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New pathway towards treatments for inflammatory diseases

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A molecule thought to play a key role in some inflammatory diseases can be switched off by two widely used medicines, new research has shown.

Scientists at the Universities of Bradford and Glasgow (UK) have identified a new biochemical pathway that can be controlled using metformin - a medicine used by diabetics to control blood sugar levels - and salicylate - the main ingredient in aspirin.

The researchers now hope to conduct further studies and eventually clinical trails with the drugs, which are already prescribed to millions of patients around the world, for a range of inflammatory disorders.

Professor Tim Palmer, a pharmacologist at the University of Bradford who led the research, said: "While our studies are at a very early stage, we've identified a new biochemical process that suggests certain anti-diabetic drugs could potentially be repurposed to treat diseases caused by activated Janus kinase proteins."

Janus kinase (JAK) proteins - named after the ancient Roman two-faced god - are involved in controlling inflammation in certain tissues. They act like gatekeepers at the surface of cells, reacting to signals released by the immune system and transmitting these messages inside the cell.

These Janus kinase proteins, however, can also carry mutations that make them faulty so they are permanently turned on and become overactive. A fault like this in Janus kinase 1 (JAK1) has been found to

occur in several diseases.

Professor Palmer and his colleagues have found another protein, known as AMP-activated protein kinase (AMPK), is able to turn JAK1 off - even when it is faulty.

According to their findings, published in the journal *Science Signaling*, it does this by chemically altering two key amino acids in the JAK1 protein in a process called phosphorylation. They also showed metformin and salicylate can activate AMPK so it turns off JAK1 in this way.

Professor Palmer said: "We found this AMPK pathway is able to profoundly inhibit JAK signalling and it seems to work in a way that other drugs that target the JAK proteins do not."

The researchers believe this approach could also be used to turn off other Janus kinase proteins, which are known to be overactive in other diseases.

Co-author Dr Ian Salt, a senior lecturer at the Institute of Cardiovascular and Medical Sciences at the University of Glasgow, added: "Although it is still early in our work, our findings suggest we can design future therapies for those disorders that target this pathway. Indeed, as AMPK is known to be stimulated by a number of existing anti-diabetic drugs, these should be investigated as potential drugs to treat those disorders."

More information: C. Rutherford et al, Phosphorylation of Janus kinase 1 (JAK1) by AMP-activated protein kinase (AMPK) links energy sensing to anti-inflammatory signaling, *Science Signaling* (2016). DOI: 10.1126/scisignal.aaf8566