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Study reveals how cancer drug causes diabetic-like state

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Scientists at Dana-Farber Cancer Institute have discovered why diabetic-like symptoms develop in some patients given rapamycin, an immune-suppressant drug that also has shown anti-cancer activity and may even slow ageing.

Rapamycin is widely used to prevent organ rejection and is being tested as a cancer treatment in clinical trials.

About 15 percent of patients, however, develop insulin resistance and glucose intolerance after taking the drug; until now, scientists had not identified the reason.

In a study published in Cell Metabolism, the researchers report that normal mice given rapamycin were more likely to have trouble regulating their blood sugar because of a drop in insulin signaling, which in turn was triggered by activity of a protein called Yin Yang 1, or YY1. But animals in which the YY1 protein was "knocked out" in their muscles had no such response to rapamycin – they were protected against the development of diabetes-like symptoms. This result pinpointed YY1 as the target of rapamycin responsible for the loss of normal insulin function.

One of the finding's implications is that physicians should consider giving anti-diabetes drugs along with rapamycin, says Pere Puigserver, PhD, senior author of the report.

The results also raise a caution flag for researchers and non-scientists who are excited about the potential for rapamycin to extend life, based on recent studies in animals including mammals, he notes.

"The possibility of increased diabetes risk needs to be taken into account" in further research on the anti-ageing properties of rapamycin and related compounds, says Puigserver.

Rapamycin is a drug derived from bacteria found on Easter Island, and was approved in 1999 by the FDA as an immunosuppressant in transplant patients.

One of its actions is to inhibit the important mTOR signaling pathway in cells (mTOR stands for "mammalian target of rapamycin"). The mTOR pathway is a critical factor in regulating the growth, proliferation, survival and motility of cells; elevated mTOR activity is a hallmark of many cancers.

In clinical trials rapamycin and a related drug are being evaluated in kidney cancer, brain tumors, and mantle cell lymphoma, among others. Intriguingly, rapamycin has been found in some experiments to extend healthy lifespan in yeast, flies and mammals, and delays age-related diseases, including cancer and atherosclerosis. But the raised risk of deleterious pre-diabetes symptoms has been a concern and something of a mystery. In 2007, Puigserver and colleagues reported in Nature that mTOR causes an increase in mitochondria – the cell's power plants – in skeletal muscles; suppressing mTOR activity with rapamycin led to a diabetic state. That research also revealed that among the proteins "downstream" of mTOR in the signaling pathway is Yin Yang 1 (YY1), a transcription factor – a protein that controls the expression of genes.

"We thought that maybe YY1 was responsible for the diabetic effects," says Puigserver. An increase in YY1 activity caused by rapamycin could

suppress the production of insulin and related hormones which are necessary for muscles to take up glucose (sugar) for energy and keep blood sugar levels stable.

To test that idea, they bred mice that lacked the YYI gene and protein in their skeletal muscles. When these mice were given rapamycin, it didn't affect their muscles' glucose uptake or insulin signaling – in effect, they were immune to the diabetic effects of rapamycin.

The investigators are continuing their studies: one goal is to discover why only a minority of human patients develop diabetes-like conditions with rapamycin treatment. One possibility that the risk is modulated by dietary factors, Puigserver says.

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