The hierarchy of transcriptional activation: from enhancer to promoter

Disturbance of gene expression underlies many diseases. Deciphering how genes are normally switched on and off in healthy cells during development and cell differentiation is helping to shed light on the molecular basis of diseases such as anaemia.

Gene expression is often under the control of regulatory DNA sequences called “enhancers” or “silencers”, depending on their activities, which can be located in a chromosome far away from the gene that they regulate. These regulatory regions of an individual’s genetic code are in turn controlled by interactions with proteins called “transcription factors” which determine whether a gene is switched on or off.

Remote control of long and short distance delivery
(Clip arts from Noun Project. Authors: Mike Ashley, Nicholas Menghini, Drue McCurdy, Irene Hoffman, Ryan Mather, Alex Auda Samora, Michal Beno, Rflor)

In a recently published review in Trends in Genetics, Doug Vernimmen and Wendy Bickmore explain how enhancer sequences control the expression of genes during development and differentiation. Enhancers have a key role in recruiting and increasing the amount of enzymes required for the transcription of a target gene. These enhancers may be local or remote and the mechanisms on how these DNA sequences communicate are now emerging. The authors argue that the mechanism involved in enhancer-target gene interaction may depend on the physical distance separating them.

To use an analogy, this can be compared with a delivery system (see Figure). Enhancers are stores (warehouses) and effectors dealing with orders planning the delivery of a parcel (a specialized transcription factor, an enzyme) to the appropriate address (target gene). Depending on the delivery address, the parcels can be shipped by plane, by van or in person. For large distances, it is more convenient to use a plane whereas for modest distances, a van would be used (warehouse 1). Once the parcel has arrived to the local store (warehouse 2), it can be delivered by hand. Scientists now have molecular/pharmacological tools that allow them to test the transport method being used for that delivery. For example, they can use so-called terminators to ‘block’ the road and if the parcel doesn’t arrive at its destination, they can conclude that a van was used, not a plane.

Understanding these delivery paths is important for the understanding of the molecular basis of genetic diseases. Indeed if one path is defective in a disease, an alternative route could be used to ensure the parcel reaches its destination.

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