Perspectives on GBP5 transcriptional bursting, chromatin structure, and transcriptional condensates

Clayton W. Seitz

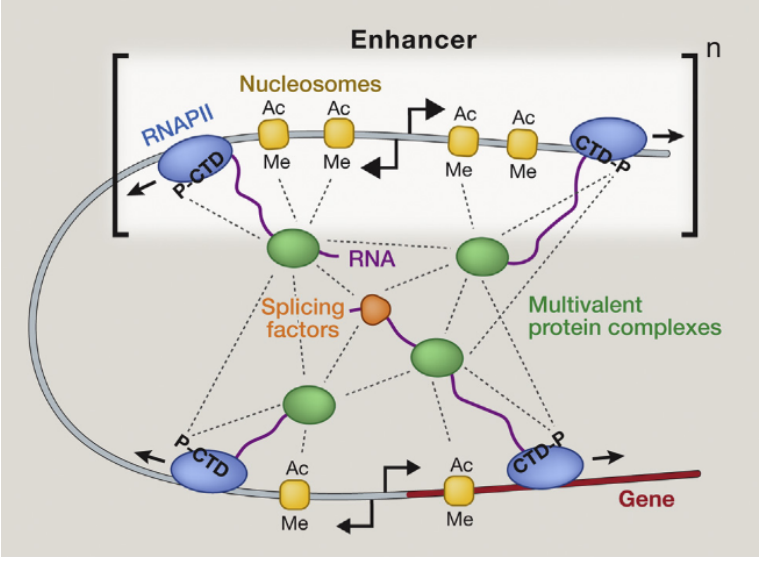
March 25, 2023

Current events

- GBP5 transcriptional kinetics are changed after Interferon-γ priming (Siwek 2020; Molecular Cell) - we have now observed this also
- HiC data shows Interferon-γ causes chromatin reorganization at GBP5 locus (Platinitis 2022; Science)
- Phase separated condensates are responsible for decrease in the degree of disorder of chromatin at macrophage GBP5 locus during bacterial infection (Lin 2022; Nature Comm)

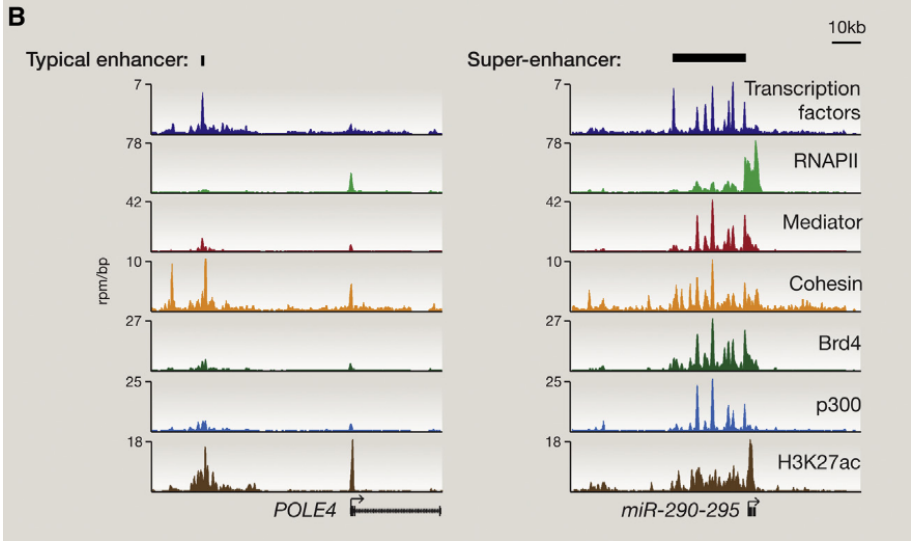
Are persistent transcriptional condensates responsible for the change in GBP5 transcriptional kinetics?

A modern view of transcriptional control

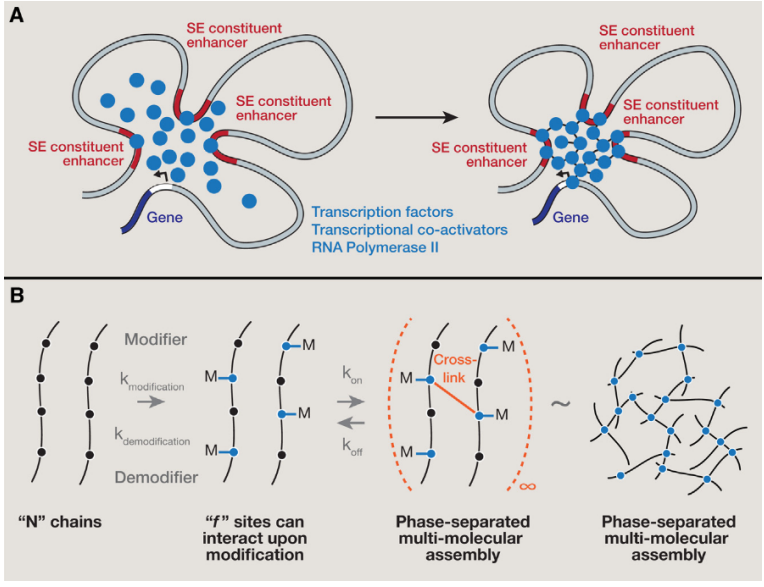


Hnisz et al. A phase separation model of transcriptional control. Cell 2017

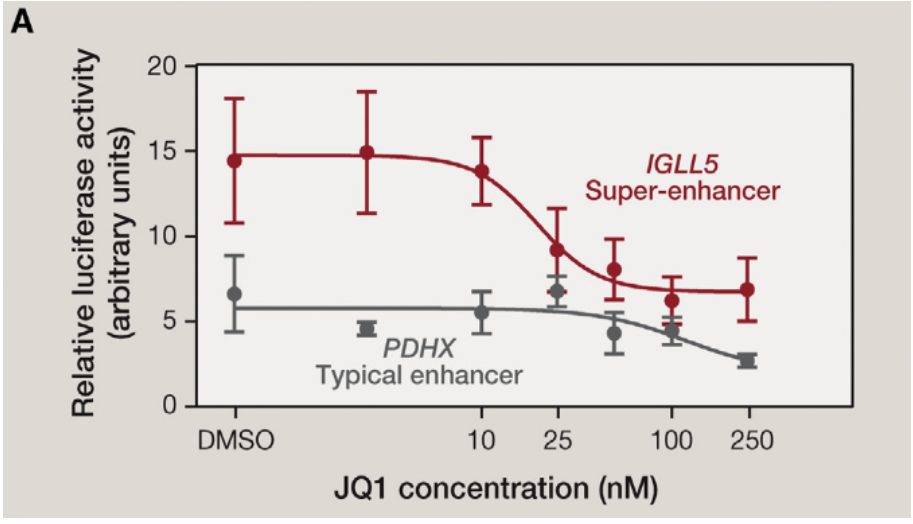
Super-enhancers host large molecular complexes that facilitate transcription



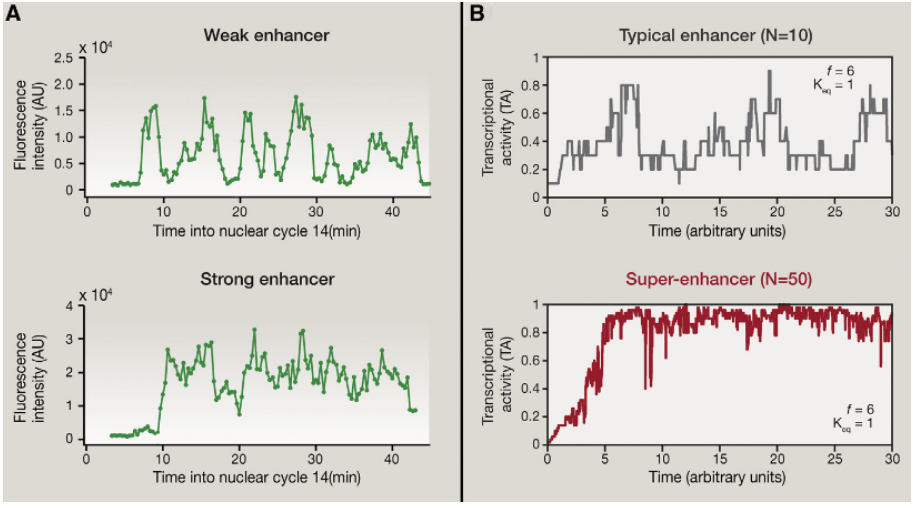
Structural modeling of phase-separated aggregates



BRD4 inhibitor JQ1 reduces transcription



Super-enhancers reduce transcriptional variability in *Drosophila* embryos



For details see *Fukaya et al. Enhancer control of transcriptional bursting. Cell 2016*

Mediator and RNA polymerase II clusters associate in transcription-dependent condensates

Won-Ki Cho[1]*, Jan-Hendrik Spille[1]*, Micca Hecht[1], Choongman Lee[1], Charles Li[2,3], Valentin Grube[1,4], Ibrahim I. Cisse[1]†

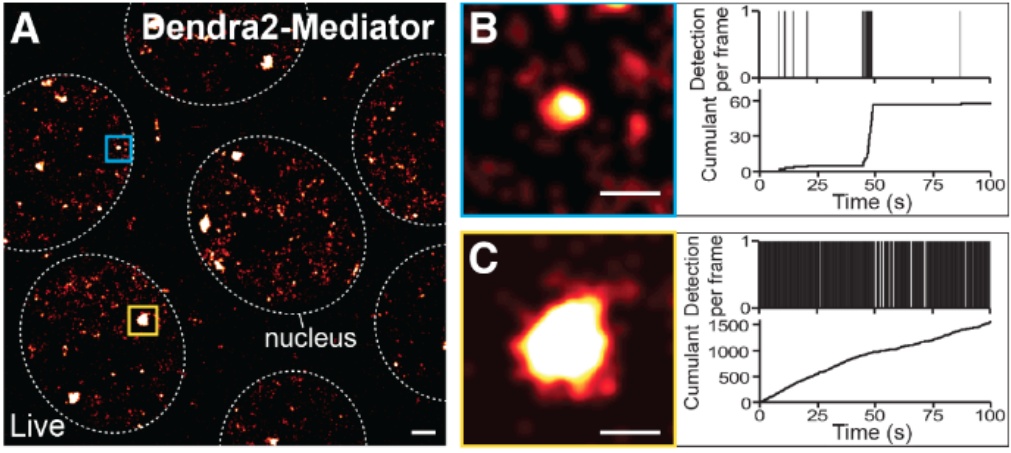
[1]Department of Physics, MIT, Cambridge, MA 02139, USA. [2]Department of Biology, MIT, Cambridge, MA 02139, USA. [3]Whitehead Institute for Biomedical Research, Cambridge, MA 02139, USA. [4]Department of Physics, LMU Munich, Geschwister Scholl Platz 1, 80539 Munich, Germany.

*These authors contributed equally to this work.

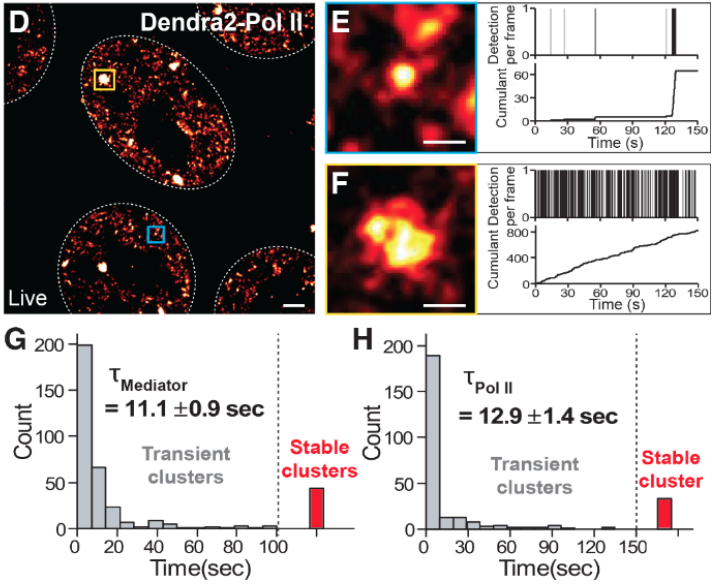
†Corresponding author. Email: icisse@mit.edu

Models of gene control have emerged from genetic and biochemical studies, with limited consideration of the spatial organization and dynamics of key components in living cells. Here we used live cell super-resolution and light sheet imaging to study the organization and dynamics of the Mediator coactivator and RNA polymerase II (Pol II) directly. Mediator and Pol II each form small transient and large stable clusters in living embryonic stem cells. Mediator and Pol II are colocalized in the stable clusters, which associate with chromatin, have properties of phase-separated condensates, and are sensitive to transcriptional inhibitors. We suggest that large clusters of Mediator, recruited by transcription factors at large or clustered enhancer elements, interact with large Pol II clusters in transcriptional condensates in vivo.

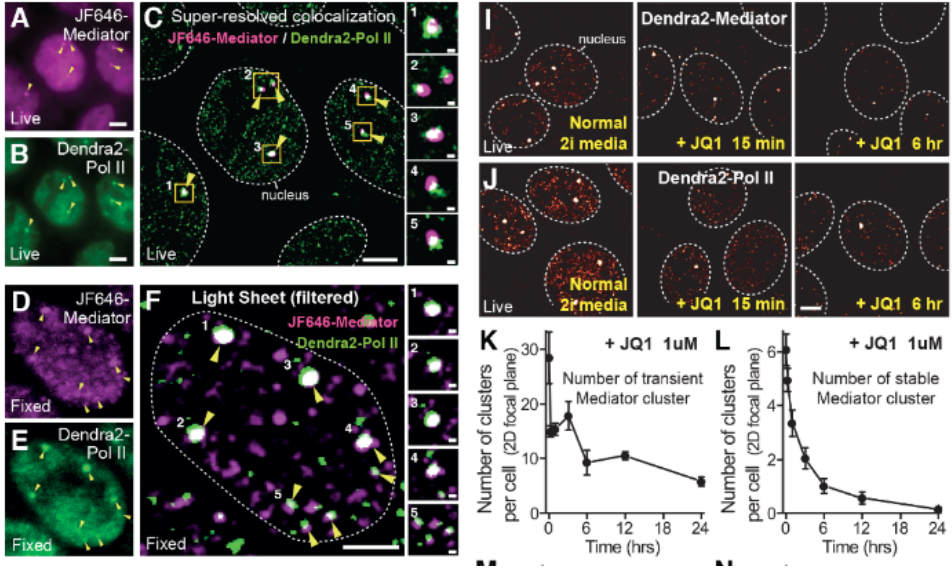
Mediator and Pol II form transient and stable clusters



Mediator and Pol II form transient and stable clusters



Mediator and Pol II clusters colocalize in a transcription dependent manner



Mediator clusters dynamically kiss actively transcribing SE-controlled genes