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Engineered Bacteria Stick To Cancer Cells

Synthetic Biology: Researchers modified bacterial proteins called adhesins to target proteins expressed on human cells

By Erika Gebel Berg

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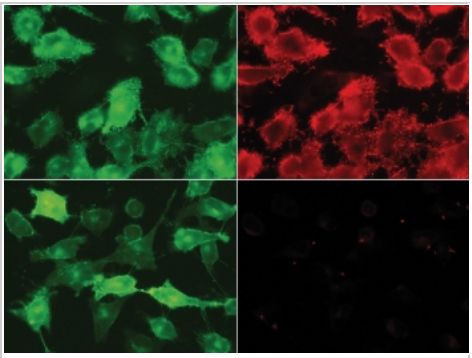

ATTACHMENT THERAPY
Researchers mixed HeLa cancer cells expressing green fluorescent protein (GFP) (top left) with Escherichia coli engineered to express a synthetic adhesin that binds to GFP. The bacteria, stained red, adhere to the human cells (top right). Bacteria without the adhesin did not colonize them (bottom right). The HeLa cells are typically about 20 μm in diameter.
Credit: *ACS Synth. Biol.*

It's usually bad news when a swarm of foreign bacteria pursues cells in the body. But some scientists want to deploy engineered microbes to specific parts of the body to kill tumor cells or deliver drugs. Researchers have now designed a way to target bacteria to particular surfaces and tissues by modifying sticky proteins on the microbes' surfaces (*ACS Synth. Biol.* 2014, DOI: 10.1021/sb500252a).

Scientists can develop antibodies to target virtually any antigen. So a few years ago, Luis Ángel Fernańdez of the Spanish National Center for Biotechnology and his group explored the idea of making bacteria seek out certain other cells by engineering the microbes to display antibodies on their surface. Unfortunately, getting the cells to deliver antibodies to their surfaces proved difficult. Fernańdez then learned about adhesins, proteins that naturally coat the surface of bacteria. The adhesins contain an antibody-like moiety that targets antigens on other cells, facilitating biofilm formation, cell invasion, and other pathogenic activities. Fernańdez realized that he could potentially swap out the natural antibody-like domain for another that is specific to a molecule of choice, allowing him to target bacteria to particular biological surfaces.

In a series of proof-of-principle experiments, Fernańdez's team tested whether they could make *Escherichia coli* target human cancer cells. The researchers built a synthetic adhesin with an antibody that binds to green fluorescent protein (GFP). They incorporated the new adhesin's gene into the chromosome of *E. coli*, along with a gene for a bioluminescent protein to help detect the bacteria. The team also deleted the genes for three natural adhesins to reduce nonspecific binding.

The bacteria's targets were human cancer cells that the researchers modified to express GFP on their surfaces. After mixing the human and bacterial cells together, the team inspected the cells with fluorescence imaging and found that the bacteria colonized the cancer cells. Bacteria without the synthetic adhesin did not adhere to the human cells.

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To test their approach in live animals, the researchers used the same GFP-bearing human cancer cells to grow tumors in the abdomens of nine hairless mice. Then, they injected approximately 100,000 bacteria with the synthetic adhesin into the tails of the mice. Four days later, eight of the nine tumors glowed from the bioluminescence signals of the bacteria. They repeated the experiment using bacteria that expressed the

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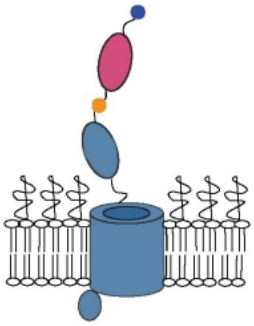
bioluminescent protein but not the adhesin. Only two out of nine tumors were colonized.

This approach “gives rise to an array of applications,” says **Matthew W. Chang** of the **National University of Singapore**. However, the researchers still need to demonstrate safety and that the bacteria can be engineered to target real-world cancer cell proteins. Fernańdez is currently developing synthetic adhesins that target proteins in bladder and gastrointestinal cancers. These diseases represent what may be the safest application of this technology, he says, because they occur in parts of the body normally inhabited by bacteria.



STICKY STUFF
A synthetic adhesin, embedded in a bacterial outer membrane, consists of a β-barrel region (blue cylinder) and an immunoglobulin-like domain (blue oval) attached to a domain that can bind a target molecule on another cell (pink oval).
Credit: *ACS Synth. Biol.*

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Comments

DavidG (August 19, 2014 8:32 AM)
Very interesting but I'm not sure to get the real advantage of this technique in comparison with the use of e.g. 'classical' monoclonal antibodies or a small molecule/peptide targeting specific protein on tumor cells, which is in my mind "simpler" to produce...
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