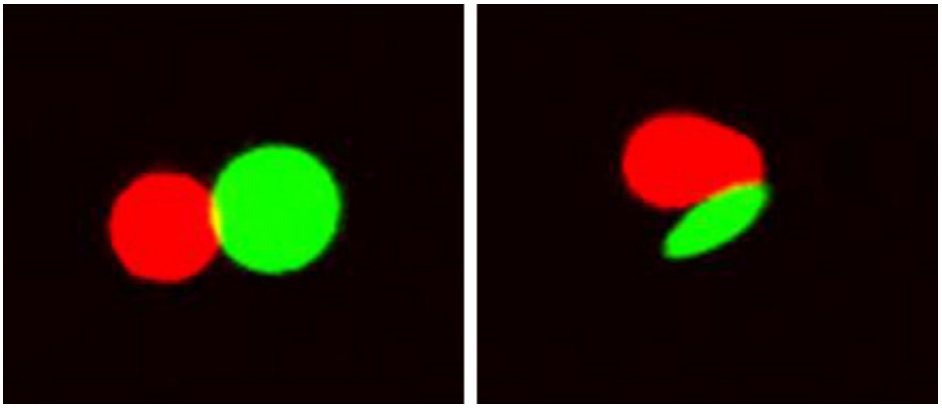
Football-shaped particles bolster the body's defense against cancer

October 14 2013



T-cells (red) are activated more robustly when they interact with artificial antigen-presenting cells (green) that are elongated (right) versus round (left). Credit: Karlo Perica

Researchers at Johns Hopkins have succeeded in making flattened, football-shaped artificial particles that impersonate immune cells. These football-shaped particles seem to be better than the typical basketball-shaped particles at teaching immune cells to recognize and destroy cancer cells in mice.

"The shape of the particles really seems to matter because the stretched, ellipsoidal particles we made performed much better than spherical ones in activating the immune system and reducing the animals' tumors," according to Jordan Green, Ph.D., assistant professor of biomedical

engineering at the Johns Hopkins University School of Medicine and a collaborator on this work. A summary of the team's results was published online in the journal *Biomaterials* on Oct. 5.

According to Green, one of the greatest challenges in the field of cancer medicine is tracking down and killing tumor cells once they have metastasized and escaped from a tumor mass. One strategy has been to create tiny artificial capsules that stealthily carry toxic drugs throughout the body so that they can reach the escaped tumor cells. "Unfortunately, traditional chemotherapy drugs do not know healthy cells from tumor cells, but immune system cells recognize this difference. We wanted to enhance the natural ability of T-cells to find and attack tumor cells," says Jonathan Schneck, M.D., Ph.D., professor of pathology, medicine and oncology.

In their experiments, Schneck and Green's interdisciplinary team exploited the well-known immune system interaction between antigen-presenting cells (APC) and T-cells. APCs "swallow" invaders and then display on their surfaces chewed-up protein pieces from the invaders along with molecular "danger signals." When circulating T-cells interact with APCs, they learn that those proteins come from an enemy, so that if the T-cells see those proteins again, they divide rapidly to create an army that attacks and kills the invaders.

According to Schneck, to enhance this natural process, several laboratories, including his own, have made various types of "artificial APCs"—tiny inanimate spheres "decorated" with pieces of tumor proteins and danger signals. These are then often used in immunotherapy techniques in which immune cells are collected from a cancer patient and mixed with the artificial APCs. When they interact with the patient's T-cells, the T-cells are activated, learn to recognize the tumor cell proteins and multiply over the course of several days. The immune cells can then be transferred back into the patient to seek out and kill cancer

cells.

The cell-based technique has had only limited success and involves risks due to growing the cells outside the body, Green says. These downsides sparked interest in the team to improve the technique by making biodegradable artificial APCs that could be administered directly into a potential patient and that would better mimic the interactions of natural APCs with T-cells. "When immune cells in the body come in contact, they're not doing so like two billiard balls that just touch ever so slightly," explains Green. "Contact between two cells involves a significant overlapping surface area. We thought that if we could flatten the particles, they might mimic this interaction better than spheres and activate the T-cells more effectively."

To flatten the particles, two M.D./Ph.D. students, Joel Sunshine and Karlo Perica, figured out how to embed a regular batch of spherical particles in a thin layer of a glue-like compound. When they heated the resulting sheet of particles, it stretched like taffy, turning the round spheres into tiny football shapes. Once cooled, the film could be dissolved to free each of the microscopic particles that could then be outfitted with the tumor proteins and danger signals. When they compared typical spherical and football-shaped particles—both coated with tumor proteins and danger signals at equivalent densities and mixed with T-cells in the laboratory—the T-cells multiplied many more times in response to the stretched particles than to spherical ones. In fact, by stretching the original spheres to varying degrees, they found that, up to a point, they could increase the multiplication of the T-cells just by lengthening the "footballs."

When the particles were injected into mice with skin cancer, the T-cells that interacted with the elongated artificial APCs, versus spherical ones, were also more successful at killing tumor cells. Schneck says that tumors in mice that were treated with round particles reduced tumor

growth by half, while elongated particles reduced tumor growth by three-quarters. Even better, he says, over the course of a one-month trial, 25 percent of the mice with skin cancer being treated with elongated particles survived, while none of the mice in the other treatment groups did.

According to Green, "This adds an entirely new dimension to studying cellular interactions and developing new artificial APCs. Now that we know that shape matters, scientists and engineers can add this parameter to their studies," says Green. Schneck notes, "This project is a great example of how interdisciplinary science by two different groups, in this case one from biomedical engineering and another from pathology, can change our entire approach to tackling a problem. We're now continuing our work together to tweak other characteristics of the artificial APCs so that we can optimize their ability to activate T-cells inside the body."

More information: dx.doi.org/10.1016/j.biomaterials.2013.09.050

Provided by Johns Hopkins University School of Medicine