Differential effects of chromatin regulators and transcription factors on gene regulation: a nucleosomal perspective

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Genome analysis

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Differential effects of chromatin regulators and transcription factors on gene regulation: a nucleosomal perspective

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Motivation

gene transcription in the cell is tightly regulated

- optimize the expression level at different physiological conditions
- capacity to quickly adjust in response to external signals and perturbations

effects of CR and TF regulation on nucleosomes are minimally understood

(Does DNA determine nucleosome binding?)

Data

Saccharomyces cerevisiae

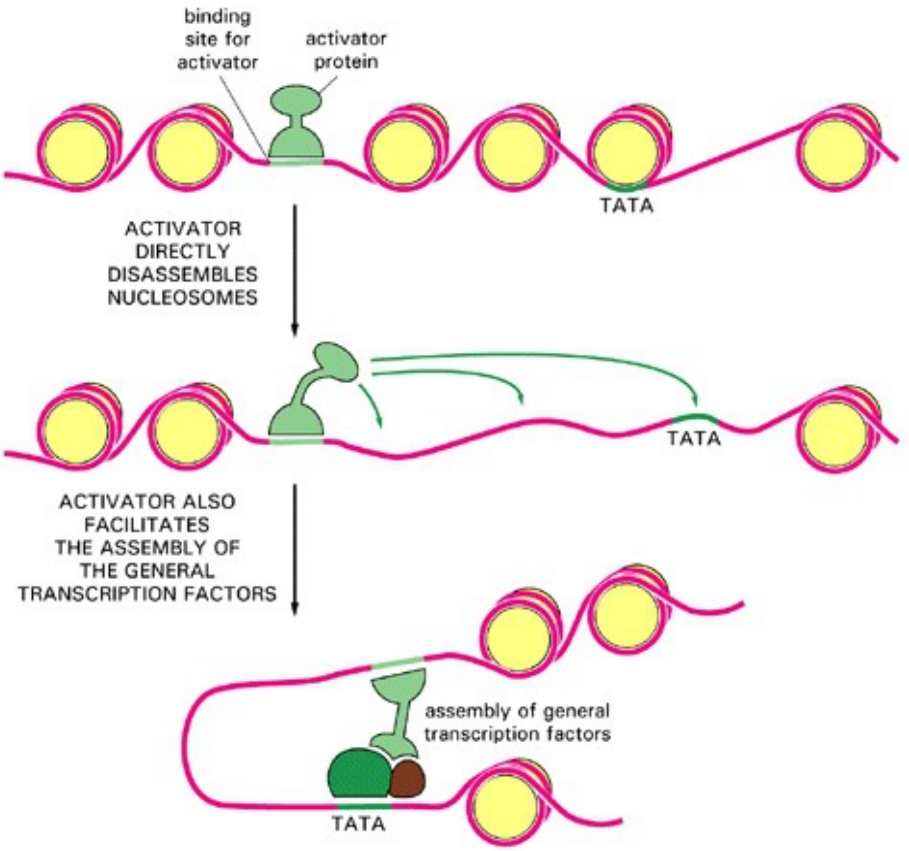
- Gene expression
- Nucleosome occupancy and fuzziness
- Epigenetic marks
- TF binding sites and TATA box genes

All data from previous studies

CR Chromatin regulators

- histone modification
- chromatin remodeling
- histone variants
- histone eviction

TF compete with nucleosomes!



Gene expression data

from Hu *et al.,* 2007, Steinfeld *et al.*, 2007

- CRE– expression profiles from deletion of CR proteins
- TRE– expression profiles from deletions of 269 Tfs
- Genes with >10% missing expression data were excluded

  we normalized the refined expression data under each perturbation condition, and then calculated CR and TF regulation effects as the average of absolute values of logarithm of the expression changes across these trans-acting factors perturbations, respectively.
- CR-sensitive and TF-sensitive – differentially expressed genes in CRE and TRE datasets

  top 20% genes by ranking in TRE and CRE
- Genes categorized in both cohorts were excluded

Table 1. Comparison of the influences of CR and TF regulation effect on transcription plasticity, mRNA abundance and transcription frequency in *S.cerevisiae*

	Transcription plasticity	mRNA abundance	Transcription rate
CRE			
TRE uncontrolled	0.68 (<1e-20)	0.05 (0.18)	0.06 (0.13)
TRE controlled	0.61 (<1e-20)	−0.01 (0.88)	−0.01 (0.86)
TRE			
CRE uncontrolled	0.28 (<1e-20)	0.27 (1e-14)	0.25 (1e-13)
CRE controlled	0.24 (<1e-20)	0.26 (1e-14)	0.23 (1e-13)

Note: when TRE and CRE were uncontrolled, Spearman's correlation coefficients were shown; when CRE or TRE was controlled, partial correlation coefficients were shown; the numbers in parentheses are *P*-values measured based on the null hypothesis that there is no significant relationships.

Nucleosome data

- Nucleosome occupancy

  Lowest average nucleosome occupancy across any 100bp window in 200bp region upstream of TSS

- Nucleosome dynamics

  Normal and heat-shock conditions

  Two cross-platform datasets in same conditions

  Different growth medium

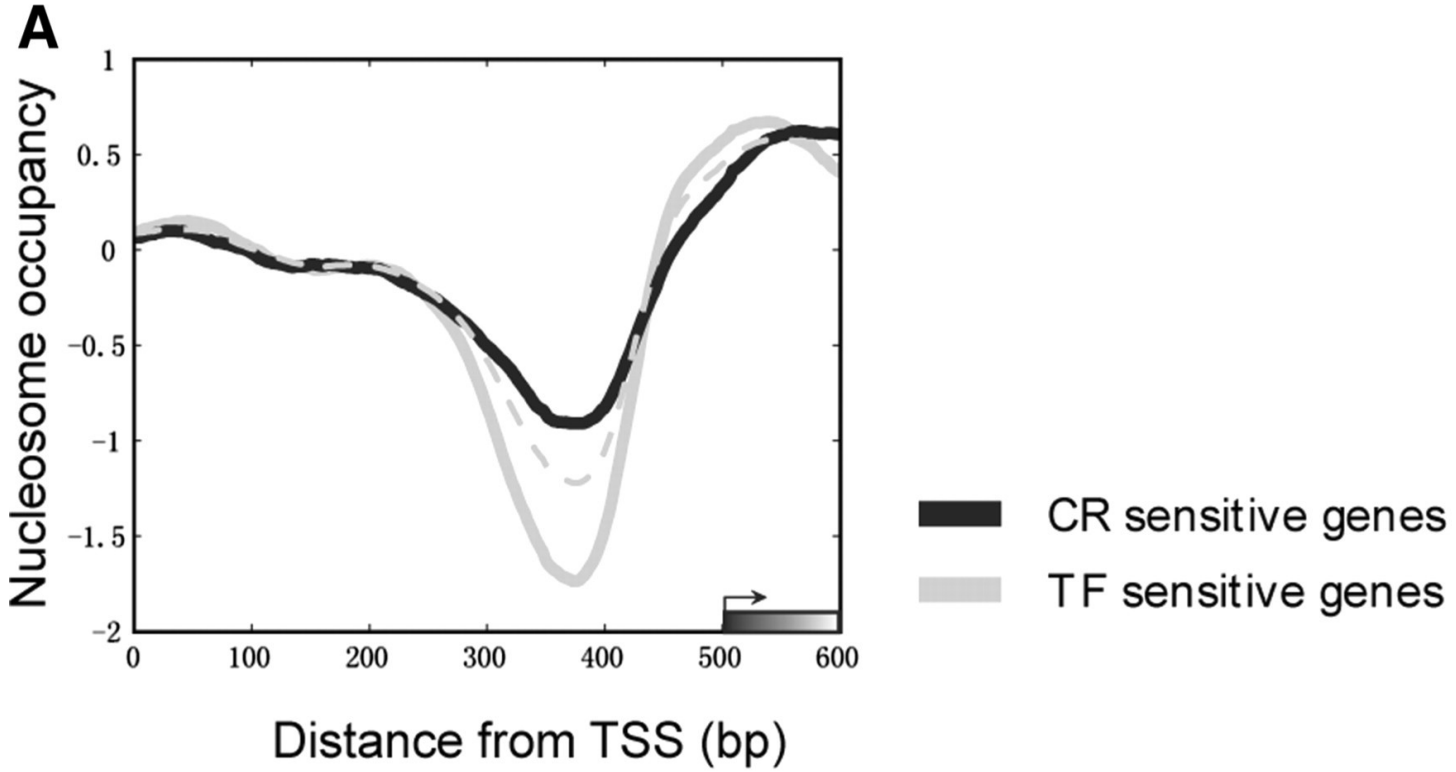
- Nucleosome fuzziness

  Unoccupied linker region

  Fuzzily positioned nucleosomes

  Well-positioned nucleosomes

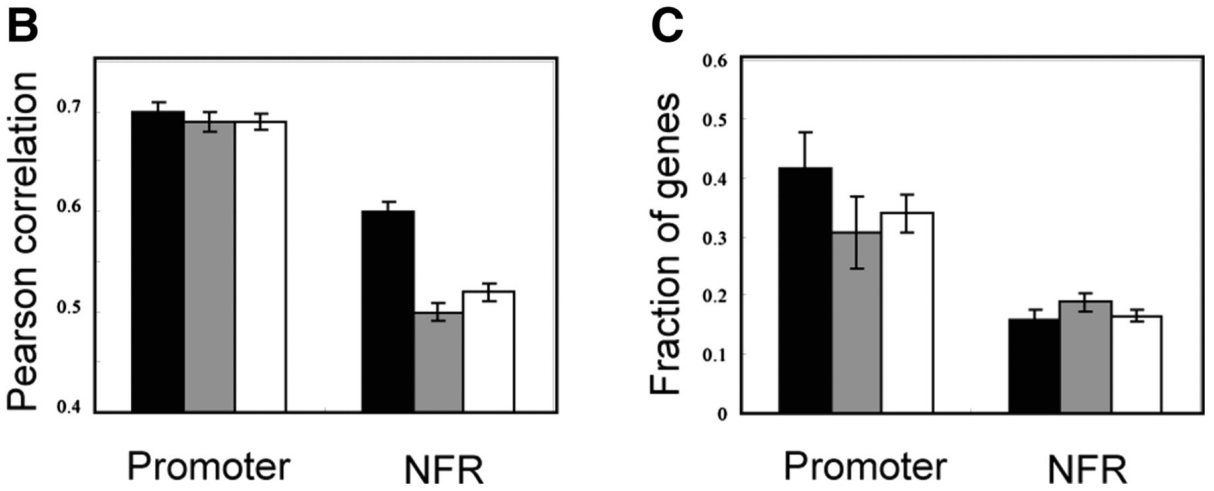
Nucleosome occupancy of the promoter regions



- The promoter regions (500 bp upstream, ~100 bp downstream relative to TSS) of TF-sensitive genes show a nucleosome-free region, whereas the promoter regions of CR-sensitive genes reflect nucleosome occupied organization.

  The dash curve represents the nucleosome occupancy of all yeast genes.

Promoter regions and nucleosome-free regions

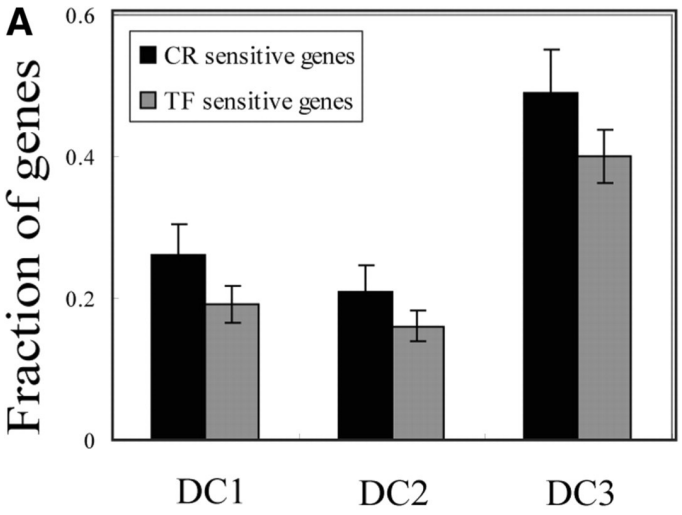


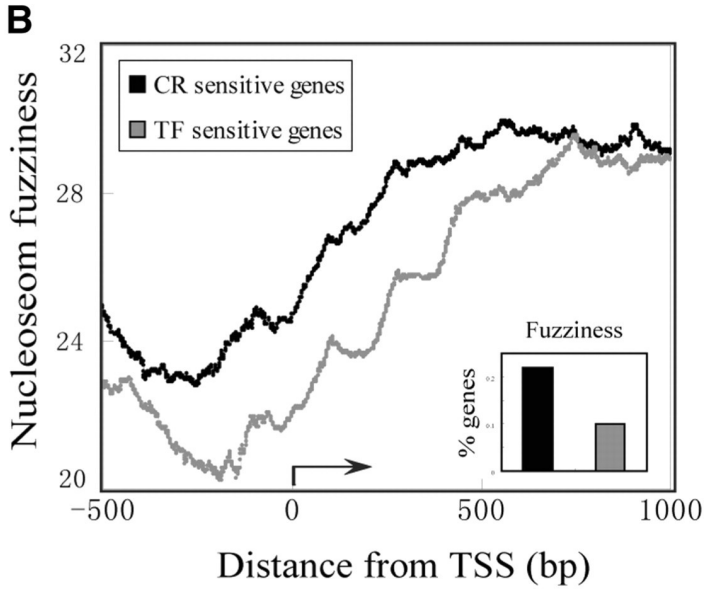
B Pearson's correlation of promoter regions and nucleosome-free regions (NFR, 200 bp upstream, ~50 bp upstream relative to TSS) of nucleosome occupancy measured in vivo and in vitro.

C TF binding sites of CR- and TF-sensitive genes under the promoter regions and nucleosome-free regions (NFR).

The white bars represent the results for all yeast genes, and the black and gray bars represent the results for CR- and TF-sensitive genes, respectively.

Dynamic characteristics (DC) of nucleosome organization.





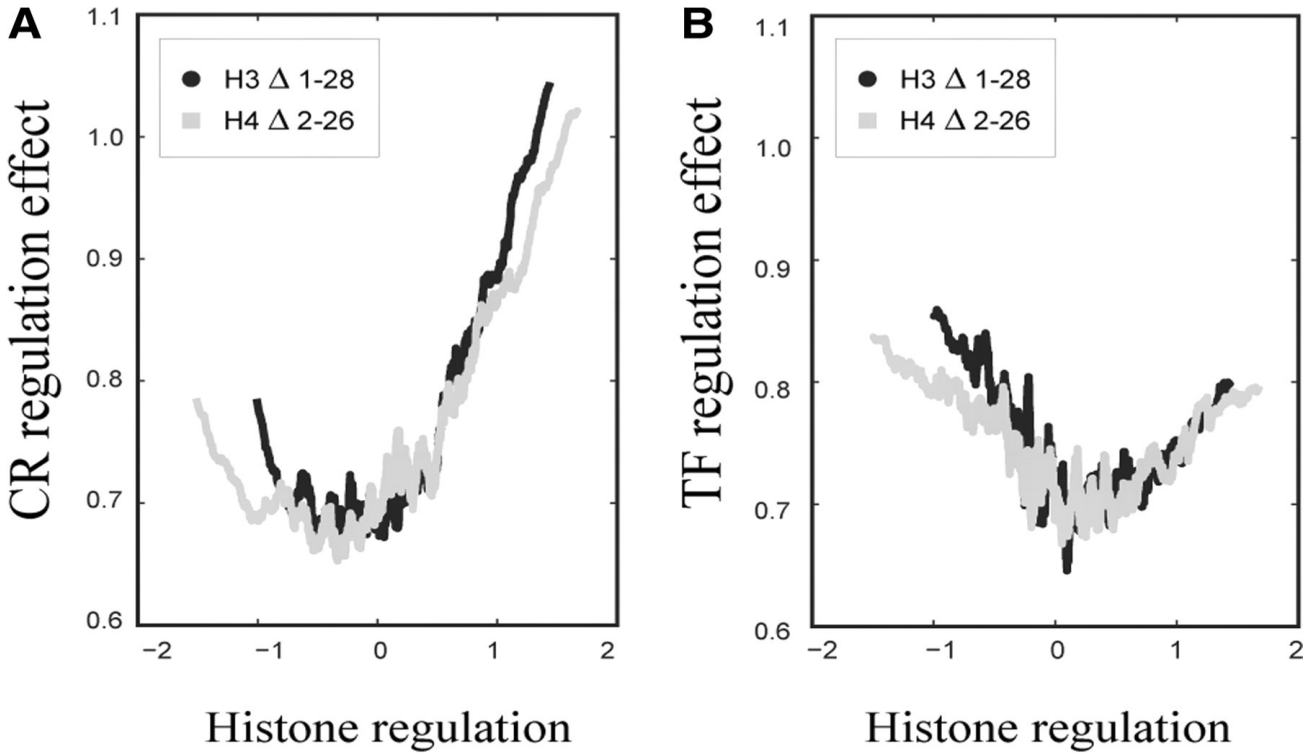
A DC of nucleosome organization in the promoter regions.

- DC1 - nucleosome positioning before and after heat shock
- DC2 - nucleosome positioning between different cross-platform datasets
- DC3 - nucleosome occupancy among cells grown at different conditions

B Nucleosome fuzziness relative to TSS.

Fuzziness is reported as the standard deviation of nucleosome locations for each individual reference nucleosome. The distribution of nucleosome fuzziness is plotted by binning nucleosomes together moving along the genes. The inset figure shows the fraction of genes with linker region longer than 50 bp in the promoter region (500 bp upstream to 1000 bp downstream to TSS).

Impact of CR and TF regulation effect on the activity of histones
Histone modification



Impact of CR and TF regulation effect on the activity of histones. (A) CR and (B) TF regulation effect with the varying sensitivity to histone regulation. Genes were ordered by expression changes resulting from histone H3 (H3Δ1−28) and H4 (H4Δ2-26) amino terminus depletion. Both the average values of CR and TF regulation effect were obtained by a sliding window of 200 ordered genes.

Conclusion

- Nucleosome depleted region ~100-200bp upstream of TSS
- Distinct patterns in promoter region under CR and TF regulation
- CR capable of remodeling chromatin structures
- CR genes tend to have dynamic characteristics of nucleosomes

CR and TF work jointly