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X-marks the spot: X-chromosome identification during dosage compensation[☆]

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Abstract

Dosage compensation is the essential process that equalizes the dosage of X-linked genes between the sexes in heterogametic species. Because all of the genes along the length of a single chromosome are co-regulated, dosage compensation serves as a model system for understanding how domains of coordinate gene regulation are established. Dosage compensation has been best studied in mammals, flies and worms. Although dosage compensation systems are seemingly diverse across species, there are key shared principles of nucleation and spreading that are critical for accurate targeting of the dosage compensation complex to the X-chromosome(s). We will highlight the mechanisms by which long non-coding RNAs function together with DNA sequence elements to tether dosage compensation complexes to the X-chromosome. This article is part of a Special Issue entitled: Chromatin and epigenetic regulation of animal development.

Keywords

Dosage compensation; *Drosophila*; Mammals; *C. elegans*

1. Introduction

Assuring that all genes are transcribed at the correct gene dosage across the genome is a key process because protein and RNA components of large macromolecular complexes are encoded on different chromosomes. Altering the stoichiometry of macromolecular complexes causes severe phenotypes [1]. The most commonly known disease of gene dosage is Down's syndrome, which is caused by trisomy of chromosome 21 [2–4]. Furthermore, copy number variation throughout the genome has been linked to diverse diseases from autism to schizophrenia, and neurons are particularly sensitive to copy number changes [5].

There is a naturally occurring situation in which there is a seeming imbalance in gene dosage: the sex chromosomes in heterogametic species. Sex-chromosome dosage compensation is an essential process that evolved to regulate the levels of transcription of X-linked genes in heterogametic species [6–8]. In the eutherian mammals (humans and mice)

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and *Drosophila*, the male is heterogametic (XY) and the female is homogametic (XX) [1]. In contrast, *Caenorhabditis elegans* (*C. elegans*) hermaphrodites are XX and males are XY. In mammals, dosage compensation occurs by silencing one of the two female X chromosomes [9]. In *Drosophila*, the genes along the length of the single male X-chromosome are upregulated two-fold to equalize transcript levels between males and females [10,11]. In *C. elegans*, the levels of transcription from each of the two X chromosomes in hermaphrodites are downregulated two-fold [12]. Despite these diverse mechanisms, there are commonalities including nucleation of dosage compensation on the X-chromosome followed by spreading along its length [13–15] (*Drosophila*); [16] (mammals); [17] (worm). Furthermore, recent work has revealed a key commonality among dosage compensation mechanisms in all organisms, which is the mechanism by which transcription levels of genes on the single active X-chromosome are equalized to those on autosomes: the acetylation of histone H4 at lysine 16 [18,19].

In mammals, *C. elegans* and *Drosophila*, the process of dosage compensation is essential for proper development [10,12,20,21]. In humans, imbalance in sex chromosome number has strong phenotypic consequences including infertility [22]. Humans that lack one X chromosome (XO) develop Turner syndrome and show symptoms of ovarian failure, infertility, short stature, and similar congenital malformations [23]. Males with an extra X chromosome (XXY), termed Klinefelter syndrome, are sterile [22]. Similarly males with two Y chromosomes (YYX), Double Y Syndrome, are sterile if the extra Y is not lost early in sperm cell development. In addition, neurons are very sensitive to gene dosage and autism and schizophrenia have been linked to deletions of a single copy of several genetic loci that each contain many genes [9]. In *C. elegans* and *Drosophila*, dosage compensation is essential for viability.

2. Sex determination

The process of sex determination occurs upstream of dosage compensation and is directly linked to dosage compensation in *Drosophila* and *C. elegans*. In contrast, in mammals, it is not known how dosage compensation is linked to sex-determination. Master regulators such as *Sry* in mammals, *sex-lethal* (*slx*) in *Drosophila*, *xol* in *C. elegans*, and *Dmrt1* conserved in flies, mammals, and worms regulate the process of sex determination. Because sex determination has been reviewed elsewhere [24–27], we will provide only a brief summary below.

In mammals the *Sry* gene on the Y-chromosome encodes the SRY protein that determines the male fate by acting on the Sox9 gene. A positive feedback mechanism ensures continual expression of Sox9 leading to testis differentiation. In the absence of SRY or temporal mis-expression of SRY, Sox9 is silenced and follicle cell and ovary formation occurs.

In *Drosophila*, the ratio of the sex chromosomes to autosomes determines sex. The gene dosage of the *sisterless* genes that are encoded on the X-chromosome results in the differential regulation of the master regulator of sex determination, the *sex-lethal* gene. *sex-lethal* (*slx*) determines sexual fate by using different promoters to produce sex-specific products at precise developmental stages, and the SXL protein to control alternative splicing

of the female specific *tra* protein. The Tra protein, in turn, regulates sexual dimorphism [26]. Once initiated, the female fate is continually maintained through autoregulation of the *sxl* gene by the SXL protein. Furthermore, in females SXL translationally represses the *male-specific lethal-2* (MSL2) protein, a core component of the male specific lethal (MSL) complex that upregulates expression of the single X chromosome in males [13]. In this way, sex determination is linked to dosage compensation.

Like *Drosophila*, in *Caenorhabditis elegans* (*C. elegans*), it is the ratio of sex chromosomes to autosomes that determines sex. The ratio of 2X:2A and 3X:4A defines the hermaphrodite, while the male is defined by 1X:2A and 2X:3A ratios [27]. The key sex-determining factor is the XO-lethal gene (*xol*), which activates the cascade for the male fate. In hermaphrodites (2X:2A), *xol* is repressed by X-signal elements (XSEs) encoded on the X chromosome. In hermaphrodites, repression of *xol* allows activation of the sex determination and dosage compensation complex (SDC-2), which is involved both in establishing hermaphrodite sexual development as well as dosage compensating the XX state [27,28].

Dmrt1, a conserved transcription factor in worms, flies, and mammals, is critical for maintaining the male fate. In mice, *Dmrt1* inhibits activation of the female fate genetic network through suppression of key female fate factors such as the FOXL2 transcription factor and WNT4/ β -catenin [24]. In the absence of *Dmrt1* and upregulation of female fate genes, male specific cells such as the Sertoli cells, differentiate into female-specific granulosa cells producing estrogen [24]. Subsequent to the initial steps of the sex determination process, dosage compensation mechanisms begin.

3. Identification of the X-chromosome during dosage compensation

Due to the haploinsufficiency of many loci throughout the genome, the cell is sensitive to dosage of a large number of genes including those that encode critical transcription and translation factors [1,5]. However, there is a widespread naturally occurring haploinsufficiency in all heterogametic species: genes that are encoded on the sex chromosomes. Dosage compensation mechanisms have evolved to specifically distinguish the X chromosome from autosomes for subsequent transcriptional modulation. X chromosome identification involves the following factors: 1) long non-coding RNAs that are likely to serve as nucleation centers [29–34]; 2) DNA sequence elements; 3) chromatin marks that alter packed chromatin; and 4) proteins that read and write the chromatin marks [30,35–39]. Below we discuss how each of these factors contributes to specifically target the dosage compensation machinery to the X-chromosome.

3.1. Long noncoding RNAs that function during dosage compensation in mammals and flies

Sex chromosome dosage compensation in mammals, flies, and worms is achieved either by upregulation or downregulation of a single or two sex chromosomes. While there are differences between the dosage compensation mechanisms among these species, the establishment of nucleation centers is required to initially identify the whole X-chromosome for dosage compensation. In mammals and flies, a key structural scaffold of these nucleation centers is the use of long non-coding RNAs (lncRNAs) as targeting platforms [40,41].

lncRNAs, are defined as RNAs that are larger than 200 nucleotides and do not code for functional protein [30,31,42]. The ability for the secondary structure and location of lncRNAs to be preserved in the absence of sequence conservation [30,33] makes them attractive targeting platforms because this is likely to decrease the frequency of spatial temporal error in the establishment of a domain of coordinate gene regulation. lncRNAs also have the capacity to bring different factors in close proximity [30]. Furthermore, lncRNAs can function in *cis* and *trans*, interact with multiple proteins, and shuttle between the nucleus and cytoplasm [30,42,43]. For example, the *roX* lncRNAs (RNA on X) can induce transcription of nearby genes when ectopically inserted onto autosomes [44,45]. Using the transcription of lncRNAs as a means of regulating expression of other genes is also supported by the observation that promoters of lncRNAs are the regions of lncRNAs under the greatest selective pressure [30,33]. In summary, lncRNAs are an ideal system by which to nucleate chromatin domains in a spatially and temporally regulated manner (Fig. 1).

The dosage compensation system in mammals uses lncRNAs to control X-chromosome identification. In mammals, dosage compensation is achieved by silencing one of two X chromosomes in female (XX), a process called X-chromosome Inactivation (XCI) [35]. XCI is controlled by the X inactivation center (Xic), which is a 100–500 kb region found on the chromosome to be silenced, Xi, and the active chromosome, Xa [9]. The Xic is a rich source of lncRNAs that are involved in X chromosome choice, counting, pairing, and silencing [9]. Xic regulation involves an intricate network of RNA and protein interactions. In the first steps of XCI, the X-specific-inactive-transcript (*Xist*) is transcribed only from the Xic on Xi into a 17–20 kb noncoding RNA and coats Xi in *cis*. Silencing of Xi requires *Xist* expression as *Xist* utilizes its conserved repeat motif (Rep A) to bind directly to Polycomb repressive complex 2 (PRC2) to target PRC2 to Xi. PRC2 deposits the silencing mark: trimethylation of histone H3 at lysine 27 (H3K27me3), facilitating chromatin compaction of DNA from active transcription [35]. *Xist* function however is regulated by its antisense transcript, *Tsix* another lncRNA. *Xist* upregulation requires *Tsix* downregulation [46]. *Tsix* inhibits *Xist* by silencing *Xist* through recruitment of a DNA methyltransferase (Dnmt3a) and inhibiting *Xist* binding to the PRC2 repressor protein [47,35,9]. In addition to *Tsix*, other lncRNAs encoded at the Xic repress *Xist* function. These include the X-inactivation intergenic transcription element (*Xite*) and the testis-specific X-linked gene (*Tsx*). A recently identified lncRNA called *Linx* (large intervening transcript in the Xic) may also have a role in *Tsix* regulation via modulating *Xite* [41]. There are also a number of lncRNAs encoded at the Xic that activate *Xist*. These include the RepA RNA and the *Jpx* RNA that can function both in *cis* and *trans* to activate *Xist* [46]. Overall, an intricate network of inter-dependent lncRNAs nucleates mammalian dosage compensation.

Drosophila sex chromosome dosage compensation also utilizes lncRNAs to establish local neighborhoods of regulation. In contrast to mammals, *Drosophila* sex chromosome dosage compensation is achieved by upregulating transcription of the single X-chromosome two-fold in males [11,48]. The male specific lethal (MSL) complex, which releases paused RNA polymerase into active elongation, mediates transcriptional upregulation by increasing histone H4 acetylation [49,50]. As described earlier, the MSL2 core complex component is translationally repressed in females by SXL and is therefore only expressed in males [13,51]. The MSL complex is a ribonucleoprotein complex composed of five proteins:

MSL1, MSL2, MSL3 (male-specific lethal 1, 2, and 3), MOF (males absent on the first), MLE (maleless), and two lncRNAs: *roX1* and *roX2*, which are required for dosage compensation [10,52,53].

Although *roX1* and *roX2* differ in sequence and size (*roX1* is 3.7 kb and *roX2* is 0.5–1.2 kb), they are functionally redundant [54–56]. The presence of one *roX* RNA in the genome is required for MSL complex recruitment to the X-chromosome [11,55,57]. However, unlike mammalian *Xist* RNA, *roX* RNAs can travel *in trans* to the X-chromosome from an autosomal location [58]. Furthermore, insertion of *roX* RNAs onto autosomes is sufficient to target MSL complex to autosomes leading to spreading of MSL complex and upregulation of autosomal genes within 200 kb of the ectopically inserted *roX* gene [44,45]. *roX1* and *roX2* RNAs are essential for MSL complex to spread from the initial sites of binding called Chromatin Entry Sites (CES) to regions of active transcription [59]. Although the precise mechanism by which *roX* RNAs distinguish the X chromosome for MSL complex recruitment is unclear, it is thought that MSL complex can be site-specifically targeted to the X chromosome by co-transcriptionally incorporating the *roX* RNAs into the MSL complex [58,60,61]. Therefore, it is likely that the loci from which *roX* RNAs are transcribed are the initial platforms that target MSL complex to the X chromosome. MSL complex spreads from these sites to coat the X chromosome (see below) [53]. This model for X chromosome targeting is supported by the findings that *roX* RNAs localize to sites of MSL complex enrichment and the number of *roX* loci present and *roX* transcription levels alter both how much and how often MSL complex spreads [58,62–64].

In summary, the studies of non-coding RNA function during mammalian and *Drosophila* dosage compensation have revealed the advantages of using lncRNAs as regulatory factors to nucleate a chromatin domain on a single chromosome. lncRNAs have a short half-life and can site specifically target. The short half-life of some lncRNAs (e.g. 30–60 min for *Tsix* [35]) is likely to supply the maximum amount of RNA directly at the site of nucleation with minimal concern for diffusion, which could lead to mis-targeting. Since lncRNAs are restricted to specific sites in the genome, targeting of transcription complexes utilizing transcription of lncRNAs can occur locally and specifically at the site of lncRNA transcription [9,33,29,30].

3.2. DNA sequence elements that function during dosage compensation

Although lncRNAs play a central role in establishing nucleation centers where transcriptional regulation occurs, DNA elements are also critical for targeting to the appropriate sites. Dosage compensation in mammals, *Drosophila*, and worms utilize specific DNA sequences during the process of X-chromosome identification. In mammals, a tandem cluster of three of the binding motifs for the zinc finger protein YY1 is required for *Xist* RNA binding to Xi that nucleates the silencing process [65]. Furthermore, long interspersed elements (LINES), enriched on the X chromosome relative to autosomes facilitate the establishment of heterochromatin that forms the silent compartment of Xi [66]. Transient expression of these LINES also appears to promote *Xist* mediated silencing of Xi [66].

In *Drosophila*, the MSL dosage compensation complex localizes most strongly to Chromatin Entry Sites (CES), also called High Affinity Sites (HAS), which are 1.5 kb regions that are

sufficient to recruit MSL complex to autosomal regions [14,67,68]. GA-rich motifs called MSL Recognition Elements (MREs) are present within almost all CES and are required for MSL complex recruitment across *Drosophila* species [69]. Recent work has indicated that MRE elements evolved from transposon insertions and by expansions of GA-rich sequences likely through replication errors [70]. MREs are enriched two-fold on the X chromosome overall and approximately four-fold enriched at the 3' end of active genes [14]. Although, MREs are X-enriched, they are not X-specific sequences. Therefore, additional factors are required to increase X-specificity including a DNA binding protein that recognizes MREs (see protein–protein interactions section below).

Worms also utilize specific DNA motifs for identification of the X-chromosomes in hermaphrodites. Similar to *Drosophila*, which initially recruits MSL complex to CES that contain MREs followed by spreading in *cis*, *C. elegans* first recruits their dosage compensation complex (DCC), to recruitment elements on X (*rex* sites) that are found at only 200 sites on the X chromosome [27,71]. Clustered within the *rex* sites is a 12-bp consensus motif, MEX, which is enriched on the X-chromosome relative to autosomes and necessary for DCC recruitment to the X chromosome [27,71,72]. Importantly, MEX motifs distinguish the *rex* sites as the regions to be targeted [27]. A second set of sites is important for recruiting the DCC; and these are the *dox* sites (dependent on X) [27,71,72]. There are many more *dox* sites than *rex* sites and these sites do not have the MEX motif. However, DCC occupancy of *dox* sites requires binding to *rex* sites. While *rex* sites are mostly found in intergenic regions, *dox* sites are often located in actively transcribed promoters [71]. *Rex* and *dox* sites are separated by 2–90 kb distances suggesting that long-range interactions between the sites may facilitate dosage compensation across the whole chromosome [27]. In summary, the use of specific DNA motifs in mammals, *Drosophila*, and *C. elegans* to recruit the dosage compensation machinery highlights the critical role of DNA elements in specifying domains of coordinate gene regulation [73].

3.3. The role of chromatin regulation during dosage compensation

While lncRNAs and DNA sequence elements are important for the initial identification of the X-chromosome, accessibility of these elements to dosage compensation complexes is regulated by chromatin [38]. The genome-wide profiling of chromatin marks has revealed two types of chromatin marks: 1) Chromatin marks that are important for the identification of the X-chromosome; and 2) A chromatin mark that is associated with the dosage compensation process across species, H4K16ac (Fig. 2).

The chromatin landscape of *Drosophila melanogaster* was analyzed on a genome-wide scale by comparing regions enriched for histone marks to domains with engaged RNA Polymerase II, lncRNAs, and DNA accessibility [38,74]. In this way, actively transcribed genes were found to have distinct chromatin features involving specific combinations of histone marks [74]. A computational model defined nine chromatin states distinguished by enrichment of histone marks associated either with activation such as H3K4me2/3 and H3K36me3 or repression such as H3K9me3 and H3K27me3. The MSL complex associates with the bodies of active genes and uses H3K36me3 as a means of spreading from CES to bodies of active genes [15,75]. The Polycomb repressive complex (PRC2), which facilitates Xi silencing in

mammals, associates with H3K27me3 mark as a means of spreading from its initial sites of recruitment [16,76].

Although there are several chromatin marks that categorize active versus silent states, the H4K16ac mark is specifically associated with activation in the context of dosage compensation across species. This chromatin mark specifically disrupts inter-nucleosome interactions and therefore nucleosomes are more loosely packed in the presence of this mark [77–79].

In *Drosophila*, H4K16ac is deposited by the MOF protein that is part of the MSL dosage compensation complex [56,80,81]. The opening of chromatin structure by H4K16ac is thought to be involved in the mechanism of transcriptional upregulation by promoting the entry of RNA Polymerase II into gene bodies [50]. Similarly in mammals, H4K16ac, deposited by MOF upon the X chromosome, is associated with increased transcription of the single active X chromosome [19]. *C. elegans* also modulate H4K16ac during dosage compensation. However, it is depletion rather than enhancement of H4K16ac that correlates with the downregulation of the hermaphrodite X chromosomes [82]. Like *Drosophila* and mammals, this acetylation is regulated in tandem with a methylation mark. In *C. elegans*, this decrease in H4K16ac is coupled with enrichment of monomethylation of lysine 20 at histone 4, H4K20me1 [82].

Ubiquitylation of histones and other proteins can change the chromatin landscape by altering the chromatin environment. Recently, ubiquitination has been linked to the dosage compensation process. The Rnfl12 ubiquitin ligase stabilizes the *Xist* RNA by degrading Rex1, a repressor of *Xist* transcription [83]. Also the RING finger of MSL2, which is required to initiate the upregulation of the X chromosome in male *Drosophila*, was recently identified to be a histone ubiquitin E3 ligase with specificity for both histone H2B and ubiquitylation of MSL complex components [84,85].

Recently, it was determined that higher order chromatin structure also contributes to establishing a chromatin domain during the dosage compensation process [40]. The X chromosome in mammals is arranged into 200 kb–1 Mb topologically associated domains (TADS) that align with chromatin marks and coordinately regulated genes [41]. Interference with TAD structure leads to misregulation of gene expression through disruption of chromosomal contacts [41]. Early sites of X-chromosome identification after induction of the *Xist* gene in male cells are primarily regions that are topologically associated with each other [40]. In summary, individual chromatin marks and higher order chromatin structure contribute to both the identification of the X-chromosome and its subsequent regulation for dosage compensation.

3.4. Interactions between proteins and chromatin that are involved in dosage compensation

In addition to a permissive chromatin landscape, interactions between components of the dosage compensation complexes and DNA are required to establish dosage compensation. Chromatin interacting proteins are required to integrate all of these signals and mediate the process and accurate targeting of dosage compensation across species. Zinc finger proteins

are a large class of transcriptional regulators that are attractive targeting factors given their ability to sequence specifically bind to DNA.

In mammals, both an initial targeting step involving the YY1 zinc finger protein and chromatin altering proteins are involved in X-inactivation. The YY1 protein tethers *Xist* RNA to the XIC to establish the nucleation centers [65]. Furthermore, the *Xist* RNA recruits the PRC2 chromatin remodeling complex and this recruitment is stabilized by the YY1 protein. After tethering to the XIC by YY1, PRC2 spreads to an initial 150 “canonical” sites, which contain CpG islands and a high occupancy of EZH2, the PRC2 enzymatic subunit that deposits the H3K27me3 mark [16]. PRC2 further spreads by binding to 4000 “noncanonical sites” that are devoid of H3K4me3 and CpG islands [16]. Therefore, the function of DNA, lncRNAs, chromatin remodelers and zinc finger proteins are integrated during the process of X-chromosome inactivation.

In *Drosophila*, the initial stage of MSL complex targeting involves the MSL1 and MSL2 proteins forming a core protein complex that is sufficient to identify the initial binding sites called CES [86]. Recent work has shown that MSL1 dimerizes and MSL2 binds this dimer to form the core complex that first targets the CES that recruit MSL complex [87]. However, none of the well-studied components of the MSL complex directly binds to DNA with sequence specificity [88]. However, a recently identified zinc finger protein, called CLAMP (Chromatin Linked Adaptor for MSL Protein) is required to recruit MSL complex to the CES sites [89,90]. CLAMP binds directly to the MRE sequences that are required for MSL complex recruitment [90], and associates with the MSL complex [90,91]. Similar to YY1, this factor can bind sequence specifically to DNA, and tether a dosage compensation complex to its target sites of regulation.

The *Drosophila* MSL complex includes three proteins that mediate the spreading process and interactions with chromatin and lncRNAs: MSL3, MLE, and MOF. MSL3 is a chromo domain containing protein that binds to nucleosomes and H3K36me3, a mark of active transcription associated with active gene bodies, thereby targeting MSL complex to active gene bodies [92,93]. MLE is an ATP-dependent RNA/DNA helicase that unwinds short double-stranded RNA or DNA/RNA hybrids [77,94]. MLE specifically interacts with *roX* RNAs via known interaction domains and facilitates the interaction between *roX* RNAs and the MSL2 core MSL complex component [94,95]. MOF is the histone acetyltransferase that deposits the H4K16ac mark at active genes to facilitate up-regulation of the male X chromosome [56,81,96,97].

In *C. elegans*, the dosage compensation complex (DCC) shares protein subunits with complexes that are involved in condensing chromatin [98]. This suggests that the DCC works similarly to condensin complexes to restructure chromosomes as a means of facilitating transcriptional regulation. For example, DPY-27, a protein involved in condensing chromatin, associates with the X-chromosome as part of the DCC [99]. DPY-30, an integral subunit of the DCC, is crucial for recruiting DCC to the X chromosome [21,98]. However, DPY-30 exhibits similar levels of binding to the X-chromosomes and autosomes and also functions in histone modification as part of the activator MLL/COMPASS complex [98]. In contrast, DPY-27, which is specific to the DCC, exhibits greater binding on X than

autosomes [98]. While the DCC binds at low levels to promoters of expressed genes, optimum binding of DCC to the X chromosomes requires the SDC-2 and SDC-3 subunits [98]. Additionally, SDC-3 is a zinc finger protein involved in assembling the DCC complex [100]. It is not known how the MEX DNA sequences that are important for dosage compensation are specifically recognized. In summary, mammals, *Drosophila* and *C. elegans* all use a combination of zinc finger proteins and chromatin interacting proteins to promote X-chromosome identification and spreading along the length of the X-chromosome.

4. Conclusion

The dosage compensation process is a paradigm for how non-coding RNAs, DNA elements, chromatin landscape and protein factors function together to regulate gene expression. There are several common principles that we have highlighted above: 1) long-noncoding RNAs that act as spatial and temporal platforms to nucleate dosage compensation in both mammals and *Drosophila*; 2) specific DNA sequences that are involved in X-chromosome identification across species; 3) chromatin landscape marks that facilitate spreading across the X-chromosome such as K27me3 in mammals and K36me3 in *Drosophila*; and 4) protein factors that associate with chromatin, DNA, and RNAs. H4K16ac has been implicated in the transcriptional regulatory process of dosage compensation across species. In mammals, higher order chromatin structure is thought to contribute to X-chromosome identification. Protein–protein interactions including tethering of dosage compensation complexes to X-chromosomes by zinc finger proteins also contribute to X-chromosome identification. To conclude, dosage compensation serves as a paradigm for understanding how chromatin domains are established within highly complex eukaryotic genomes.

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Fig. 1.

lncRNA transcription generates an environment favorable for coordinate regulation. Recruitment of polymerase for lncRNA transcription leads to more open chromatin state. Nucleosomes are displaced and DNA is made more accessible, exposing transcription factor motifs for DNA binding. Once transcription factors bind to their motifs, this serves as a signal for regulation through recruitment of other co-activators and complex assembly. lncRNAs facilitate the process through their own transcription, sequestration of heterochromatin, creation of pockets of activity in nucleus, and scaffolding different components into closer proximity to facilitate interactions favorable for regulation.

Fig. 2.

MOF deposits H4K16acetylation, decondensing chromatin to favor the X chromosome for active transcription. As nucleosomes are displaced and histones are acetylated, specifically H4K16acetylation in X chromosome dosage compensation primes the X chromosome for active transcription and upregulation.