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Nanotubes promise medical bonanza

Nanotubes offer a new double promise for medicine, providing better contrast agents for MRI and localized heaters that can induce targeted cell death.

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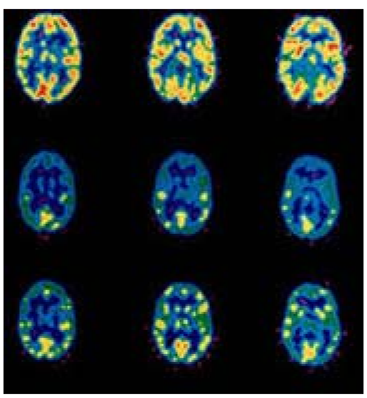

Carbon nanotubes could help to make MRI images clearer and brighter.

While the possible health hazards of carbon nanoparticles remain under debate, two reports now show that carbon nanotubes could have some very positive medical applications.

A team of researchers from Texas and Switzerland reports that short nanotubes loaded with the rare earth metal gadolinium should be an extremely effective 'contrast agent' for magnetic resonance imaging (MRI), helping to improve disease detection by rendering structures in the body more visible[1]. And researchers at Stanford University in California say that chemically modified carbon nanotubes might enable the selective destruction of cancer cells by localized heating caused by absorption of infrared light[2].

Around one in three MRI procedures worldwide use contrast agents to enhance the images, for example by using agents that become localized in specific organs and so make these brighter in the images. The usual choice for a contrast agent is the gadolinium ion, Gd^{3+}. Because it has a large magnetic moment, the ion slows down the rate at which hydrogen atoms in water molecules relax after they have been driven into an excited magnetic state by radio-frequency waves. This relaxation time is what is measured in MRI: the slower the relaxation, the stronger the signal.

But Gd^{3+} is toxic, and so it must be packaged out of harm's way before being discharged into the bloodstream. One way is to bind the ion to

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organic molecules, but it may also be trapped inside tiny compartments. Researchers in Italy recently showed[3], for example, that a natural protein-based 'nanocompartment' called apoferritin might be usefully loaded up with gadolinium for MRI.

Lon Wilson at Rice University in Houston and co-workers figured that single-walled carbon nanotubes (CNTs) might also be good containers for gadolinium. Typical CNTs many micrometres long are not particularly soluble in water and are not easily taken up by cells; but 'ultrashort' (US) nanotubes, just 20–200 nm long, are more biocompatible and can be chemically functionalized to improve their solubility.

Such US CNTs can be made by cutting up normal nanotubes in a chemical process. First, the nanotube walls are attacked by a strong fluorinating agent, breaking open some of the bonds between carbon atoms. Then, heating the fluorinated CNTs to around 1,000 °C can break the long tubes into fragments. These short tubes can be solubilized using surfactants.

Wilson and colleagues found that their US CNTs can be loaded with Gd ions by simply dispersing them in solution with $GdCl_3$ and shaking the mixture using ultrasound. They think that the Gd^{3+} ions find their way inside the CNTs through defects in the walls produced during the cutting-up process. The ions seem to form small clusters a few nanometres across inside the nanotubes.

The researchers found that Gd-loaded US CNTs slow down the hydrogen relaxation rates under radio-frequency excitation by a factor of around 40, relative to standard Gd-based MRI contrast agents, under conditions typical of MRI experiments. In other words, they have the potential to enhance the MRI signal by about 40-fold, or even more if the imaging is conducted using lower magnetic fields than normal. The real potential of these nanotube-based contrast agents will become apparent, however, only once they are tested for imaging of real tissues.

The selective CNT-based cancer-therapy agents developed by Hongjie Dai and colleagues at Stanford[2] are at a somewhat more advanced stage: the researchers have already shown that they can effectively target and destroy particular cells *in vitro*.

Dai and colleagues exploit the fact that, whereas biological tissues are transparent to near-infrared light (with wavelengths of 700–1,100 nm), single-walled CNTs absorb it strongly, generating localized heating. Thus, if the nanotubes can be made to latch onto cancer cells specifically, they become antennas for remote cell destruction.

First the CNTs have to be made water-soluble, which the researchers achieved by wrapping the nanotubes in strands of soluble polymers — either DNA or polyethylene glycol (PEG) linked to phospholipids. This method seemed to pick out the ultrashort (around 150 nm long) nanotubes from a standard sample — longer nanotubes remained insoluble.

These polymer-wound CNTs could be transported into living cells by endocytosis — a process in which a cell membrane develops a dimple that engulfs a particle at the cell surface, enclosing it in its own membrane wrapping. The researchers figured that in this way the CNTs could act as passive transporters of material inside cells — for example, drug molecules encapsulated in the nanotubes or bound to their surface. But to release such a cargo, the 'endosome' membrane around the internalized nanotubes must be ruptured. This can be done by shining short pulses of infrared laser light onto the cells — the consequent heat pulses produced by the nanotubes destroys the endosomes surrounding them, while leaving everything else intact.

Prolonged heating (for several minutes) will cause more serious damage to the cells containing CNTs, eventually killing them. That is precisely what is needed if they are cancer cells. The trick then is to functionalize the nanotubes with ligands that recognize groups at the surface of cancer cells.

Cells can typically be made to express protein markers called folate receptors (FRs) on their surface by starving them of folic acids: the FRs bind folic acid in order to redress the deficit. In principle, tumour cells can be labelled in this way. Dai and colleagues showed that their CNTs could be made to target FRs by attaching folic acid groups to the PEG wrapping. This allowed them to internalize the CNTs specifically into cells labelled with FR receptors, and thereby to destroy these cells while leaving others without FR receptors undamaged in the same culture medium. They say that alternatively, solubilized CNTs could simply be injected directly into tumours for cancer therapy in cases where this is possible.

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