Dosage Compensation

Dosage compensation is the process by which organisms equalize the expression of genes between members of different biological sexes. For example, in animal world, females have two X chromosomes and male have one X chromosome. There are mechanisms by which the expression of genes on X chromosome are equalized in male and female sexes. Dosage compensation can occur by three processes as reported so far.

1. Random Inactivation of one X chromosome of female, e.g. Mouse, Human
2. Two fold translation of single X chromosome of male (hypertranscription), e.g. Drosophila
3. Decrease (half) transcription of both X chromosomes (hypotranscription), e.g. C. elegans (Fig 1)

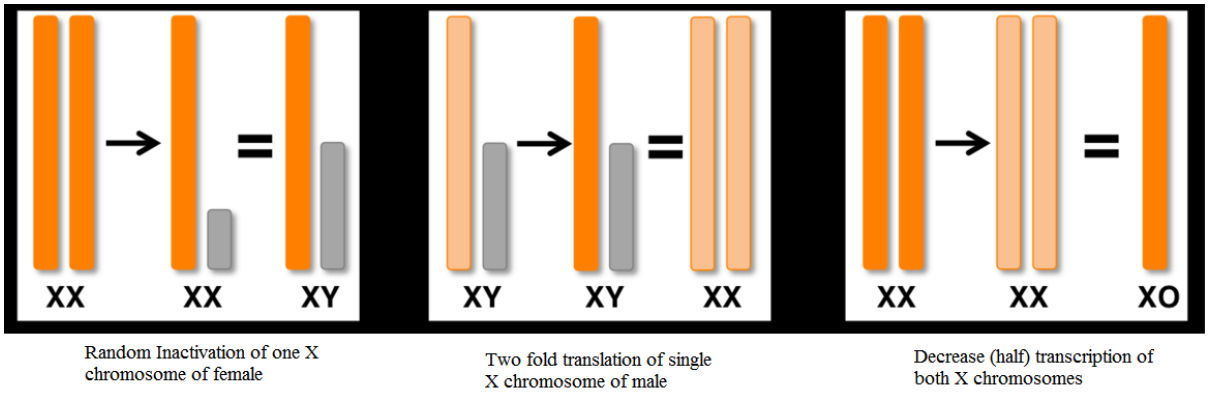

Fig 1: Different mechanisms of dosage compensation. [source: From Wikimedia Commons, the free media repository]

Dosage compensation in Drosophila

Dosage compensation in *Drosophila* increases the transcription of genes on the single X chromosome in males to equal that of both X chromosomes in females. This is done by the site-specific histone acetylation and activation of genes along the length of male X chromosome by male-specific lethal complex (MSL).

A> Sex determination and dosage compensation

Sex determination and dosage compensation in Drosophila are parallel process and regulated during the embryonic development. If the X/A ratio is equal to 1, a regulatory cascade leads to female sexual development. In female, the presence of the Sxl gene product prevents the translation of the msl2 mRNA and assembly of the MSL complex. If the X/A ratio is only 0.5, absence of the cascade leads by default to male sexual development and to the formation of the MSL complex or Dosage Compensation Complex (DCC). (Fig 2)

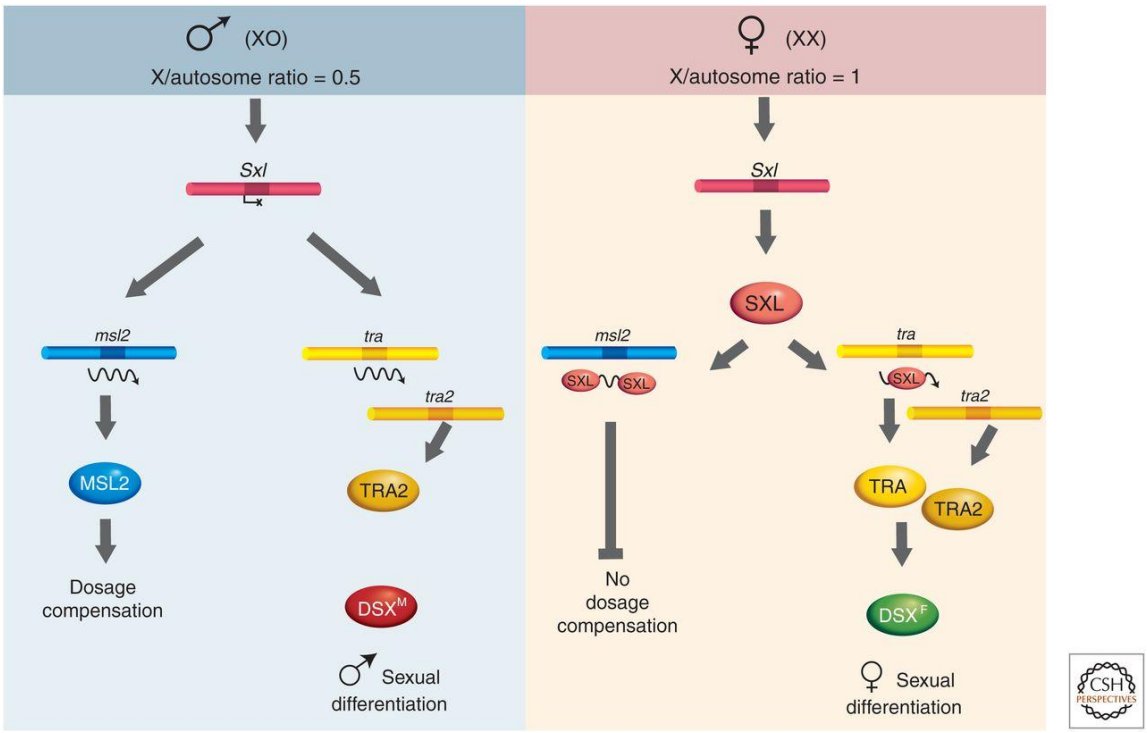

Fig 2: Diagram of the control of sex determination and dosage compensation. [source: Cold Spring Harb Perspect Biol. 2015]

B> MSL complex and associated proteins

The MSL complex, consists of five known protein subunits and two noncoding RNAs (ncRNAs). The unifying function of the individual components of the MSL complex appears to be the targeting of histone H4K16 acetylation and additional chromatin-modifying activities to active X-chromosomal genes. The members of MSL complex are MSL1, MSL2, MSL3, MLE, MOF and noncoding RNA like roX1 and roX2. The MSL or the male-specific complex promotes enrichment of the general factors JIL-1 and Topoisomerase II to the male X chromosome. The functions of the MSL components are as follows: (Fig 3)

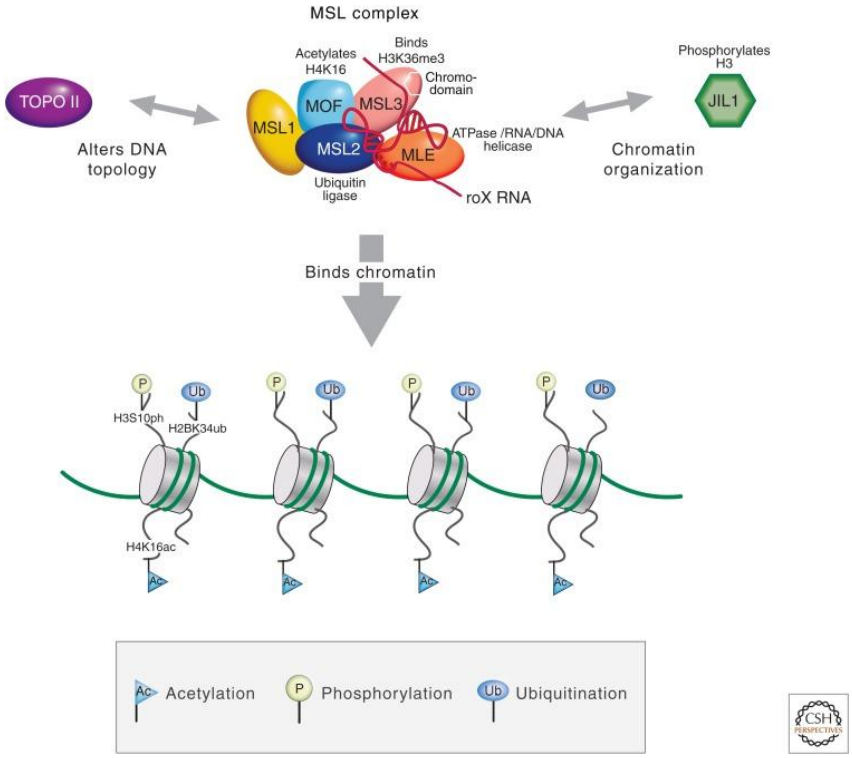

Fig 3: The various components of MSL complex. [source: Cold Spring Harb Perspect Biol. 2015]

MSL 1 and MSL 2: These are DNA binding proteins. Association of MSL1 and MSL2 is essential for assembly of MSL complex and binding of the MSL complex to chromatin. MSL2 in association with MSL1 ubiquitinate histone H2B at Lysine 34 (H2BK34)

MSL3: MSL3 has chromodomain by which it interact with methylated histone H3 at lysine 36 (H3K36me) and help the MSL complex to locate target genes.

MOF: Acetylate histone H4 at lysine 16 (H4K16).

MLE: MLE shows RNA/DNA helicase, adenosine triphosphatase (ATPase), and single-stranded RNA/single-stranded DNA binding activities. Thus, MLE has two fold activity. Single-stranded RNA/single-stranded DNA binding activities recruite noncoding RNAs (rox1 and rox2) to the MSL complex and helicase/ ATPase activity support spreading of the complex along the X chromosome.

roX noncoding RNAs (roX1 and roX2): These have secondary stem-loop structure. roX RNAs are required to stimulate assembly of MSL complex and spreading of it.). Assembly of the complex is initiated when the secondary structure of the roX RNAs is

modified. This allows the binding of MSL2 and provides the core for the full recruitment of the other MSL subunits

JIL-1: JIL-1 phosphorylates histone H3.
Topoisomerase I: Topo I alters DNA topology for spreading of MSL complex.

C> Site of association of MSL complex to X-chromosome

The question is what is the location on X-chromosome, MSL complex targets or associate with. This is explained by a model which depicts that MSL complexes assemble at High affinity sites (HASs) or Chromosome entry sites (CESs), in particular, the sites of roX RNA transcription, and subsequently access flanking and distant sites on the X chromosome. (Fig 4)

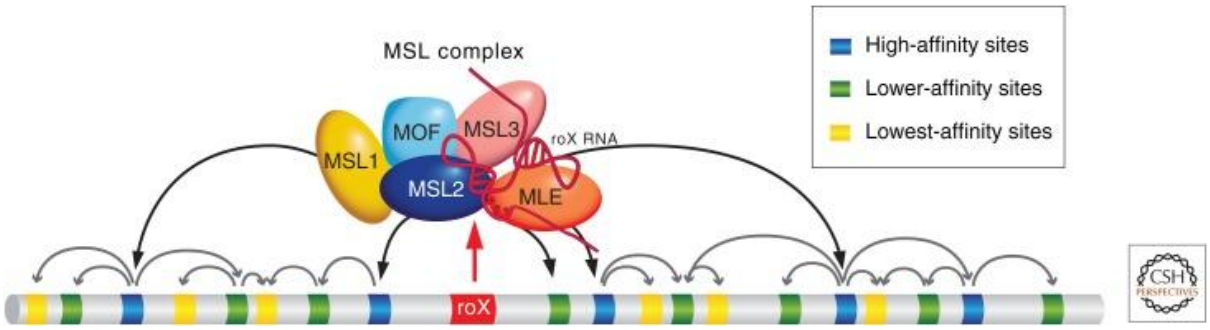

Fig 4: Model for the targeting of the MSL complex to the X-chromosome. [source: Cold Spring Harb Perspect Biol. 2015]

D> Mechanism of Dosage Compensation

Gene expression can be regulated at multiple steps, particularly during (1) transcription initiation, (2) release from pausing, or (3) elongation. The transcriptional enhancement of X-linked genes responsible for dosage compensation in Drosophila occurs at the elongation step of transcription rather than at initiation. The high level of H4K16 acetylation mediated by the MSL complex occurs throughout the length of transcriptional units with a bias that favors their 3′ ends rather than the promoter regions. Furthermore, genes with "weak" promoters and genes with "strong" promoters coexist on the X chromosome. In males, the activity of both types of genes is enhanced approximately twofold by the dosage compensation mechanism.

[Ref: Dosage Compensation in *Drosophila* by John C. Lucchesi and Mitzi I. Kuroda]