DNA structure influences the function of transcription factors

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A depiction of the double helical structure of DNA. Its four coding units (A, T, C, G) are color-coded in pink, orange, purple and yellow. Credit: NHGRI

Substances known as transcription factors often determine how a cell develops as well as which proteins it produces and in what quantities. Transcription factors bind to a section of DNA and control how strongly a gene in that section is activated. Scientists had previously assumed that gene activity is controlled by the binding strength and the proximity of the binding site to the gene. Researchers at the Max Planck Institute for Molecular Genetics in Berlin have now discovered that the DNA segment to which a transcription factor binds can assume various spatial arrangements. As a result, it alters the structure of the transcription factor itself and controls its activity. Neighbouring DNA segments have a significant impact on transcription factor shape, thus modulating the activity of the gene.

For a car to move, it is not enough for a person to sit in the driver's seat: the driver has to start the engine, press on the accelerator and engage the transmission. Things work similarly in the cells of our body. Until recently, scientists had suspected that certain proteins only bind to specific sites on the DNA strand, directing the cell's fate in the process. The closer and more tightly they bind to a gene on the DNA, the more active the gene was thought to be. These proteins, known as transcription factors, control the activity of genes.

A team of scientists headed by Sebastiaan Meijsing at the Max Planck Institute for Molecular Genetics have now come to a different conclusion: The researchers discovered that transcription factors can assume various shapes depending on which DNA segment they bind to. "The shape of the bond, in turn, influences whether and how strongly a gene is activated," Meijsing explains.

Consequently, transcription factors can bind to DNA segments without affecting a nearby gene. As in our car analogy, the mere presence of a "driver" is evidently not sufficient to set the mechanism in train. Other factors must also be involved in determining how strongly a transcription

factor activates a gene.

Glucocorticoid receptor is also a transcription factor

One example is glucose production in the liver. If the blood contains too little glucose, the adrenal glands release glucocorticoids, which act as chemical messengers. These hormones circulate through the body and bind to glucocorticoid receptors on liver cells. The receptors simultaneously act as transcription factors and regulate gene activity in the cells. In this way, the liver is able to produce more glucose, and the blood sugar level rises again.

"Sometimes glucocorticoid receptor binding results in strong activation of neighbouring genes, whereas at other times little if anything changes," Meijsing reports. The scientists found that the composition of DNA segments to which the receptors bind help determine how strongly a gene is activated. However, these segments are not in direct contact with the receptors acting as transcription factors; they only flank the binding sites. Yet, that is evidently enough to have a significant influence on the interaction.

"The structure of the interface between the transcription factor and genome segments must therefore play a key role in determining gene activity. In addition, adjacent DNA segments influence the activity of the bound transcription factors. These mechanisms ultimately ensure that liver cells produce the right substances in the right amounts," Meijsing says.

Medical applications

The findings could also have medical applications. Many DNA variants associated with diseases belong to sequences that evidently control the

activity of transcription factors. "Scientists had previously assumed that these segments exert an effect by inhibiting the binding of transcription factors, thus impeding the activity of neighbouring genes," Meijsing says. "Our findings have now shown that some of these segments may not influence the contact directly but nevertheless reduce the activation state of the associated transcription factor."

More information: Stefanie Schöne et al, Sequences flanking the core-binding site modulate glucocorticoid receptor structure and activity, *Nature Communications* (2016). DOI: 10.1038/ncomms12621

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