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► **To cite this version:**

Salvatore Spicuglia, Alvaro Rada-Iglesias. Understanding enhancer function to understand human disease. 2023, 10.1002/bies.202300149 . hal-04288514

HAL Id: hal-04288514

<https://amu.hal.science/hal-04288514>

Submitted on 16 Nov 2023

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Editorial

Understanding enhancer function to understand human disease

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In multicellular organisms, spatial and temporal regulation of gene expression is crucial for development, cellular differentiation, and homeostasis. Cell-type-specific regulation of gene expression is achieved through the interaction between regulatory elements that are either proximal (promoters) or distal (enhancers, silencers, insulators) to gene transcription start sites (TSSs). Enhancers, which primarily function in a cell type-specific manner, are short (100-1000 bp) DNA sequences that contain binding sites for transcription factors and increase the expression of their target genes in *cis*. Four decades after their first discovery, enhancers are now widely considered key elements in the spatiotemporal control of gene expression underlying human development and homeostasis. Furthermore, enhancers play a significant role in disease, evolution, and phenotypic diversity. From a medical point of view, accumulating evidence indicate that a wide spectrum of human disorders, known as enhanceropathies, are influenced by enhancer malfunction caused by genetic, structural, or epigenetic alterations. These processes can directly cause cancer or Mendelian disorders, while they can also underpin the susceptibility to many common diseases. Despite recent advances in our understanding of enhancer biology and function, our capacity to foresee how enhancer dysfunction affects gene expression and, thus, human disease, is still limited. Therefore, elucidating the molecular basis of enhancer function in healthy and disease states has far-reaching translational implications, as it can help improving the diagnosis and therapeutic intervention of a broad range of human disorders.

Despite their functional and medical relevance, there are fundamental questions about enhancers that remain unsolved: (i) what is an enhancer?; (ii) how does an enhancer control gene expression?; (ii) how do enhancers specifically control the expression of their target

genes?; (iv) what are the different pathomechanisms whereby enhancers can contribute to human disease?. In this focus issue of BioEssays, several experts in the fields of functional genomics, medical genetics, and bioinformatics, discuss these important issues, which need to be addressed to fully understand the role of enhancer dysfunction in disease.

What is an enhancer and how it controls gene expression? Enhancers can be defined in different ways depending on the methods used to identify them. On the one hand, operational definitions are based either on the ability of a given region to enhance transcription in a reporter assay or to harbor biochemical marks associated with enhancer activity. On the other hand, the biological definition requires that a distally-located DNA sequence regulates the transcription of a *cis*-located gene, in its native *in vivo* context. Although there is a fair overlap between these assays, operational-defined enhancers are not necessarily functioning in their endogenous context and *vice versa*. In a “Problems & Paradigms” essay Thomas and Buecker discuss the different types of enhancers and the methods to identify them (<https://doi.org/10.1002/bies.202300044>). Higgs and colleagues illustrate how the detailed characterization of the enhancers involved in the regulation of the α -globin gene cluster, a model locus involved in α -thalassemia, has provided important lessons about the molecular basis of enhancer function (<https://doi.org/10.1002/bies.202300047>).

How do enhancers specifically control the expression of their target genes? It is often assumed that distal enhancers have to come into physical proximity to their target gene in order to function. However, not all enhancers seem to establish physical contact with their target genes and, thus, alternative regulatory mechanisms might also exist. Furthermore, enhancers and their target genes often occupy the same regulatory domains, which enables specific enhancer-gene communication and the establishment of appropriate gene expression programs. Thus, a major challenge is to understand the mechanisms controlling the interplay between enhancers and other regulatory elements, including promoters and insulators, and how the joint activity of a regulatory domain is influenced by disruptions of individual enhancers. Two essays of this focus issue discuss the role of the nuclear organization in the control of gene expression. Plewczynski and collaborators review the role of the cohesin complex in the regulation of higher-order chromatin structure, as well, as the experimental and bioinformatic methods to assess the 3D organization of the genome (<https://doi.org/10.1002/bies.202200240>). Zippo and collaborators describe how by studying proteins mutated in a group of rare Mendelian diseases known as chromatinopathies, it is possible to gain important insights into the role of

chromatin condensates and the genome's spatial organization in enhancer function and human disease (<https://doi.org/10.1002/bies.202300075>).

Which are the different pathomechanisms whereby enhancers can contribute to human disease? As mentioned above, enhancer dysfunction has emerged as a central mechanism in the pathogenesis of certain diseases. In particular, point mutations or structural variants that affect enhancer function can lead to pathological changes in gene expression that are directly involved in the etiology of several human cancers and Mendelian diseases. Moreover, the large majority of genetic variants associated with common diseases are found within *cis*-regulatory elements, including enhancers. In this context, genetic variation at Epromoters, a new type of *cis*-regulatory element harboring both promoter and enhancer functions, are thought to play pleiotropic roles in disease by regulating proximal and distal genes at the same time, as suggested by Spicuglia and colleagues in a “Hypothesis” article (<https://doi.org/10.1002/bies.202300012>). Depending on the nature of the genetic alteration, enhancer dysfunction can be classified into two main types. The first type involves small single nucleotide variants (SNVs) and indels in the enhancer sequence that lead to changes in enhancer activity. Such variations can for instance alter the affinity of bound TFs or create new binding sites. The second type involves structural variants that lead to deletion, duplication, or relocation of the entire enhancer, which impacts chromatin topology and enhancer function. In a “Review essay”, Allou and Mundlos discuss the various mechanisms by which structural variants result in altered gene regulation or gene-intergenic fusion transcripts and how these mechanisms are involved in the etiology of rare genetic disorders (<https://doi.org/10.1002/bies.202300010>). Chromosomal rearrangements can lead to the rewiring of enhancer-gene connections, which may involve both enhancer adoption/hijacking (gain-of-function) and enhancer disconnection (loss-of-function). Rico and collaborators discuss how enhancer hijacking results in the formation of broad H3K4me3 domains, a chromatin signature associated with the expression of cell-type-specific genes in healthy cells as well as with the ectopic expression of oncogenes in cancer cells (<https://doi.org/10.1002/bies.202200239>). Last but not least, it is important to consider that, in addition to genetic and epigenetic alterations, environmental factors also contribute to the etiology of human disease. In this regard, in their “Ideas & Speculations” article, Robert and Rada-Iglesias discuss how the effects of certain non-coding genetic variants affecting enhancer function might be only or preferentially manifested under certain environmental conditions (<https://doi.org/10.1002/bies.202300038>).

We hope that the articles in this focus issue will assist the readers in a better understanding of enhancer function and its involvement in human disease.

Funding information

The preparation of the special issue has been done with the support of the “Enhpathy” Marie Skłodowska-Curie actions (MSCA) - Innovative Training Network (ITN) funded by the European Union’s Horizon 2020 research and innovation program (Grant Number: 860002).