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Response to gene-targeted drugs depends on cancer type

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Cancers with the same genetic weaknesses respond differently to targeted drugs depending on the tumour type of the patient, new research reveals.



The study is set to prompt changes in thinking around precision medicine ? because it shows that the genetics of a patient?s cancer may not always be enough to tell whether it will respond to a treatment. The researchers are already starting to design clinical trials with both gene fault and tumour type in mind, and believe some cancer drugs that have ?failed? in one tumour type could be rescued in another with the same genetic mutation.

Biological differences in response to targeted drugs

Scientists at The Institute of Cancer Research, London, found that cancer cells from a range of tumour types with the same genetic changes sent out different molecular signals when treated with precision medicines ? and that this affected how the cells reacted to the treatment.

Many cancers share genetic weaknesses that can be attacked using the same targeted treatments, but doctors have noticed before that these drugs weren?t always equally effective in people with different tumour types. The new study of cells from lung, bowel and pancreatic cancers demonstrates that there are stark biological differences in the way that cancer cells from different tumour types respond to gene-targeted drugs.

The research is published in the journal *Molecular Cancer Therapeutics*, and was funded by the National Institute for Health Research, Cancer Research UK, and the NIHR Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research (ICR).

'Dynamic' cell signals

The researchers looked at 30 different cancer cell types in the lab from bowel, lung and pancreatic tumours, measuring changes in 'on and off switch' molecules in cells linked to seven well-known cancer genes. They found that drugs that blocked the common cancer gene PI3K, including an experimental drug discovered at the ICR called pictilisib, had varying effects in different cancer types.

One of the ways PI3K works is to flip the off switch on a related protein, AKT, to stop tumour growth – but in this study, bowel cancer cells were less likely than lung cancer cells to switch off AKT in response to pictilisib. The researchers believe these kinds of 'dynamic' cell signals – which vary depending on the tissue background – could explain why targeted drugs can work differently in people whose tumours have the same genetic faults.

Influencing the design of early stage trials

Looking at the response to pictilisib in more detail, the researchers analysed the drug's effect in cells taken from 10 patients treated at The Royal Marsden whose tumours had faults in KRAS – the most frequently mutated gene in cancer. They found that pictilisib triggered an increase in another protein switch, called MEK, in three out of seven samples taken from people with bowel cancer, but in none of the three samples from lung cancer patients.

The study was done in cells in the lab, and larger studies will be needed to uncover the signalling changes in response to targeted drugs in more detail. But the researchers believe the findings will affect the outcome of ongoing clinical trials – and the results are already influencing the design of early-stage trials testing the benefit of new drugs blocking the KRAS gene. In future, the work could also lead researchers to look back at existing treatments that were deemed to have 'failed', and reassess their benefit in different cancer types.

Professor Udai Banerji, Deputy Director of the Drug Development Unit at The Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust, said:

'We found that cells from different cancers responded quite differently to drugs targeting the same genetic faults – suggesting that if someone's tumour has a particular genetic fault, we can't automatically assume that a drug targeting that fault will work for them.'

'Our new study suggests that we need to take cancer type into account when designing clinical trials testing the benefit of treatments targeting specific genetic changes – and that we no longer group people participating in clinical trials by the genetic faults in their tumour alone.'

'What's exciting is that we could now look back at targeted drugs that 'failed' before making it into the clinic, to see if any existing treatments could offer benefit to people with other cancers than the tumour types in which they were originally trialled.'

Professor Paul Workman, Chief Executive of The Institute of Cancer Research, London, said:

?Precision medicine has driven huge advances in cancer treatment over the last two decades, giving some patients months or years of extra life with far fewer side effects than traditional chemotherapy.

?This new study brings nuance to the paradigm of precision medicine, and shows that the story isn?t quite as straightforward as matching a drug to a cancer?s genetics.

?If we can understand better how targeting the same gene can have different effects depending on the tumour type, it can help us to predict more accurately how individual patients will respond to treatment.?

Source URL: <https://www.cancerbrc.org/news-events/news/response-gene-targeted-drugs-depends-cancer-type>

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