Metformin could one day be used to treat malignant tumors

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A*STAR researchers have provided strong evidence, using patient tumor grafts, that metformin, a common diabetes drug, might help fight colorectal cancer in humans.

Metformin's potential as a tumor-suppressing agent, to prevent the growth of breast, colon, lung and prostate cancers, has been demonstrated in pre-clinical studies. However, the experimental models used in these studies do not accurately recreate the natural manifestations of the disease, and require toxic levels of metformin to demonstrate beneficial effects.

Min-Han Tan and a group of researchers from A*STAR's Institute of Bioengineering and Nanotechnology (IBN), the Biological Resource Centre, and the Genome Institute of Singapore, with collaborators from hospitals across Singapore, have now tested metformin's cancer-fighting abilities on a model of colorectal cancer that is more representative of how the disease appears in humans.

The team took samples of cancer tissue from two patients and implanted them in mice, then assessed how the tumors responded to metformin as well as 5-fluorouracil, the current front-line treatment for colorectal cancer.

They found that metformin inhibited tumor growth by at least 50 per cent after 24 days and, when combined with 5-fluorouracil, inhibited the tumor grafts from one patient by 85 per cent. The experiments used concentrations of metformin equivalent to that used to treat diabetes in humans.

In previous studies, scientists typically injected cancer cells into host animals rather than transplanting tissue directly. In these models, high glucose, insulin, and growth factor levels are needed to establish cell cultures for injection. Tan's group suspects that this artificial environment meant previous studies needed higher levels of metformin to stunt tumor growth as, in this study, they were able to demonstrate response using therapeutic doses of the drug: "We tested a wide range of concentrations down to the physiological," says Tan. "It was important to show that there was a response at that level, as many studies have not documented that."

The IBN-led collaboration discovered that metformin enacted its therapeutic benefits by activating a cellular pathway implicated in the inhibition of cancer, and by reducing cancer cell oxygen consumption. Using next-generation genetic sequencing, the team also provided evidence that direct patient tissue grafts in mice retain the genetic, molecular, and tissue features of the original tumor—making them ideal platforms to study colorectal cancer and its treatment.

It's believed that this is the first investigation into metformin and colorectal cancer using patient tumor grafts. Tan says that future studies could shed light on metformin's relevance as a therapeutic agent for cancer: "Our study shows that metformin has a possible activity against colorectal cancer, using gold-standard materials, and provides a mechanism to explain this. Further clinical trials are now needed."

More information: Nur-Afidah Mohamed Suhaimi et al. Metformin Inhibits Cellular Proliferation and Bioenergetics in Colorectal Cancer Patient–Derived Xenografts, *Molecular Cancer Therapeutics* (2017). DOI: 10.1158/1535-7163.MCT-16-0793

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