Дозовая компенсация *Drosophila melanogaster* – ключ к пониманию кооперативности в эпигенетике

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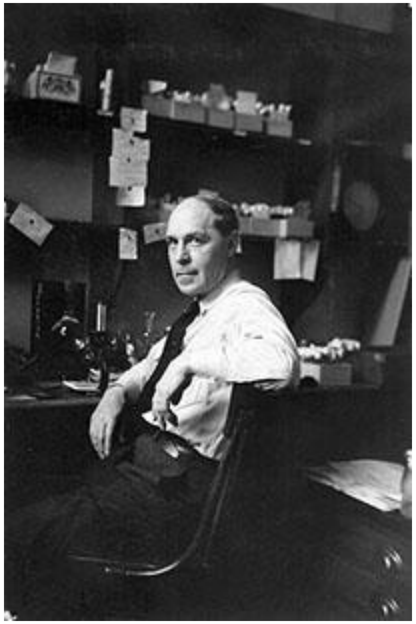
‘Dosage compensation’ – a mechanism that is responsible for the equality of expression of X-linked genes in male and female *Drosophila*. (Muller, 1932)



1949 – Barr & Bertram: Barr body
1956 – Dobzhansky: equality of DNA-polymerase amount in 1 male and 2 female X
1959 – Ohno: XCI (X chromosome inactivation)
1961 – Lyon, Russel: random choice of XCI (1962, Lyon – DC in mammals)
1966 – Komma: autosomal activators
1973 – Maroni & Plaut: global chromosome regulation
1985 – Wood: *C. elegans*

Dosage compensation: different modes

During the course of evolution, an ancestor to the placental mammals must have escaped a peril resulting from the hemizygous existence of all the X-linked genes in the male by doubling the rate of product output of each X-linked gene. Once this step was accomplished, the female no longer needed two X's in her somatic cells. Hence, the dosage compensation mechanisms by random inactivation of one or the other X evolved.

In the case of Drosophila, on the other hand, it appears that a needed increase of the rate of product output by the individual X-linked genes did not take place in their evolutional past. Thus, two alleles at each X-linked gene locus are still needed by the female. The presence of modifier genes is required primarily to raise the efficiency of individual X-linked genes in the hemizygous state as a means of minimizing a peril encountered by the male.

Sex Chromosomes and Sex-Linked Genes, Ohno, 1967

Dosage compensation: different modes

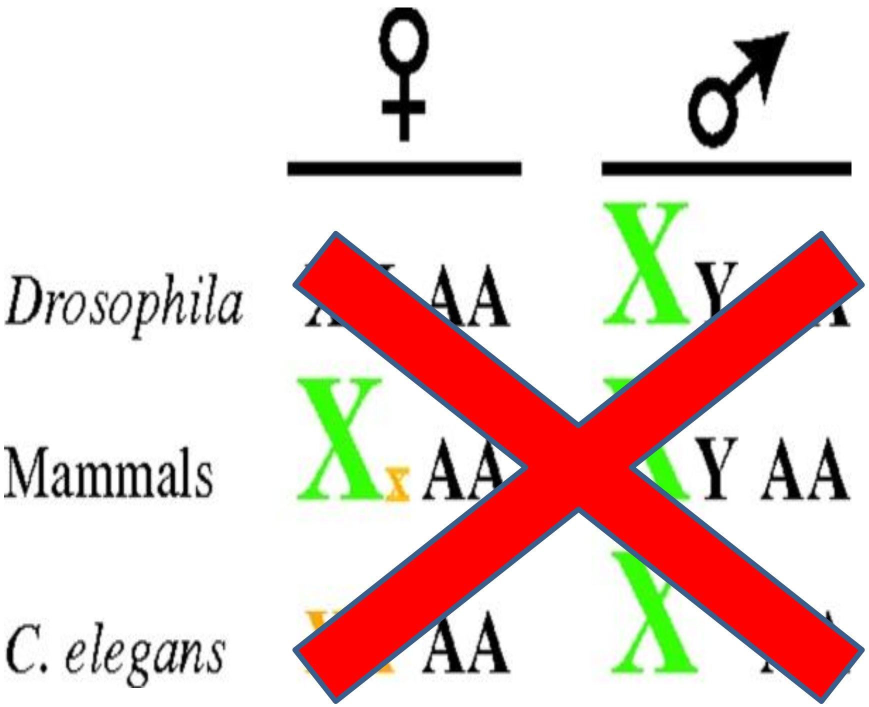
- Selection will favor tight linkage between the sex determining locus and sexually antagonistic alleles benefiting the heterogametic sex. (Gu and Walters, 2017)
- Ohno proposed that dosage compensation in mammals evolved as a two-step mechanism with (1) a twofold expression increase of the X chromosome in both sexes, which solves the gene dose imbalance problem in males, and (2) inactivation of one of the two X chromosomes by XCI in females to restore optimal dosage. (Pessia et al, 2014)

Dosage compensation: different modes

Sex Determination	SCDC Pattern	Taxon (number of species surveyed)
Male heterogamety (XX/XY)	Type I (X = XX = Ancestral)	True bugs (Hemiptera) (4)
		Strepsipteran (1)
		Beetle (Coleoptera) (1)
		Flies and mosquitoes (Diptera) (7)
	Type II (X = XX < Ancestral)	Nematodes (2)
		Therian mammals (9)
	Type III (X < XX = Ancestral)	Three-spined stickleback (1)
		Platypus (1)
Female heterogamety (WZ/ZZ)	Type II (Z = ZZ < Ancestral	Moths and butterflies (Lepidoptera) (5)
	Type III (Z < ZZ = Ancestral)	Blood-fluke (Schistosoma) (1)
		Tonguefish (1)
		Snakes (2)
		Birds (5)

(Gu and Walters, 2017)

Dosage compensation: different modes



(Gelbart & Kuroda, 2009)

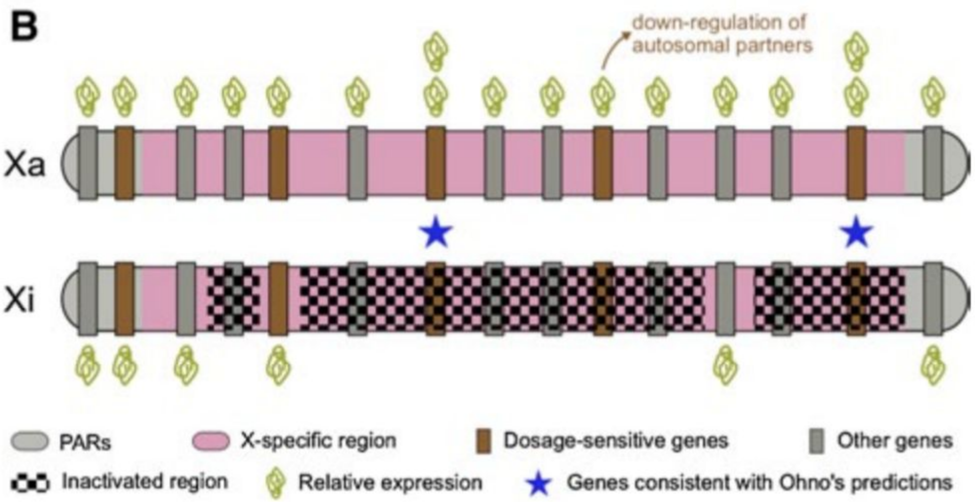
	♀	♂
Drosophila	XX AA	XY AA
Eutherians	xX AA	XY AA
Marsupials	???	
Prototherian	xX AA	XY AA
C. elegans	xx AA	XY AA

Dosage compensation: complete and incomplete DC. DC≠XCI!

The well-studied mammalian X chromosome inactivation system, to which we have habitually compared other systems, is unique in vertebrates and perhaps not a useful comparator. It remains unclear what special selective forces drove the evolution of global control of X inactivation in therian mammals. In other vertebrates, the dosage compensation of genes on differentiated sex chromosomes is gene-specific and *partial*.

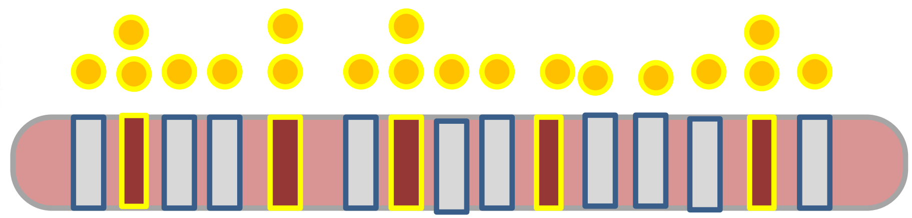
(Graves, 2016)

Dosage compensation: complete and incomplete DC

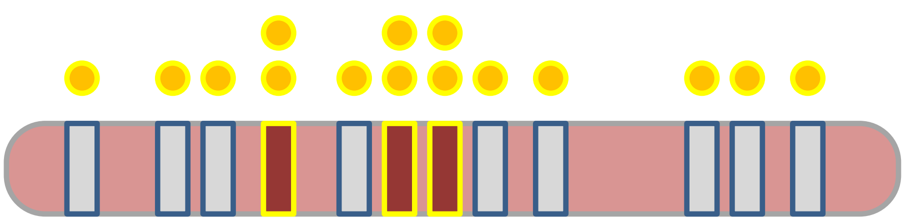


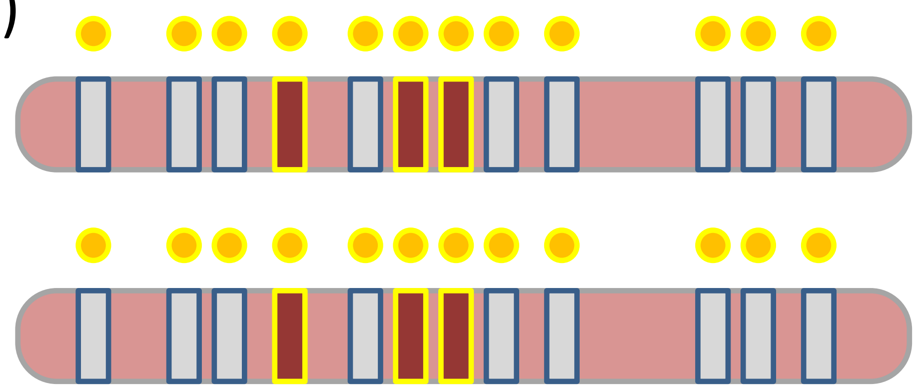
(Pessia et al, 2014)

XCI in mammals (placental)

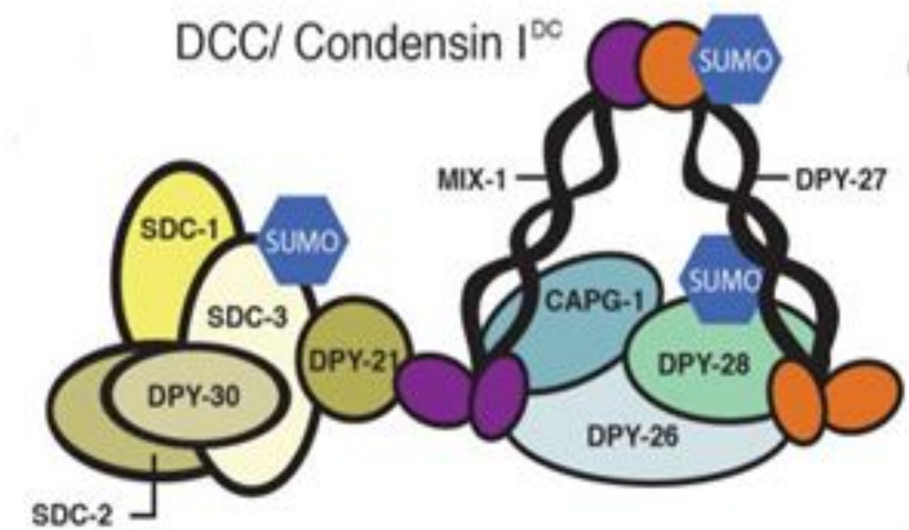


DC in birds, snakes and fish (Z)





Amazing and so different DCCs



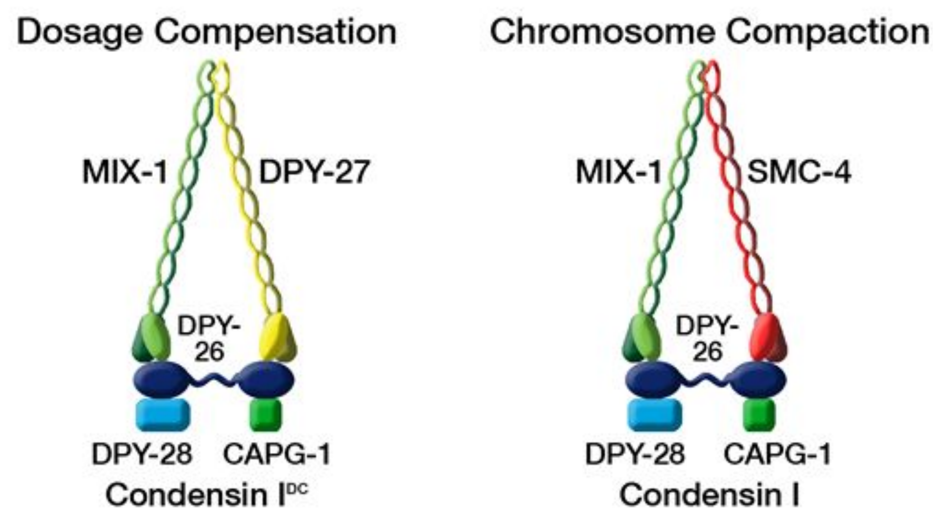
(Lau & Csankovszki, 2015)

C. elegans

Cooperation of rex sites of C. elegans (0.1-1Mb)

Recruit complexes MES2/3/6 (H3K27me) and SET1 (H4K20me)
on strong (200 bp clusters with HOT-sites)
Then spreading through weak sites
(12 bp motif or tRNA gene)

Albritton & Ercan, 2018



(Mets & Meyer, 2009)

Questions from *C. elegans*

- What proteins recognize the 12-bp DNA sequence motif at the recruitment sites? What are the mechanisms that regulate condensin DC ring loading to the X chromosome?
- What is the molecular mechanism by which the DCC spreads along chromatin?
- How does the DCC reduce RNA Pol II binding to X chromosome promoters?

Albritton & Ercan, 2018

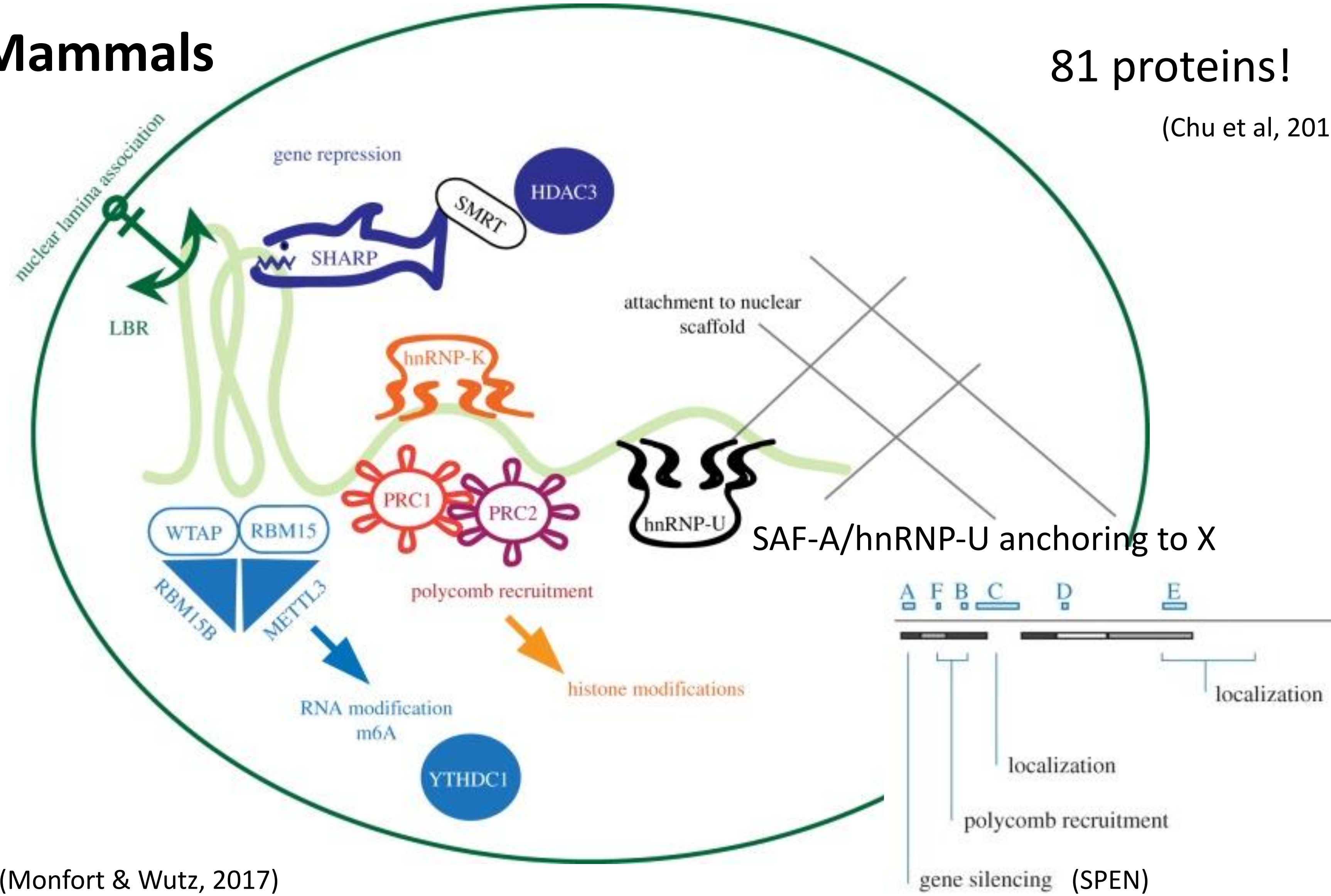
Amazing and so different DCCs

Mammals

81 proteins!

(Chu et al, 2016)

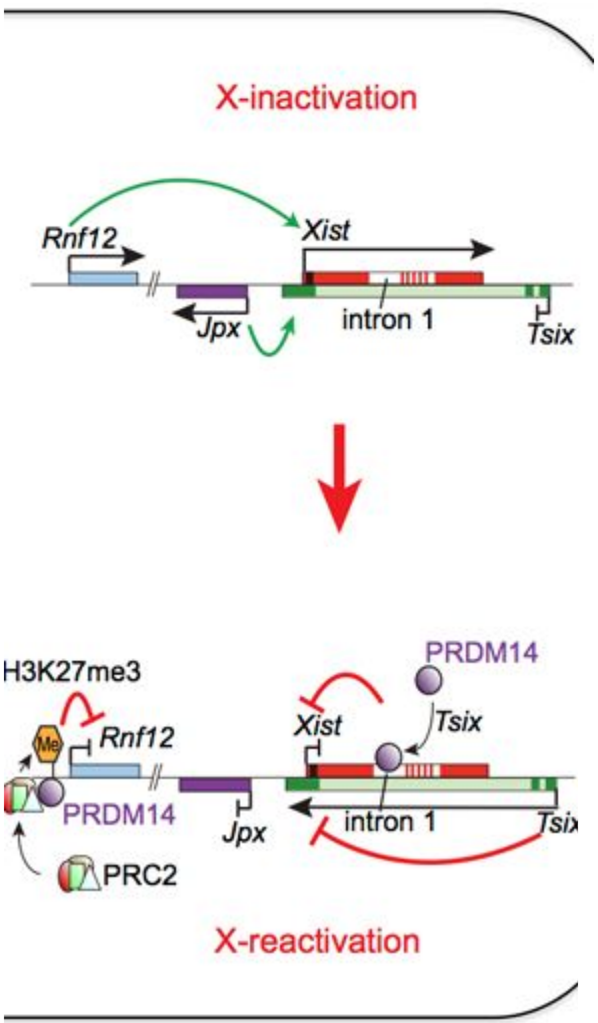
SAF-A/hnRNP-U anchoring to X



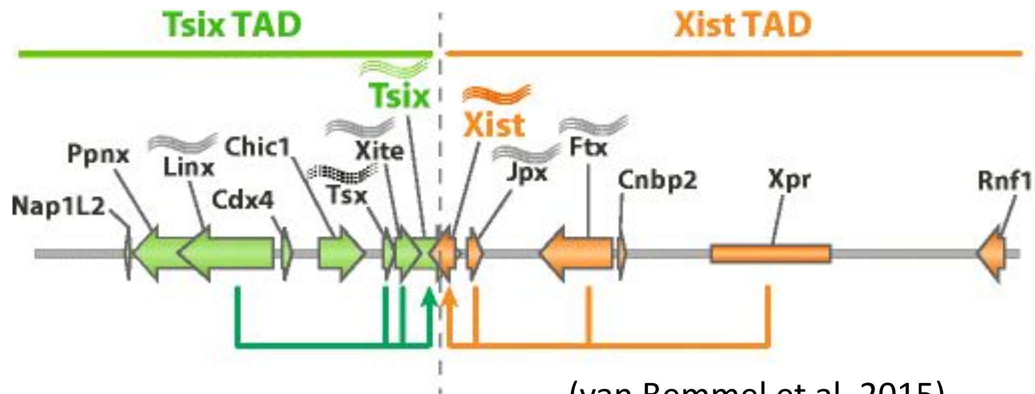
(Monfort & Wutz, 2017)

(SPEN)

Amazing and so different DCCs



(Payer, 2015)



(van Bemmel et al, 2015)

Feature	Mouse	Human
Xist expression at onset	Only on future Xi in female. It is always X^P	On all X chromosomes in males and females
Upregulation of Xist on Xi	Four to eight cells; Selective, as only the future inactive X is upregulated	Not until sometime after Day 7; on all X chromosomes but one
Imprinted XI	Yes, in trophectoderm	No
Random XI	Only in embryo proper	In placenta and embryo proper
Tsix functional	In imprinted XI	Nonfunctional
XACT	Not present	May inhibit *XIST* upregulation early, but not later
Repression of Xist on future active X	*Tsix* early. Later, not known	Some other dosage-sensitive *XIST* repressor

(Migeon, 2017)

Amazing and so different DCCs

It has been surprising then that the DNA sequences (and proteins) required for *XIST* RNA binding and silencing are not restricted to the X chromosome. *We conclude that XIST does not recognize the chromosome sequence, but somehow recognizes the underlying nuclear chromosome structure of its parent chromosome*. (Creamer & Lawrence, 2017)

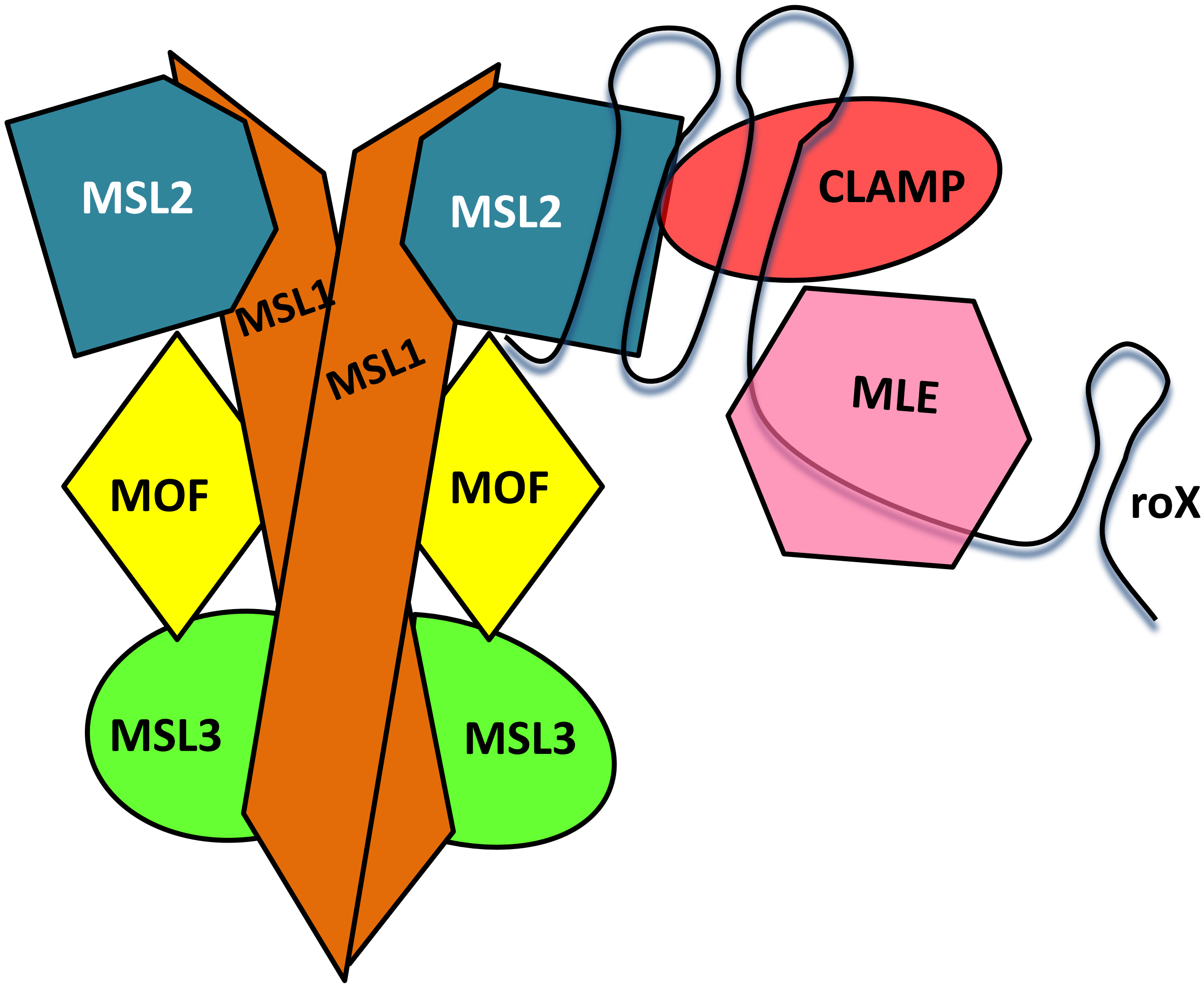
Questions from mammals

- How does Xist propagate along X-chromosome? Why its propagation is confined?
- How does Xist inactivate X chromosome?
- Many questions about Xist regulation

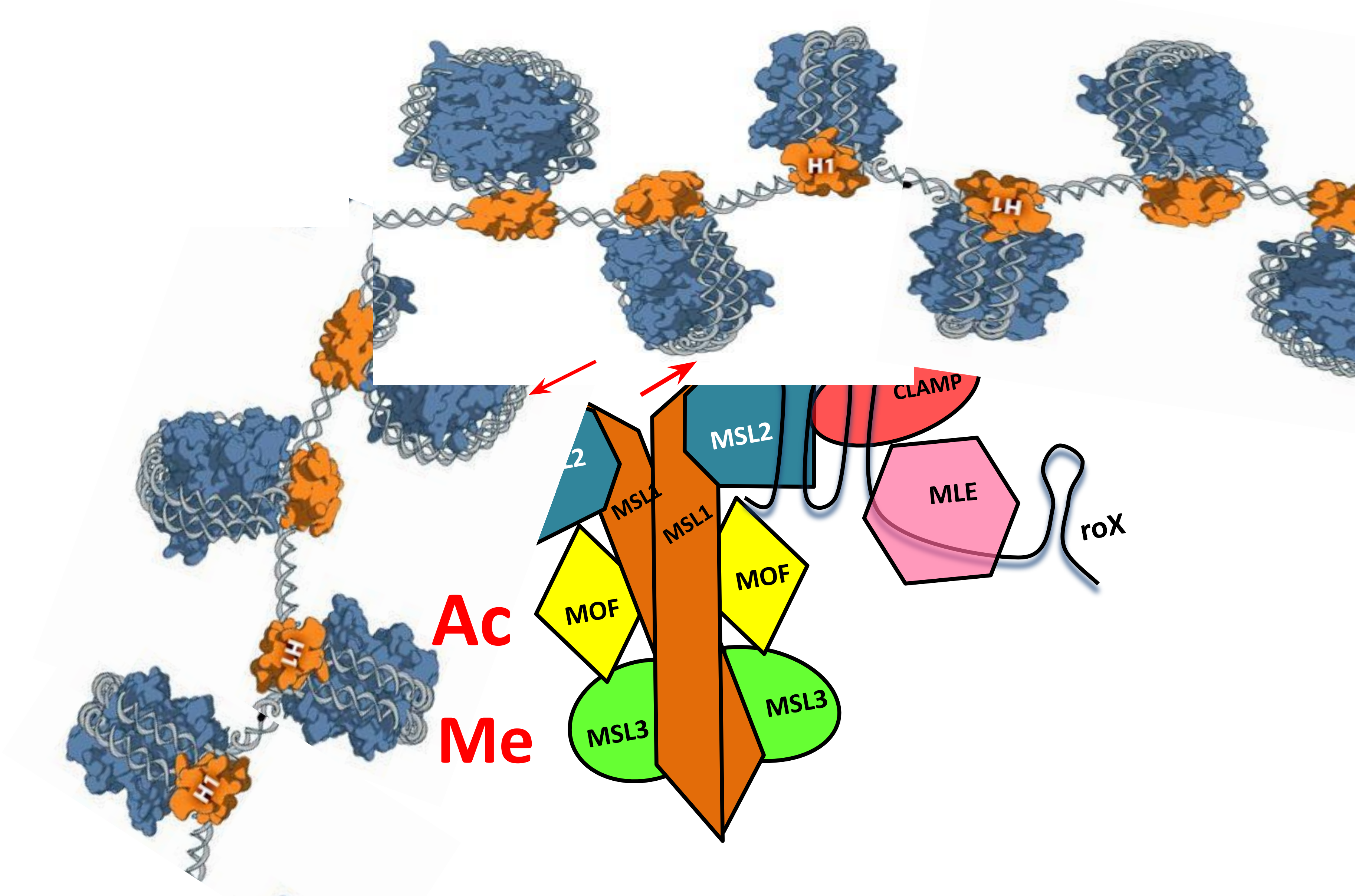
Dosage compensation in *Drosophila melanogaster*

Component	Function
MSL1	Dimeric scaffold protein (big, coiled-coil)
MSL2	DNA- and RNA-binding protein, ubiquitin-ligase, recruiter?
MSL3	H3K36me-binding protein
MLE	RNA-helicase
MOF	**HAT (H4K16ac)**
CLAMP	DNA-binding protein with Zn-fingers
roX 1 и 2	lncRNAs with conservative secondary structure

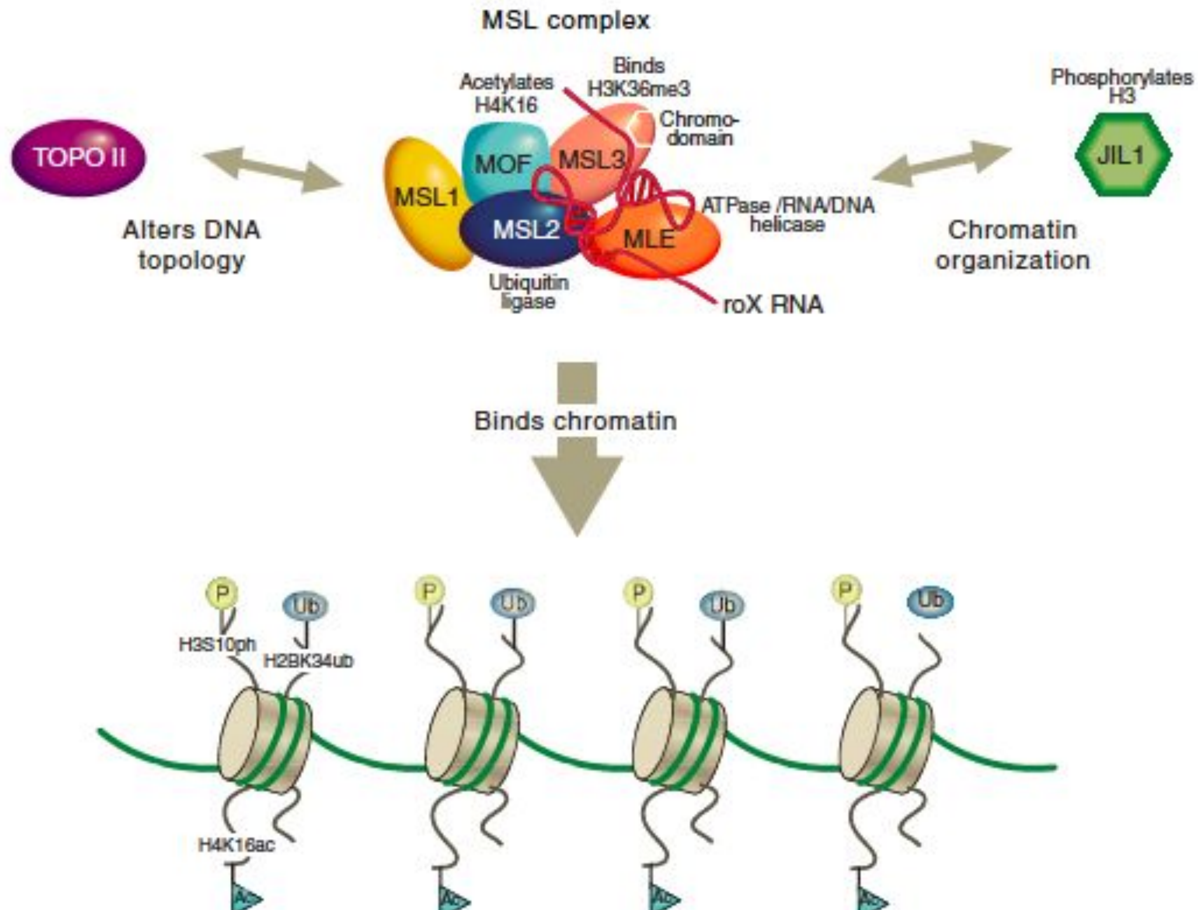
DCC (MSL-complex)



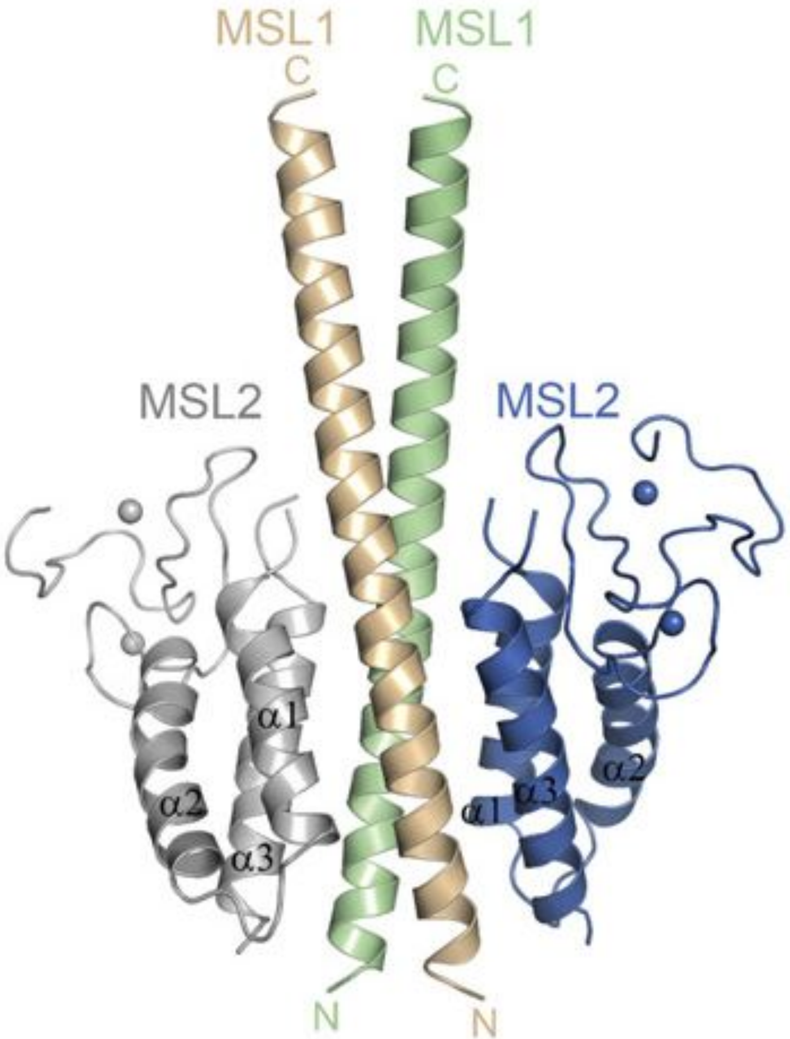
DCC (MSL-complex)

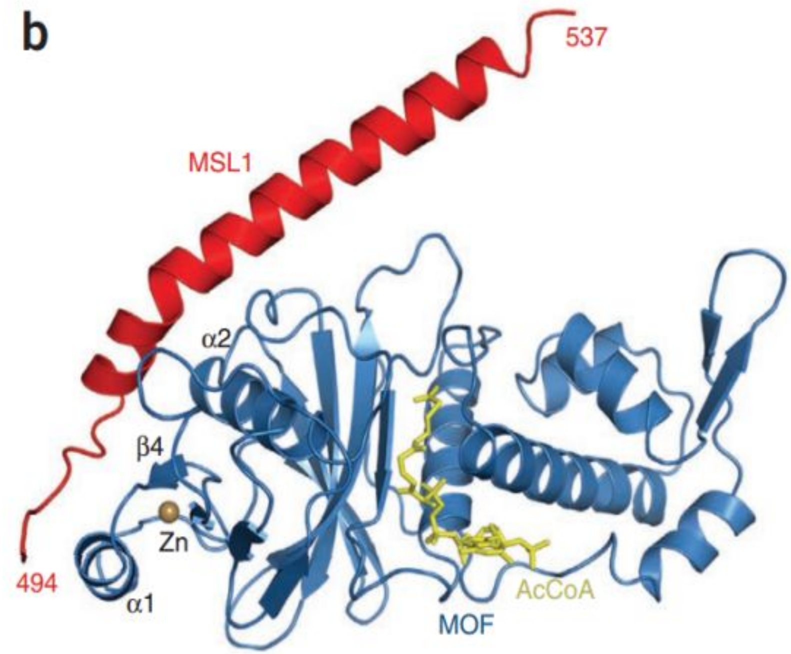


DCC (MSL-complex)



MSL-compex structure

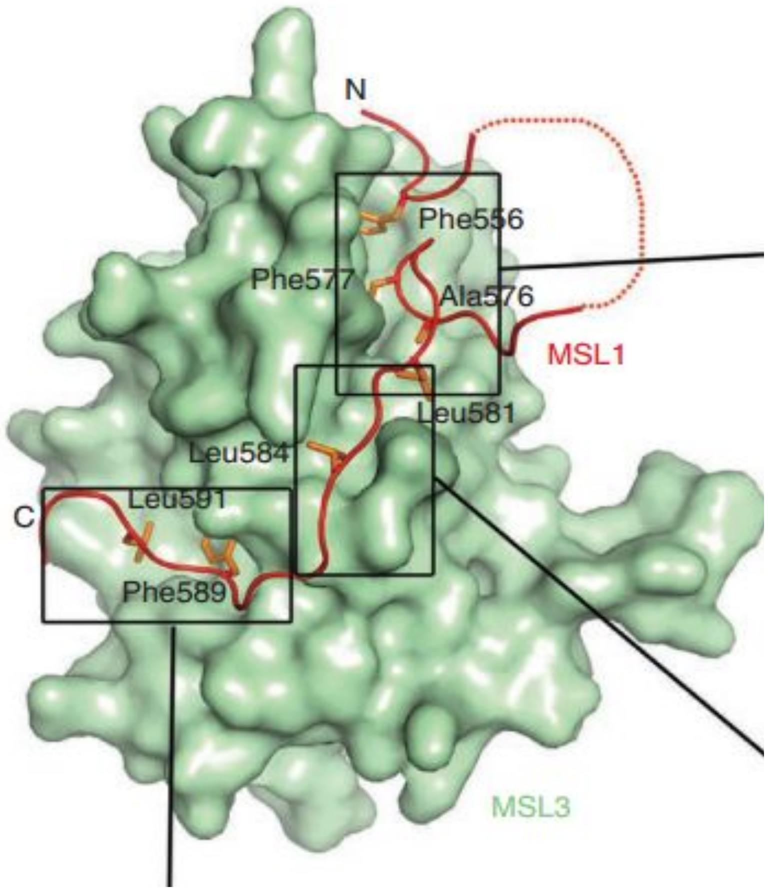




(Kadlec *et al*, 2011)

(Hallacli et al., 2012)

MSL-compex structure



(Kadlec *et al*, 2011)

MSL2

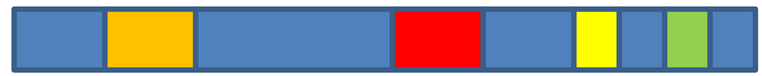
Ubiq

MSL1

RING-Zn

Coiled coil Cys

Pro



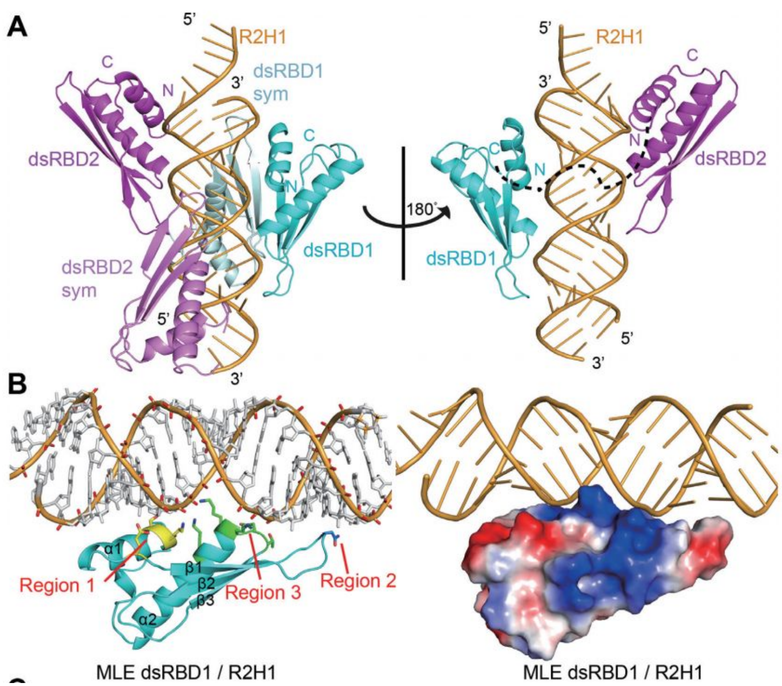
MLE

dsRBD

Helicase

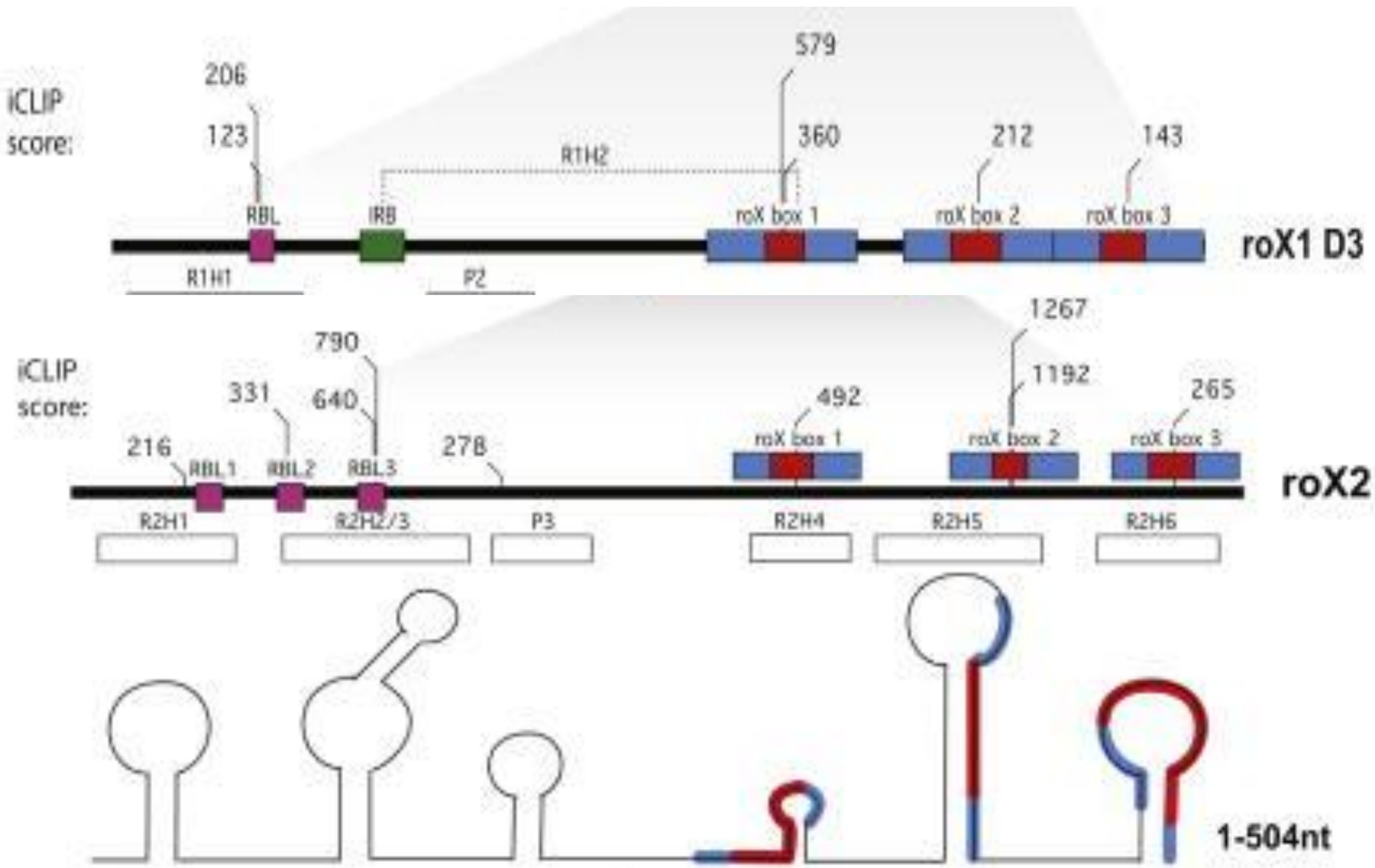
roX1 and 2

(Maenner et al, 2013)



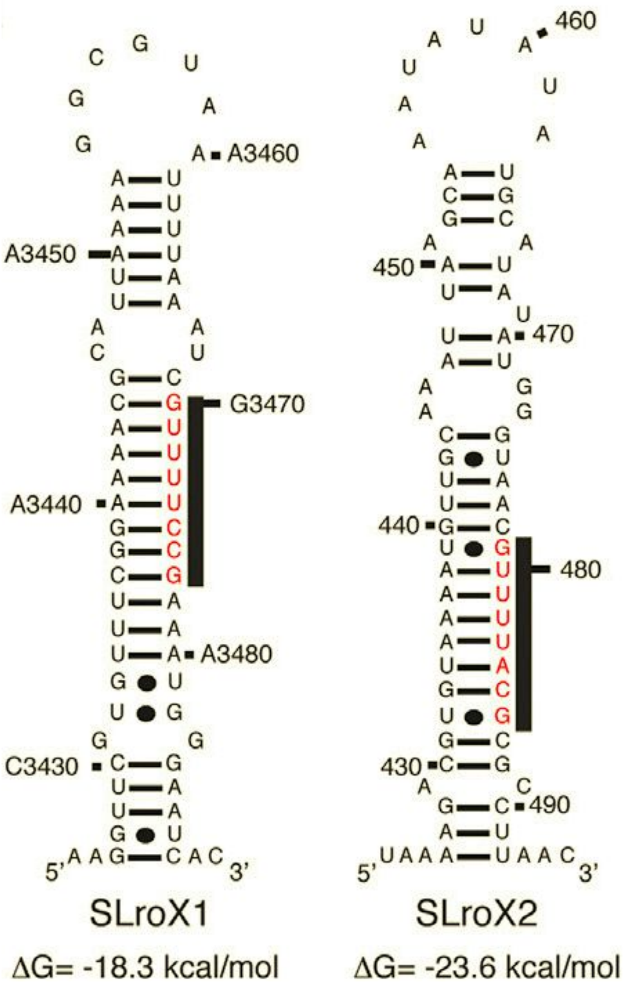
Lv et al, 2019

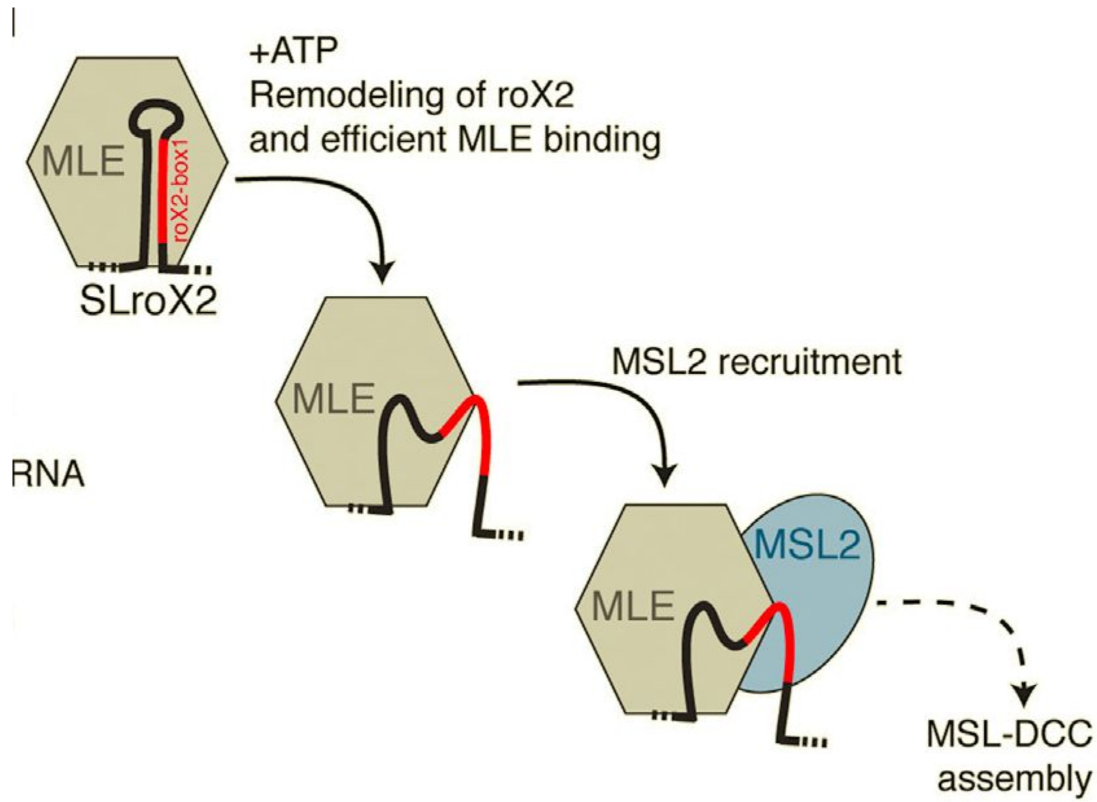
roX1 and 2



(Ilik *et al*, 2013)

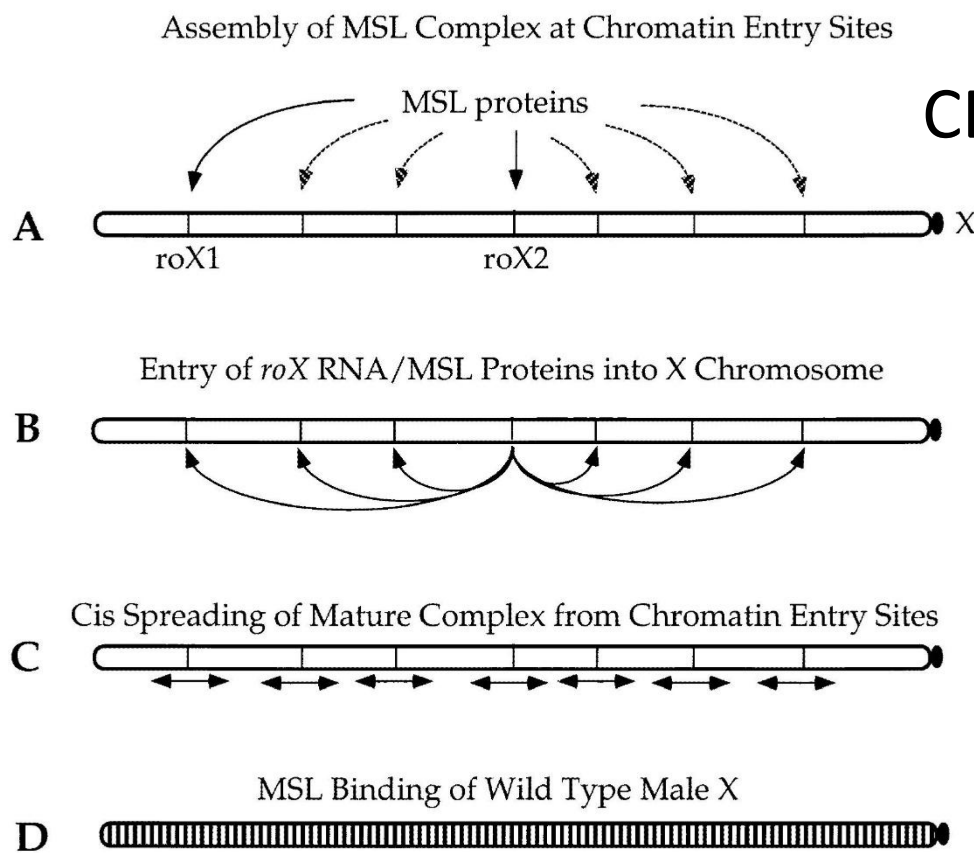
MLE





(Ilik et al, MolCell, 2013
Maenner et al, MolCell, 2013)

DCC propagation



CES/HAS

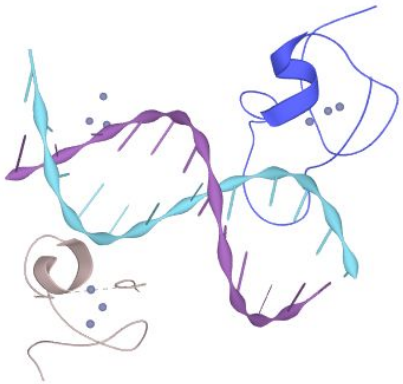
PionX?

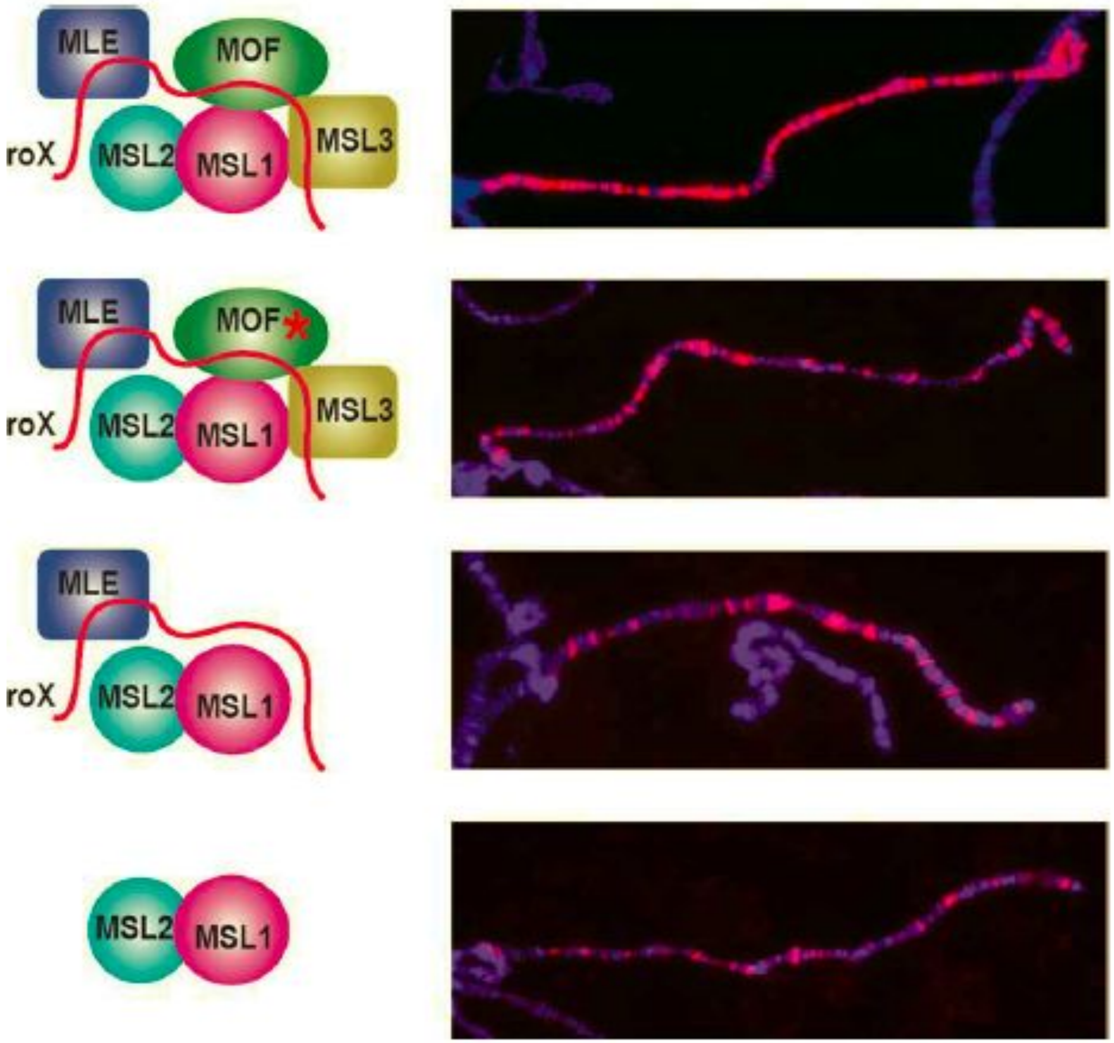
(Villa et al, 2016)

(Kelley et al, 1999)

DCC targeting and propagation

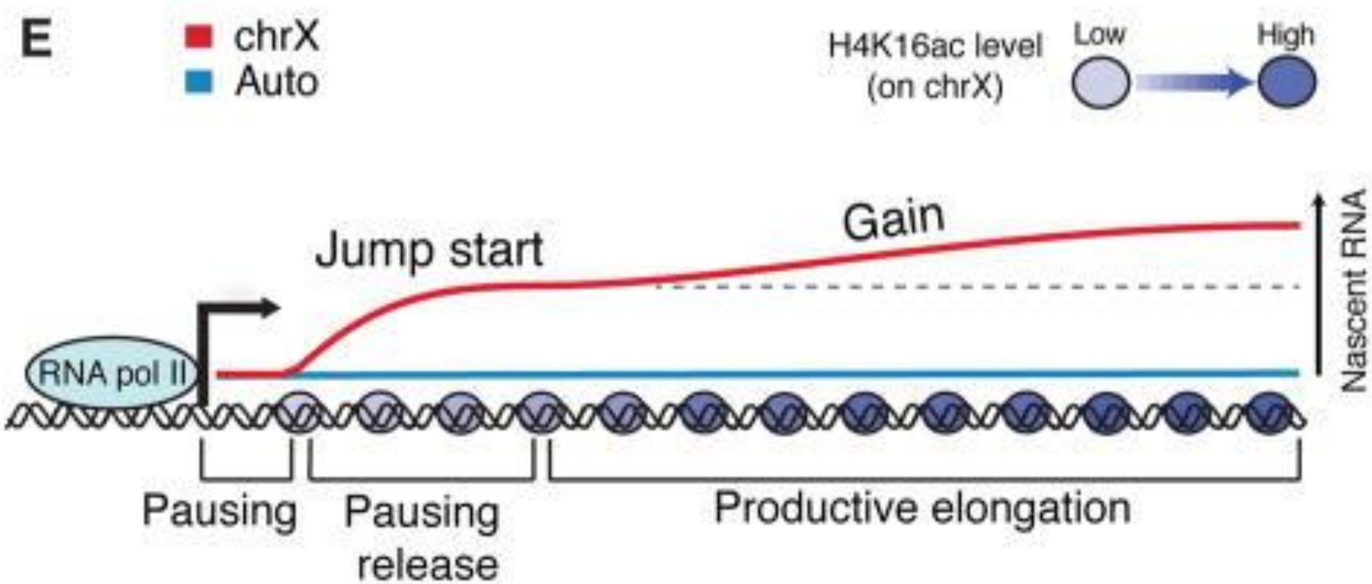
MSL2 and DNA





(Gilfillan et al., FEBSLet, 2004)

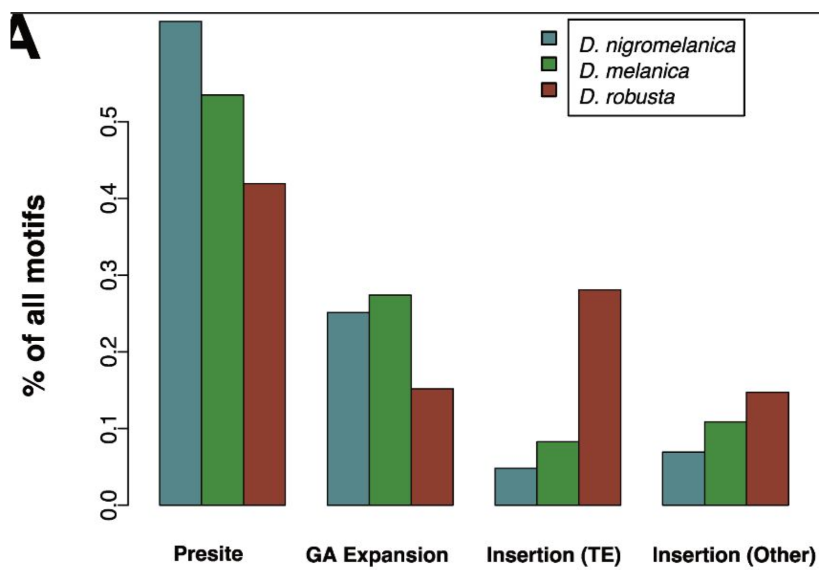
Two-fold up-regulation «Jumpstart and gain» model



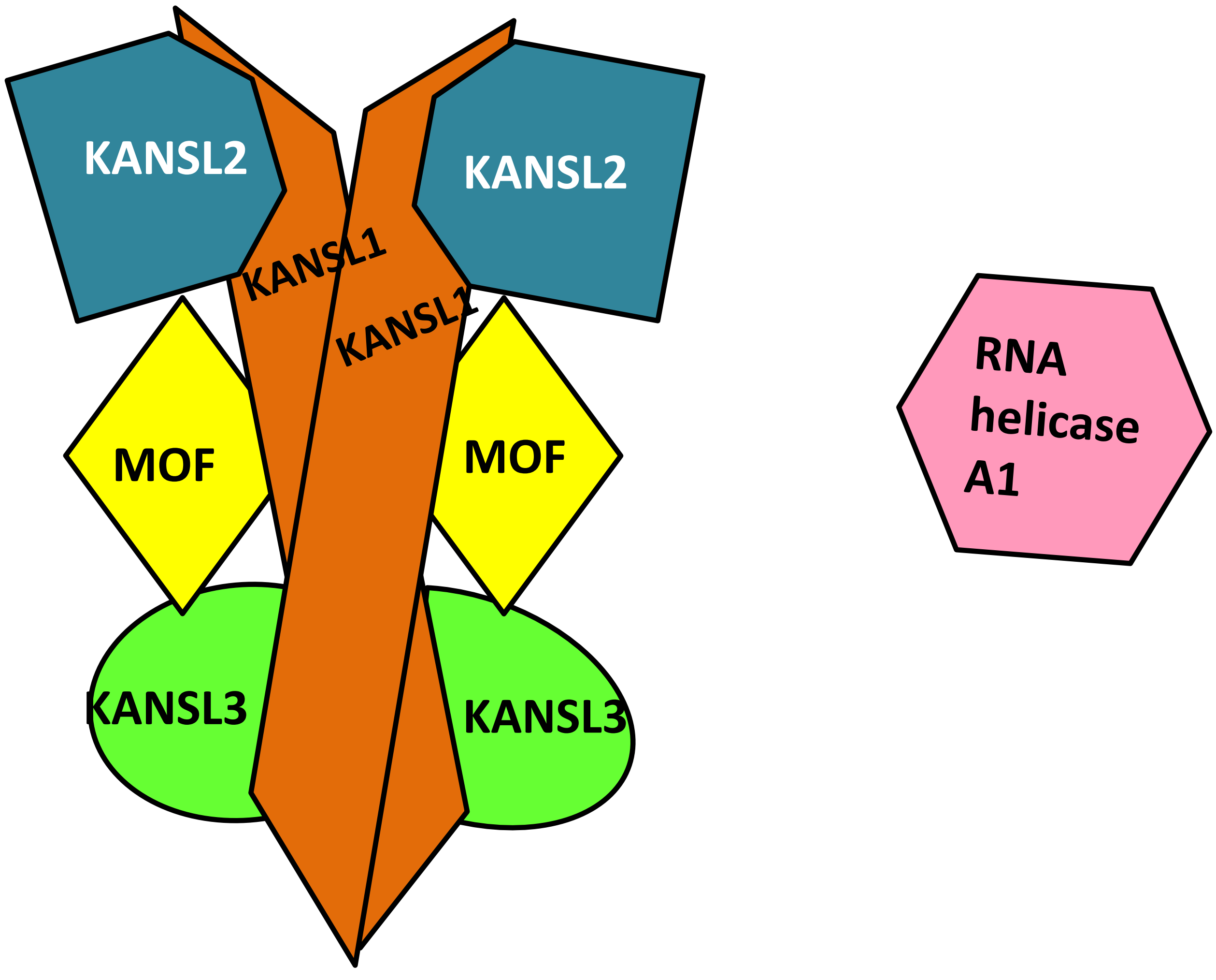
(Ferrari *et al*, 2013)

Evolution of MRE

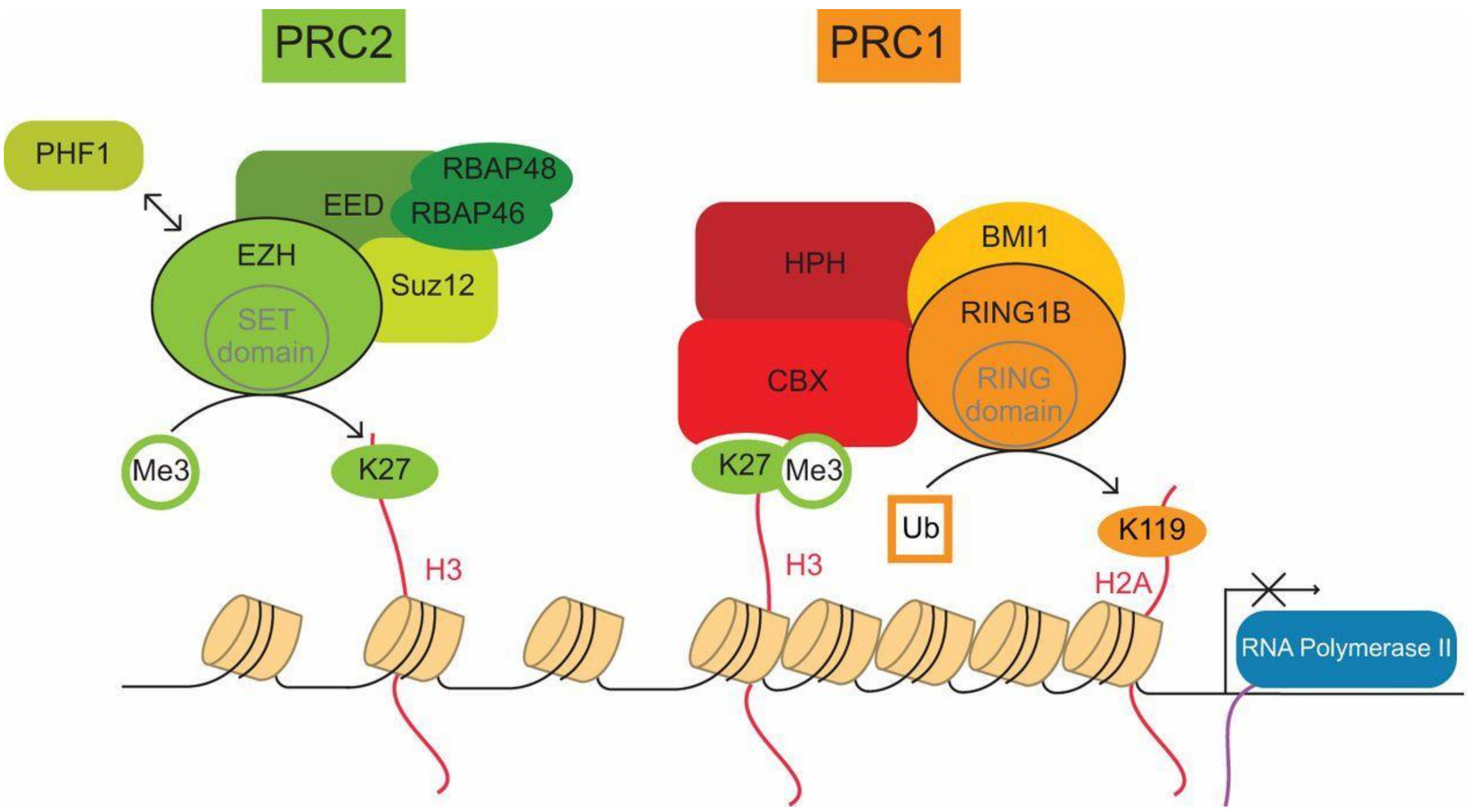
- Presites (epistatic capture) (Ellison & Bachtrog, 2019)
- Slippage and generation of GA repeats (Kuzu, 2016)
- Transposable elements (cheat-code) (Ellison & Bachtrog, 2013, 2019)



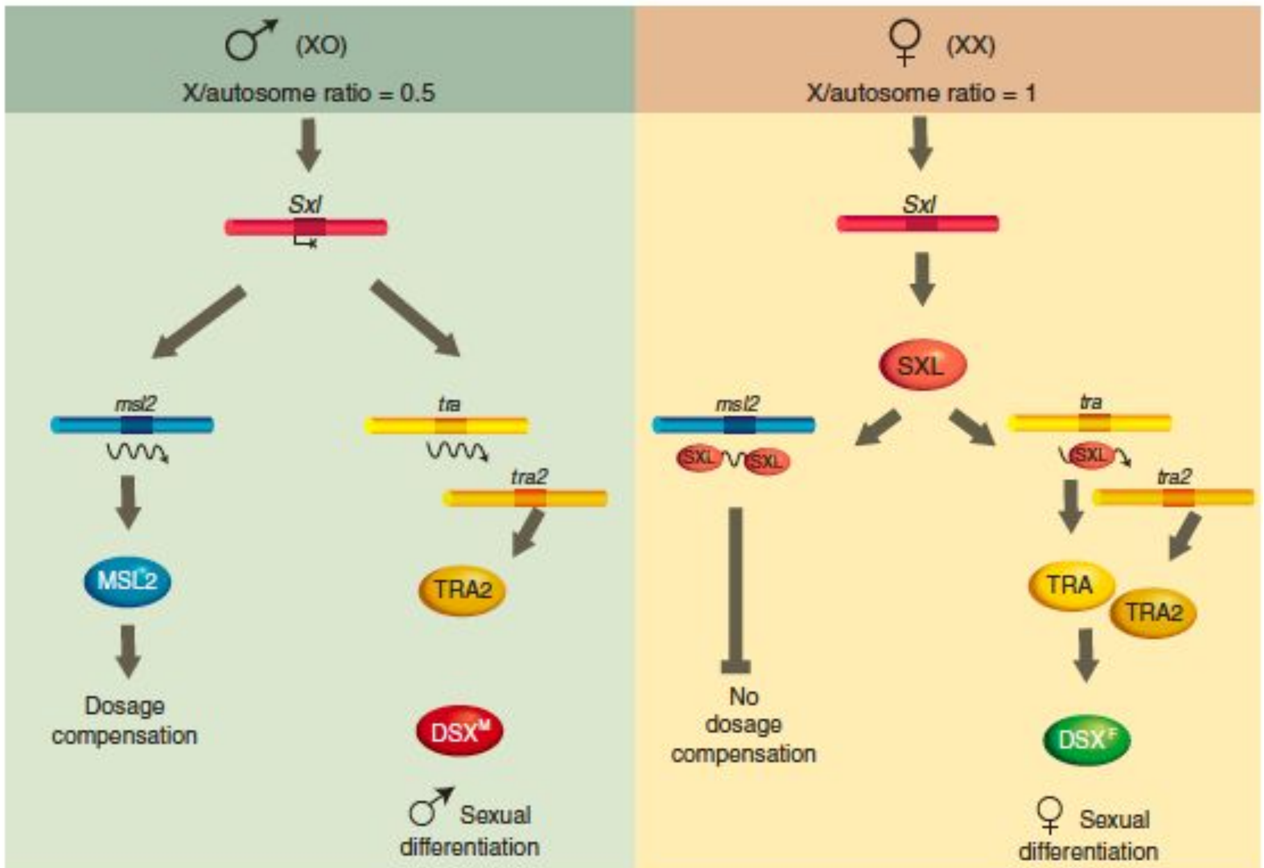
NSL complex (mammals)



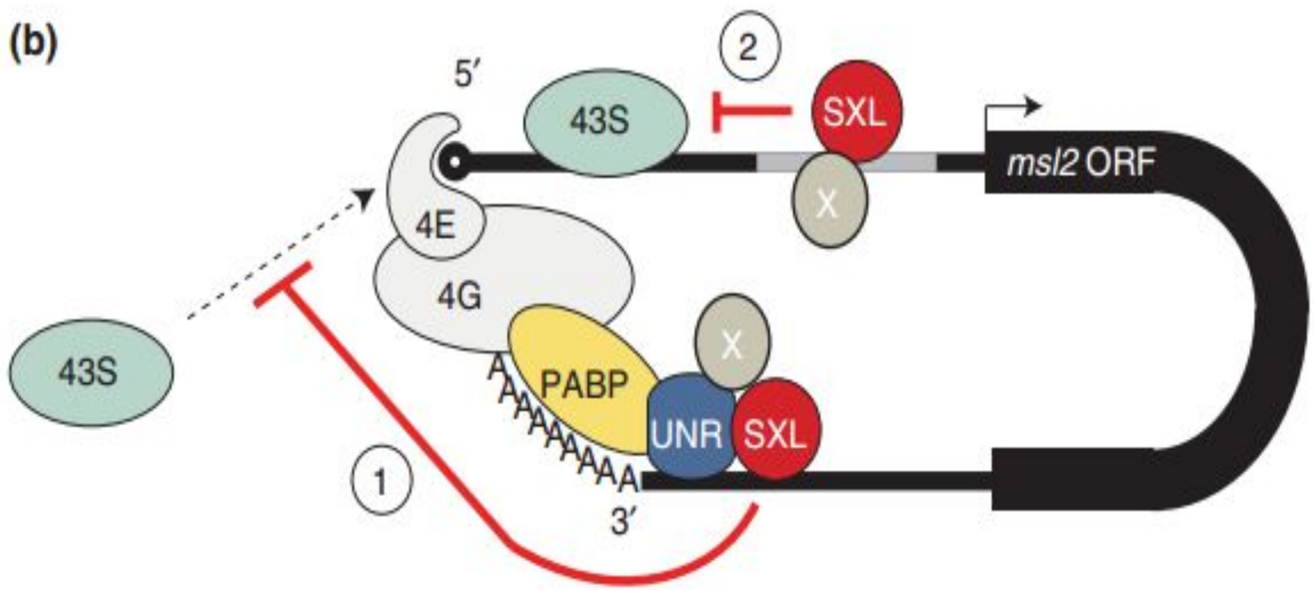
Polycomb complexes



DC regulation in males and females



DC regulation in males and females



(Graindorge *et al*, 2011)