Common diabetes drug reverses inflammation in the liver

Salk researchers made new inroads into understanding how the commonly prescribed drug metformin works in the body

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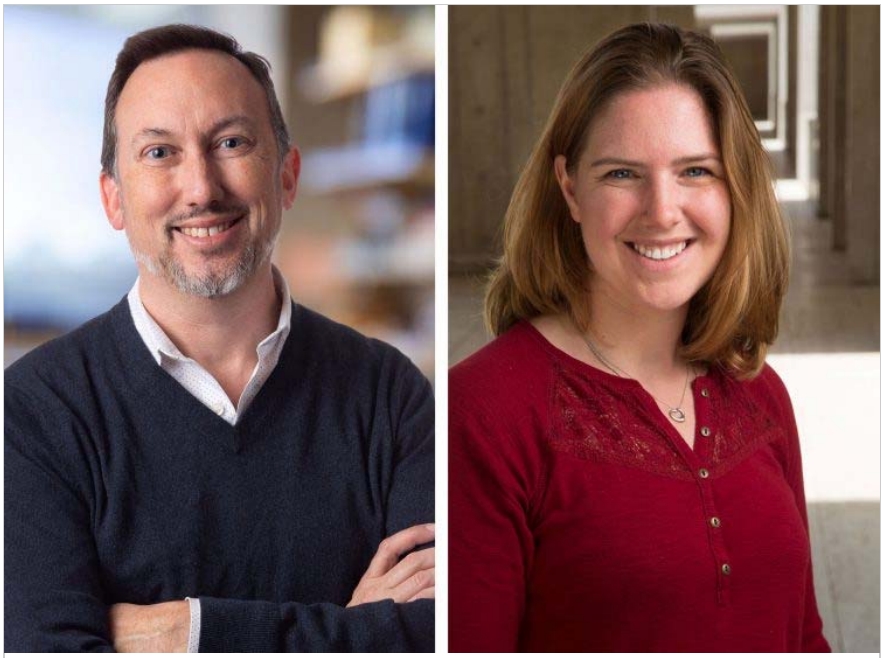
LA JOLLA—The diabetes drug metformin—derived from a lilac plant that's been used medicinally for more than a thousand years—has been prescribed to hundreds of millions of people worldwide as the frontline treatment for type 2 diabetes. Yet scientists don't fully understand how the drug is so effective at controlling blood glucose.

Now, researchers at the Salk Institute have shown the importance of specific enzymes in the body for metformin's function. In addition, the new work showed that the same proteins, regulated by metformin, controlled aspects of inflammation in mice, something the drug has not typically been prescribed for. Apart from clarifying how metformin works, the research, which appeared in the journal ***Genes & Development*** on September 10, 2020, has relevance for many other inflammatory diseases.

"These findings let us dig into precisely what metformin is doing at a molecular level," says **Reuben Shaw**, a professor in Salk's Molecular and Cell Biology Laboratory and the senior author of the new paper. "This more granular understanding of the drug is important because there is increasing interest in targeting these pathways for not only diabetes but immune diseases and cancer."

Researchers have known for 20 years that metformin activates a metabolic master switch, a protein called AMPK, which conserves a cell's energy under low nutrient conditions, and which is activated naturally in the body following exercise. Twelve years ago, Shaw discovered that in healthy cells, AMPK starts a cascade effect, regulating two proteins called Raptor and TSC2, which results in a block of the central pro-growth protein complex called mTORC1 (mammalian target of rapamycin complex 1). These findings helped explain the ability of metformin to inhibit the growth of tumor cells, an area of research that began to generate excitement after Shaw and others connected AMPK to a bona fide cancer gene in the early 2000s.



From left: Reuben Shaw and Jeanine Van Nostrand.
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Credit: Salk Institute

But in the intervening years, many additional proteins and pathways that metformin regulates have been discovered, drawing into question which of the targets of metformin are most important for different beneficial consequences of metformin treatment. Indeed, metformin is currently entering clinical trials in the United States as a general anti-aging treatment because it is effects are so well established from millions of patients and its side effects are minimal. But whether AMPK or its targets Raptor or TSC2 are important for different effects of metformin remains poorly understood.

In the new work, in mice, Shaw and his colleagues genetically disconnected the master protein, AMPK, from the other proteins, so they could not receive signals from AMPK, but were able to otherwise function normally and receive input from other proteins.

When these mice were put on a high-fat diet triggering diabetes and then treated with metformin, the drug no longer had the same effects on liver cells as it did in normally diabetic animals, suggesting that communication between AMPK and mTORC1 is crucial for metformin to work.

By looking at genes regulated in the liver, the researchers found that when AMPK couldn't communicate with Raptor or TSC2, metformin's effect on hundreds of genes was blocked. Some of these genes were related to lipid (fat) metabolism, helping explain some of metformin's beneficial effects. But surprisingly, many others were linked to inflammation. Metformin, the genetic data showed, normally turned on anti-inflammatory pathways and these effects required AMPK, TSC2 and Raptor.

"We didn't go looking for a role in inflammation, so for it to come up so strongly was surprising," says Salk postdoctoral fellow and first author Jeanine Van Nostrand.

People suffering from obesity and diabetes often exhibit chronic inflammation, which further leads to additional weight gain and other maladies including heart disease and stroke. Therefore, identifying

an important role for metformin and the interrelationship between AMPK and mTORC1 in control of both blood glucose and inflammation reveals how metformin can treat metabolic diseases by multiple means.

Metformin and exercise elicit similar beneficial outcomes, and research has previously shown that AMPK helps mediate some of the positive effects of exercise on the body, so among other questions, Shaw and Van Nostrand are interested in exploring whether Raptor and TSC2 are involved in the many beneficial effects of exercise, as well.

“If turning on AMPK and shutting off mTORC1 are responsible for some of the systemic benefits of exercise, that means we might be able to better mimic this with new therapeutics designed to mimic some of those effects,” says Shaw, who holds the William R. Brody Chair.

In the meantime, the new data suggest that researchers should study the potential use of metformin in inflammatory diseases, particular those involving liver inflammation. The findings also point toward AMPK, Raptor and TSC2 more broadly as potential targets in inflammatory conditions, suggesting the need for a deeper investigation of metformin, as well as newer AMPK agonists and mTOR inhibitors, the researchers say.

Other researchers on the study were Kristina Hellberg, Alina Dayn, Jingting Yu, Maxim Shokhirev and Yelena Dayn of Salk; and En-Ching Luo, Eric Van Nostrand and Gene Yeo of the University of California San Diego. The work was supported by grants from the National Institutes of Health and the Damon Runyan Cancer Research Foundation.

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