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A unifying model of epigenetic regulation:

Single-cell tracking reveals a common “algorithm” of operation used by chromatin regulators

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Expression of the genome is controlled by an intricate “web” of proteins, chemical modifications, and RNA that together organize genomic DNA into chromatin. Molecular studies of the various forms and levels of chromatin organization are advancing rapidly, revealing an increasing number of connections between chromatin and cellular and disease processes, as well as a fast-expanding web of known chromatin factors (1). On page 720, Bintu *et al.* take a radically different approach to dissecting chromatin, focusing not on molecular but on “algorithmic” chromatin biology (2). By studying how individual chromatin regulators (CRs) operate to produce distinct gene expression outputs within individual cells, they find that chromatin’s complexity can be reduced into an elegant and unifying model of gene regulation.

In eukaryotic organisms, gene expression states are established in part by a system of CRs that act on chromatin in diverse ways (3). The principal questions posed by Bintu *et al.* concern how these CRs modulate gene expression, how permanent these expression changes are, and how the CRs’ “operations” relate to one another. To study this, the authors developed a framework for quantitatively interrogating the input-output relationship between the presence (or absence) of a CR and gene expression in live mammalian cells. The framework combines artificial recruitment of CRs to a target reporter locus with precise temporal control—an increasingly popular strategy for focusing the activity of CRs (4–8)—with time-lapse microscopy to track reporter activity in individual cells.

The authors used this framework to compare four repressive CRs that use distinct chromatin modifications. The embryonic ectoderm development (EED) protein of Polycomb repressive complex 2 catalyzes histone H3 lysine 27 (H3K27) methylation. The Krüppel associated box (KRAB) protein promotes H3K9 methylation. DNA methyltransferase 3b (DNMT3B) catalyzes DNA methylation. The histone deacetylase 4 (HDAC4) enzyme directs histone deacetylation. Previous work has shown that different types of repressed chromatin are generally associated with distinct time scales of repression. For example, DNA methylation is widely associated with heritable gene repression (9), whereas histone acetylation is typically transient (10). However, by comparing these distinct CRs side by side, Bintu *et al.* were able to bring them under a unified quantitative model.

What is key to the authors' approach are the longitudinal measurements they make of single cells via time-lapse microscopy. In this way, they could track not only changes in reporter protein levels in individual cells, but also changes in protein production rate during and after recruitment of the CRs to chromatin. This approach revealed that all the CRs silence the reporter gene in all-or-none fashion, as characterized by an abrupt change in protein production rate in individual cells. Moreover, when the CRs are released from chromatin, reactivation of the reporter gene also occurs in all-or-none fashion. This leads to a general and simplified model in which cells are stochastically switching between active and silent states, rather than transitioning gradually through different activity levels.

The key distinction among the four CRs is how quickly a proportion of the cells in a population transition to the silent state. To complete the model, the authors extended their tracking of silent cells over longer times to quantify the heritable stability of the silent state. This revealed a third state, ultimately yielding a model in which cells can stochastically transition between active, reversibly silent, and irreversibly silent states. Consistent with other studies (5), the proportion of cells entering the final, irreversibly silent state is controlled by varying the duration of time that the CR is recruited to the gene.

From conceptually simple but technically exquisite experiments, the authors have produced an elegant model for capturing the dynamics of epigenetic regulation. What is compelling about this work is the minimalism of the three-state model, and the fact that CRs with diverse molecular identities and mechanisms can be collapsed into it. Dynamic control of fractions of a population would seem to be an effective way of transmitting and recording environmental signals, and suggests distinct advantages of CRs over canonical transcriptional networks. It is intriguing to consider how cells potentially exploit this rate control mechanism to link specific CRs and associated chromatin modifications with specific cellular processes, such as selectively turning off genes in the right cells during development. Additionally, we know that CRs and modifications rarely exist or act in isolation (11). Thus, it will be interesting to see how this rate control framework extends to combinatorial contexts.

The simplicity of the model is less suited for problems involving a higher level of biochemical detail, given that there is little direct connection to molecular mechanisms. Connecting aspects of the model to the wealth of existing chromatin data [derived from chromatin immunoprecipitation sequencing (ChIP-seq), biochemistry, etc.] will represent an exciting area of investigation. Yet this work is a critical step in our efforts to find logic within the regulatory complexity of chromatin. Distilling complex processes into phenomenological models has been historically central to our understanding of biology. For example, simplified descriptions such as the FitzHugh-Nagumo model have been used for decades to describe the behavior of neurons without full molecular details (12). Finally, this work nicely illustrates the importance of synthetic approaches for providing a functional view of biology, in this case revealing CRs as sophisticated "devices" inherently capable of controlling the time scale and epigenetic memory of gene expression.

References

1. ENCODE Project Consortium. *Nature*. 2012; 489:57. [PubMed: 22955616]
2. Bintu L, et al. *Science*. 2016; 351:720. [PubMed: 26912859]
3. Kouzarides T. *Cell*. 2007; 128:693. [PubMed: 17320507]
4. Audergon PN, et al. *Science*. 2015; 348:132. [PubMed: 25838386]
5. Hathaway NA, et al. *Cell*. 2012; 149:1447. [PubMed: 22704655]
6. Keung AJ, et al. *Cell*. 2014; 158:110. [PubMed: 24995982]
7. Mendenhall EM, et al. *Nat Biotechnol*. 2013; 31:1133. [PubMed: 24013198]
8. Ragunathan K, Jih G, Moazed D. *Science*. 2015; 348:1258699. [PubMed: 25831549]
9. Bird A. *Genes Dev*. 2002; 16:6. [PubMed: 11782440]
10. Katan-Khaykovich Y, Struhl K. *Genes Dev*. 2002; 16:743. [PubMed: 11914279]
11. Bernstein BE, et al. *Cell*. 2006; 125:315. [PubMed: 16630819]
12. FitzHugh R. *Biophys J*. 1961; 1:445. [PubMed: 19431309]

Figure 1. Unifying epigenetic regulation

(A) A proposed three-state model of gene regulation by repressive CRs, in which cells stochastically transition between active, reversibly silent, and irreversibly silent states. (B) The model is obtained by quantifying silencing events in individual cells during CR recruitment, and reactivation events upon release of the CR, by means of time-lapse microscopy. Filmstrips for two CRs are shown. DNMT3B induces slow but complete commitment to irreversibly silent states, whereas HDAC4 leads to rapid silencing and reactivation. (C) Duration-dependent fractional control of long-term (irreversible) silencing.