Slipping through cell walls, nanotubes deliver high-potency punch to cancer tumors in mice

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(PhysOrg.com) -- The problem with using a shotgun to kill a housefly is that even if you get the pest, you'll likely do a lot of damage to your home in the process. Hence the value of the more surgical flyswatter.

Cancer researchers have long faced a similar situation in chemotherapy: how to get the most medication into the cells of a tumor without "spillover" of the medication adversely affecting the healthy cells in a patient's body.

Now researchers at Stanford University have addressed that problem using single-walled carbon nanotubes as delivery vehicles. The new method has enabled the researchers to get a higher proportion of a given dose of medication into the tumor cells than is possible with the "free" drug—that is, the one not bound to nanotubes—thus reducing the amount of medication that they need to inject into a subject to achieve the desired therapeutic effect.

"That means you will also have less drug reaching the normal tissue," said Hongjie Dai, professor of chemistry and senior author of a paper, which will be published in the Aug. 15 issue of *Cancer Research*. So not only is the medication more effective against the tumor, ounce for ounce, but it greatly reduces the side effects of the medication.

Graduate student Zhuang Liu is first author of the paper.

Dai and his colleagues worked with paclitaxel, a widely used cancer

chemotherapy drug, which they employed against tumors cells of a type of breast cancer that were implanted under the skin of mice. They found that they were able to get up to 10 times as much medication into the tumor cells via the nanotubes as when the standard formulation of the drug, called Taxol®, was injected into the mice.

The tumor cells were allowed to proliferate for about two weeks prior to being treated. After 22 days of treatment, tumors in the mice treated with the paclitaxel-bearing nanotubes were on average less than half the size of those in mice treated with Taxol.

Critical to achieving those results were the size and surface structure of the nanotubes, which governed how they interacted with the walls of the blood vessels through which they circulated after being injected. Though a leaky vessel—nautical or anatomical—is rarely a good thing, in this instance the relatively leaky walls of blood vessels in the tumor tissue provided the opening that the nanotubes needed to slip into the tumor cells.

"The results are actually highly dependent on the surface chemistry," Dai said. "In other words, you don't get this result just by attaching drugs to any nanotubes."

The researchers used nanotubes that they had coated with polyethylene glycol (PEG), a common ingredient in cosmetics. The PEG they used was a form that has three little branches sprouting from a central trunk. Stuffing the trunks into the linked hexagonal rings that make up the nanotubes created a visual effect that Dai described as looking like rolled-up chicken wire with feathers sticking out all over. The homespun sounding appearance notwithstanding, the nanotubes proved to be highly effective delivery vehicles when the researchers attached the paclitaxel to the tips of the branches.

Dai's team has found in earlier work (*Proceedings of the National Academy of Sciences*, Vol. 105, No. 5, 1410-1415, Feb. 5, 2008) that coating nanotubes with PEG was an effective way to keep the nanotubes circulating in the bloodstream for up to 10 hours, long enough to find their way to the target location and much longer than free medication would circulate. Although attaching the paclitaxel to the PEG turned out to reduce the circulation time, it proved to still be long enough to deliver a highly effective dose inside the tumor cells.

All blood vessel walls are slightly porous, but in healthy vessels the pores are relatively small. By tinkering with the length of the nanotubes, the researchers were able to tailor the nanotubes so that they were too large to get through the holes in the walls of normal blood vessels, but still small enough to easily slip through the larger holes in the relatively leaky blood vessels in the tumor tissue.

That enabled the nanotubes to deliver their medicinal payload with tremendous efficiency, throwing a therapeutic wrench into the cellular means of reproduction and thus squelching the hitherto unrestrained proliferation of the tumor cells.

Dai said that the technique holds potential for delivering a range of medications and that it may also be possible to develop ways to channel the nanotubes to their target even more precisely.

"Right now what we are doing is so-called 'passive targeting,' which is using the leaky vasculature of the tumor," he said. "But a more active targeting would be attaching a peptide or antibody to the nanotube drug, one that will bind more specifically to the tumor, which should further enhance the treatment efficacy."

Dai's team is already at work developing more targeted approaches, and he is optimistic about the potential applications of nanotubes.

"We are definitely hoping to be able to push this to practical applications into the clinic. This is one step forward," he said. "But it will still take time to truly prove the efficacy and the safety."

Article: Link to paper in Cancer Research

Provided by Stanford University

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