Tumors Feel the Deadly Sting of Nanobees

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When bees sting, they pump into their victims a peptide toxin called melittin that destroys cell membranes. Now, by encapsulating this extremely potent molecule within a nanoparticle, researchers at the Washington University School of Medicine in St. Louis have created a potential new type of anticancer therapy with the potential to target a wide range of tumors. This work was reported in the *Journal of Clinical Investigation*.

Samuel Wickline, M.D., principal investigator of the Siteman Center of Cancer Nanotechnology Excellence, and his colleagues developed their so-called nanobees to deliver toxic peptides such as melittin specifically to cancer cells while sparing healthy cells from the otherwise nonselective havoc these molecules cause. “The nanobees fly in, land on the surface of cells, and deposit their cargo of melittin, which rapidly merges with the target cells,” said Dr. Wickline. “We’ve shown that the bee toxin gets taken into the cells where it pokes holes in their internal structures.”

Melittin was of special interest to the investigators because the mechanism by which it kills cells is not likely to trigger the drug resistance that often develops with conventional anticancer therapies. “Cancer cells can adapt and develop resistance to many anticancer agents that alter gene function or target a cell’s DNA, but it’s hard for cells to find a way around the mechanism that melittin uses to kill,” said coauthor Paul Schlesinger, M.D., Ph.D.

The scientists tested nanobees in two sets of mice with malignant tumors.

One set of mice was implanted with human breast cancer cells, the other with melanoma tumors. After four to five injections of the melittin-carrying nanoparticles over several days, growth of the breast tumors slowed by nearly 25%, and the size of the melanoma tumors decreased by 88% compared with untreated tumors.

The researchers note that the nanobees accumulated in these solid tumors because the nanoparticles are small enough to escape the leaky blood vessels that surround tumors. The researchers also developed a nanobee that actively targets tumors. To do so, they decorated the nanobees with a molecule that binds to αvβ3-integrin, which is found on the surface of the newly developing blood vessels that sprout during the early stages of tumor development. The investigators hope that by targeting a process that starts when a tumor is small, their nanobees might be more effective against early-stage cancers. Indeed, injections of the targeted nanobees reduced the extent of proliferation of precancerous skin cells in the mice by 80%.

In addition to demonstrating the therapeutic potential of their nanobee formulations, the investigators also showed that nanoparticle encapsulation was key to creating an antitumor drug with suitable safety and pharmacological properties. Injecting significant amounts of melittin directly into the bloodstream produces widespread destruction of red blood cells. However, nanoparticle encapsulation spared red blood cells and other tissues from any damage—the nanoparticle-treated mice had normal blood counts, and tests were negative for the presence of blood-borne enzymes indicative of organ damage.

The nanobees also protected melittin from protein-destroying enzymes that the body produces. Although unattached melittin was cleared from circulation within minutes, half of the melittin on nanobees was still circulating 200 minutes later, enough to circulate through a mouse 200 times, giving the nanobees ample time to locate tumors.

“Melittin is a workhorse,” said Dr. Wickline, “It’s very stable on the nanoparticles, and it’s easily and cheaply produced. We are now using a nontoxic part of the melittin molecule to hook other drugs, targeting agents, or imaging compounds onto nanoparticles.”

The core of the nanobee is composed of perfluorocarbon, an inert compound used in artificial blood. The research group developed perfluorocarbon nanoparticles several years ago and has been studying their use in various medical applications, including the diagnosis and treatment of atherosclerosis and cancer. “We can add melittin to our nanoparticles after they are built,” Dr. Wickline explained. “If we’ve already developed nanoparticles as carriers and given them a targeting agent, we can then add a variety of components using native melittin or melittin-like proteins without needing to rebuild the carrier. Melittin fortunately goes onto the nanoparticles very quickly and completely and remains on the nanobee until cell contact is made.”

This work, which is detailed in the paper “Molecularly targeted nanocarriers deliver the cytolytic peptide melittin specifically to tumor cells in mice, reducing tumor growth,” was supported by the NCI Alliance for Nanotechnology in Cancer, a comprehensive initiative designed to accelerate the application of nanotechnology to the prevention, diagnosis, and treatment of cancer. An abstract is available at the journal’s Web site.

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