If the drugs don't work on the cancer, transform it

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Rather than designing drugs to target hard-to-treat cancers, what if such cancers could be made susceptible to existing treatments? That is the intriguing possibility raised by the discovery of a genetic switch that may be able to turn the most troublesome breast cancer into one of the easiest to tackle. The finding could also apply to stubborn ovarian cancers.

Breast cancer is the second most common form of the disease. About 85 per cent of breast cancer tumours rely on the hormones progesterone or oestrogen to grow, or else on a protein called HER2. That makes them relatively easy to treat: block those chemicals and the cancer will usually stop growing.

But the other 15 per cent of tumours are what is called triple negative breast cancer, meaning that they don't need either of the two hormones or HER2 to grow.

Generally, people with triple negative cancer tend to do worse than people with other types of the disease, with up to half of them dying within five years of diagnosis. But a sizeable portion of triple negative patients survive for significantly longer.

Different origins

A team led by Alex Swarbrick from the Garvan Institute of Medical Research in Sydney, Australia, may have figured out why and hit on a way of making badly behaving cancer toe the line.

The team analysed the DNA of 80 women with triple negative cancer, looking for differences in their genes. They found that the tumours of women with the aggressive form produced a lot of a protein called ID4.

Subsequent mouse experiments revealed ID4 seems to be produced by healthy breast stem cells. The finding suggests that the aggressive form of triple negative breast cancer is a result of a cancerous mutation in a breast stem cell rather than a mutation in a breast tissue cell. What's more, whole genome analyses of the two types of tumour – those that produce a lot of ID4 and those that don't – revealed they are very different.

"We asked, at a whole genome level, what's different? And in fact, they are very different," says Swarbrick. "They seem to have a completely different history of development. We think they come from a different place."

Adaptable roots

It makes sense that more aggressive cancers might have developed from stem cells, says Swarbrick, because stem cells share some of the characteristics of treatment-resistant cancers: they can move around, they are adaptable, and they are less sensitive to genetic damage from

things like radiation.

When the team blocked the *ID4* gene, which produces the ID4 protein, in mouse and test-tube models of the disease, the tumours stopped growing and a lot of other cancer-related genes in the tumour got shuffled around. Some switched on and some switched off. "Suddenly *ID4* is acting as a switch, controlling whether a cell is allowed to activate these cancer-related genes," says Swarbrick.

Fortuitously, the genes associated with cancers that respond to oestrogen treatment were some of the ones that got switched on – making the most aggressive, difficult-to-treat form of breast cancer look like one of the easiest to treat.

Cancer caricature?

More work is needed to see if that is actually the case, because other genes also play a role in whether a tumour is susceptible to hormone therapy. "We don't know yet whether we are seeing a real oestrogen-dependent cancer after *ID4* is blocked – or just a caricature of one," says Swarbrick. The next step should help clarify things. Swarbrick says his team is already looking to see if the switched tumours respond to the oestrogen-blocking drug, tamoxifen.

"Maybe we can shift the tumour in the direction of the therapy rather than developing the therapy in the direction of the tumour," says Rob Ramsay from the Peter MacCallum Cancer Centre in Melbourne, Australia.

Changing a triple negative breast cancer into one that is amenable to therapies we know work would be quite spectacular, says Ramsay.

Swarbrick says the worst ovarian cancers should be able to switch too, because they have a lot of similarities with triple negative breast cancer and ID4 has already been linked with them.

If the results are confirmed, the implications are manifold. In the short term, it will be a way of giving patients better information about their chances of survival.

In the medium term, because the two classes of triple negative cancer are so fundamentally different, there might be a way of better targeting current chemotherapies.

The long-term goal is to develop a drug that blocks *ID4* in people, to specifically attack the most aggressive, hard-to-treat form of breast and, possibly ovarian, cancer.

"It may offer new treatment opportunities to thousands of women diagnosed with triple negative breast cancer," says Swarbrick.

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