How context-specific factors control gene activity

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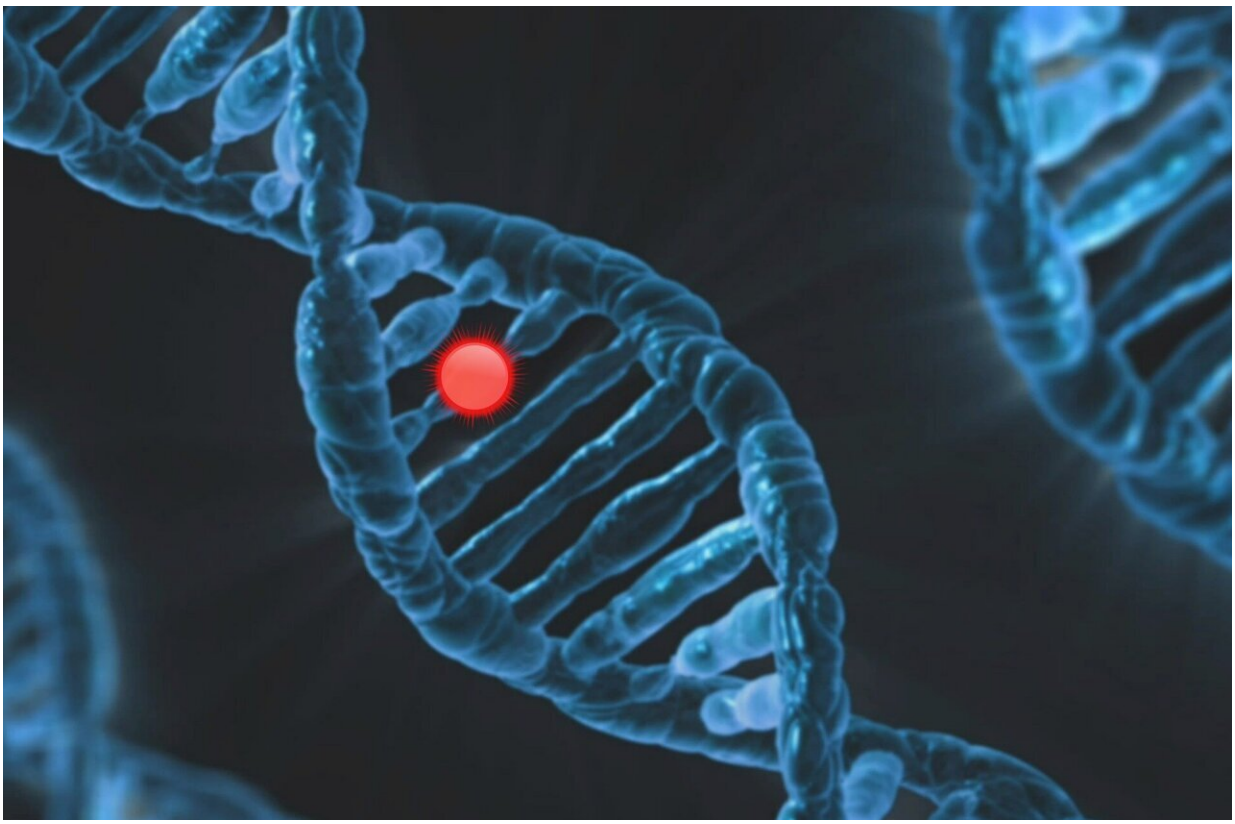

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Every cell in our body contains the same DNA, yet liver cells are different from brain cells, and skin cells differ from muscle cells. What determines these differences? It all comes down to gene regulation;

essentially how and when genes are turned on and off to meet the cell's demands. But gene regulation is quite complex, especially because it is itself regulated by other parts of DNA.

There are two important components that control gene regulation: the first are enhancers, which are short bits of DNA that increase the likelihood that a gene will be activated—even if that gene is far away from the enhancer on the genome.

The second are specialized proteins, generally referred to as "transcription factors" (TFs), which bind to enhancers and, put crudely, control gene expression by "flipping" the genes' on/off switches. TFs come in many different varieties, with current studies estimating over 1600 of them in the human genome alone.

Enhancer 'motifs'

Despite the critical role of enhancers and TFs, scientists have struggled to understand the details of how they interact. Traditional approaches focus on what geneticists refer to as DNA "motifs": specific sequences, or patterns, of DNA that can be found across different parts of the genome, like a recognizable musical motif that appears in different parts of a symphony.

The current strategy is to find motifs within enhancers that are recognized by particularly potent TFs. However, it has so far failed to explain the complexity of gene regulation.

It seems that finding these individual motifs is not enough; the overall "enhancer context" in which these motifs are embedded also matters. This has led to a search for new methods to better understand how multiple TFs cooperate at enhancers to tune gene expression.

A new approach

A team of scientists at the group of Bart Deplancke at EPFL has now developed a new approach for studying the interplay between enhancers and TFs. They identified a new type of "context-only" TFs—proteins that seem to boost the activity of those TFs that establish cellular identity (e.g., liver, blood, or brain cell).

The research was led by Judith Kribelbauer, and provides a new understanding of the cooperative environments that TFs create to regulate genes effectively. It is published in *Nature Genetics*.

The researchers used data from a type of genetic analysis called "chromatin accessibility quantitative trait loci (caQTL) mapping." caQTLs are population-specific variations in DNA sequences that influence how accessible a region of the genome will be to gene regulators such as TFs, which in turn influences gene expression.

Focusing on enhancers that contain caQTLs, the team assessed the motif location of different TFs. This led to the discovery of 'context-only' TFs, a name that reflects the fact that these DNA motifs are found close to the caQTL within the respective enhancer.

"The existence of 'context-only' TFs surprised us, as previous studies that looked into how DNA variation affects gene regulation focused on TFs that are directly affected by the caQTL," says Kribelbauer.

"Naturally, we were curious about what exactly these TFs do in the context of caQTLs, and whether they may play a role in deciding which of the numerous DNA mutations in our genomes affect gene regulation."

The study found that context-only TFs, which do not directly initiate gene activity, are nonetheless crucial in enhancing the effects of the

caQTL-linked TFs that initiate changes in enhancer status—basically, they help create a cooperative environment which is more efficient for the regulation of important genes.

The team also discovered that context-only TFs do not need to be in direct proximity to the TFs they enhance, which suggests that they work through a more flexible and dynamic collaborative mechanism than previously thought.

Another important finding was that context-only TFs may contribute to the formation of regulatory factor clusters, which are essential for maintaining cell identity. These clusters can form complex networks of enhancers that work together to regulate gene expression, making the process highly adaptable to different cellular needs.

By uncovering the role of context-only TFs, scientists can now have a better understanding of how genes are regulated in health and disease and how this regulation goes awry, for example, as a result of DNA mutations often present in complex diseases like cancer.

The study also provides a framework for inferring how different TFs cooperate in various cellular contexts, which could lead to more targeted and effective genetic therapies, for example through synthetic enhancer design.

More information: Context transcription factors establish cooperative environments and mediate enhancer communication. *Nature Genetics*(2024). DOI: 10.1038/s41588-024-01892-7 , www.nature.com/articles/s41588-024-01892-7 . On *bioRxiv*: DOI: 10.1101/2023.05.05.539543

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