Scientists discover promising off-switch for inflammation

28 March 2018

Scientists have discovered a new metabolic process in the body that can switch off inflammation. They have discovered that 'itaconate'—a molecule derived from glucose—acts as a powerful off-switch for macrophages, which are the cells in the immune system that lie at the heart of many inflammatory diseases including arthritis, inflammatory bowel disease and heart disease.

The scientists, working in the School of Biochemistry and Immunology in the Trinity Biomedical Sciences Institute at Trinity College Dublin, hope their discovery will have relevance for inflammatory and infectious diseases—and that their findings may also help to develop much-needed new drugs to treat people living with these conditions.

Professor of Biochemistry at Trinity, Luke O'Neill, was, along with Dr. Mike Murphy of the University of Cambridge, the joint leader of the work just published in leading international journal *Nature*. The discoveries were made using both human cells and mice as a model organism.

Professor O'Neill said: "My lab has been exploring metabolic changes in macrophages for the past six years and we've come across what we think is the most important finding yet."

"It is well known that macrophages cause inflammation, but we have just found that they can be coaxed to make a biochemical called itaconate. This functions as an important brake, or off-switch, on the macrophage, cooling the heat of inflammation in a process never before described."

Dr. Evanna Mills, who, with Dylan Ryan was joint first author of the work, said: "The macrophage takes the nutrient glucose, whose day job it is to provide energy, and surprisingly turns it into itaconate. This then blocks production of inflammatory factors, and also protects mice from the lethal inflammation that can occur during infection."

Dylan Ryan added: "We've found that itaconate can directly modify a whole host of proteins important for inflammation in a chemical reaction never before described, and that this reaction is important for the anti-inflammatory effects of itaconate."

The discovery is very much on the frontier of inflammation research and Professor O'Neill and his collaborators are now exploring its relevance to the onset and development of inflammatory and infectious diseases. They are also keen to explore whether the findings can be exploited in the effort to develop new anti-inflammatory medicines.

The work was a collaboration with Harvard Medical School, the University of Cambridge, the University of Oxford, Johns Hopkins University, the University of Dundee, and GlaxoSmithKline, where both Professor O'Neill and Dr. Mills spent time on sabbatical.

Professor O'Neill said: "This discovery and the new research pathways it has opened up will keep us busy for some time but we are hopeful that it will one day make a difference to patients with diseases that remain difficult to treat."

More information: Evanna L. Mills et al, Itaconate is an anti-inflammatory metabolite that activates Nrf2 via alkylation of KEAP1, *Nature* (2018). DOI: 10.1038/nature25986

Provided by Trinity College Dublin