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DISSERTATION SUMMARY

The different role of ADA2b proteins in genome-wide acetylation and specific gene activation

Tibor Pankotai

Department of Genetics and Molecular Biology, University of Szeged, Szeged, Hungary

In eukaryotes the genetic material is present in a compact chromatin structure consisting of DNA and histone proteins. This chromatin structure must be opened in the early transcription steps to enable the binding of transcription factors to the promoter region. This process is regulated by the histone acetyltransferases. One of these acetyltransferases is the GCN5 subunit of GANT histone acetyltransferase complexes. GCN5 is one of the most intensively studied histone acetyltransferase and it is the catalytic component of a number of protein complexes. Other components of the GCN5-containing complexes are adaptor proteins like ADA2 and ADA3.

Recently, our group has reported that the Drosophila genome contains two distinct genes encoding ADA2 homologs. Biochemical characterization of the two ADA2 proteins demonstrated that both of them interact with the HAT GCN5 and participate in transcription activation. On the other hand, ADA2a and ADA2b exhibit marked differences, e.g., they participate in distinct high-molecular-weight HAT-containing protein complexes, are localized to different chromosomal loci, and have at least partly different partners of interaction.

Here we demonstrated that the complexity of ADA proteins is even higher and the Drosophila Ada2b gene produces two types of Ada2b mRNAs. The two proteins translated from the mRNAs are localized in different parts of the cells. The ADA2b1 protein is presented in the cytoplasm while the ADA2b2 is presented in the nucleus.

I generated Ada2b mutations which permit studying the role of the two ADA2b proteins together and separately as well. Ada2b mutations caused lethality in the late-pupa stage and reduced H3 K14 and H3 K9 acetylation. Interestingly, only the ADA2b1 isoform is required for the general H3 K14 and K9 acetylation. The absence of ADA2b2 did not affect the level of these acetylations.

The Ada2b mutation affects TAF10 localization at some, but not all, specific bands on Drosophila polytene chromosomes. The introduction of an Ada2b transgene into Ada2b mutant animals restored a staining pattern of polytene chromosomes identical to that seen in wild-type animals, providing further evidence that the loss of TAF10 localization at these sites derived from ADA2b depletion. This suggests that in certain complexes the presence of ADA2b is required for the incorporation of TAF10.

The mutation of Ada2b caused dramatical changes in specific gene function. Comparison of the pigment contents of Ada2b heterozygotes and wild-type animals indicated that Ada2b mutation affected the pigment contents of the eyes of adult animals. In concert with this, the mRNA level of rosy, a gene encoding xanthene dehydrogenase, which is involved in the formation of red eye pigments, exhibited a significant reduction in Ada2b mutant animals compared to wild-type animals. The two isoforms of ADA2b differ in regulation of rosy, the presence of ADA2b2 is necessary for normal expression level of rosy gene. On the other hand the ADA2b1 and ADA2b2 act differentially in the regulation of mitotic specific genes. The Ada2b mutation abolishes the Map205 expression but the presence of ADA2b2 rescues the Map205 mRNA level, while the ADA2b1 does not.

The Dmp53 function is essential for radiation-induced apoptosis. DNA damage leads to Dmp53 activation, which causes apoptosis through the transcriptional activation of proapoptopic factors. For Ada2b mutants, the number of cells undergoing apoptosis was significantly lower than that in wild type animals. For the tested Ada2b, the number of acridine orange-stained cells was decreased significantly. Interestingly, high-dose X-ray irradiation, which resulted in a decrease in apoptosis in wing imaginal disks, induced the reaper message level similarly (a three- to fourfold increase compared to the non-irradiated controls) in wild-type and Ada2b larvae.

The mutation of Ada2b causes dramatical changes in specific gene activations. Approximately six percent of the known Drosophila genes showed decreased (368 genes) or increased expression (461 genes) in the absence of Ada2b. These results indicate that the ADA2b containing complexes coordinate the regulation of genome wide expression through specific genes.

Supervisor: Imre Boros
E-mail: ptibor@bio.u-szeged.hu