Enhancer activity: The indirect chromatin modulation that reshapes gene expression

Written by The Life Science Feed Editorial Team · Published 27 July 2026 · Edited by Mara Voss

The precise control of gene expression dictates cellular function and differentiation, a process often initiated by enhancers. These regulatory elements, once activated, are known to directly influence their target genes. But the full scope of their influence, particularly on genes not immediately adjacent, has remained a subject of mechanistic inquiry, challenging the conventional understanding of transcriptional regulation. A deeper understanding of these indirect effects could reshape our approach to diseases driven by aberrant gene expression.

New insights into this intricate regulatory dance come from research published in eLife, which explored how ligand-dependent enhancer activation can indirectly modulate non-target promoters within a shared chromatin domain. This work delineates a mechanism where enhancer activity extends beyond direct gene activation, influencing a broader transcriptional landscape through chromatin remodeling.

KEY TAKEAWAYS

- The Pivot: Enhancer activation does not solely act on direct target genes; it also indirectly modulates non-target promoters within the same chromatin domain.
- The Data: Indirect modulation of non-target promoters occurred via changes in chromatin accessibility and histone modifications, specifically H3K27ac.
- The Action: Clinicians should consider the broader, indirect effects of transcriptional modulators, as therapeutic interventions targeting specific enhancers may have unforeseen systemic impacts on gene expression.

Gene regulation is a hierarchical process, with enhancers playing a critical role in dictating when and where genes are expressed. These short DNA sequences, often located far from the genes they regulate, recruit transcription factors and coactivators to boost gene transcription. The prevailing model posits a direct interaction, where an activated enhancer physically loops to its target promoter, facilitating RNA polymerase recruitment and subsequent gene transcription. This direct interaction is well-established, but the possibility of more diffuse, indirect effects within the larger chromatin architecture has been less thoroughly explored. Understanding these broader regulatory networks is essential for developing targeted therapies that avoid off-target effects.

The investigation focused on understanding the spatial and temporal dynamics of enhancer-promoter interactions, particularly how a ligand-activated enhancer might influence genes beyond its immediate, canonical target. Researchers employed a combination of molecular biology techniques, including chromatin immunoprecipitation sequencing

(ChIP-seq), RNA sequencing (RNA-seq), and chromosome conformation capture (3C) assays, to map these interactions. The study utilized specific cellular models where enhancer activation could be precisely controlled through ligand binding, allowing for a clear observation of downstream effects on gene expression and chromatin state. The goal was to dissect the mechanisms by which a localized signal (ligand binding to an enhancer) could propagate its influence across a larger genomic region.

Unpacking the Enhancer's Reach

The initial observations confirmed that ligand-dependent enhancer activation indeed led to the expected upregulation of its direct target gene. This direct effect involved the recruitment of specific transcription factors and coactivators to the enhancer, followed by the formation of a chromatin loop that brought the enhancer into close proximity with the target gene's promoter. This is the canonical pathway, a well-understood mechanism of gene activation. But the researchers also noted changes in the expression of several other genes located within the same topologically associating domain (TAD) as the activated enhancer, but not directly interacting with it. These non-target genes showed altered expression patterns, some upregulated, others downregulated, suggesting a more complex regulatory landscape than previously assumed. The changes in expression for these non-target genes were less pronounced than for the direct target, but consistently observed across replicates.

To investigate these indirect effects, the team performed detailed chromatin analyses. They found that the activation of a specific enhancer, in response to its cognate ligand, induced changes in the chromatin landscape across the entire local domain. Specifically, there was an increase in histone H3 lysine 27 acetylation (H3K27ac) marks not only at the activated enhancer and its direct target promoter but also at the promoters of several non-target genes within the same TAD. H3K27ac is a well-established marker of active enhancers and promoters, indicating an open and transcriptionally permissive chromatin state. This widespread increase in H3K27ac suggested a global shift in chromatin accessibility within the domain, rather than just localized changes at the direct interaction sites. The magnitude of H3K27ac enrichment at non-target promoters was typically 2-fold to 3-fold lower than at the direct target, but still statistically significant ($p<.01$).

The researchers then explored the implications of these chromatin modifications for gene expression. RNA-seq data confirmed that genes within the affected chromatin domain, even those without direct enhancer contact, exhibited altered transcriptional profiles. Some non-target genes showed a modest but consistent increase in expression, while others displayed a subtle decrease. This bidirectional modulation suggests that the indirect effects are not simply a uniform upregulation but a more finely tuned adjustment of gene activity. The average fold change for indirectly modulated genes ranged from 1.2-fold to 1.8-fold, compared to a 5-fold to 10-fold increase for the direct target gene. These smaller changes, while not as dramatic as direct activation, could still have cumulative biological consequences over time, particularly in processes requiring precise gene dosage.

The Mechanism of Indirect Influence

The mechanism underlying this indirect modulation appears to involve a global relaxation of chromatin structure within the TAD. When the enhancer is activated, it recruits chromatin remodeling complexes and histone acetyltransferases (HATs) to its immediate vicinity. These enzymes not only act locally but also appear to spread their activity, albeit to a lesser extent, across the entire chromatin domain. This spreading leads to a more open chromatin conformation, making

the DNA more accessible to transcription factors and RNA polymerase at other promoters within the domain, even those not directly looped to the enhancer. The study used DNase I hypersensitivity assays to confirm increased chromatin accessibility across the domain, with an average 1.5-fold increase in hypersensitive sites at non-target promoters ($p<.005$).

But the influence is not purely permissive. The study also identified instances where non-target gene expression was downregulated. This suggests that while chromatin opening might generally facilitate transcription, the specific combination of transcription factors present at each non-target promoter, coupled with the altered chromatin environment, ultimately dictates the final transcriptional output. It is a complex interplay of accessibility and specific factor binding. The precise mechanisms for downregulation remain less clear, but could involve competition for limiting transcription factors or the induction of repressive chromatin marks at specific sites as a secondary effect.

The implications of these findings extend beyond basic molecular biology. Many therapeutic strategies aim to modulate gene expression by targeting specific transcription factors or epigenetic modifiers. If enhancer activation can indirectly influence a broader set of genes within a chromatin domain, then interventions designed to activate or repress a single gene might have unintended consequences on a network of other genes. This highlights the need for a holistic view of gene regulation when designing drugs that interact with the epigenome or transcriptional machinery. For instance, a drug intended to upregulate a tumor suppressor gene might inadvertently alter the expression of other genes critical for cellular homeostasis, leading to off-target effects. Understanding these domain-wide effects is crucial for predicting and mitigating such outcomes.

Where the Data Falls Short

While the study provides compelling evidence for indirect enhancer modulation, it relies heavily on in vitro cellular models. The complexity of chromatin organization and gene regulation in a living organism, with its myriad cell types and dynamic environmental cues, is far greater than what can be replicated in a cell culture dish. Whether these domain-wide indirect effects manifest with the same magnitude and consistency in vivo remains an open question. The specific cell lines used may also exhibit unique chromatin architectures or regulatory factor expression profiles that are not universally applicable. Future research will need to validate these findings in more complex biological systems, including animal models and primary human tissues, to confirm their physiological relevance. The current data provides a mechanistic foundation, but the clinical translation requires further validation.

The resolution of the chromatin conformation capture techniques, while advanced, still provides an averaged view of interactions across a population of cells. Single-cell approaches might reveal greater heterogeneity in enhancer-promoter dynamics and indirect modulation, potentially uncovering cell-specific regulatory patterns that are masked in bulk analyses. The study also focused on a limited number of enhancers and their associated domains. A more comprehensive analysis across the entire genome, encompassing a wider variety of enhancer types and cellular contexts, would be necessary to establish the universality of this indirect modulation phenomenon. The specific ligands and transcription factors investigated represent only a fraction of the vast regulatory machinery at play in human cells. Still, the mechanistic insights gained here provide a valuable framework for future, broader investigations into the epigenome and its regulatory reach.

CLINICAL IMPLICATIONS

The notion that enhancer activation can indirectly modulate non-target promoters within a chromatin domain adds a layer of complexity to our understanding of gene regulation. Clinicians often consider therapies that target specific gene pathways, but this research suggests that such interventions might have broader, less predictable effects on the transcriptome. A drug designed to activate a particular gene via its enhancer could inadvertently alter the expression of other genes in the same domain, leading to unforeseen therapeutic benefits or, more concerningly, off-target toxicities.

This expanded view of enhancer function demands a more comprehensive assessment of transcriptional modulators in drug development. Pharmaceutical companies developing epigenetic drugs or transcription factor modulators must now consider not just the direct targets, but the entire chromatin domain's response. This could necessitate broader genomic profiling in preclinical and clinical trials to identify and characterize these indirect effects, moving beyond single-gene expression analysis to a more systems-level approach.

For patients, this means that therapies aimed at correcting a specific gene dysregulation might come with a wider array of effects, some beneficial, others potentially detrimental. Understanding these indirect modulations could help explain variability in patient responses to targeted therapies. It underscores the need for personalized medicine approaches that account for individual chromatin landscapes and the unique regulatory networks within a patient's cells, rather than assuming a uniform response to a given intervention.

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