EPIGENETICS

Sequence-guided entry for MSL

> “...the combination of a sequence element and a particular chromatin context could explain the X chromosome specificity of MSL.”

IMAGE100

Protein–DNA interactions govern a vast array of biological processes, and the specificity of these interactions can be determined by both genetic and epigenetic information. A process that requires such interactions, and that is a classic model for how specific chromatin domains are established, is dosage compensation: an important mechanism for balanced gene expression between the sexes. A new study has found that both a specific DNA motif and the chromosomal context are important for the role of a DNA-binding factor in establishing dosage compensation in *Drosophila melanogaster*.

In *Drosophila*, expression of genes on the single male X chromosome is increased to match the output from the two X chromosomes present in females. This upregulation is largely dependent on binding of the male-specific lethal (MSL) protein complex to the male X chromosome. The complex contains a histone acetyltransferase, which can help to form active chromatin domains. A two-step model for MSL binding has been proposed, whereby the complex is first attracted to specific chromatin entry sites and then spreads to surrounding genes. Now, Alekseyenko and colleagues have put this model to the test.

To define features of MSL entry sites, the authors ran motif-searching algorithms on MSL-binding sites that were identified using chromatin immunoprecipitation followed by microarray analysis (ChIP–chip) and by sequencing (ChIP–seq). They found a 21-bp sequence with a core GAGA (or TCTC) repeat that seems to constitute an MSL recognition element (MRE). When tested in reporter-gene and transgenic experiments, MREs were able to recruit the MSL complex and mutation of the core motif abolished this function, indicating that the sequence element is both necessary and sufficient for MSL binding.

However, the MRE consensus sequence is found at thousands of sites within the genome where there is no evidence of MSL binding — so what additional factors determine where MSL actually binds? The authors found that genuine MSL-binding sites are located within active genes and are typified by nucleosome depletion. Indeed, when an active gene location was added to the criteria for identifying a genuine MRE, four times as many MREs were found on the X chromosome compared with an autosome (chromosome 2L), suggesting that the combination of a sequence element and a particular chromatin context could explain the X chromosome specificity of MSL.

In addition to increasing our mechanistic understanding of dosage compensation in *Drosophila*, this work might provide a framework for identifying potential interaction sites for other chromatin-organizing complexes. It also re-emphasises the need for sequence-motif identification to be coupled with studies of genomic location and the chromatin environment to appreciate fully how binding-site selection is achieved.

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ORIGINAL RESEARCH PAPER Alekseyenko, A. A. *et al.* A sequence motif within chromatin entry sites directs MSL establishment on the *Drosophila* X chromosome. *Cell* **134**, 599–609 (2008)

FURTHER READING Straub, B. & Becker, P. B. Dosage compenstation: the beginning and end of generalization. *Nature Rev. Genet.* **8**, 47–57 (2007)