Scientists develop approach for exploiting cancer's dietary demands

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Numerous studies in mice and cancer cells have shown cancer growth can be reduced in response to diets lacking serine. But results have been variable because some cancer cells are efficient in making their own serine, particularly those with a KRAS mutation which is found in several hard-to-treat cancers.

The scientists in a new study, funded by Cancer Research UK, found that restricting the amount of serine in the diet of mice, when given alongside a drug that prevents the body from making it, reduced tumor cell growth in several different models of bowel cancer.

If future work shows the limitation of serine in healthy people is possible, then it could lead to a new precision medicine approach to exploiting cancers' dietary weaknesses as cancer treatments.

Serine is an amino acid that is found in many foods, but can also be made by the body, and is one of the building blocks for making proteins. Cancer cells have been found to be more dependent on serine than their healthy counterparts due to their accelerated growth, suggesting a weakness that might be exploited for cancer therapy.

Scientists based at the Francis Crick Institute, and led by Professor Karen Vousden, Cancer Research UK's chief scientist, wanted to see if restricting serine in the diet in combination with a drug called PH755, which prevents cancer cells from making the amino acid, would be more effective at blocking cancer cell growth.

The researchers were able to inhibit bowel cancer cell growth, both in cell cultures in the lab as well as in organoids—3-D models of tumors which mimic some of the complexity of organs, using this dual approach.

Critically, in bowel cancer xenografts, where human bowel cancer cells are studied in a mouse model of the disease, they found that the combined approach significantly reduced the tumors' growth compared to either approach alone.

Encouragingly, PH755 had few side effects in the animal models.

Professor Karen Vousden said: "The idea of being able to develop dietary interventions, based on the understanding of mechanisms behind how changes

in nutrients affect tumors, has the potential to unlock a powerful way to treat cancer.

"In the future this could provide a basis for developing a precision medicine approach to diet as a cancer therapy, much as we do with targeted drugs. Personalizing each individual's diet to target the nutritional demands of cancer could, alongside other therapies, give people the best opportunity to respond to treatment."

The researchers hope that this two-pronged approach could work in a range of cancers, including those with KRAS mutations, and could provide an additional way to tackle the disease alongside current treatments, such as chemotherapy.

Michelle Mitchell, chief executive at Cancer Research UK, said: "Understanding the fundamental biology of cancer through studies like this is vital for revealing the true complexity of the disease, and can shed light on new treatment avenues. This research has given us a tantalizing glimpse into how we can turn cancer's dietary dependencies against it, and we look forward to seeing if the approach works in people."

Martin Ledwick, Cancer Research UK's head information nurse, said: "While it's encouraging to see the potential of targeting cancer's nutritional demands to help treat the disease, it's important to remember that this is early research in mice and cells, and people with cancer shouldn't change their diets in light of this. We need to see if this work translates into cancer in humans before testing to see if diet changes are helpful."

More information: Mylène Tajan et al. Serine synthesis pathway inhibition cooperates with dietary serine and glycine limitation for cancer therapy, *Nature Communications* (2021). DOI: 10.1038/s41467-020-20223-y