Coordinated changes of histone modifications and HDAC mobilization regulate the induction of MHC class II genes by Trichostatin A.

The deacetylase inhibitor Trichostatin A (TSA) induces the transcription of the Major Histocompatibility Class II (MHC II) DRA gene in a way independent of the master coactivator CIITA. To analyze the molecular mechanisms by which this epigenetic regulator stimulates MHC II expression, we used chromatin immunoprecipitation (ChIP) assays to monitor the alterations in histone modifications that correlate with DRA transcription after TSA treatment. We found that a dramatic increase in promoter linked histone acetylation is followed by an increase in Histone H3 lysine 4 methylation and a decrease of lysine 9 methylation. Fluorescence recovery after photobleaching (FRAP) experiments showed that TSA increases the mobility of HDAC while decreasing the mobility of the class II enhanceosome factor RFX5. These data, in combination with ChIP experiments, indicate that the TSA-mediated induction of DRA transcription involves HDAC relocation and enhanceosome stabilization. In order to gain a genome-wide view of the genes responding to inhibition of deacetylases, we compared the transcriptome of B cells before and after TSA treatment using Affymetrix microarrays. This analysis showed that in addition to the DRA gene, the entire MHC II family and the adjacent histone cluster that are located in chromosome 6p21-22 locus are...
strongly induced by TSA. A complex pattern of gene reprogramming by TSA involves immune recognition, antiviral, apoptotic and inflammatory pathways and extends the rationale for using Histone Deacetylase Inhibitors (HDACi) to modulate the immune response.