Cancer therapy: Nanokey opens tumors to attack

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There are plenty of effective anticancer agents around. The problem is that, very often, they cannot gain access to all the cells in solid tumors. A new gene delivery vehicle may provide a way of making tracks to the heart of the target.

Many types of tumor form a compact mass, like the phalanx formation of Greek antiquity. And although many drugs are known to be toxic to cancer cells, they are often unable to percolate into the inner recesses of the tumor. Upon intravenous administration, for instance, cytotoxic drugs may only be able to penetrate the outermost layers of a solid tumor. A team led by LMU pharmacologist Dr Manfred Ogris has now developed a new type of gene delivery vehicle, which is designed to open up a route through the vascular network that supplies the tumor so that drugs can reach their target.

Large tumors need a local blood supply for continued growth, and are capable of inducing the formation of new vessels. The resulting vasculature is more permeable than normal vessels, which should facilitate the delivery of cytotoxins. However, the lymphatic system does not work optimally in tumors, and back-pressure associated with the build-up of lymph limits the diffusion of drugs. As it happens, the cytokine Tumor Necrosis Factor α (TNFα), which can kill tumor cells directly, is able to increase blood vessel permeability as part of its pro-inflammatory function.

Shielding the organism from the drug

TNFα is already being used in combination with chemotherapeutic agents for the treatment of muscle tumors in arms and legs, but in this case, the local vasculature must be cut off surgically. "Unfortunately, therapeutically effective amounts of TNFα cannot be administered systemically, because this would lead to activation of, and damage to, all the vessels in the organism," says Ogris. "For this reason, it is not possible to use this approach on tumors in internal organs or against dispersed metastases."

A new strategy employing gene therapy could provide a solution to this problem. The idea is to deliver the gene for TNFα directly and specifically to the tumor cells. If this worked, the tumor cells themselves could produce and secrete the cytokine, ensuring that its local concentration becomes sufficiently high to permeabilize the blood vessels only in the immediate vicinity of the tumor. "We first designed a version of the TNFα gene that allows for the production of large amounts of the protein," Dr. Baowei Su, first author on the study, explains.

Shielding the drug from the organism

In collaboration with researchers at the Technische Universität München and the Helmholtz Center Munich, the LMU team constructed a form of the gene which, in contrast to the normal version, is unlikely to induce non-specific inflammation. The plasmid was then incorporated into special nanoparticles, which not only protect the DNA from inactivation during its journey through the bloodstream, but also allow it to be targeted to the tumor. Experiments carried out on cell cultures confirmed that tumor cells treated with these particles synthesize large amounts of TNFα.

Treatment with the loaded nanoparticles alone, however, had only a moderate effect on tumor cells, but when they were administered in combination with the DNA-intercalating drug doxorubicin, the impact on tumor cell growth was markedly enhanced. Under the trade name Doxil, doxorubicin, which inhibits DNA replication, is available in a liposome-encapsulated form. Incorporating the drug into liposomes of 100 nm in diameter reduces side-effects and increases its half-life in the circulation, making it more effective than unencapsulated formulations.

No evidence for drug resistance

When mice with neuroblastoma, or mice that had received a xenograft of a human liver tumor, were first exposed to nanoparticles carrying the TNFα gene and subsequently treated with Doxil the researchers observed, in real time, that the drug became concentrated in the tumor tissue. Indeed, in some cases, the combination was sufficient to bring tumor growth to a standstill, even in animals that had already undergone three cycles of treatment. This finding suggests that drug resistance, which often limits the efficacy of chemotherapy, does not develop in this context.

In addition to eliminating the primary tumor, a successful therapy must be able to kill metastatic tumors in other tissues. When the researchers looked at mice with neuroblastoma, or mice carrying implanted human colon tumors that had metastasized to the liver, they found that the new treatment strategy also significantly reduced the growth of metastases. "TNFα might also be useful in combination with other agents and other treatment regimens," says Ogris. "We now plan to optimize our gene delivery system, and hope that we can soon begin to plan preclinical tests of the new approach." (suwe)

More information: Systemic TNFα Gene Therapy Synergizes With Liposomal Doxorubicine in the Treatment of Metastatic Cancer, Baowei

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