How cells in developing embryos change the way they use enhancers to regulate gene expression

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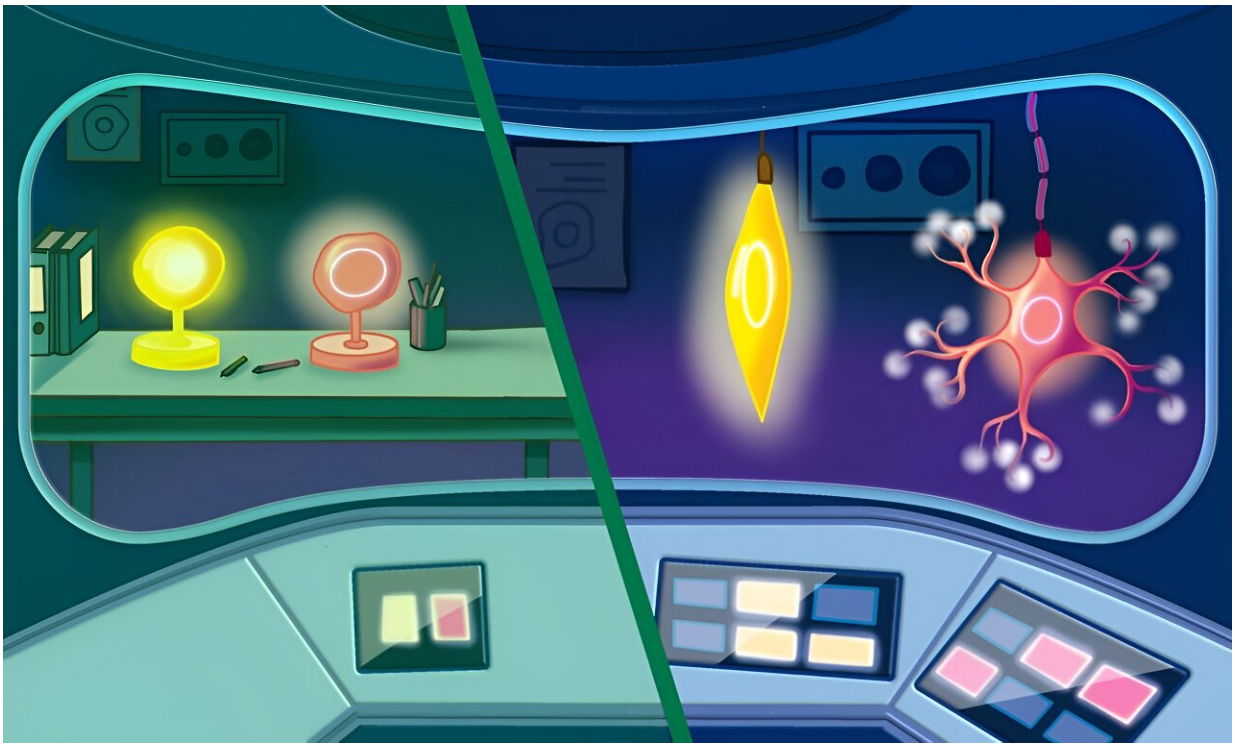

As cells mature and differentiate (right), they use a much more elaborate and cell-type specific 'switchboard' to control their gene expression, especially when compared to earlier, immature stages (left). Credit: Isabel Romero Calvo/EMBL

If you look at a nerve cell, a muscle cell, or a skin cell under the microscope, they appear strikingly different. However, every cell in our body has the same DNA and has descended from a common ancestorâ€"the fertilized egg cell. The diversity we observe arises due to differentiationâ€"a process during development where cells mature into their final functional forms.

New research from the Furlong group at EMBL Heidelberg has identified a shift in how genes are regulated by DNA control regions called enhancers during the differentiation process, as cells go from the specified precursor stages (e.g., myoblasts) to more mature, functional forms (e.g., muscle). The study was recently published in *Nature Genetics*.

The Furlong group studies the fundamental principles that drive genome regulation during embryonic development. One of their main areas of focus is enhancersâ€"DNA control regions that regulate gene expression, often despite being located a long way (in DNA terms) from the genes they control. In this, enhancers are like light switches that can turn genes "on" or "off" from a distance.

"Once considered to be part of the 'junk' non-coding DNA that makes up about 97% of our genomes, enhancers are now understood to be critical for cellular function and development. However, more than 40 years after their discovery, there's still a lot we don't understand about how they function," said Eileen Furlong, Group Leader and Head of the Genome Biology Unit at EMBL Heidelberg.

Scientists currently believe that enhancers convey information to the genes they regulate as part of large DNA loops or hubs. This allows the enhancers to physically interact with "promoters"â€"regulatory

DNA regions located at the beginning of genes. In one of the largest studies of its kind during embryonic development, Furlong and her team recently examined nearly 600 enhancers and promoters in developing nerve and muscle cells in the fruit fly embryo to determine how enhancer-promoter interactions are related to when they regulate gene expression.

Previous studies in the field had shown two distinct modes of regulation. In some cases, enhancer-promoter interactions only happened when the gene was expressed, so the physical proximity between the two directly affected gene expression. This is known as an "instructive" mode of regulation. But in other contexts, scientists observed that enhancers begin interacting with a gene's promoter hours before the gene is expressed. This, known as a "permissive" mode of regulation, allows a gene to be ready for activation long before it is expressed.

"It wasn't clear why one form of regulation was found in some contexts, while a different one was reported in another," said Tim Pollex, Research Staff Scientist at EMBL and the first author of this study. "Our study directly addressed this conundrum, and we show that both types of regulation co-exist during embryogenesis. Developmental stage is the key to determining which is the more dominant mode of regulation."

In their study, the researchers examined when hundreds of enhancers interact with their gene's promoter during both muscle and neuronal development in fruit fly embryos, specifically during the times when gene expression is switched on or off.

The scientists first looked at the stages when cells are specified, i.e., when the embryo determines which cells will form which cell types. At this stage, when the cells are not yet in their mature, differentiated forms, the researchers found that the way in which many developmental enhancers or gene promoters interact is strikingly similar between a

future nerve cell or a future muscle cell (analogous to a shared control system, as shown in the left side of the illustration above).

At this point, enhancers and promoters function within these "permissive" environments to regulate which genes are switched on or off. The scientists speculate that this might allow gene expression patterns to undergo rapid changes. It may also help the cells to be much more flexible, and even change their fate if necessary.

However, once the embryo develops further and these cells differentiate to their final formâ€"a more mature nerve or muscle cell, enhancer-promoter interactions become more diverse, complex and long-range. They also only emerge when and where a gene is expressed, being "instructive" rather than "pre-formed" or permissive. Additionally, in differentiated neurons and muscles, enhancer-promoter interactions become distinct for neuronal or muscle-specific genes (more complex and tissue-specific control systems, as shown on the right side of the illustration above).

"A complementary study from Evgeny Kvon's lab at UC Irvine, examined the relationship between enhancer-promoter activity in differentiated mouse tissues and came to a similar conclusion," said Furlong.

"They show that in differentiated tissues, enhancer-promoter interactions are different between different tissues and that they occur at the time of gene expression. Such instructive enhancer-promoter regulation therefore appears to be an ancient feature of tissue differentiation ensuring the development of tissues with distinct functions."

More information: Tim Pollex et al, Enhancer–promoter interactions

become more instructive in the transition from cell-fate specification to tissue differentiation, *Nature Genetics* (2024). DOI: 10.1038/s41588-024-01678-x