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Optogenetic technology developed at UMMS uses light to trigger immunotherapy

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A new optogenetic technology developed by scientists at the University of Massachusetts Medical School and Texas A&M Health Science Center Institute of Biosciences & Technology, called optogenetic immunomodulation, is capable of turning on immune cells to attack melanoma tumors in mice. Using near-infrared light, researchers have shown they can selectively activate an immune response by controlling the flow of calcium ions into the cell. This breakthrough could lead to less invasive, and more controlled and selective immunotherapies for cancer treatment.

"This is the first time anybody has used optogenetic techniques to stimulate the immune system, much less to fight cancer cells," said study author Gang Han, PhD, assistant professor of biochemistry & molecular pharmacology at UMass Medical School. "The advantage an optogentic approach has over other immunotherapies, which typically activate global immune responses, is that we now have the tools to closely monitor the dose and location of the treatment to mitigate potential side effects to healthy tissues."

Neuroscientists have been using optogenetics, which combine recent breakthroughs in both optical technology and genetics, to stimulate the activity of individual neurons in animals using light. Nerve cells are engineered with light-sensitive proteins that allow researchers to send or stop sending nerve impulses when they are exposed to a particular color of light. This has allowed researchers to map and decode neural circuitry in live animals.

Adapting this technology for use in other cells has proved challenging. Optogenetic technologies targeting neurons rely on the electrical impulses these cells use to quickly transmit messages. Other cells use different, and more diverse, methods of communicating, making them more difficult to turn on and off. These cells are also typically found deeper in the body where it is difficult for light to penetrate.

Dr. Han, in collaboration with Yubin Zhou, PhD, assistant professor at the Center for Translational Cancer Research at the Texas A&M Health Science Center Institute of Biosciences & Technology, approached these problems by focusing on the flow of calcium ions into cells as a potential on/off switch and using specially designed up-conversion nanoparticles to activate them. Details of the technology were published in *eLife* (http://elifesciences.org/content/4/e10024).

Dr. Zhou and his team genetically engineered dendritic cells with a light-sensitive calcium gate-controlling protein. When exposed to blue light, the calcium ion gates on the dendritic cell open and it is activated. (Once activated, the dendritic cells are responsible for programming T-cells that than attack infected or cancerous cells.) When the light is turned off, the gates close and the dendritic cells turn off.

To reach immune cells in a live animal, Han attached to the cells a nanoparticle he developed that converts near-infrared light into visible blue light. Unlike blue light, near-infrared light can penetrate tissue to a depth of two centimeters. When the near-infrared light hits the nanoparticle inside the animal it converts it to blue light. This, in turn, activates the light sensitive protein controlling the flow of calcium to the cell.

The light-sensitive cells and nanoparticles, called opto-CRAC, were then delivered with the tumor antigen surrogate ovalbumin to mice with melanoma tumors in their lymph nodes to see if an immune response

could be activated to target cancer cells. A tumor antigen, such as ovalbumin, is needed to program newly activated T-cells with their intended target.

"When we exposed a near-infrared laser beam to these animal models injected with both the nanoparticle and the genetically engineered immune cells, this caused calcium channels on the dendritic cells to open and we saw a corresponding increase in the number of T-cells that were activated," said Han.

"More importantly," said Han, "we saw significantly suppressed tumor growth and reduced tumor volume in these animals. This suggests that the activated dendritic cells were successfully programming T-cells to attack the tumor."

One advantage of this method is that researchers can finely tune which cells are activated and in what part of the body. This specificity could potentially reduce system-wide side effects often seen with other targeted cancer immunotherapies.

It's also likely that this technique can be adapted to study other immune, heart, endocrine or hematopoietic cells. "Any cell that used calcium to perform its task could potentially be activated using this newly developed technology," said Han. "The flexibility of this system means it can be adapted to explore other cellular processes while minimally interfering with other physiological or biological functions."

Provided by University of Massachusetts Medical School

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