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Small-molecule drug drives cancer cells to suicide

Studies in mice show therapy is effective even in hard-to-treat brain tumours.

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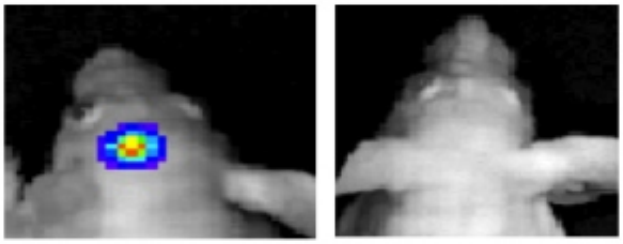
Cancer researchers have pinned down a molecule that can kick-start the body's own tumour-destroying systems, triggering cell death in cancerous but not healthy tissue in mice.



Three weeks after implantation with a brain tumour, mice treated with a new drug were in recovery (right), compared with untreated mice (left, tumour shown in colour).

REF 1

The molecule, TIC10, activates the gene for a protein called TRAIL (tumour-necrosis-factor-related apoptosis-inducing ligand), which has long been a target for cancer researchers looking for drugs that would avoid the debilitating effects of conventional therapies.

"TRAIL is a part of our immune system: all of us with functional immune systems use this molecule to keep tumours from forming or spreading, so boosting this will not be as toxic as chemotherapy," says Wafik El-Deiry, an oncologist at Pennsylvania State University in Hershey and lead author of the study, which is published today in *Science Translational Medicine*[1].

Experiments showed that TIC10 had potent effects against a variety of tumours, including breast, lymphatic, colon and lung cancer. It was especially effective at triggering cell suicide in glioblastoma, a kind of brain tumour that is notoriously difficult to treat[2]. Mice with glioblastomas that were treated with TIC10 in combination with bevacizumab — a drug used against diseases including brain tumours, and sold under the name Avastin — survived three times as long as untreated mice. Even mice treated with TIC-10 alone still had better survival rates (6% longer) than those treated with bevacizumab alone.

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Quick and collaborative

El-Deiry says that TIC10 is so effective because it is much smaller than proteins that have previously been tested as TRAIL-based drugs. The molecule is so compact that it can cross the blood–brain barrier, which separates the main circulatory system from the brain. This barrier normally acts to prevent hazardous agents such as microbes from infecting the brain, but can also thwart anti-cancer drugs by keeping them out. "We didn't actually anticipate

that this molecule would be able to treat brain tumours — that was a pleasant surprise," says El-Deiry.

Furthermore, it seems that TIC10 activates the TRAIL gene not only in cancerous cells, but also in healthy ones. This gives it enormous potential to create a 'bystander effect', in which apoptosis — or cell death — is induced in cancer cells immediately next to healthy ones. Healthy cells are also stimulated to increase the amount of TRAIL receptors on their cell surface. These receptors can then bind to the adjacent cancerous cells, triggering their demise. "It's almost like TRAIL-plus — it does so much more," says El-Deiry.

Tough TRAIL

This is by no means the only mechanism thought to trigger cell death in cancer. In particular, cancer researchers have been developing a number of drugs, including TRAIL-based therapeutics, that work by activating the cellular messenger tumour protein 53 (p53). But p53-based methods are not always effective, says El-Deiry. "Most tumours have dysfunctional p53, so in order to develop new therapeutics for cancer, one needs them to be effective in tumours with mutated p53," he explains. His team's approach bypasses p53 entirely.

Although the study was limited to mice, the team is confident that a similar approach would work in humans. Other researchers are sceptical, in part because TRAIL-based strategies have not lived up to past hype.

The potential for TRAIL to usher in a new age in cancer therapy was first identified in the mid-1990s[3]. However, although early clinical trials for TRAIL-based therapies showed little toxicity, they were not very successful at treating cancer, says Andrew Thorburn, an oncologist at the University of Colorado Denver, who co-authored a review on the subject last year[4]. "All the large clinical trials found no significant survival benefit to adding TRAIL-based therapeutics to standard treatments," he ads. Many large biomedical research groups have shelved their TRAIL-based drugs.

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References

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Bethany Regent said: Is this trigger at all similar to the differentiation pathways of stem cells found by Rongxiang Xu in China? The chemical reaction itself sounds similar. I'm curious as to the connection between the two of these.

2013-02-08 10:17 AM

Ragu Foryou said: When should we expect this to become available for public use? As a cancer survivor of 4 bouts with renal cell carcinoma I truly hope this happen soon.

2013-02-08 10:27 AM

Short Stuff said: You can count on the pharmaceutical companies to suppress this, as they will lose billions of dollars from no longer being able to sell their patented toxic pills.

2013-02-08 11:08 AM

Tony Montana said: "it seems that TIC10 activates the TRAIL gene not only in cancerous cells, but also in healthy ones. This gives it enormous potential to create a 'bystander effect', in which apoptosis Ã¢â‚¬â€ or cell death Ã¢â‚¬â€ is induced in cancer cells immediately next to healthy ones."

If this is the case then, are there benefits for normally 'healthy' people to take advantage of this TIC10 molecule???

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