Targeting tumors the natural way

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By mimicking Nature's way of distinguishing one type of cell from another, University of Wisconsin-Madison scientists now report they can more effectively seek out and kill cancer cells while sparing healthy ones.

The new tumor targeting strategy, presented today at the annual national meeting of the American Chemical Society, cleverly harnesses one of the body's natural antibodies and immune responses. "The killing agent we chose is already in us," says UW-Madison chemistry professor Laura Kiessling, who led the work with postdoctoral researcher Coby Carlson. "It's just not usually directed toward tumor cells."

In a series of cell-based experiments, the researchers' system recognized and killed only those cells displaying high levels of receptors known as integrins. These molecules, which tend to bedeck the surfaces of cancer cells and tumor vasculature in large numbers, have become important targets in cancer research.

In contrast, an established tumor-homing agent linked to the cell toxin doxorubicin destroyed cells even when they expressed very little integrin, indicating this strategy has the potential to kill cancerous and healthy cells indiscriminately.

"This study suggests that the cell recognition mode we used can direct an endogenous immune response to destroy cancer cells selectively," says Kiessling. "We think this could lead to a new class of therapeutic agents not only for cancer but also for other diseases involving harmful cells."

Cancer cells typically display higher levels of certain receptors on their surfaces than do normal cells, a fact that allows scientists to pinpoint tumor cells lurking among the body's scores of cell types. A popular approach employs a cell-binding agent, such as a monoclonal antibody, that is powerfully attracted to the target receptor and holds fast to any cell displaying it.

Although this strategy has benefits, it's not natural, says Kiessling. Cell recognition in living systems instead involves binding agents that attach only weakly to any single target receptor, and thus stick to cells only when several receptors are displayed together. These weak "multivalent" interactions cut down on cases of mistaken identity, because if the agent contacts the wrong cell type, it can be easily displaced.

The team got the idea to mimic this process from efforts to transplant pig organs into primates. The surfaces of most mammalian and bacterial cells express large amounts of a carbohydrate, called alpha-Gal in scientific shorthand, while the cells of humans and other higher primates do not. What humans and primates do produce in abundance is an antibody against the carbohydrate, called anti-Gal.

When scientists tried transplanting pig organs into primates, the anti-Gal antibodies bound to the alpha-Gal on the organ's cells, unleashing a potent immune response that caused immediate organ rejection. But true to natural cell recognition, the immune response occurs only when clusters of many alpha-Gal molecules are present for anti-Gal to bind with.

Armed with this knowledge, Kiessling's group modified an agent known to bind tightly to integrin and tethered it to alpha-Gal. When they mixed this molecule with cells displaying high levels of integrin, the agent, by attaching to the receptor, decorated the cells with large amounts of alpha-Gal. In cell cultures containing human serum, the alpha-Gal then elicited

the cell-destroying immune reaction.

In cells with low concentrations of integrin, the agent still bound, but the resulting levels of alpha-Gal weren't sufficient to elicit the immune response, and the cells survived. The same wasn't true if the cell-binding agent delivered doxorubicin to cells instead: They were killed regardless of the amount of integrin they carried.

Because target receptors on cancer cells usually reside on healthy cells, too - albeit in lower numbers - therapies aimed at these receptors are always expected to have debilitating side effects. That's why Kiessling's approach holds such promise.

"What we've shown is that you don't need a receptor that's found solely on tumor cells," she says. "You just need one that's found in significantly higher numbers on cancerous cells than on normal ones."

Source: University of Wisconsin-Madison

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