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Super-powered switches may decide cell fate

Long chunks of DNA improve efficiency of gene activators.

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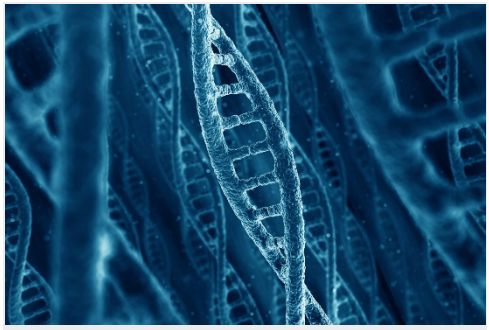
Cancer cells, stem cells, muscle cells and more may owe their unique identities to powerful gene-regulating structures called super-enhancers, two studies suggest. These structures are long stretches of DNA to which many proteins attach, souping up activity of the genes that they are near.



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The discovery of super-enhancers follows studies on cancers that are fuelled by an over-active *MYC* gene.

Different cell types in the body contain the same genetic information but have different genes activated. Short stretches of DNA in the genome called enhancers act like switches for these genes, flipping them 'on' when certain proteins attach to them. Two studies published in *Cell* now show that enhancers become even more powerful when many of them join together[1,2]. Richard Young, a cancer researcher at the Whitehead Institute in Cambridge, Massachusetts, and senior author of both papers, has dubbed these giant groupings super-enhancers.

In the study led by Jakob Lovén at the Whitehead Institute the team looked at cancer cells that owe their out-of-control growth to a notorious gene named *MYC*[1]. They found that super-enhancers had formed within the cells near the *MYC* gene, and that the structures catalysed high production of MYC protein. They also found that the super-enhancers could easily be perturbed, causing MYC protein levels to plummet. The Whitehead Institute's Warren Whyte and his colleagues then went on to show that ordinary, healthy cells also seem to depend on super-enhancers[2].

Bigger is better

Young says that the fragility of the super-enhancers means that scientists may have a fruitful new way to study cancers. Rather than designing drugs that block MYC — a technique that has thus far been unsuccessful — he suggests that investigators try to hinder the super-enhancer complex that brings *MYC* to power. (Young is a founder and director of Syros Pharmaceuticals, a new company in Cambridge, Massachusetts, that has announced a US$30-million venture-capital investment aimed at developing new cancer drugs, perhaps based on super-enhancers.)

Young's teams discovered super-enhancers while pursuing a conundrum. Back in 2011, scientists had reported that blocking a protein called Brd4 in mice with leukaemia would cause the amounts of Myc protein in cancer cells to diminish sharply and stop the cancer cells from proliferating[3]. But Brd4 is known to help activate enhancers in both healthy and cancerous cells, so how could the Brd4 inhibitors be leaving normal cells unscathed? "I thought, maybe BRD4 does something special to *MYC* that it does not do to other genes," says Young.

Lovén and his colleagues showed that BRD4 was in fact binding to an abnormally long stretch of DNA. Enhancers are usually about 500 base pairs in length — but BRD4 was binding to a stretch of 40,000 base pairs near the *MYC* gene.

Whyte and his colleagues then went on to show that super-enhancers might also be at work in healthy, non-cancerous cells. They found that genes known to be key to keeping stem cells pluripotent — able to develop into many different types of cell — are controlled by super-enhancer DNA sequences. Super-enhancer DNA sequences also control the genes that make muscle proteins[2].

Last year, a multicentre effort called the Encyclopedia of DNA Elements (ENCODE) reported that it had identified about a million enhancer switches in the human genome. Based on his teams' findings, Young speculates that some of these enhancers act not on their own, but clustered together into large groups. The location and identity of these super-enhancers would differ according to the type of cell, so that the genes that give each cell type its unique identity (such as *MYC* in a cancer cell) are activated appropriately. "This looks like a very cool biological phenomenon in which a cluster of enhancers seem to function as a unit," says John Stamatoyannopoulos, a cancer researcher at the University of Washington in Seattle and a lead investigator on the ENCODE project.

Young predicts that learning more about the super-enhancers operating in each cell type will be key to manipulating gene expression within cells without too many side effects, just as was the case for BRD4 and *MYC* in mice. It would also mean that rather than exploring some 10,000 enhancers operating in a cell, researchers might be able to focus on super-enhancers, the masterminds running the show.

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References

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