Aneuploidy compensatory mechanisms and genome-wide regulation of gene expression in *Drosophila melanogaster*

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av filosofie doktorsexamen framläggs till offentligt försvaret i sal E04, Byggnad 6E, Umeå Universitet onsdagen den 5 juni, kl. 09:00. Avhandlingen kommer att försvaras på engelska.

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Stimulation or repression of gene expression by genome-wide regulatory mechanisms is an important epigenetic regulatory function which can act to efficiently regulate larger regions or specific groups of genes, for example by compensating for loss or gain of chromosome copy numbers. In Drosophila melanogaster there are two known chromosome-wide regulatory systems; the MSL complex, which mediates dosage compensation of the single male X-chromosome and POF, which stimulates expression from the heterochromatic 4th chromosome. POF also interacts with the heterochromatin inducing protein HP1a, which represses expression from the 4th chromosome but which also has been assigned stimulatory functions. In addition to these two, there is another more elusive and less well-characterized genome-wide mechanism called buffering, which can act to balance transcriptional output of aneuploidy regions of the genome (i.e. copy number variation).

In my thesis, I describe the presence of a novel physical link between dosage compensation and heterochromatin; mediate by two female-specific POF binding sites, proximal to roX1 and roX2 on the X chromosome (the two non-coding RNAs in the MSL complex). These sites can also provide clues to the mechanisms behind targeting of chromosome-specific proteins. Furthermore, to clarify the conflicting reports about the function of HP1a, I have suggested a mechanism in which HP1a has adopted its function to different genomic locations and gene types. Different binding mechanisms to the promoter vs. the exon of genes allows HP1a to adopt opposite functions; at the promoter, HP1a binding opens up the chromatin structure and stimulates gene expression, whereas the binding to exons condense the chromatin and thus, represses expression. This also causes long genes to be more bound and repressed by HP1a. Moreover, I show that buffering of monosomic regions is a weak but significant response to loss of chromosomal copy numbers, and that this is mediated via a general mechanism which mainly acts on differentially expressed genes, where the effect becomes stronger for long genes. I also show that POF is the factor which compensates for copy number loss of chromosome 4.

Keywords
Genome-wide gene regulation, aneuploidy, buffering, HP1a, POF, SETDB1, Su(var)3-9, MSL, roX