UMEÅ UNIVERSITET

Regulation of gene expression in fruit flies;

How does it start, and will it be remembered?

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av filosofie doktorsexamen framläggs till offentligt försvar i Astrid Fagreus lecture hall (A103), byggnad 6A .

Fredagen den 07 December, kl. 13:00.
Avhandlingen kommer att försvaras på engelska.
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Abstract

One of the most distinctive features of eukaryotic chromosomes is the bundling of DNA together with functionally associated RNA and proteins in chromatin. This allows huge amounts of DNA to be packed inside the very tiny space of the nucleus, and alterations in the structure of chromatin enable access to the DNA for transcription ("reading" genes by production of RNA copies). Much of the current knowledge of chromatin structure and regulation comes from studies of Drosophila melanogaster. When the chromatin structure is open the transcription of a gene can start after recruitment of the necessary factors. The main enzyme for gene transcription is Polymerase II (Pol II). For successful gene transcription, Pol II must not only be recruited to the gene's promoter, but also escape from a pausing state which occurs soon after transcription initiation. CBP/P300 is one of the co-activators involved in transcriptional activation. In the studies this thesis is based upon, my colleagues and I (hereafter we) discovered a new function for CBP in transcription activation. Using high throughput sequencing techniques, we found that CBP directly stimulates recruitment of Pol II to promoters, and facilitates its release from the paused state, enabling progression to the elongation stage of transcription.

For cells to remember their identity following division during development, the transcriptional state of genes must be transmitted. Intensively studied players involved in this memory are the Polycomb group (PcG) proteins, responsible for maintaining the repressed state of important developmental genes. The core members are Polycomb repressive complex 1 and 2 (PRC1 and PRC2), which are recruited in flies through poorly known mechanisms to target genes by so-called Polycomb response elements (PREs). Using Drosophila mutant cell lines, we showed that (in contrast to previous models) some PREs can recruit PRC1 even when PRC2 is absent. We also observed that at many PREs, PRC1 is needed for recruitment of PRC2 and concluded that targeting PRC complexes to PREs is a much more flexible and variable process than previously thought.

Some phenotypic effects of environmental changes can be transferred to subsequent generations. Previous efforts to identify the mechanisms involved have focused on material (mainly, but not only, DNA) transferred through germ cells. However, organisms' microbiomes are also transferred to the next generation. Thus, to investigate possible contributions of microbiomes to such transfer, we used fruit flies as the microbiomes they inherit can be easily controlled. We altered some parents' environmental conditions by lowering the temperature, then grew offspring that received microbiomes from cold-treated and control parents in control conditions and compared their transcriptional patterns. Our results suggest that most of the crosstalk between the microbiome and the fly happens in the gut, and that further investigation of this previously unsuspected mode of inheritance is warranted.

Keywords
Drosophila, epigenetics, transcription, gene regulation, transcription maintenance, CBP, polymerase pausing, Polycomb group proteins, transgenerational inheritance of transcriptional response, gut microbiome

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