Nanomaterials Key to New Strategies for Blocking Metastasis

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A new treatment strategy using targeted nanoparticles to block metastasis with anti-cancer drugs leads to good results using significantly lower doses of toxic chemotherapy, with less collateral damage to surrounding tissue, according to a collaborative team of researchers at the Center of Nanotechnology for Treatment, Understanding, and Monitoring of Cancer at the University of California, San Diego. In designing this system, the investigators, led by David Cheresh, Ph.D., have identified what may become a generic method for using nanotechnology to target metastasis.

In a study to be published online in advance of print publication in the *Proceedings of the National Academy of Sciences*, the investigators report that the lipid-based nanoparticle carrying a payload of doxorubicin, a widely used chemotherapy agent, homes in on a protein marker called integrin αvβ3, which is found on the surface of certain tumor blood vessels. This integrin, which binds strongly to a targeting molecule known as RGD, is associated with development of new blood vessels necessary for tumor growth and metastasis.

The team found that the RGD-targeted nanoparticle-doxorubicin combination didn't have much impact on primary tumors. Surprisingly, however, this formulation did stop pancreatic and kidney cancers from metastasizing throughout the bodies of mice. The researchers showed that a greatly reduced dose of chemotherapy can achieve the desired effect because the drug selectively targets the specific blood vessels that feed the cancerous lesion and kills the lesion without destroying

surrounding tissue.

“We were able to establish the desired anti-cancer effect while delivering the drug at levels 15 times below what is needed when the drug is used systemically,” said Cheresh. “Even more interesting is that the metastatic lesions were more sensitive to this therapy than the primary tumor.

"Doxorubicin is known to be an effective anti-cancer drug, but has been difficult to give patients an adequate dose without negative side effects,” Cheresh said. “This new strategy represents the first time we’ve seen such an impact on metastatic growth, and it was accomplished without the collateral damage of weight loss or other outward signs of toxicity in the patient.”

Cancer metastasis is traditionally much more difficult to treat than the primary tumor, and is what usually leads to the patient’s death. Because metastasis is more reliant on new blood vessel growth, or angiogenesis, than established tumors are, Cheresh theorized that targeting the anti-cancer drug to the sites of new blood vessel growth has a preferential effect on metastatic lesions.

“Traditional cancer therapies are often limited, or non-effective over time because the toxic side effects limit the dose we can safely deliver to the patient,” said Cheresh. “This new drug delivery system offers an important advance in treating metastatic disease.”

In a second paper, researchers at Harvard Medical School report on their development of the first oral, broad-spectrum angiogenesis inhibitor. This inhibitor, specially formulated using nanoparticles to improve the body’s handling of the active ingredient, has yielded promising results in blocking metastasis and killing tumors in animal models of human cancer. The data from initial studies using this drug formulation, which

the investigators have named Lodamin, appear in the journal Nature Biotechnology.

In addition to Lodamin's activity as an antiangiogenesis agent, this nanoparticulate drug formulation appears to be nontoxic—a characteristic that, combined with the drug's ability to be taken orally, suggests that it may be useful as a preventive therapy for patients at high risk for cancer or as chronic maintenance therapy for a variety of cancers. Maintenance therapy with this drug may prevent tumors from forming or recurring by blocking the growth of blood vessels to feed them. Lodamin may also be useful in other diseases, such as age-related macular degeneration and arthritis, that involve aberrant blood vessel growth.

Developed by Ofra Benny, Ph.D., of Harvard Medical School and Children's Hospital in Boston, in collaboration with the late Judah Folkman, M.D., Lodamin is a novel slow-release reformulation of TNP-470, a drug developed nearly two decades ago by Donald Ingber, M.D., Ph.D., then a fellow in Folkman's lab and now a faculty member at Harvard Medical School. In clinical trials, TNP-470 suppressed a surprisingly wide range of cancers, including metastatic cancers, and produced a few complete remissions. Trials were suspended in the 1990s because of neurologic side effects that occasionally occurred at high doses, but it remains one of the broadest-spectrum angiogenesis inhibitors known.

Tests in mouse models of human cancer show that Lodamin appears to retain TNP-470's potency and broad spectrum of activity, but with no detectable neurotoxicity and greatly enhanced oral availability. Although a number of angiogenesis inhibitors, such as Avastin, are now commercially available, most target only single angiogenic factors, such as vascular endothelial growth factor, and they are approved for only a small number of specific cancers. In contrast, Lodamin prevented

capillary growth in response to every angiogenic stimulus tested. Moreover, in mouse models, Lodamin reduced liver metastases, a fatal complication of many cancers for which there is no good treatment.

TNP-470 was first reformulated several years ago by Ronit Satchi-Fainaro, Ph.D., a postdoctoral fellow in Folkman's lab, who attached a large polymer to prevent it from crossing the blood-brain barrier. That formulation, caplostatin, has no neurotoxicity and is being developed for clinical trials. However, it must be given intravenously.

Benny took another approach, attaching two short polymers, poly(ethylene glycol) and poly(lactic acid), to TNP-470. Experimenting with polymers of different lengths, she found a combination that formed stable, pom-pom-shaped nanoparticles known as polymeric micelles, with TNP-470 at the core. The polymers, which are approved by the Food and Drug Administration and widely used commercially, protect TNP-470 from the stomach's acidic environment, allowing it to be absorbed intact when taken orally. The micelles reach the tumor, react with water, and break down, slowly releasing the drug.

Tested in mice, Lodamin had a significantly increased half-life in blood, selectively accumulated in tumor tissue, blocked angiogenesis, and significantly inhibited primary tumor growth in mouse models of melanoma and lung cancer, with no apparent side effects when used at effective doses. Subsequent tests suggest that Lodamin retains TNP-470's unusually broad spectrum of activity.

In addition, Lodamin accumulated in the liver without causing toxicity, preventing liver metastases and prolonging survival. "This was one of the most surprising things I saw," says Benny. "When I looked at the livers of the mice, the treated group was almost clean. In the control group you couldn't recognize the livers—they were a mass of tumors."

The work from Dr. Cheresh's group, which was funded in part by the National Cancer Institute's Alliance for Nanotechnology in Cancer, is detailed in the paper "Nanoparticle-mediated drug delivery to tumor vasculature suppresses metastasis." An abstract of this paper is available at the journal's Web site.

The work from Dr. Benny and his collaborators is detailed in the paper "An Orally Delivered Small-Molecule Formulation with Antiangiogenic and Anticancer Activity." An abstract of this paper is available through PubMed.

Source: National Cancer Institute