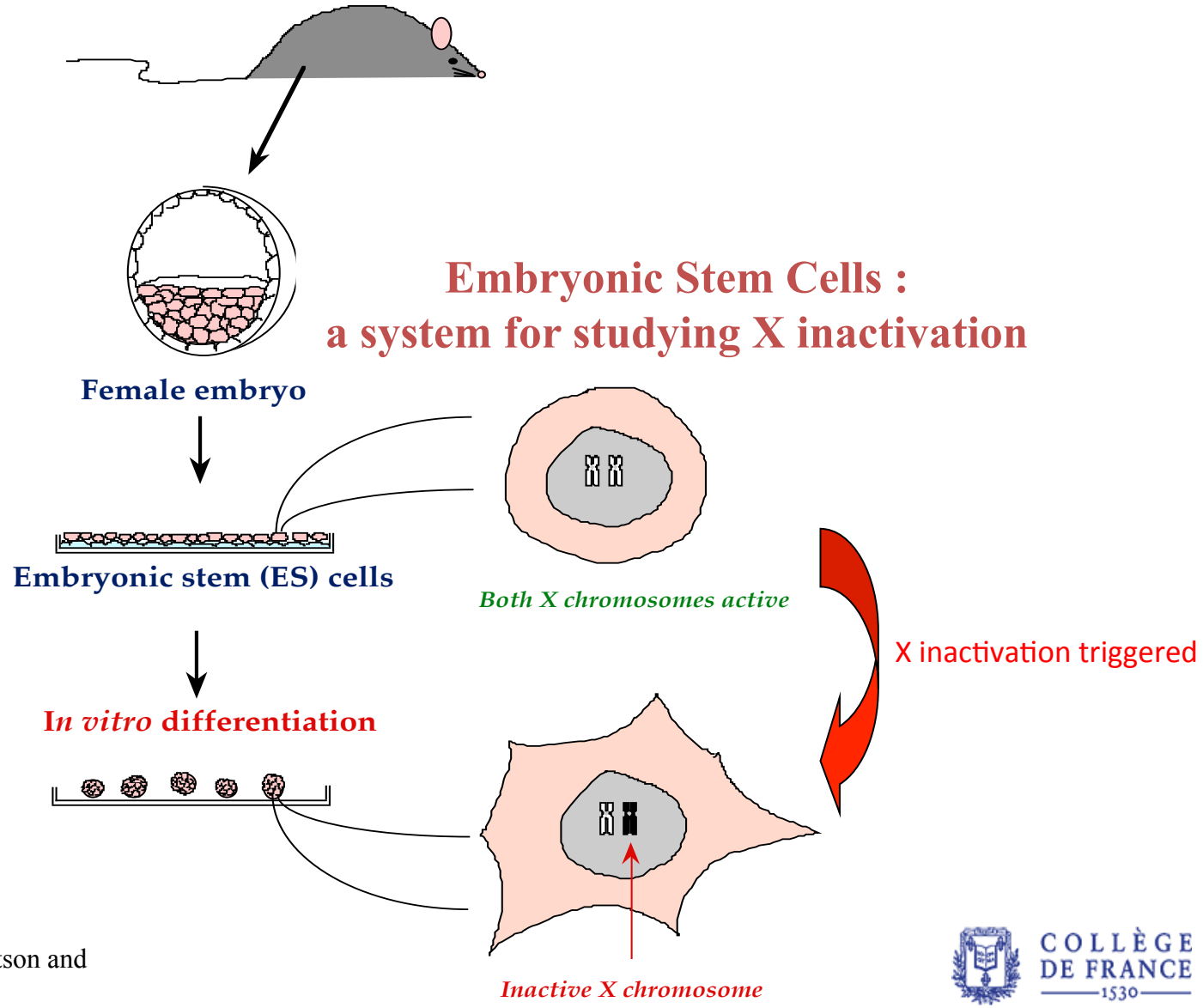
⇒ Polycomb is involved in maintaining the inactive state of the paternal X chromosome in these tissues but not initiation.

Note that nevertheless, there is substantial escape from X inactivation for some X-linked genes in trophoblast giant cells even in the presence of Polycomb (Corbel et al, 2013)
and that DNA Methylation is generally thought to be lacking from X-linked promoters in extraembryonic tissues



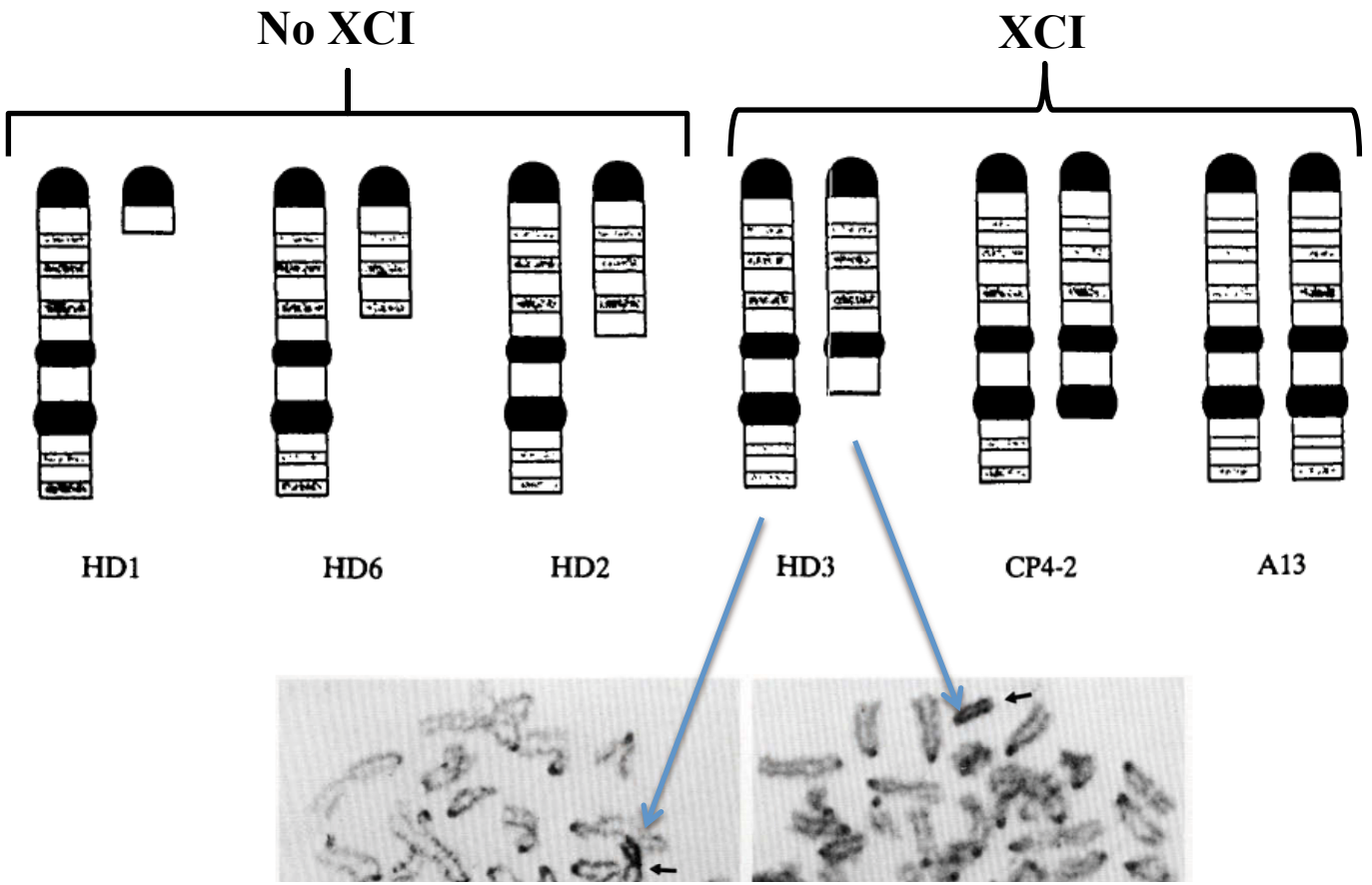
Dissecting the Mechanisms underlying X inactivation

Dissecting the Mechanisms underlying X inactivation



Initial studies in EK cells : Liz Robertson and Sohaila Rastan in the 1980's

Mechanisms underlying the initiation of X inactivation?

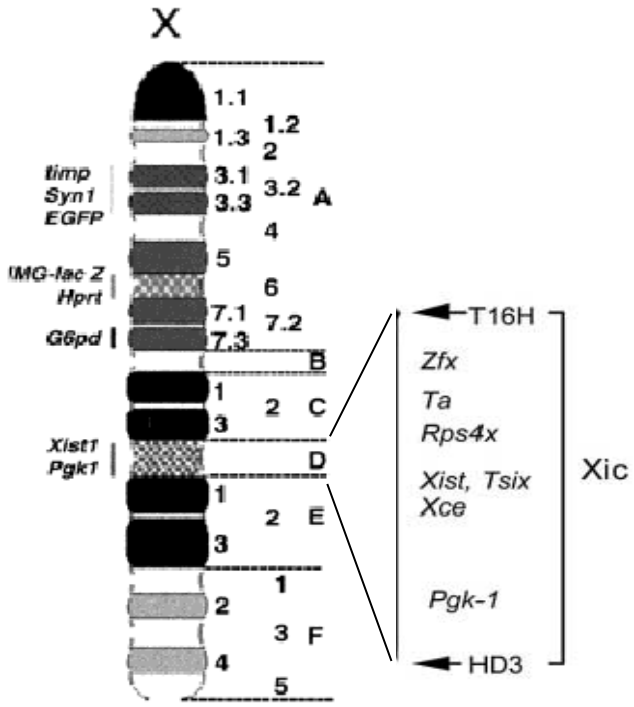


X-autosome translocation data showed that inactivation can spread into autosomal regions physically contiguous with an X fragment carrying an Xce

NB (a) spreading into autosomal sequences does occur

(b) the spreading is limited and probably less stable.

The X-inactivation center (*Xic*)



- Two or more Xics required for X inactivation to be triggered
- A counting mechanism proposed, whereby one X stays active per diploid cell
- The Xce locus which overlaps with the Xic, affects choice of Xp or Xm
- Cis-inactivation must require a cis-limited trigger and self-templating process?

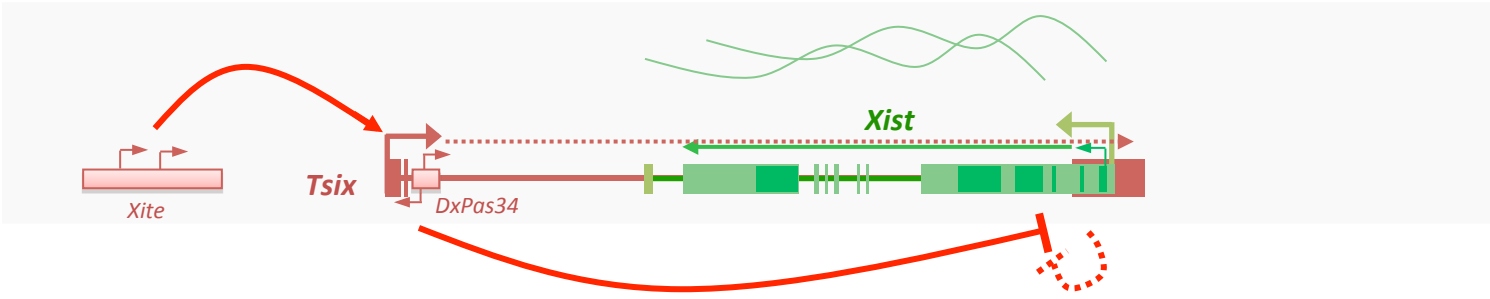
Rastan, 1983

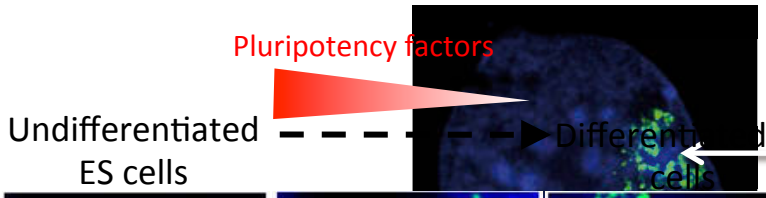
Rastan and Robertson, 1985

Work of Russell, Lyon, Cattanach, Rastan, Willard and others

The X-inactivation center (*Xic*)

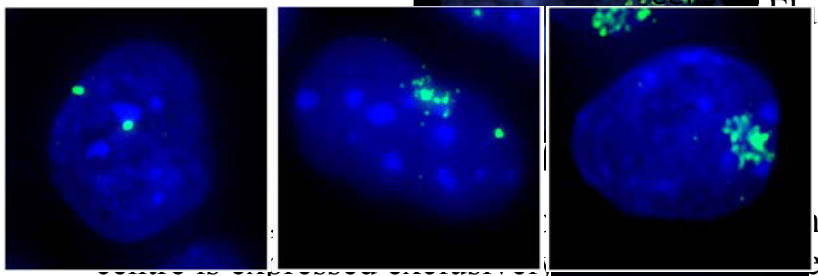
Antisense *Tsix* transcription represses *Xist* expression during early differentiation





RNA

orescence *in situ* hybridisation (FISH)



RNA FISH
Xist probe

Avner
Brockdorff
Gribnau
Heard
Jaenisch
Lee
Rougeulle
Sado
Wutz

XX

XY

e human X inactivation
X chromosome.

ysis of a 17kn inactive
and is highly localised

See Augui et al, Nat. Rev. Genet. 2011 for review

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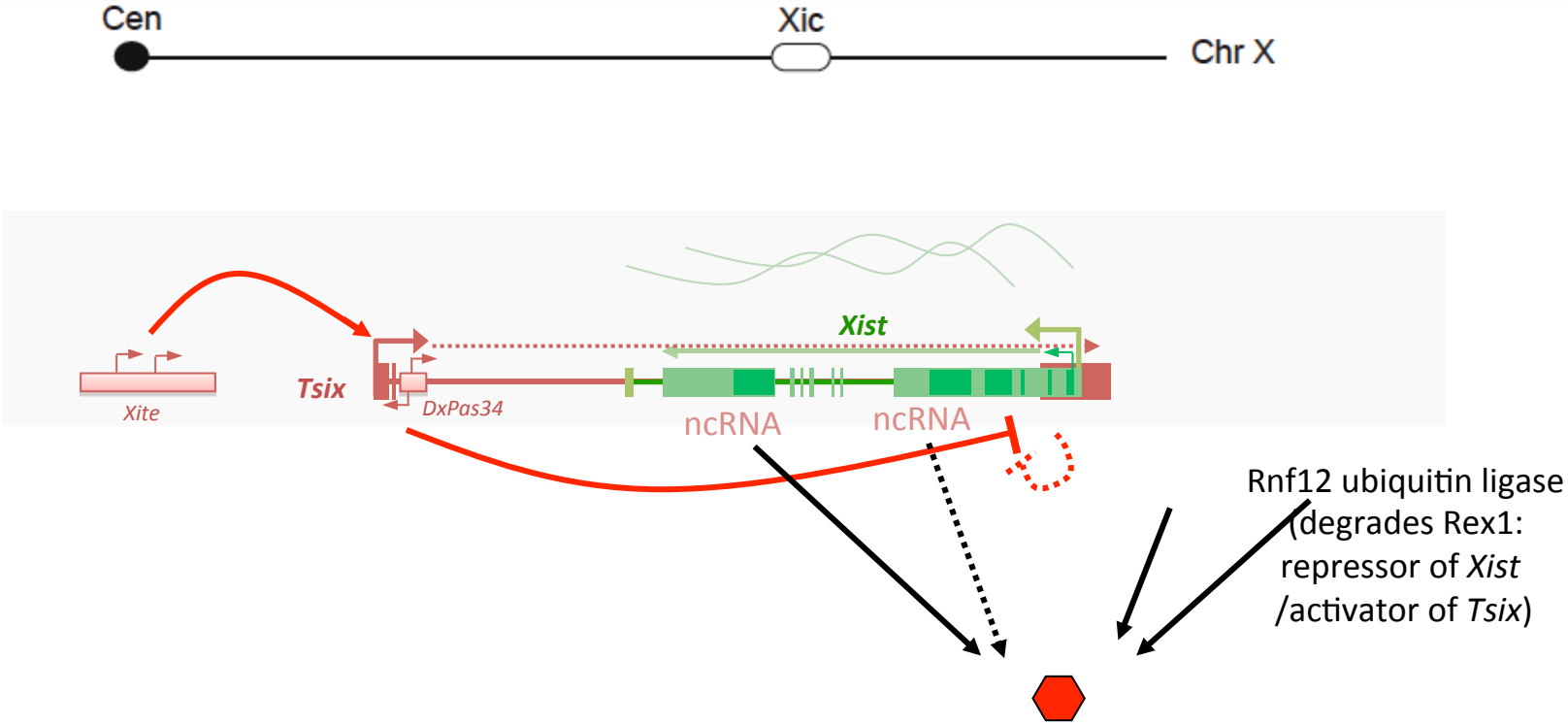
The X-inactivation center (*Xic*)



Avner
Brockdorff
Gribnau
Heard
Jaenisch
Lee
Rougeulle
Sado
Wutz

- ***Xist*** **activators (Rnf12), pairing elements (Xpr), ncRNAs, enhancers (*Ftx*? *Jpx*?…)**
- **Down-regulation of repressors (pluripotency factors, *Tsix*…)**
- **Monoallelic *Xist* up-regulation –> via monoallelic *Tsix* expression?**

See Augui et al, Nat. Rev. Genet. 2011 for review

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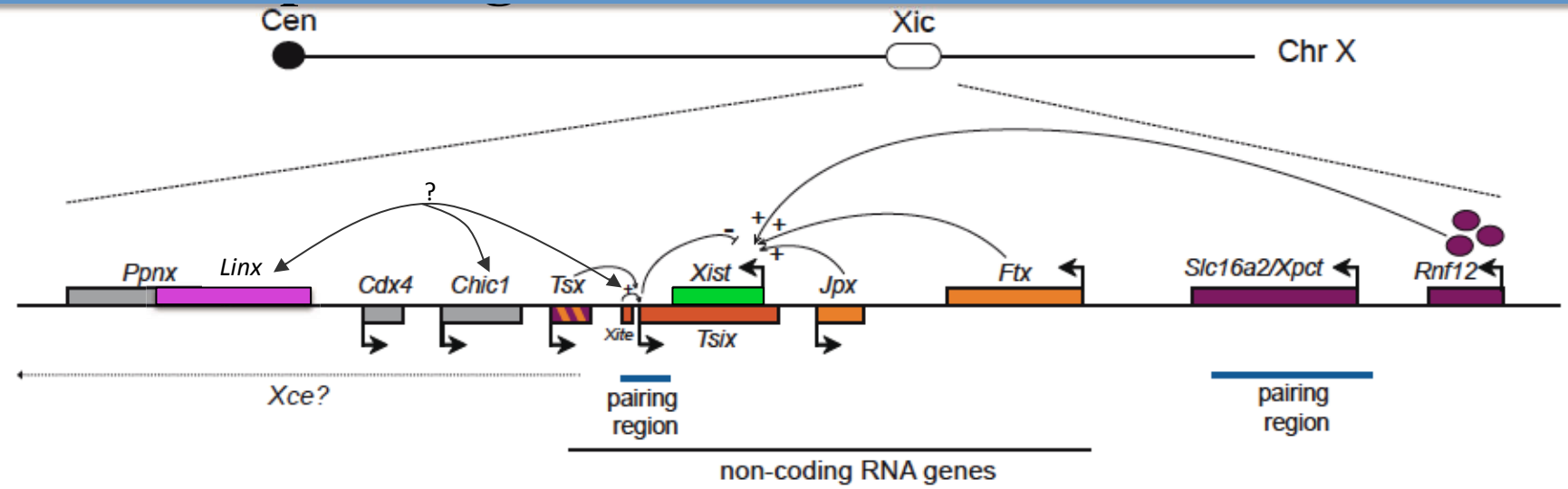
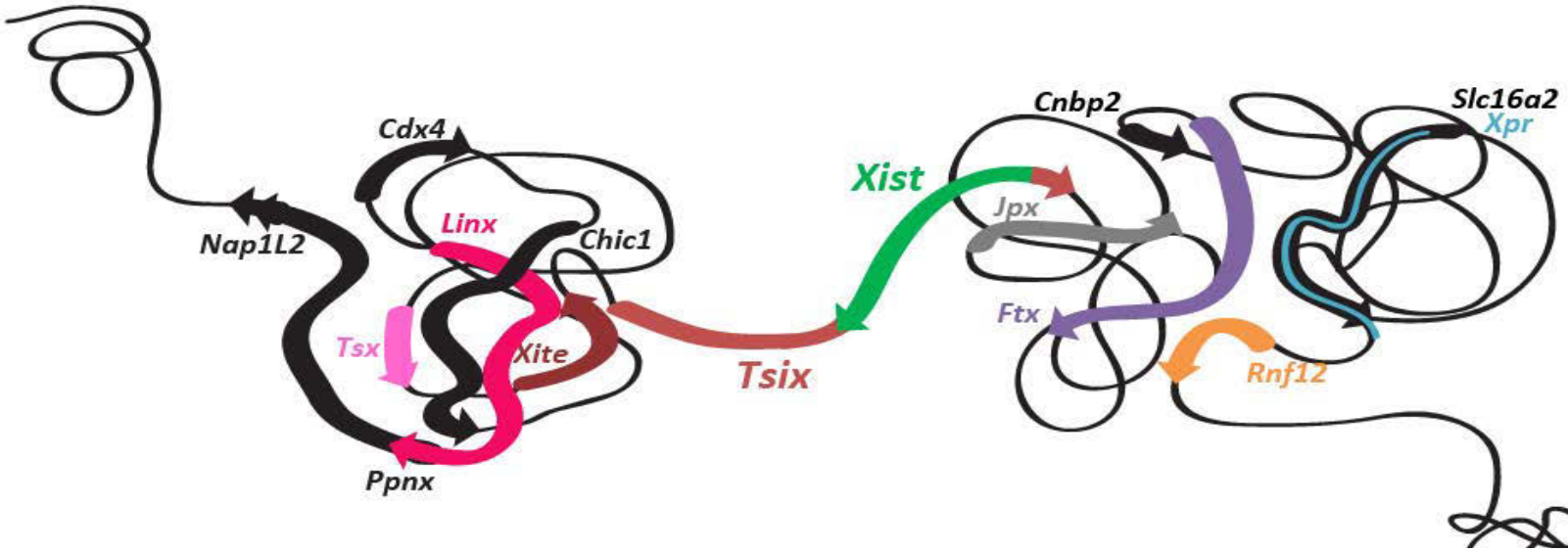
The Xic : a complex Regulatory Landscape spanning several hundred kilobases

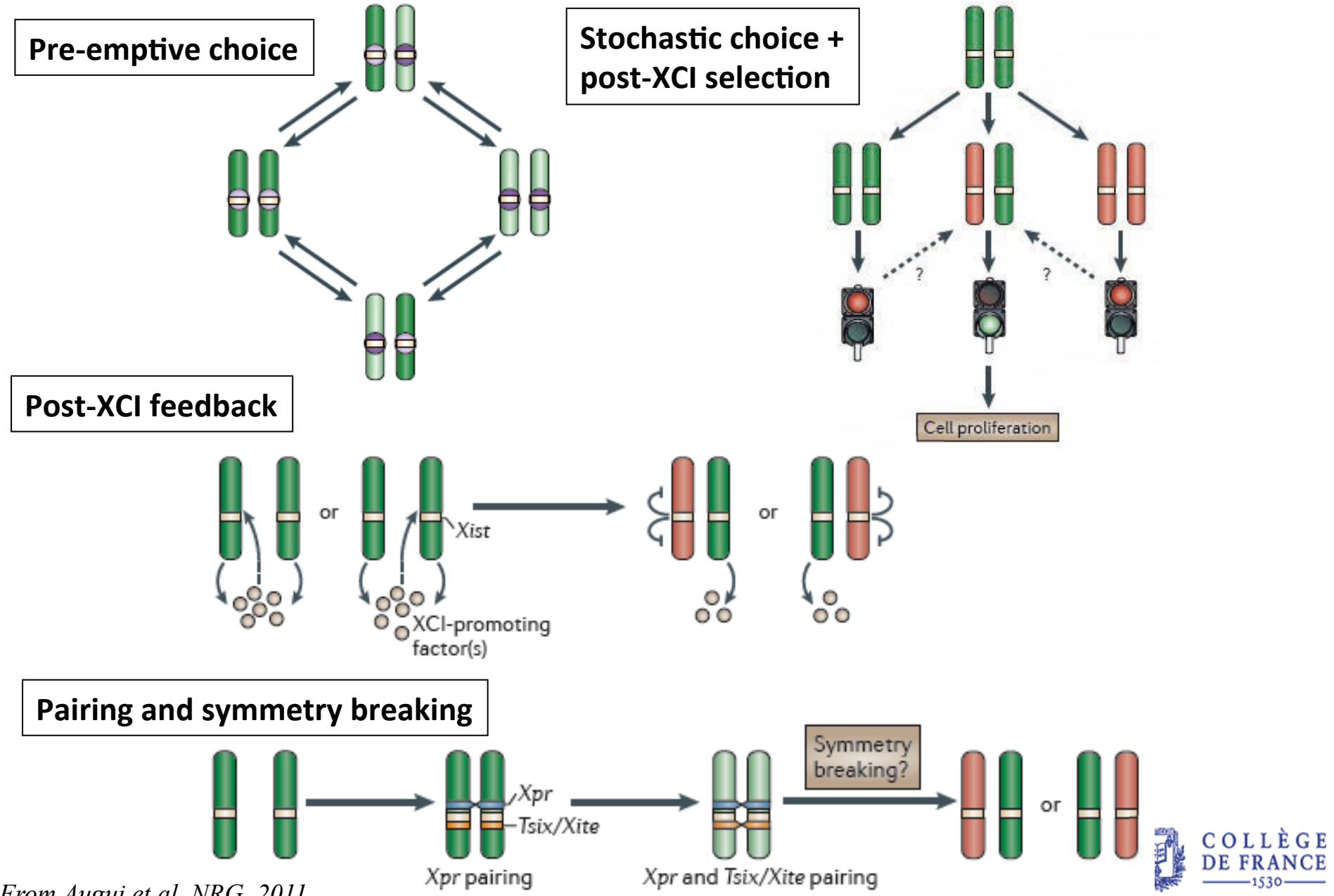


DOWN-regulated **UP-regulated**



Nora et al (2012) Spatial partitioning of the regulatory landscape of the X-inactivation center. *Nature* 485, 381-385.

Recent Models for the Initiation of X inactivation



From Augui et al, NRG, 2011

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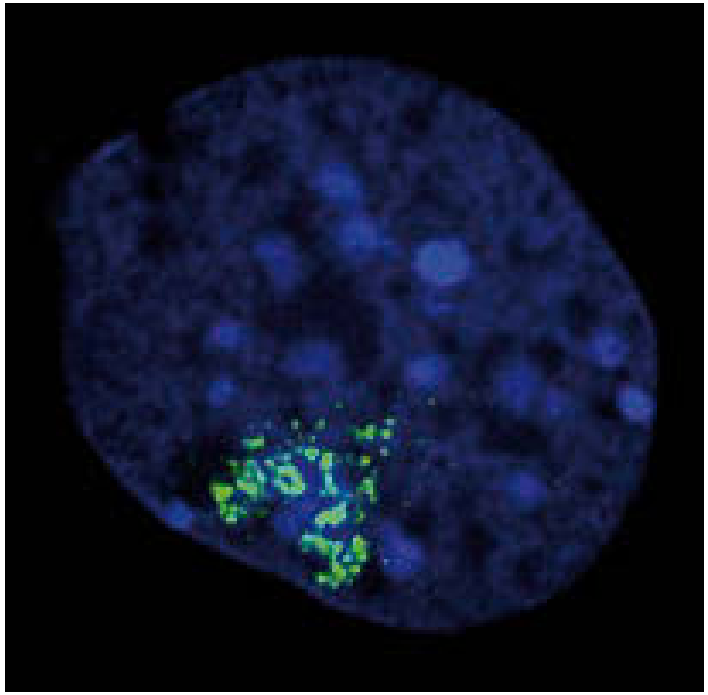
The Role(s) of XIST?

Non-coding, ~19000 nt spliced, capped nuclear RNA
Xist RNA is necessary and sufficient to trigger XCI
Coats chromosome in *cis* and triggers gene silencing
Induces chromatin changes (directly or indirectly?)
Creates a silent nuclear compartment



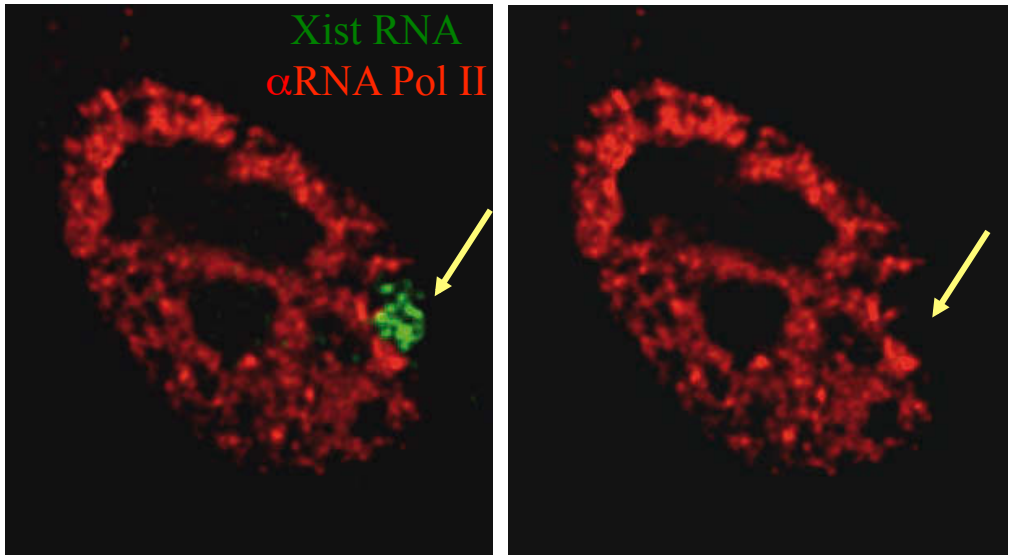
For recent review
see Wutz, NRG, 2011

COLLÈGE DE FRANCE 1530

The Role(s) of XIST?

Non-coding, ~19000 nt spliced, capped nuclear RNA
Xist RNA is necessary and sufficient to trigger XCI
Coats chromosome in *cis* and triggers gene silencing
Induces chromatin changes (directly or indirectly?)
Creates a silent nuclear compartment

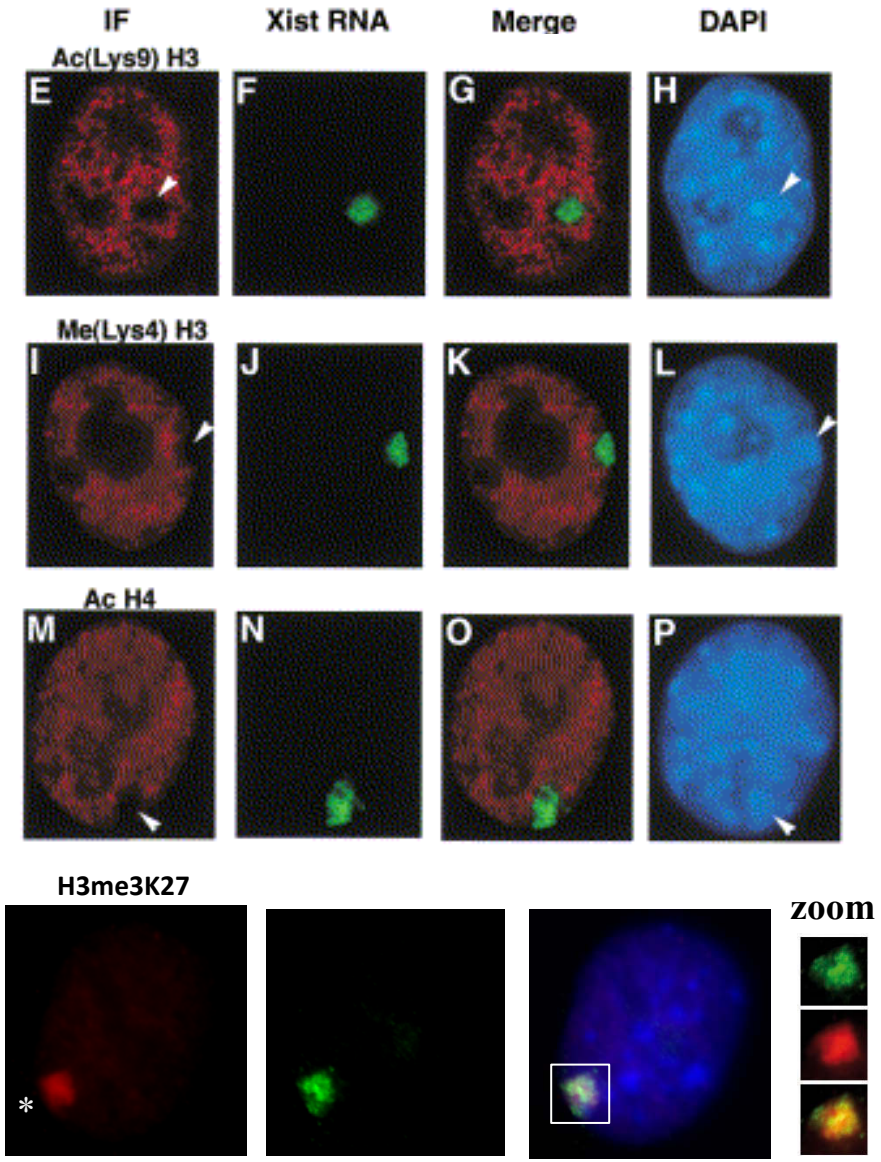
- *Made up of repetitive elements*
- *Into which genes become recruited as silencing proceeds*



Chaumeil et al., 2006
Clemson et al,, 2006
Chow et al, 2010

For recent review see Wutz, NRG, 2011

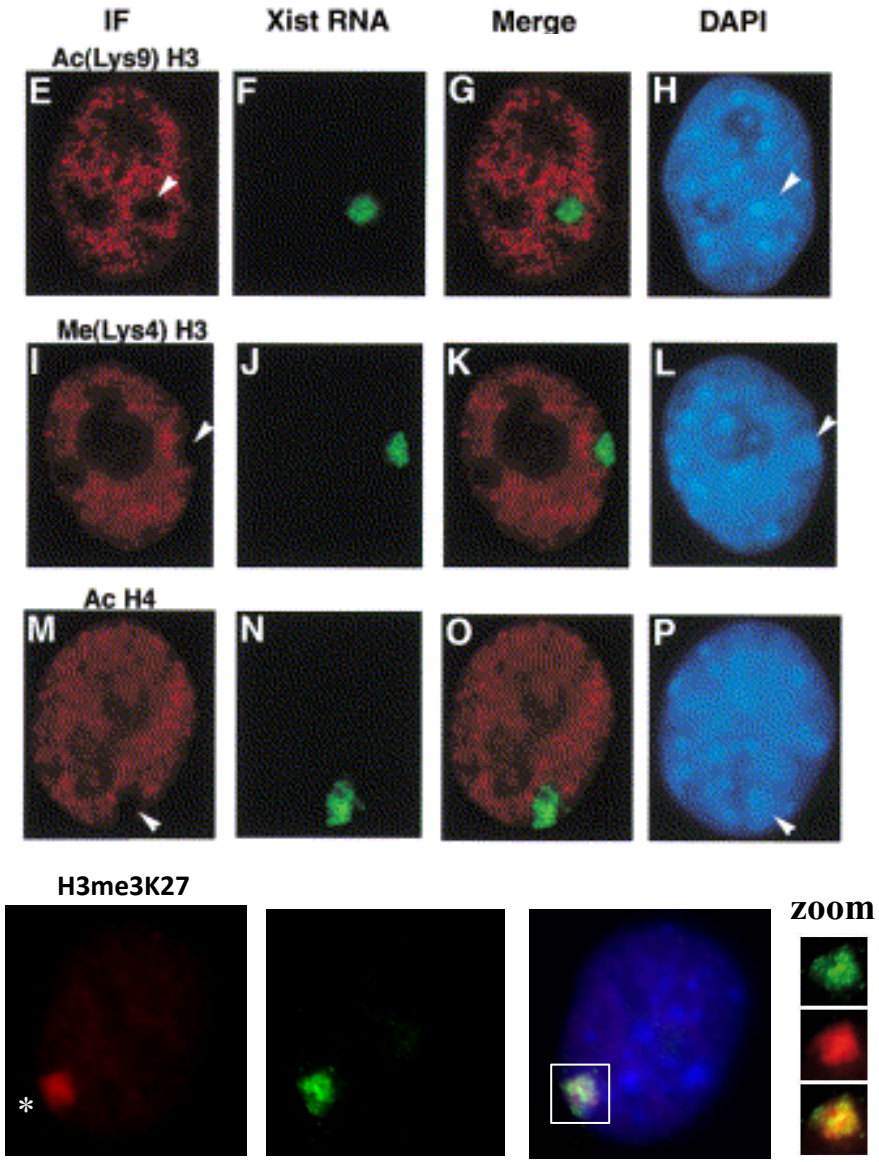
Xist RNA coating is followed by numerous chromatin changes on the X

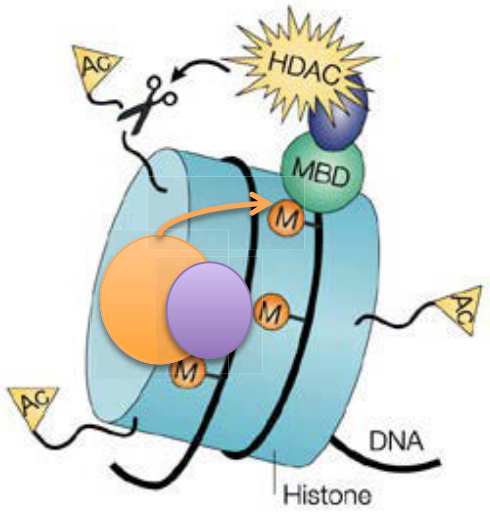


- Exclusion of euchromatic marks from the Xist RNA-coated chromosome
- Enrichment for H3K27me3, H3K9me2, H4K20me1, macroH2A
  Polycomb complexes PRC2, PRC1
- Chromatin modifications on the X(i) are Xist RNA dependent initially
  – *some become Xist-independent eg H4Ac*

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

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

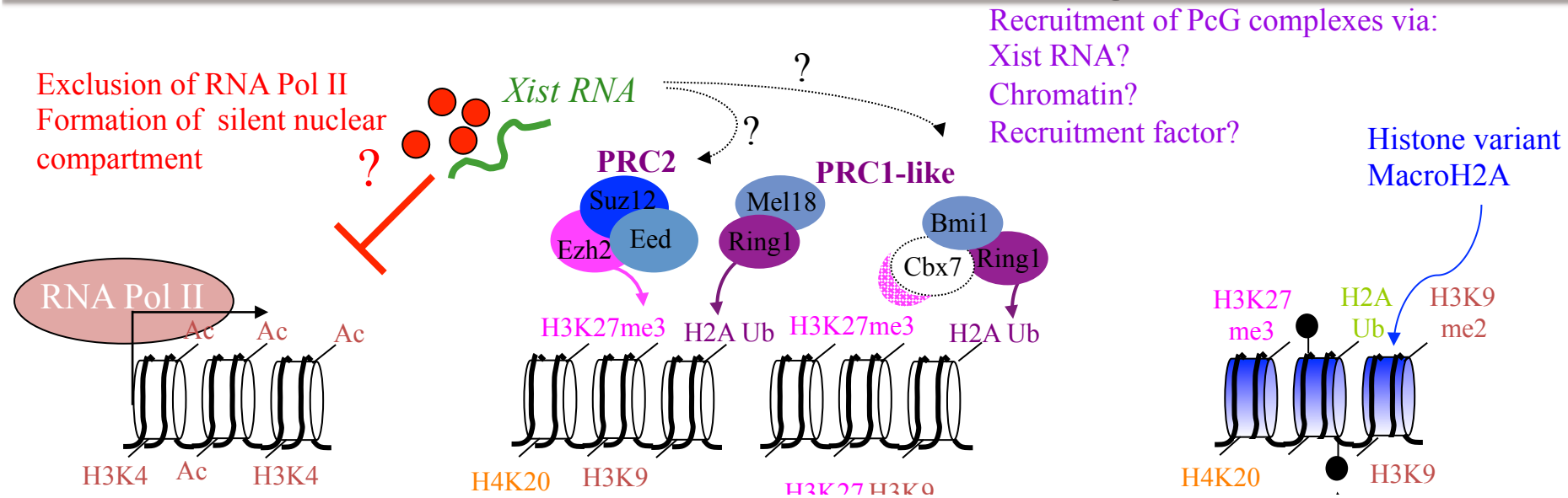




Histone 'readers' and 'writers' of the Xi ?

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

Exploring Heterochromatin Formation during X inactivation in differentiating ES cells



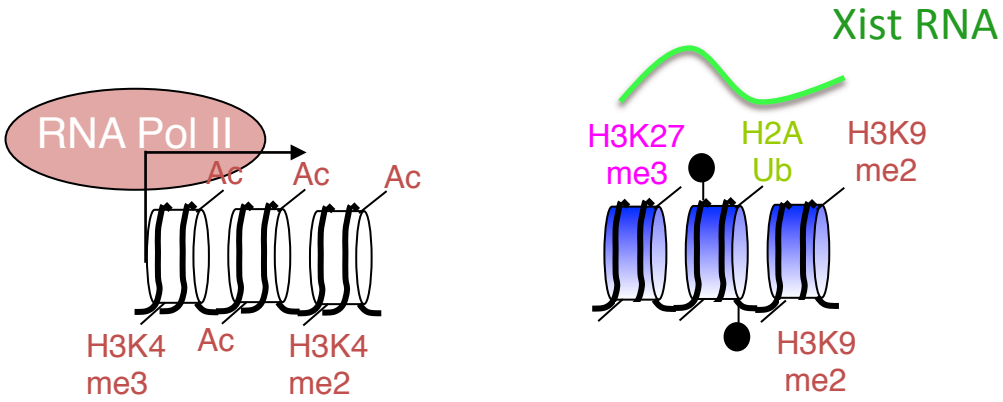
Once X inactivation has been established, Xist RNA is no longer required for the stable propagation of the inactive state

(Wutz and Jaenisch (2000) *Mol. Cell*, 5, 695–705)

F

The Epigenetics of X inactivation

Identical DNA sequences
Opposite gene activity states



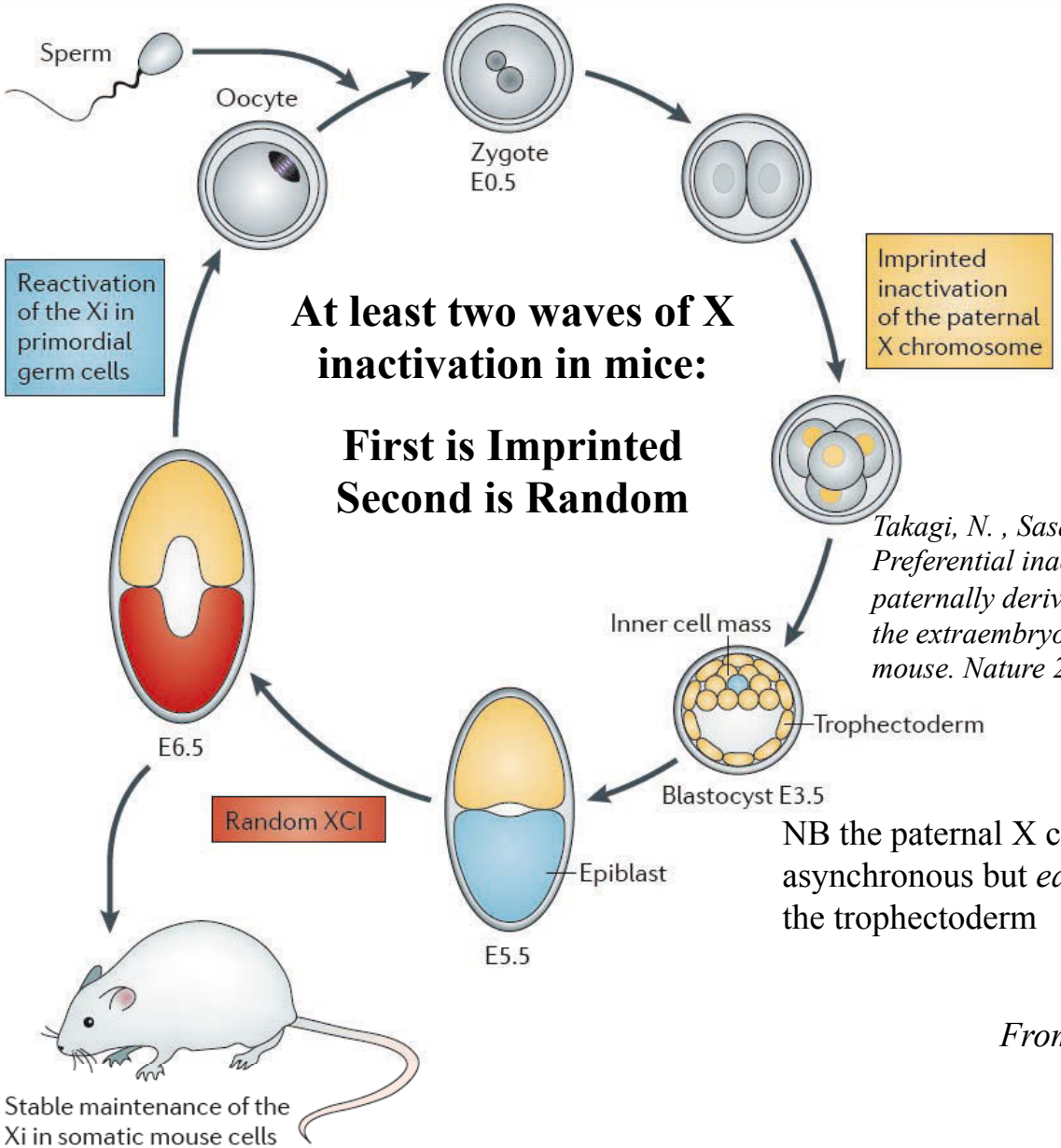
Active X chromosome Inactive X chromosome

Synergy of epigenetic marks, nuclear compartmentalization and asynchronous replication timing,
provides extremely stable, heritable
silencing over hundreds of cell divisions.

Csankovski et al, 2001
Zhang et al, 2007
Wutz, 2011 for review

The inactive state is fully reversible in the germ line,
during early development
and during induced pluripotency (iPS) *(to be covered in future courses!)*

The Developmental Dynamics of X inactivation



Takagi, N. , Sasaki, M. 1975. Preferential inactivation of the paternally derived X chromosome in the extraembryonic membranes of the mouse. Nature 256, 640-642

Kay et al, 1994
Huyhn and Lee, 2003
Okamoto et al, 2004
Mak et al, 2004
Patrat et al, 2009

NB the paternal X chromosome is asynchronous but *early* replicating in the trophectoderm

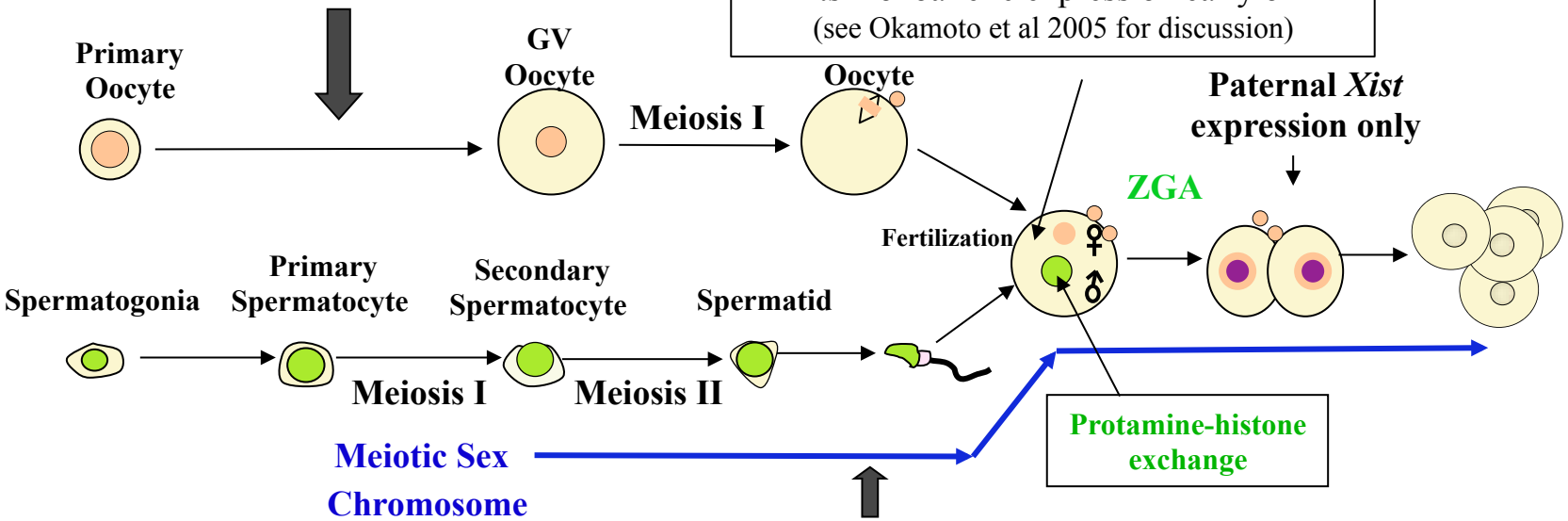
From Wutz, 2011

Imprint(s) underlying paternal X inactivation in Mice?

Maternal Imprint :
Prevents maternal X chromosome inactivation
(Rastan and Lyon, 1984,Tada et al, 2000)
Repressive *Xist* imprint?

Rnf12 is essential for initiation of imprinted XCI (Shin et al, 2010)

The maternal pool of Rnf12 and early ZGA in mice may have led to the requirement for an *Xist* imprint to regulate its monoallelic expression early on
(see Okamoto et al 2005 for discussion)

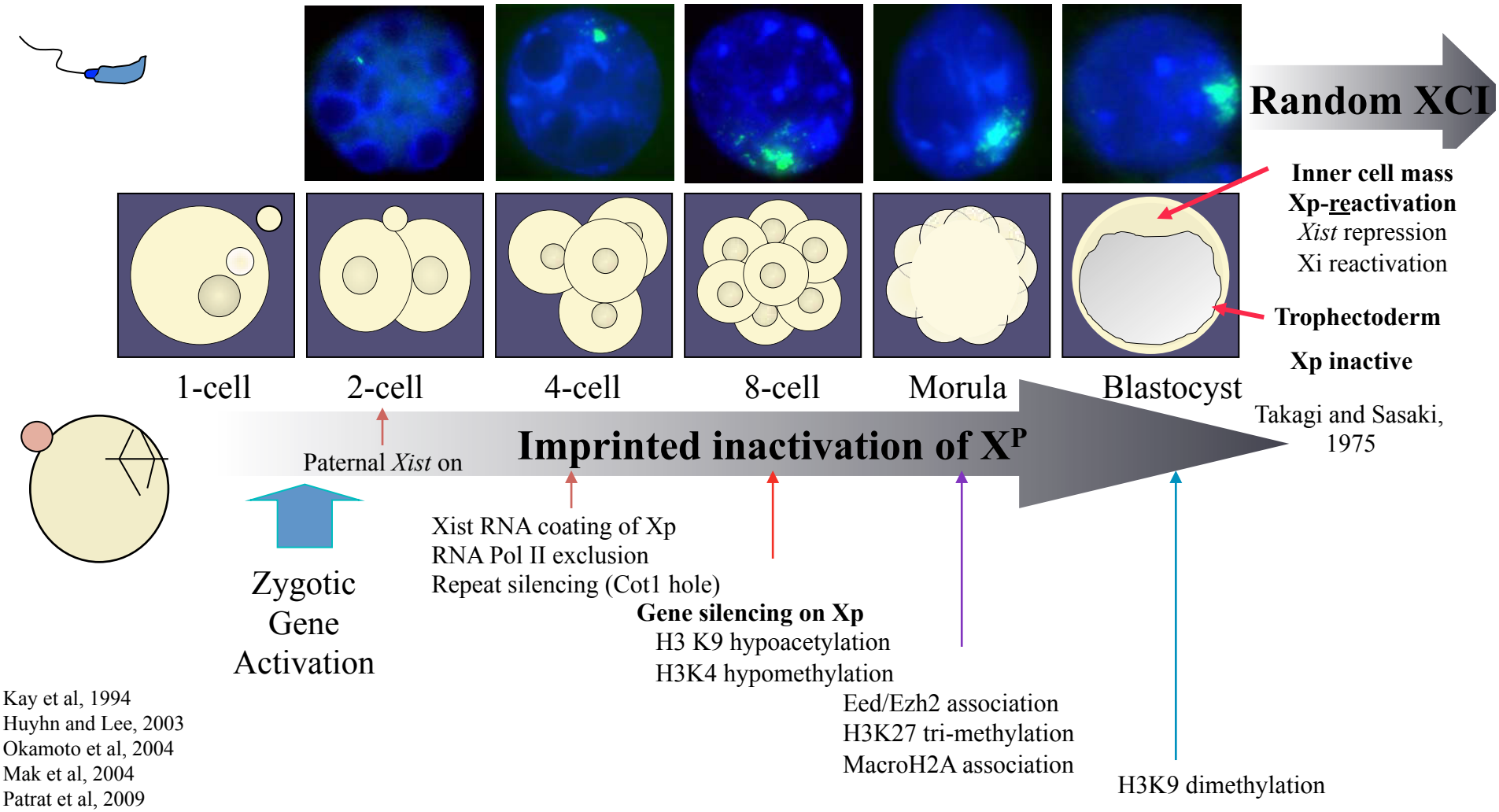


Paternal Imprint :
Xp Pre-inactivation (continuity of silencing)
(Huyhn and Lee,, 2003)
Xp predisposition (chromatin imprint)
(Monk and McLaren, 1983)

The Xp chromosome is genetically active in the zygote
***Xist* transgenes on autosomes can trigger imprinted cis-inactivation *without* prior MSCI**
(Okamoto et al, 2005; Patrat et al, 2009; Namekawa et al, 2011)

Imprinted Paternal XCI during Pre-implantation Mouse Development

Xist is expressed from paternal X only (never biallelic)



Kay et al, 1994
Huyhn and Lee, 2003
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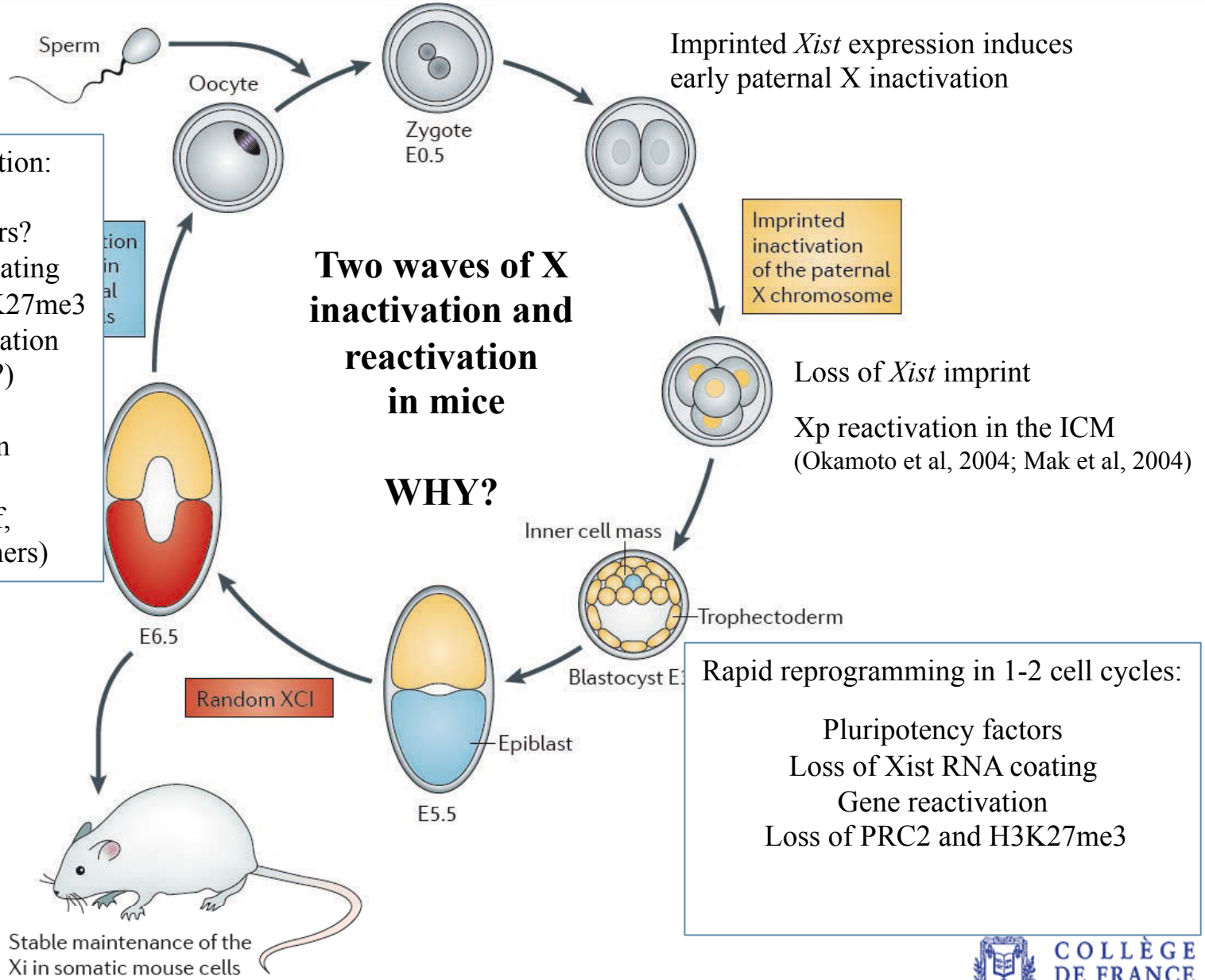
The Developmental Dynamics of X inactivation

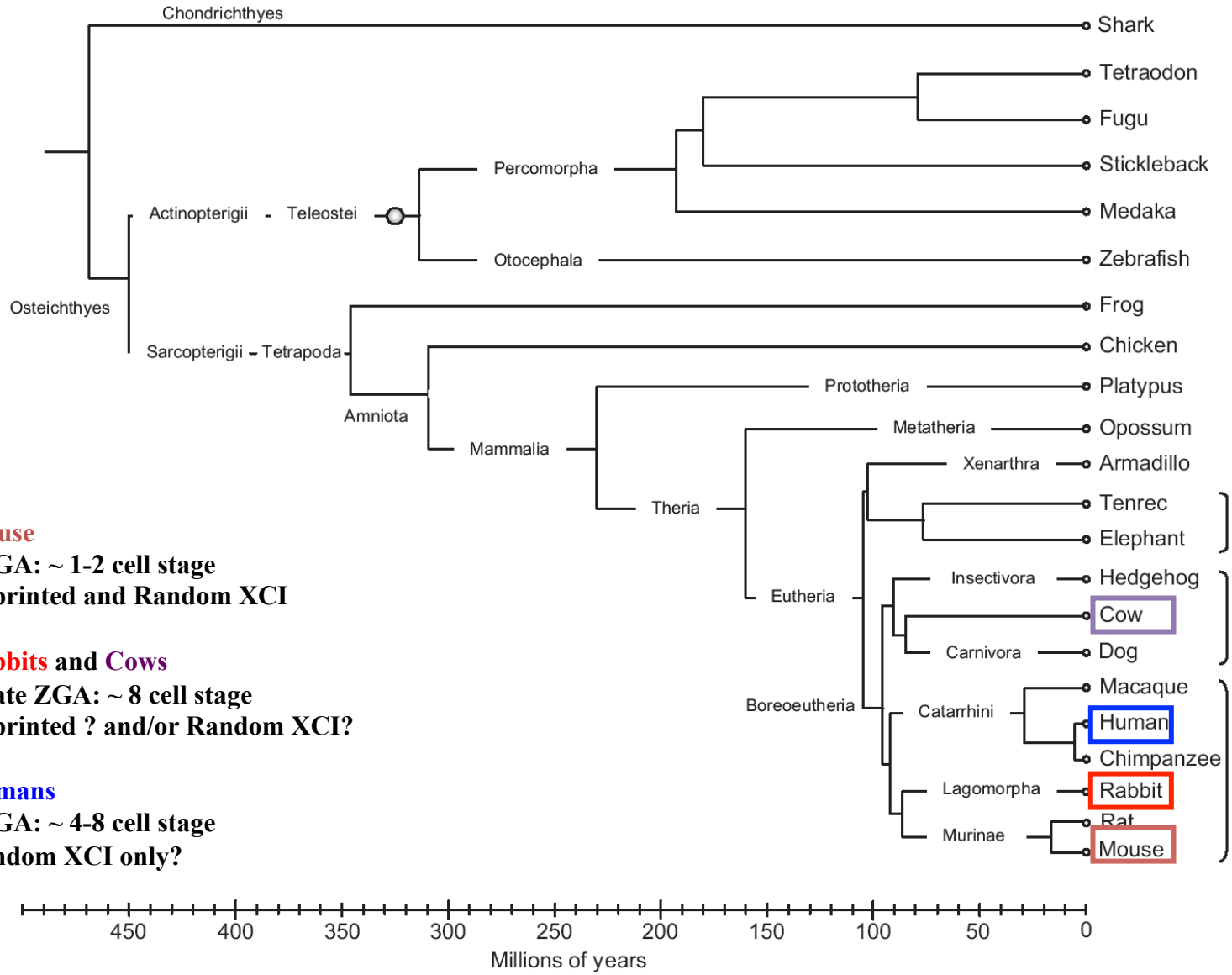


Kay et al, 1994
Huyhn and Lee, 2003
Okamoto et al, 2004
Mak et al, 2004
Patrat et al, 2009

Nothing in Biology Makes Sense Except in the Light of Evolution…

Theodosius Dobzhansky

Evolutionary conservation of X inactivation during early development in eutherian mammals?



Mouse
- **ZGA: ~ 1-2 cell stage**

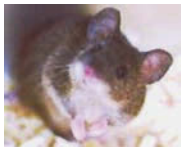
Imprinted and Random XCI

Rabbits and Cows
- **Late ZGA: ~ 8 cell stage**

Imprinted ? and/or Random XCI?

Humans
- **ZGA: ~ 4-8 cell stage**

Random XCI only?

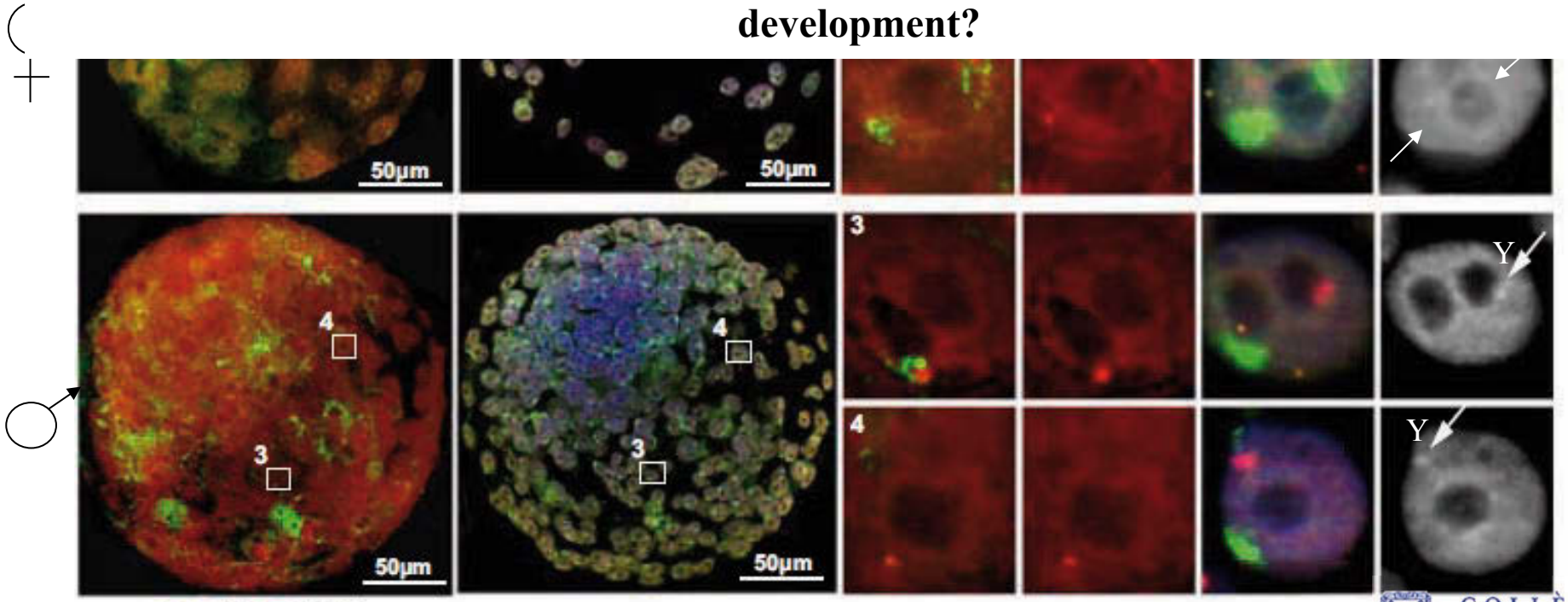


XIST RNA and X-inactivation patterns in Human embryos

XIST is initially biallelically expressed in human and rabbit embryos –> no *XIST* imprint
No signs of X inactivation or Barr body formation even at day 7 blastocyst stage in humans
No reactivation of the Xi in the inner cell mass of the blastocyst in rabbits or humans
Subsequent chromatin changes are quite similar between mammals

⇒ Very different regulation of initiation of X inactivation:
only one wave, no *Xist* imprint, post-XCI choice…

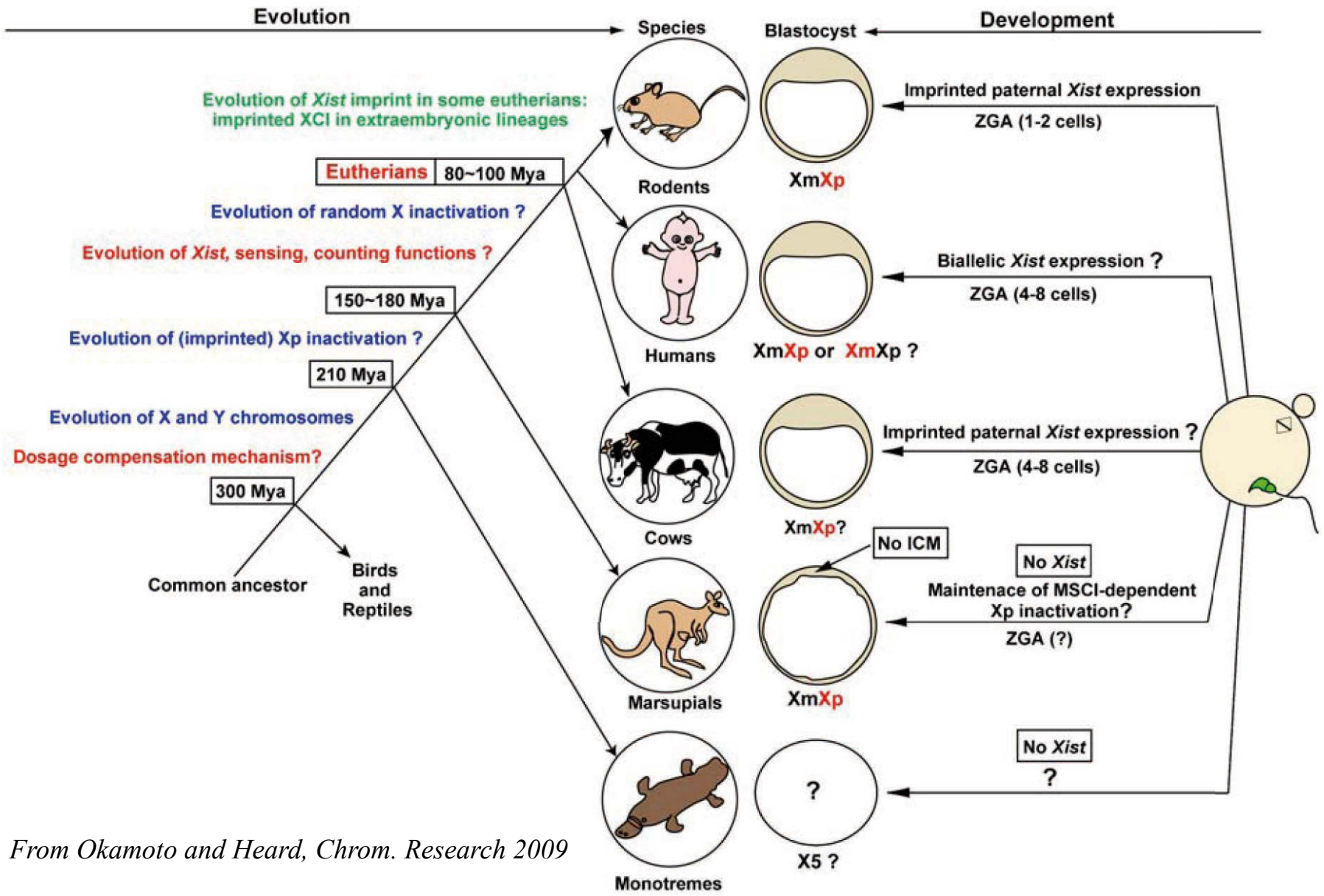
Are mice the exception to the eutherian rule due to their very early ZGA and rapid development?



XIST / ATRX RNA

Okamoto et al (2011) Evolutionary Diversity of X-chromosome Inactivation in Mammals. *Nature* 472 : 370-374

The Evolutionary Dynamics of X inactivation



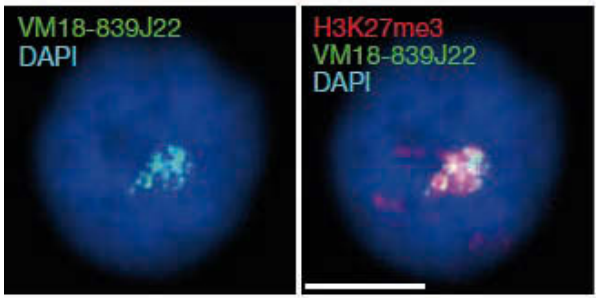
From Okamoto and Heard, Chrom. Research 2009

The Evolutionary Dynamics of X inactivation

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], Hélène Royo[1], Janine Duckworth[3], John R. McCarrey[4], John L. VandeBerg[5], Marilyn B. Renfree[6], Willie Taylor[1], Greg Elgar[1], R. Daniel Camerini-Otero[2], Mike J. Gilchrist[1] & James M. A. Turner[1]

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



Non-coding RNAs may be easy to evolve,
easy to regulate dynamically in development,
and could be useful "triggers" for epigenetic processes…
(next two lectures)

Prof. Joost Gribnau

"X-Chromosome Inactivation Mechanisms"

E. Heard, February 18th, 2013

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