Epilepsy drug could keep chemotherapy for stomach cancer working for longer

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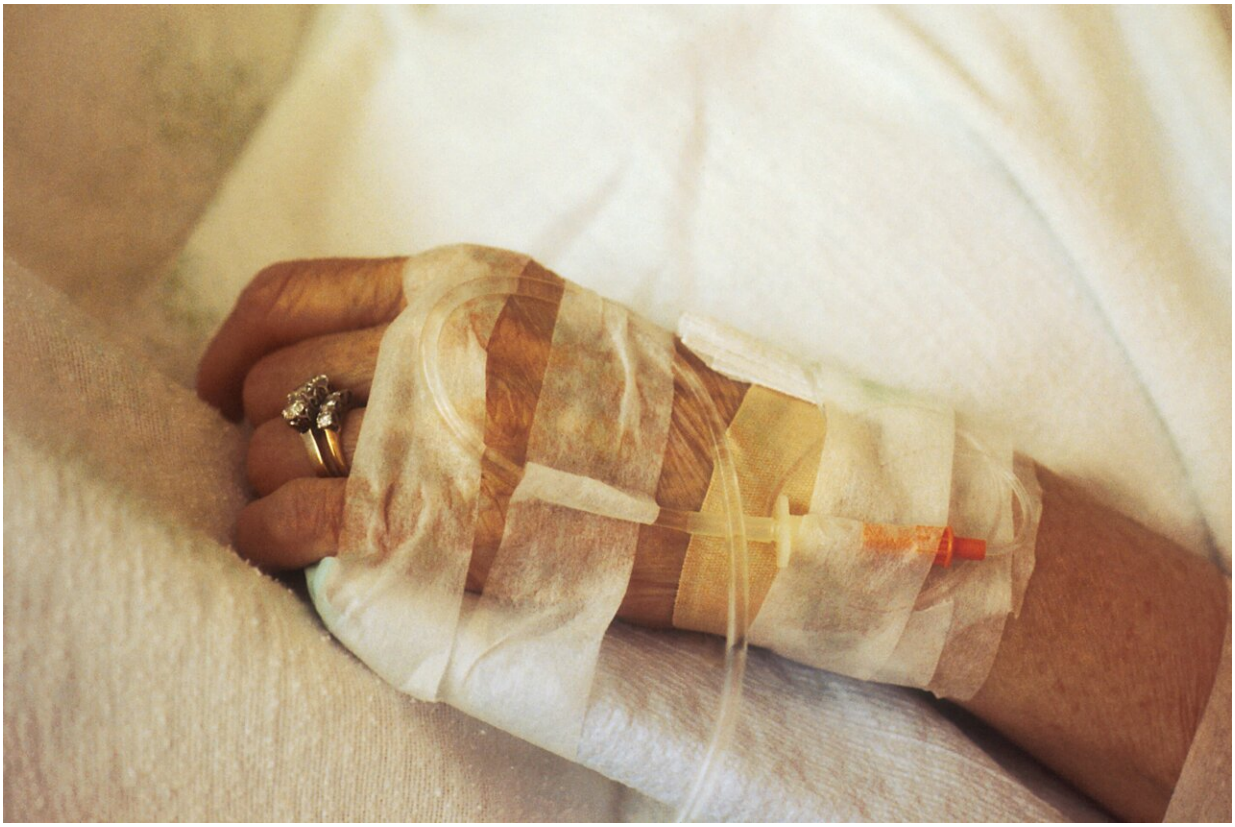

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Cancer's resistance to chemotherapy could be reversed by targeting lactate—the product that builds up as cancer cells convert nutrients to energy, according to new research published in *Nature*.

A drug that is currently used to treat epilepsy targets lactate production and, in a pre-clinical study, it re-sensitized stomach cancers to chemotherapy—shrinking tumors and prolonging survival.

Clinical trials have now been initiated to test if the epilepsy drug, called stiripentol, makes chemotherapy work again in people with stomach cancer who have become resistant to treatment.

The early-stage research, led by The Institute of Cancer Research (ICR), London, and Sun Yat-sen University, China, reveals the role that lactate plays in repairing cancer cells' DNA after chemotherapy has damaged it.

Tackling chemotherapy resistance

Chemotherapy attacks cancer by damaging cells' DNA, so cells try to rapidly repair it as they attempt to survive and continue growing.

The researchers examined tissue from 24 patients with stomach cancer, where 15 of the cancers were resistant to chemotherapy and the tumors had continued to grow.

They found that lactate—which builds up in cancer cells as they convert their food source, glucose, to energy in a process called glycolysis that doesn't require oxygen—was most abundant in the chemotherapy-resistant cancer tissues. During glycolysis when there is limited oxygen, glucose is first turned into pyruvate and then lactate, by an enzyme called LDHA.

Targeting lactate build-up

To test if preventing a build-up of lactate could keep chemotherapy working for longer, the researchers targeted the LDHA enzyme with

stiripentol. Stiripentol is currently used to treat epilepsy and stops the LDHA enzyme from working.

In mice with stomach cancer, giving stiripentol and chemotherapy reduced the size of tumors—a response which continued to last for four weeks after treatment. The tumors of mice treated with chemotherapy alone shrunk for one week, before starting to grow again.

The mice treated with stiripentol and chemotherapy also survived for longer than those with chemotherapy alone; with chemotherapy, no mice survived for longer than 40 days after treatment, while those with the combination of drugs survived for more than 70 days.

The researchers, some of whom work in the Breast Cancer Now Toby Robins Research Center at the ICR, also found that the lactate is responsible for altering the structure of a key protein involved in DNA repair, called NBS1, and affecting its efficiency.

They examined samples from 94 patients with stomach cancer, prior to chemotherapy treatment. They found that higher levels of alteration of NBS1, higher levels of the NBS1 protein, and higher levels of the LDHA enzyme were all associated with poorer prognosis of the patients after chemotherapy.

The researchers believe that lactate may be responsible for stopping chemotherapy treatment working in other cancers, as levels of LDHA are increased in pancreatic, lung and ovarian cancers.

Professor Axel Behrens, Professor of Stem Cell Biology at The Institute of Cancer Research, London, said, "This extremely promising research has uncovered a likely mechanism for how cancer evades chemotherapy. The discovery that cancer cells create energy in a process that causes a build-up of lactate won the Nobel prize in 1931.

"What we have now found, almost 100 years later, is that lactate has a fundamental impact on cancers' ability to survive, as it boosts the DNA repair process after it has been damaged by chemotherapy treatment.

"In our early-stage study we've seen that you can prevent the build-up of lactate and make a tumor that was resistant to chemotherapy become sensitive again—the treatment continues to work.

"The next step is to test this in a clinical trial, and it would be wonderful if we see the same results in people and give people with cancer precious extra time living well. As we already have a drug to target lactate in clinical use, this discovery could reach patients even sooner."

Professor Kristian Helin, CEO of The Institute of Cancer Research, London, said, "Drug resistance remains one of the biggest challenges we face in treating cancer. While chemotherapy is effective for many patients, we need to stay one step ahead to prevent cancer becoming resistant to it.

"It's clear now that some patients will require a combination of therapies to keep their cancer at bay, and this study indicates an interesting new drug target that could keep chemotherapy working for longer.

"I look forward to seeing this research taken into clinical trials, to see if it could improve the outcome for people with stomach cancer, and hopefully other cancers too."

More information: Hengxing Chen et al, NBS1 lactylation is required for efficient DNA repair and chemotherapy resistance, *Nature* (2024). DOI: 10.1038/s41586-024-07620-9

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