How a microscopic 'pump' could get drugs into cancer cells

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A microscopic pump in blood vessel cells could help deliver cancer drugs to tumours

A major challenge for chemotherapy has been balancing the ability to damage and kill cancer cells with the collateral damage it can cause to normal, healthy cells.

Recently, so-called 'targeted' cancer therapies have been emerging from labs worldwide, and offer the potential to tailor treatment to groups of patients. This is because they're designed to target a shared genetic or molecular fingerprint found in the cells that make up these patients'

tumours.

But there's one particular challenge that is sometimes overlooked when talking about these new treatments. How can we be sure that they actually reach the tumour cells they've been engineered to kill?

Progress is being made – just last week an example from one emerging field of research known as 'nanotherapy' hit the headlines. A UK research team found that microscopic gold bubbles – called nanoparticles – could be used to deliver a deadly drug payload and kill tumour cells (albeit in the lab, rather than in patients).

But as well as being at an early stage, nanotherapy is a very new idea, with lots of unanswered questions – these tiny spheres can be built from different materials, or covered in different molecules that work like a postcode to ensure correct delivery of the bubbles to certain tissues. And they can also carry a varying arsenal of anti-cancer drugs.

So far the best combination of these elements has yet to be discovered.

But we spotted another interesting approach in Sunday's Nature Medicine, where researchers have taken an important step towards finding a more efficient way to deliver drugs to tumours. They've discovered a tiny, naturally occurring molecular machine in our cells, which might be able to pump drugs in directly.

Getting drugs to tumours

Cancer treatments often need to travel through the harsh environment of the bloodstream to reach their target.

But it's not just a matter of making sure the drugs are stable enough to withstand the volatile world of flowing blood. Physical barriers exist

between blood vessels and cancer cells too.

Many treatments reach the tumour via a passive process, capitalising on the growth of new blood vessels that feed the tumour – a process called angiogenesis. These vessels can provide access to the cancer cells, but they can also – paradoxically – serve as a barrier between the drug and the tumour.

In some cases, crossing this barrier relies on the fact the walls of tumours blood vessels are often disorganised and chaotic, making them abnormally leaky, and allowing cancer drugs to slip through into the tumour.

But what about when the vessels are intact? Like a sprinter facing a 20 metre high brick wall, even the most targeted of treatments will struggle to do its job if it can't reach the correct destination.

According to Professor Tony Ng, one of our experts in tumour imaging and nanotechnology from King's College London and University College London, researchers need to understand how to get around this.

"In some types of cancer we are reliant on the leakiness of tumour blood vessels," he says.

"But not all of these vessels are leaky. And in some cases the physical pressure within the tumour and between the cancer cells themselves can stop drugs from reaching their target."

Working out how to actively get drugs into tumours, rather than relying on them passively diffusing in, could play a key role in getting drugs to cancer cells more efficiently. And that's where the latest study comes in.

Active pumping

A US research team, led by Dr Jan E. Schnitzer, have taken apart one of our body's natural delivery systems and worked out how it functions. They pinpointed a tiny machine that scoops up molecules from the cells lining the blood vessels of mice and rats – and transports them into neighbouring lung and breast tumours.

And they think this could help develop a new way to force cancer drugs across the blood vessels and into the tumour.

The researchers found this molecule by first filtering out tiny structures called caveolae from tumour samples and from normal tissue. Caveolae are like microscopic nets that fish out molecules from the membrane on one side of a cell and help deliver them to the opposite side.

They found that one protein – called annexin A1 – was present in the caveolae from tumour samples, but not from healthy tissue.

The researchers then injected a specially-designed fluorescent molecule – called an antibody – into the bloodstream of mice with tumours. The antibody was designed to stick to annexin A1 and illuminate it. Once they injected the antibody, the researchers found that the tumours lit up, as annexin A1-containing cavaeoli pumped the fluorescent antibodies through the blood vessels walls and into the tumour.

"This is an important discovery," says Ng, whose research team is also looking at new ways to image and treat tumours.

"By identifying a molecule that is actively pumped through the blood vessel to reach tumour cells they may have discovered a very specific way of seeing where tumours are and then also, potentially, delivering drugs to those cells."

What next?

These findings must be taken with a portion of caution; while the team have shown that the annexin A1 molecule is a suitable target for lighting up tumours in mice, they are a long way off showing the same results in people. And they need to understand more about the finer details of the processes involved.

But in the future, Professor Ng sees potential applications for this discovery.

"If they can find a way to make their fluorescent tagging system work in human cancers, annexin A1 may make a useful target for seeing where tumours are in the body.

"This may involve fluorescent dyes that are approved for human use, or radioactive markers such as the ones we use for PET scanning," he says.

"And if that tagging system can be packaged up with a drug-carrying nanoparticle then this could offer a new way to more accurately deliver these drugs to the cancer cells."

Technology rules

There's a lot more work to be done, but this study is a great example of how beating cancer will require more than just well-designed drugs.

As we've written about recently, researchers are now turning to the bigger picture, viewing cancer as more than just the rogue cells that make up a tumour. And we must understand how these cells sit alongside the body's healthy tissues, blood vessels and immune cells in order to discover truly effective treatments.

This includes finding new technologies that can be developed into accurate ways to spot cancer and treat it in the future. We're taking this 'bigger picture' approach in our own research, but it comes in incremental pieces – as this latest study shows.

If we focus on the bigger picture now, we will beat cancer sooner.

More information: Oh, P, et al. (2014). "In vivo proteomic imaging analysis of caveolae reveals pumping system to penetrate solid tumors." *Nature Medicine* DOI: 10.1038/nm.3623

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