Edith Heard, Sarah Tishkoff, John A Todd, Marc Vidal, Günter P Wagner, Jun Wang, Detlef Weigel, Richard Young (2010 Sep 8)

**Ten years of genetics and genomics: what have we achieved and where are we heading?**

*Nature reviews. Genetics*: 723-33 : [DOI : 10.1038/nrg2878]

**Summary**

To celebrate the first 10 years of Nature Reviews Genetics, we asked eight leading researchers for their views on the key developments in genetics and genomics in the past decade and the prospects for the future. Their responses highlight the incredible changes that the field has seen, from the explosion of genomic data and the many possibilities it has opened up to the ability to reprogramme adult cells to pluripotency. The way ahead looks similarly exciting as we address questions such as how cells function as systems and how complex interactions among genetics, epigenetics and the environment combine to shape phenotypes.

Elphège P Nora, Edith Heard (2009 Dec 1)

**X chromosome inactivation: when dosage counts.**

*Cell*: 865-7 : [DOI : 10.1016/j.cell.2009.11.009]

**Summary**

How do mammals count their X chromosomes and keep only one X active per cell? In this issue, Jonkers et al. (2009) show that Rnf12/RLIM, encoded by the X-linked gene Rnf12, induces X chromosome inactivation only when present above a certain threshold, a condition fulfilled when at least two Xs are active.

Ikuhiro Okamoto, Edith Heard (2009 Oct 6)

**Lessons from comparative analysis of X-chromosome inactivation in mammals.**

*Chromosome research*: 659-69 : [DOI : 10.1007/s10577-009-9057-7]
Summary

In most mammals, X-chromosome inactivation is used as the strategy to achieve dosage compensation between XX females and XY males. This process is developmentally regulated, resulting in the differential treatment of the two X chromosomes in the same nucleus and mitotic heritability of the silent state. A lack of dosage compensation in an XX embryo is believed to result in early lethality, at least in eutherians. Given its fundamental importance, X-chromosome inactivation would be predicted to be a highly conserved process in mammals. However, recent studies have revealed major mechanistic differences in X inactivation between eutherians and marsupials, suggesting that the evolution of the X chromosome as well as developmental differences between mammals have led to diverse evolutionary strategies for dosage compensation.

Edith Heard, Laura Carrel (2009 Sep 18)
**Foreword: Coping with sex chromosome imbalance.**
*Chromosome research* : 579-83 : [DOI: 10.1007/s10577-009-9062-x]

**Summary**

Jennifer C Chow, Constance Ciaudo, Melissa J Fazzari, Nathan Mise, Nicolas Servant, Jacob L Glass, Matthew Attreed, Philip Avner, Anton Wutz, Emmanuel Barillot, John M Greally, Olivier Voinnet, Edith Heard (2009 Aug 21)
**LINE-1 activity in facultative heterochromatin formation during X chromosome inactivation.**
*Cell* : 956-69 : [DOI: 10.1016/j.cell.2010.04.042]

**Summary**

During X chromosome inactivation (XCI), Xist RNA coats and silences one of the two X chromosomes in female cells. Little is known about how XCI spreads across the chromosome, although LINE-1 elements have been proposed to play a role. Here we show that LINEs participate in creating a silent nuclear compartment into which genes become recruited. A subset of young LINE-1 elements, however, is expressed during XCI, rather than being silenced. We demonstrate that such LINE expression requires the specific heterochromatic state induced by Xist. These LINEs often lie within escape-prone regions of the X chromosome, but close to genes that are subject to XCI, and are associated with putative endo-siRNAs. LINEs may thus facilitate XCI at different levels, with silent LINEs participating in assembly of a heterochromatic nuclear compartment induced by Xist, and active LINEs participating in local propagation of XCI into regions that would otherwise be prone to escape.

Jennifer Chow, Edith Heard (2009 May 30)
**X inactivation and the complexities of silencing a sex chromosome.**
*Current opinion in cell biology* : 359-66 : [DOI : 10.1016/j.ceb.2009.04.012]

**Summary**

X chromosome inactivation represents a paradigm for monoallelic gene expression and epigenetic regulation in mammals. Since its discovery over half a century ago, the pathways involved in the establishment of X-chromosomal silencing, assembly, and maintenance of the heterochromatic state have been the subjects of intensive research. In placental mammals, it is becoming clear that X inactivation involves an interplay between noncoding transcripts such as Xist, chromatin modifiers, and factors involved in nuclear organization. Together these result in a changed chromatin structure and in the spatial reorganization of the X chromosome. Exciting new work is starting to uncover the factors involved in some of these changes. Recent studies have also revealed surprising diversity in the kinetics and extent of gene silencing across the X chromosome, as well as in the mechanisms of XCI between mammals.

Catherine Patrat, Ikuhiro Okamoto, Patricia Diabangouaya, Vivian Vialon, Patricia Le Baccon, Jennifer Chow, Edith Heard (2009 Mar 11)

**Dynamic changes in paternal X-chromosome activity during imprinted X-chromosome inactivation in mice.**
*Proceedings of the National Academy of Sciences of the United States of America* : 5198-203 : [DOI : 10.1073/pnas.0810683106]

**Summary**

In mammals, X-chromosome dosage compensation is achieved by inactivating one of the two X chromosomes in females. In mice, X inactivation is initially imprinted, with inactivation of the paternal X (Xp) chromosome occurring during preimplantation development. One theory is that the Xp is preinactivated in female embryos, because of its previous silence during meiosis in the male germ line. The extent to which the Xp is active after fertilization and the exact time of onset of X-linked gene silencing have been the subject of debate. We performed a systematic, single-cell transcriptional analysis to examine the activity of the Xp chromosome for a panel of X-linked genes throughout early preimplantation development in the mouse. Rather than being preinactivated, we found the Xp to be fully active at the time of zygotic gene activation, with silencing beginning from the 4-cell stage onward. X-inactivation patterns were, however, surprisingly diverse between genes. Some loci showed early onset (4-8-cell stage) of X inactivation, and some showed extremely late onset (postblastocyst stage), whereas others were never fully inactivated. Thus, we show that silencing of some X-chromosomal regions occurs outside of the usual time window and that escape from X inactivation can be highly lineage specific. These results reveal that imprinted X inactivation in mice is far less concerted than previously thought and highlight the epigenetic diversity underlying the dosage compensation process during early mammalian development.
Julie Chaumeil, Sandrine Augui, Jennifer C Chow, Edith Heard (2008 Oct 28)
**Combined immunofluorescence, RNA fluorescent in situ hybridization, and DNA fluorescent in situ hybridization to study chromatin changes, transcriptional activity, nuclear organization, and X-chromosome inactivation.**
*Methods in molecular biology (Clifton, N.J.)*: 297-308 : [DOI: 10.1007/978-1-59745-406-3_18]

**Summary**

Epigenetic mechanisms lead to the stable regulation of gene expression without alteration of DNA and trigger initiation and/or maintenance of cell-type-specific transcriptional profiles. Indeed, modulation of chromatin structure and the global 3D organization of the genome and nuclear architecture participate in the precise control of transcription. Thus, dissection of these epigenetic mechanisms is essential for our understanding of gene regulation. In this chapter, we describe challenging combinations of immunofluorescence, and RNA and DNA fluorescent in situ hybridization and their application to our studies of a remarkable example of epigenetic control of gene expression in female mammals, the process of X chromosome inactivation.

Sandrine Augui, Edith Heard (2008 Jul 8)
**[Inactivation of X chromosome: cells know how to count two X chromosomes].**
*Médecine sciences : M/S*: 584-5 : [DOI: 10.1051/medsci/20082467584]

**Summary**

Edith Heard, Vincent Colot (2008 Jun 10)
**Chromosome structural proteins and RNA-mediated epigenetic silencing.**
*Developmental cell*: 813-4 : [DOI: 10.1016/j.devcel.2008.05.013]

**Summary**

Structural maintenance of chromosomes (SMC) proteins form the cohesin and condensin complexes and play important roles in sister chromatid pairing, chromosome segregation, and transcriptional regulation. Two papers in Nature Genetics now show that SMC-like proteins also participate in epigenetic processes such as X inactivation in mammals and RNA-directed DNA methylation in plants.

Year of publication 2007

Edith Heard, Wendy Bickmore (2007 May 1)
The ins and outs of gene regulation and chromosome territory organisation.
*Current opinion in cell biology* : 311-6

**Summary**

The establishment and maintenance of differential patterns of gene expression lie at the heart of development. How the precision of developmental gene regulation is achieved, despite the highly repetitive and complex nature of the mammalian genome, remains an important question. It is becoming increasingly clear that genetic regulation must be considered not only in the context of short- and long-range regulatory sequences and local chromatin structure, but also at the level of position within the nucleus. Recent studies have addressed the extent to which the location of a gene relative to its interphase chromosome territory affects its regulation or its capacity to be expressed. Two model systems have emphasized the role of this level of nuclear organization during development. Hox gene clusters have provided important insights into the dynamic repositioning of a locus relative to its chromosome territory during spatial and temporal patterning of gene expression. The inactive X chromosome has also become a useful paradigm for studying the differential chromatin status and chromosomal organization of the two X’s within the same nucleus. Recent work suggests that chromosome territory reorganisation can be an important step in the gene silencing process.

Year of publication 2006

Sandrine Augui, Edith Heard (2006 Nov 15)
[Cross talk between the Xics].
*Médecine sciences* : M/S : 910-1

**Summary**

Julie Chaumeil, Patricia Le Baccon, Anton Wutz, Edith Heard (2006 Aug 17)
*A novel role for Xist RNA in the formation of a repressive nuclear compartment into which genes are recruited when silenced.*
*Genes & development* : 2223-37

**Summary**

During early mammalian female development, one of the two X chromosomes becomes inactivated. Although X-chromosome coating by Xist RNA is essential for the initiation of X inactivation, little is known about how this signal is transformed into transcriptional silencing. Here we show that exclusion of RNA Polymerase II and transcription factors from the Xist RNA-coated X chromosome represents the earliest event following Xist RNA accumulation described so far in differentiating embryonic stem (ES) cells. Paradoxically, exclusion of the transcription machinery occurs before gene silencing is complete. However, examination of the three-dimensional organization of X-linked genes reveals that, when transcribed, they
are always located at the periphery of, or outside, the Xist RNA domain, in contact with the transcription machinery. Upon silencing, genes shift to a more internal location, within the Xist RNA compartment devoid of transcription factors. Surprisingly, the appearance of this compartment is not dependent on the A-repeats of the Xist transcript, which are essential for gene silencing. However, the A-repeats are required for the relocation of genes into the Xist RNA silent domain. We propose that Xist RNA has multiple functions: A-repeat-independent creation of a transcriptionally silent nuclear compartment; and A-repeat-dependent induction of gene repression, which is associated with their translocation into this silent domain.

Edith Heard, Christine M Disteche (2006 Jul 19)
Dosage compensation in mammals: fine-tuning the expression of the X chromosome.
*Genes & development*: 1848-67

**Summary**

Mammalian females have two X chromosomes and males have only one. This has led to the evolution of special mechanisms of dosage compensation. The inactivation of one X chromosome in females equalizes gene expression between the sexes. This process of X-chromosome inactivation (XCI) is a remarkable example of long-range, monoallelic gene silencing and facultative heterochromatin formation, and the questions surrounding it have fascinated biologists for decades. How does the inactivation of more than a thousand genes on one X chromosome take place while the other X chromosome, present in the same nucleus, remains genetically active? What are the underlying mechanisms that trigger the initial differential treatment of the two X chromosomes? How is this differential treatment maintained once it has been established, and how are some genes able to escape the process? Does the mechanism of X inactivation vary between species and even between lineages? In this review, X inactivation is considered in evolutionary terms, and we discuss recent insights into the epigenetic changes and developmental timing of this process. We also review the discovery and possible implications of a second form of dosage compensation in mammals that deals with the unique, potentially haploinsufficient, status of the X chromosome with respect to autosomal gene expression.