Light-activated genes might be precisely controlled and targeted

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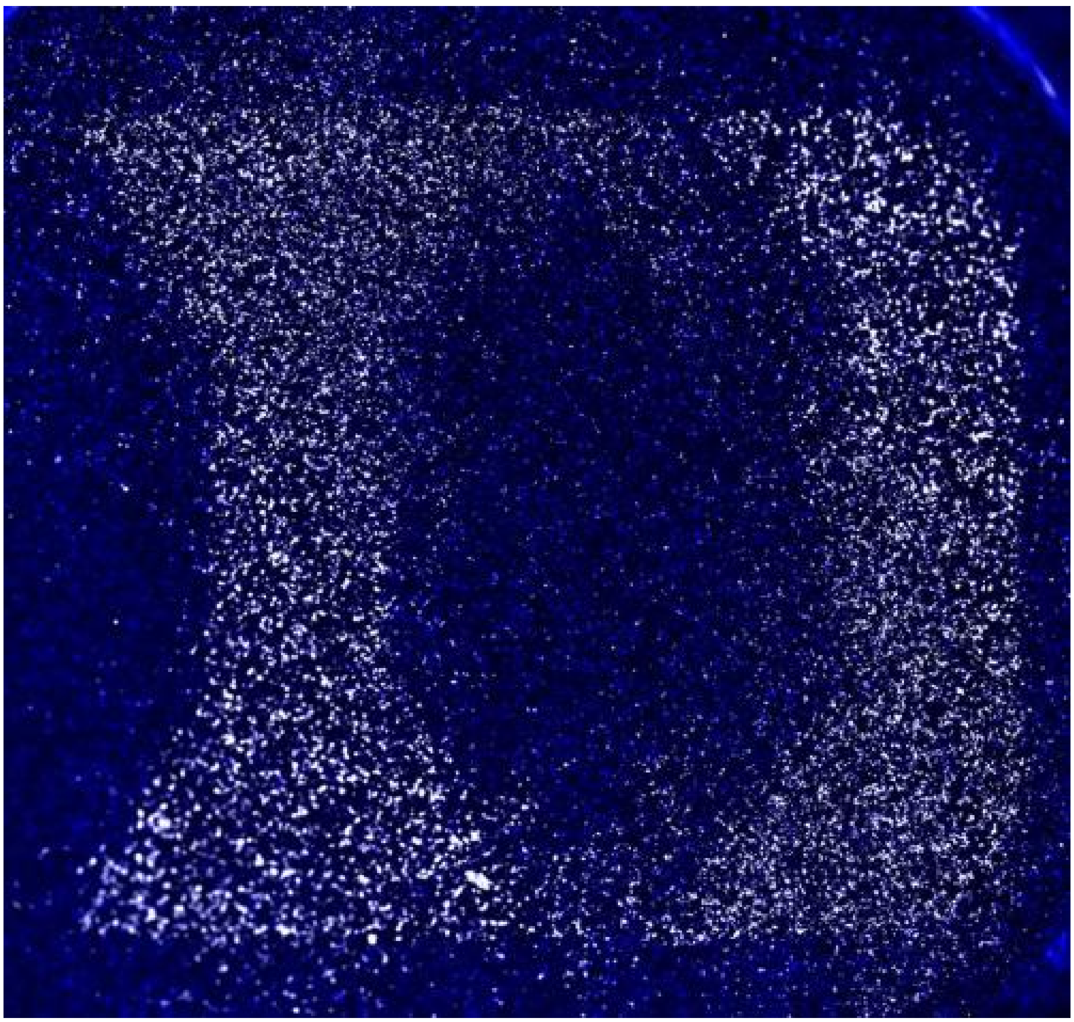

Light-activated genetic manipulation is demonstrated by shining light through a stencil to turn on fluorescent genes in cells. Credit: Charles Gersbach, Duke University

Duke University researchers have devised a method to activate genes in any specific location or pattern in a lab dish with the flip of a light switch by crossing a bacterium's viral defense system with a flower's response to sunlight.

With the ability to use light to activate genes in specific locations, researchers can better study genes' functions, create complex systems for growing tissue, and perhaps eventually realize science-fiction-like healing technologies.

The study was led by Charles Gersbach, assistant professor of biomedical engineering at Duke University, and published on February 9 in *Nature Chemical Biology*.

"This technology should allow a scientist to pick any gene on any chromosome and turn it on or off with light, which has the potential to transform what can be done with genetic engineering" said Lauren Polstein, a Duke PhD student and lead author on the work. "The advantage of doing this with light is we can quickly and easily control when the gene gets turned on or off and the level to which it is activated by varying the light's intensity. We can also target where the gene gets turned on by shining the light in specific patterns, for example by passing the light through a stencil."

The new technique targets specific genes using an emerging genetic engineering system called CRISPR/Cas9. Discovered as the system bacteria use to identify viral invaders and slice up their DNA, the system was co-opted by researchers to precisely target specific genetic sequences.

The Duke scientists then turned to another branch of the evolutionary tree to make the system light-activated.

In many plants, two proteins lock together in the presence of light, allowing plants to sense the length of day which determines biological functions like flowering. By attaching the CRISPR/Cas9 system to one of these proteins and gene-activating proteins to the other, the team was able to turn several different genes on or off just by shining blue light on the cells.

"The light-sensitive interacting proteins exist independently in plants," explained Gersbach. "What we've done is attached the CRISPR and the activator to each of them. This builds on similar systems developed by us and others, but because we're now using CRISPR to target particular genes, it's easier, faster and cheaper than other technologies."

Gersbach envisions a wide range of potential applications for the new light-activated, gene-regulating system.

Researchers could tightly and precisely control the level of a gene's activity from its natural position in the chromosomal DNA, which would allow them to get a more accurate interpretation of the gene's role. The light-induced system could also provide more control over how stem cell cultures differentiate into various types of tissues. And by creating different patterns of gene expression, Gersbach hopes the system can be used in tissue engineering.

"One of the limitations of tissue engineering right now is that typical methods make a chunk of bone, cartilage or muscle, but that's not what tissues look like naturally," said Gersbach. "There are several cell types mixed together, gradients of tissues between interfaces, and blood vessels and neurons that penetrate through them. We want to spatially control where different tissues get made in a cell population, and that way create multi-tissue constructs that potentially better represent normal physiology."

And then there's a more futuristic idea of how light-induced genetic engineering could be applied.

"It's possible to illuminate cells through the skin and control what they're doing, like growing blood vessels or regenerating tissues," said Gersbach. "Far, far down the road, you could envision the type of device you'd see on Star Trek where you wave a flashlight over a wound and it heals. Obviously that's not currently possible, but this type of technology that creates much better control over biological systems could move us in that direction."

More information: "A light-inducible CRISPR-Cas9 system for control of endogenous gene activation," Lauren R Polstein, Charles A Gersbach. *Nature Chemical Biology*, February 9, 2015. DOI: 10.1038/nchembio.1753

Provided by Duke University