Testing the super-enhancer concept

Citation: Blobel, Gerd A, Higgs, Douglas R, Mitchell, Jennifer A, Notani, Dimple and Young, Richard A. 2021. "Testing the super-enhancer concept." Nature Reviews Genetics, 22 (12).

As Published: 10.1038/S41576-021-00398-W

Publisher: Springer Science and Business Media LLC

Persistent URL: https://hdl.handle.net/1721.1/147079

Version: Author's final manuscript: final author's manuscript post peer review, without publisher's formatting or copy editing

Young, R. (2021). Testing the super-enhancer concept. Nature Reviews Genetics, 22(12). doi:10.1038/S41576-021-00398-W

1) Several enhancer clusters in the genome have been described as super-enhancers. Could you describe your thoughts on the coining of the super-enhancer term?

Three properties of enhancer clusters led us to call them super-enhancers. They regulate genes that play prominent roles in cell identity, assemble a high density of transcriptional apparatus to drive robust expression of these genes, and are highly enriched in disease-associated genetic variation (1). Super-enhancers are acquired by driver oncogenes in tumor cells, further emphasizing the roles they play in robust gene expression and in cell identity. My thoughts about coining the term super-enhancer? Similar clusters were identified in Francis Collin's lab and were called stretch enhancers (2). As William Shakespeare wrote, in Romeo and Juliet, "What's in a name? that which we call a rose by any other name would smell as sweet." We used the term super-enhancers to provoke further study of these interesting regulatory elements.

2) To what extent are the properties of super-enhancers distinct from the sum of their individual constituent enhancers? Does the concept of a super-enhancer help us to understand principles and mechanisms of gene regulation?

At some loci, super-enhancers have constituent enhancers that can act in a highly cooperative fashion and at other loci the constituents can function in a temporal manner, so super-enhancers have not evolved to serve a single mechanistic purpose.

The super-enhancer concept led us to consider a condensate model for gene regulation. Where super-enhancers cooperatively assemble a high density of transcriptional apparatus, the assembly exhibits very sharp transitions of formation and dissolution. This property, and the enrichment of condensate-promoting features in components of the transcription apparatus, led us to propose that the assembly of biomolecules at active super-enhancers is due to phase separation of the apparatus at these elements. Experimental analysis subsequently showed that transcription factors, cofactors and RNA polymerase II do form dynamic, transcriptionally active biomolecular condensates (3,4). The concept of a transcriptional condensate provides a useful model to address many mysteries in the field of gene regulation, including the functions of the intrinsically disordered activation domain of transcription factors, the ability of a single large enhancer to simultaneously activate two independent genes, the mechanism by which RNA contributes to transcriptional bursting, the preference of cellular signaling molecules to associate with super-enhancers, and the ability of cancer drugs to concentrate at specific genomic loci (5).

3) What experimental approaches are key for dissecting the functions of enhancer clusters?

The functions we might wish to study include the regulatory contributions of individual constituent enhancers and the transcription factors that bind them, roles of diverse RNA molecules in regulating condensate formation and dissociation, physicochemical features that lead to concentration of certain biomolecules and drugs, or mechanisms by which sequence variants in super-enhancers predispose to disease. There are diverse genetic, genomic, biochemical and microscopic approaches that might be employed in such studies. When considering these and other approaches, I believe the integration of concepts in physics, chemistry and biology into questions of function will provide some of the most exciting new insights into the mechanisms that contribute to gene regulation.

4) What are the most interesting aspects of the emerging interplay between enhancer clusters and transcriptional condensates?

I now consider enhancers as DNA elements that crowd transcription factors and other components of the transcription apparatus to the point where condensates can form (6), and clustered enhancers as loci where such condensates are larger (and thus easier to study), more long-lived and capable of producing more transcripts (7). The concept that enhancers can contribute to the formation of transcriptional condensates establishes a new framework for studies of transcriptional regulation in cellular homeostasis and development, investigating the dysregulated transcription that is associated with a multitude of diseases and exploring new therapeutic hypotheses. It inspires new questions about the functions of compartmentalization, concentration and regulation of large assemblies of molecules that have not been addressed with conventional molecular models (5). For example, the powerful ability of RNA molecules to regulate formation and dissolution of condensates should stimulate new questions about the roles of noncoding RNA in gene control. The ability of post-translational modifications to change the selective condensate partitioning behavior of molecules should prompt further study of the functions of epigenetic modifications of DNA, RNA and proteins. The selective drug-concentrating properties of condensates are fueling interest in the possibility that new therapeutic approaches might address diseases due to transcriptional dysregulation.

5) What are the most pressing unanswered questions and future directions in the field?

Transcriptional condensates add a layer of regulation to gene expression that extends beyond the canonical molecular mechanisms by compartmentalizing and concentrating the transcription apparatus. What physical and chemical principles might help us model and further study the roles of biomolecular polymers – DNA, RNA and proteins – in condensate behaviors?

There is evidence that protein, RNA, and small molecules can be selectively concentrated in specific condensates, and different condensates are associated with active and silent genes. What are the biomolecular components and chemical environments in condensates that contribute to this selective compartmentalization?

Diverse chemical modifications of DNA, RNA and proteins in chromatin are important for cellular homeostasis, differentiation and development. To what extent do chemical modifications contribute to cellular regulation through condensate-associated behaviors?

Many biomolecular condensates exhibit dynamic formation and dissolution. RNA molecules can contribute to both formation and dissolution of condensates. The functions of most long noncoding RNAs are not known; might these contribute to gene regulation through their modulation of condensates?

Thousands of pathological genetic variants cause disease through mechanism that are not yet understood; to what extent is condensate dysregulation the underlying cause of disease? Where condensates are dysregulated, can therapeutics be developed to suppress or reverse this dysregulation?

References:

1) Hnisz, D., Abraham, B.J., Lau A, Saint-André, V., Sigova, A.A., Hoke, H.A., Lee, T.I., and Young, R.A. Super-enhancers in the control of cell identity and disease. Cell 155: 934-947 (2013).
2) Parker, S.C., Stitzel, M.L., Taylor, D.L., Orozco, J.M., Erdos, M.R., Akiyama, J.A., van Bueren, K.L., Chines, P.S., Narisu, N., Black, B.L., Visel, A., Pennacchio, L.A., Collins, F.S. Chromatin stretch

enhancer states drive cell-specific gene regulation and harbor human disease risk variants. Proceedings of the National Academy of Sciences. 110: 17921–6 (2013).
3) Sabari, B.R., Dall'Agnese, A., Boija, A., Klein, I.A., Coffey, E.L., Shrinivas, K., Abraham, B.J., Hannett, N.M., Zamudio, A.V., Manteiga, J.C., Li, C.H., Guo, Y.E., Day, D.S., Schuijers, J., Vasile, E., Malik, M., Hnisz, D., Lee, T.I., Cisse, I.I., Roeder, R.G., Sharp, P.A., Chakraborty, A.K., and Young, R.A. Coactivator condensation at super-enhancers links phase separation and gene control. Science, 361, eaar3958 (2018).
4) Boija, A., Klein, I.A., Sabari, B.R., Dall'Agnese, A., Coffey, E.L., Zamudio, A.V., Li, C.H., Shrinivas, K., Manteiga, J.C., Hannett, N.M., Abraham, B.J., Afeyan, L., Guo, Y.E., Rimel, J.K., Fant, C., Schuijers, J., Lee, T.H, Taatjes, D.J., and Young, R.A. Transcription factors activate genes through the phase separation capacity of their activation domains. Cell 175:1842-1855 (2018).
5) Boija, A., Klein, I.A., Young R.A. Biomolecular condensates and cancer. Cancer Cell 39:174-192 (2021).
6) Shrinivas, K., Sabari, B.R., Coffey, E.L., Klein, I.A., Boija, A., Zamudio, A.V., Schuijers, J., Hannett, N.M., Sharp, P.A., Young, R.A., Chakraborty, A. Enhancer features that drive formation of transcriptional condensates. Mol Cell 75:549-561 (2019).
7) Cho, W.-K. et al. Mediator and RNA polymerase II clusters associate in transcription-dependent condensates. Science 361, 412–415 (2018).