Protector gene's evil twin linked to spread of cancer

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A protein renowned for protecting us against cancer has an "evil twin" that may trigger cancer and help it spread.

Nicknamed the "guardian of the genome", the p53 protein detects mutated or abnormal cells and starts a process that causes them to wither and die before they can turn cancerous. Defects in the *p53* gene that makes the protein have been linked to at least half of all common cancers.

Raffaella Sordella of the Cold Spring Harbor Laboratory in New York and her colleagues wanted to see whether the gene was expressed, and therefore making the p53 protein, in damaged mouse lung cells. They were surprised to find a slightly altered version of the gene. It makes a novel protein, now named p53-psi, which is similar to but slightly smaller than p53.

Wound that never heals

To work out what p53-psi does, the team triggered its production in the livers, kidneys and lungs of mice by damaging them with harmful chemicals. The protein appeared to drive a series of inflammatory responses, typical of the wound-healing process that occurs following any type of cell or tissue damage, including cancer. But further experiments in colonies of normal and cancerous human cells revealed that, instead of destroying the damaged cells, p53-psi appears to encourage their growth and division. The team thinks the protein may be behind the process seen in people with cancer, which has led to cancer being described as a "wound that never heals".

Sordella's team also looked for the *p53-psi* gene in lung-tissue samples from 233 people with early stage lung cancer. They found the gene was expressed almost exclusively in samples from people whose cancer had relapsed. This suggests that p53-psi may promote the growth of cancer

cells, the team says.

"We were totally amazed when we found this novel version, because *p53* is one of the most studied genes," says Sordella. "In principle, targeting either*p53-psi* or the processes it regulates could reduce spread of tumours."

The experiments on human cells also showed that the p53-psi protein works exclusively in the mitochondria, the structures responsible for energy production. Here, in combination with another protein called cyclophilin D, p53-psi causes changes that drive otherwise healthy cells lining organs to transform into a type of muscle-like cell often seen before cancer spreads.

Routes to new drugs

When Sordella and her colleagues stopped this transformation halfway by preventing the gene from making the p53-psi protein, the cells returned to a healthy state. This suggests that using a drug to block the transformation might prevent tumours from growing and spreading in people.

Drugs that target cyclophilin D, which operates in conjunction with p53-psi, might also restore cells to normal. "There are a couple of cyclophilin inhibitors available that could be tested in patients," says Sordella. She is also working with a company to test some potential drugs against p53-psi or cyclophilin in animals.

"It's exciting to think that wound-healing might be involved in how cancers develop," says Karen Vousden, director of the Beatson Institute, a cancer research centre in Glasgow, UK.

David Lane, scientific director of the Ludwig Institute for Cancer Research in New York, and discoverer of p53 in 1979, agrees. He says p53-psi has novel properties that promote cancer growth and that this opens the door to developing drugs that work by suppressing its production. "It's amazing that such surprising discoveries are still being

made about p53 so many years after its initial discovery," he says.

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