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on dosing and compensating

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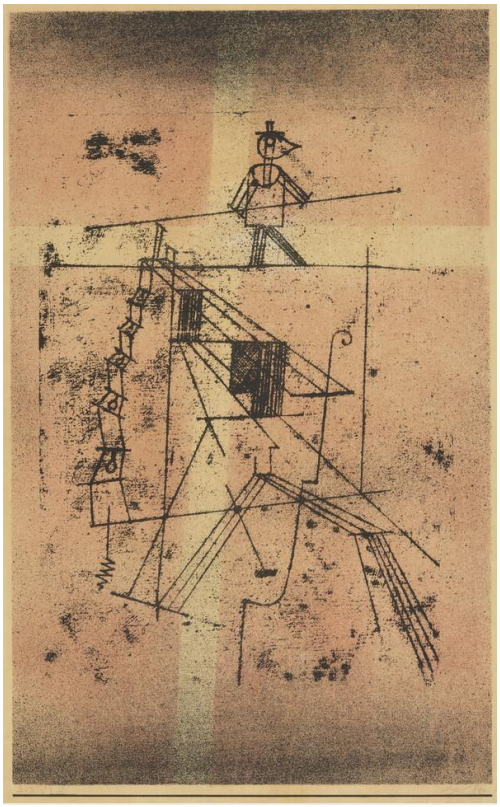
***Drosophila* flies are born with four pairs of chromosomes in each of their cells. It is the genetic heritage they receive from their genitors. Three of these pairs are simply two versions of the same chromosome, as in two copies of chromosomes 2, 3 and 4. The first pair, however, represents the sex chromosomes – of which there are two, X and Y. Female fruit flies receive an X chromosome from both parents, while male fruit flies receive an X chromosome from their female genitor and a Y chromosome from their male genitor. Just like in humans! In fact, just like all mammals. This is the system Nature uses to produce scores of male and female animals. Now give this a thought: if some fruit flies are XX and others are XY, do the former not have more of something? And the latter something else altogether? For the XY individuals, the answer is yes. That is what makes them male. For the XX individuals, however, the answer is no. Though they may carry an extra X chromosome, in *Drosophila*, researchers have discovered a protein whose role is to prevent any kind of genetic imbalance with regards, precisely, to X-linked genes. Its name? MSL2.**



Tight Rope Walker
Paul Klee (1879-1940)

Across all organisms, the expression of one gene over another, or sets of genes over others, is of crucial importance. If the natural balance of gene expression is altered – in other words the production of proteins – it will bring about disorders of some kind, either developmental or disease. The pairing of sex chromosomes is very intriguing because the natural balance of gene expression seems to have been altered from the very start. In humans, for example, X and Y do share some identical genes but really very few, barely 5%. The other 95% is unique to Y. So organisms carrying XX and those carrying XY will tend to bear different genetic potentials. How is some kind of balance restored? In *Drosophila*, for example, the expression of genes on the X chromosome in XY individuals is upregulated. In mammals, yet another dosage compensation system has been adopted. Instead of upregulating the expression of genes on the X chromosome in XY individuals, one X chromosome is inactivated in XX individuals. As a result, X chromosome expression is levelled out for everyone.

Gene expression must be one of the most intricate biological processes there is, because there are several hurdles to tackle before it can be done. DNA is a fragile molecule and is therefore highly protected. First, it is preserved in a special cellular compartment: the nucleus. Second, within the nucleus and at regular intervals, the DNA of each chromosome is coiled around multitudes of identical protein structures, or histones, much in the manner fishermen coil ropes around moors. This histone-DNA structure then coils further to create very tightly-packed chromatin (DNA and histones). This is wonderful for protecting DNA but it does not make things easy when cells need to express genes and make proteins. In order to access the DNA, cells need to unwind coils and set aside histones. Also, though we will go into no detail, besides targeting the right gene and binding to it, they still have to split apart the stable

double helix to transcribe only one side of it. Needless to say, gene expression involves hordes of different proteins, enzymes and cofactors – all of which interact at various stages.

So, in terms of dosage compensation, how do we understand the upregulation of an X chromosome in male *Drosophila*? It all has to with a complex that has been called the Male Specific Lethal (MSL) complex. MSL complex is an assembly of five protein dimers (MSL1, MSL2, MSL3, MLE and MOF) and two non-coding RNAs (ncRNA) – each of which have specific roles, such as structural, chromatin interactions, protein-protein interactions, DNA-binding and the like. In *Drosophila*, the MSL complex assembles exclusively in male (XY) flies where it acts on the X chromosome. There, it begins by modifying (acetylating) the histones around which DNA is coiled. This action opens up the overall chromatin structure, paving the way for gene expression. The MSL complex then binds to specific sites, High Affinity Sites (HAS), scattered along the X chromosome DNA. Bouncing from HAS to HAS, the MSL complex gradually coaxes the increased expression of X-linked genes.

You may be wondering, do female *Drosophila* have MSL complexes? Yes, proteins that are part of the complex are also found in female flies. However, the expression of one of its subunits – protein MSL2 – is inhibited. This not only saves female flies from the unleashed overexpression of their X chromosomes, but it must also mean that MSL2 has a central role in chromosome upregulation in male flies. MSL2 is activated when it binds to MSL1 via its RING domain – a domain composed of seven cysteine residues which coordinate two zinc atoms. Tethered to the MSL complex, MSL2 then pulls it from HAS to HAS as it binds to DNA via its CXC domain – a nucleic acid binding domain made up of a cluster of nine cysteine residues that coordinate another three zinc atoms.

This is how upregulation of the male *Drosophila* X chromosome is explained. MSL complexes also exist in mammals. Similar in their composition and assembly, they are also active in dosage compensation but not in the same circumstances. In mammals, the MSL complex does not upregulate the X chromosome in XY individuals since another system silences one of the X chromosomes in XX individuals. So what does it do? The mammalian MSL complex seems to be crucial in the event of haploinsufficiency. What does this mean? Humans receive two copies of each gene: one from our mother, the other from our father. These are called alleles. As described implicitly above, both alleles are usually expressed. A gene is haplo-insufficient when one of its alleles is inactive. In such instances, the MSL complex can be called up to activate the silenced allele, much in the way the complex upregulates the X chromosome in *Drosophila*. In mammals, the MSL complex thus retains the same role but uses it for a different purpose. Again, MSL2 is a key protein in the process but its exact role is unknown. It could be that MSL2 frees space on chromatin by preventing protective DNA methylation or perhaps heightening histone acetylation like in Drosophila, thus giving transcription factors the chance to reach genes.

Gene expression is a fascinating field of research. Silencing genes while activating others is what gives rise to an intrinsic and vital biological balance every single organism depends on. Here we have the example of a protein, or a set of proteins – the MSL complex – that evolution has retained over time. But not quite for the same purpose. Although it always involves the upregulation of gene expression, the circumstances in which it occurs is not the same. In Drosophila, the MSL complex upregulates the expression of genes on the X chromosome in XY individuals. In mammals, it seems to have been kept to upregulate the expression of alleles that have been silenced so as to restore bi-allelic expression. Loss of MSL2 can lead to developmental disorders such as eye malformation, or brain and kidney defects. So getting to know how it works in full molecular detail would help to develop novel therapies.

Cross-references to UniProt

E3 ubiquitin-protein ligase msl-2, *Drosophila melanogaster (*Fruit fly*):* P0C1R0
E3 ubiquitin-protein ligase msl-2, *Homo sapiens (*Human*):* Q9HCI7
E3 ubiquitin-protein ligase msl-2, *Mus musculus (*Mouse*):* Q69ZF8

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