Natural metabolite can suppress inflammation

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The was image inspired by draw-bridges of Saint Petersburg depicts Itaconate disrupting the TCA cycle flow. Credit: © Aleksandra Ziminova

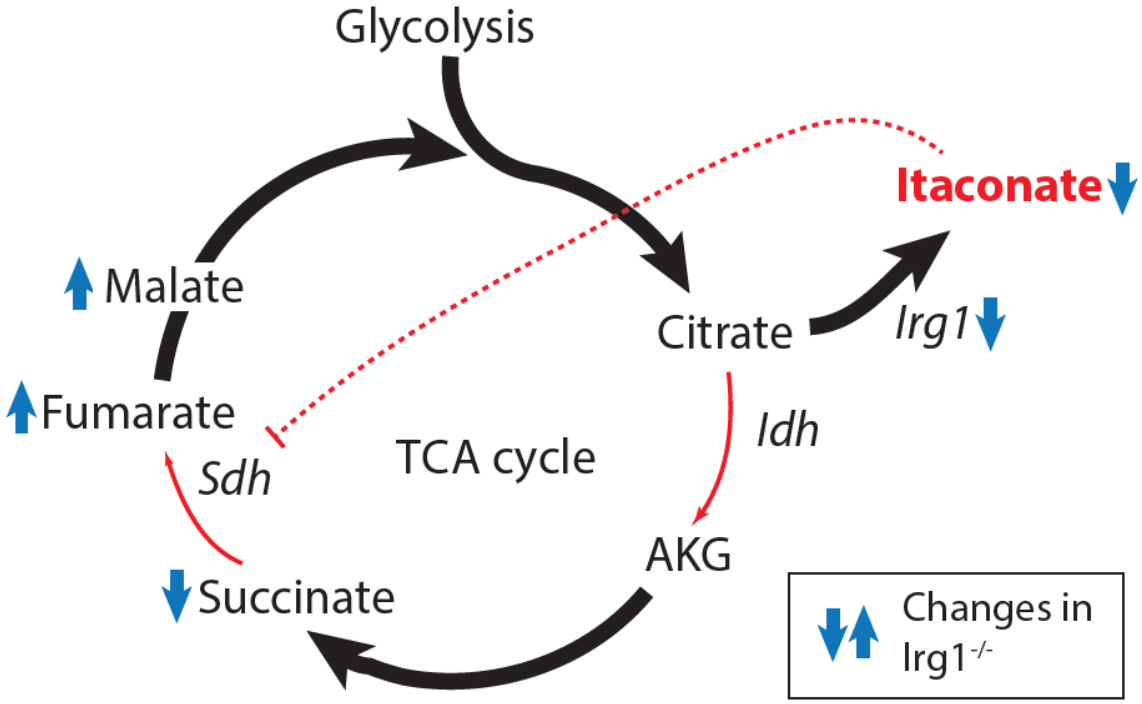
An international group of scientists from the U.S., Canada, Germany and Russia has revealed a naturally occurring organic compound that can suppress the pro-inflammatory activity of macrophages. The compound, itaconate, is released in large quantities by macrophages, but until now, its role has been poorly understood. Now, scientists have found evidence that itaconate acts as an antioxidant and anti-inflammatory agent. These properties make itaconate promising for the treatment of pathologies caused by excessive inflammation or oxidative stress. Such conditions may be associated with cardiac ischemia, metabolic disorders and perhaps autoimmune diseases. The findings were published in *Cell Metabolism*.

The work was based on the study of macrophages—immune system cells in charge of fighting pathogens. An important feature of macrophages is their ability to switch between different states depending on the concentration of substances in the body. In total, there are three such states: M0 (neutral), M1 (pro-inflammatory) and M2 (anti-inflammatory).

M1 macrophages are the first to arrive at the site of infection. As they begin to swallow viruses and bacteria, an intense inflammatory process kicks in. This process may adversely affect the entire organism if the macrophages are overly diligent. Inflammation consumes energy resources and can lead to numerous complications, or even death. In order to mitigate the negative consequences of the inflammatory response, it is important to understand how to reduce the excessive proinflammatory effect of macrophages.

An in-depth study of macrophage metabolism during the transition from inactive to proinflammatory states helped researchers identify itaconate as a substance that suppresses macrophage-related inflammations. Describing the working mechanism of itaconate resulted from a complex map of metabolic pathways in macrophages that was developed by the

group.



The metabolic cycle for energy production in a macrophage cell is shown. Credit: ITMO University

Itaconate is produced by macrophages when they switch from the M0 inactive state to the M1 pro-inflammatory state. If the concentration of itaconate increases to a defined limit, macrophage activation falls. "Itaconate sets the bar controlling M1 macrophage formation," says Alexey Sergushichev, one of the authors of the paper. "Without this substance, the inflammation would increase more than required. In the future, with the help of itaconate, it will be possible to artificially manipulate the transition of macrophages from M0 to M1, meaning the possibility of restraining inflammation. The influence of itaconate on

macrophages is a delicate mechanism that can ensure high selectivity of the immune system regulation."

Prior to the study, guesswork with respect to the function and origin of itaconate generated a lot of speculation. But the new study shows that itaconate plays the role of immune regulator. To understand how itaconate reduces the activity of immune cells, the researchers examined the so-called Krebs cycle, or tricarboxylic acid cycle, and cellular respiration (processes that produce vital substances and energy from the oxidation of glucose in cells). Having done so, the scientists identified two bottlenecks that can be influenced to reverse the reaction and send it another way.

The Krebs cycle is preceded by signal transmission between cells through oxygen-sensitive pathways. Itaconate blocks the enzyme Sdh (succinate dehydrogenase), which not only ensures the functioning of the tricarboxylic acid cycle but also links the cycle to cellular respiration and signaling pathways.

Thus, itaconate acts on both functions of the Sdh enzyme, adjusting the cells' Krebs cycle and respiration. When the enzyme is blocked in macrophages, both processes are interrupted, and this impairs the cells' activation. "Notably, itaconate acts as an anti-oxidant and anti-inflammatory agent," says Vicky Lampropoulou, the lead author of the paper and researcher at the laboratory of Maxim Artyomov at Washington University in St. Louis. "At the same time, itaconate is naturally produced by mammalian immune cells. These features make it attractive for use in adjuvant therapy for numerous diseases in which excessive inflammation and oxidative stress associate with pathology, like heart ischemia, metabolic disorders, and perhaps even autoimmunity."

The researchers have already demonstrated that they can use itaconate to

reach the desired effect in living organisms. Experiments with mice have shown that the substance reduces damage after heart attack, acting via the same mechanism of locking the Sdh enzyme. However, according to the scientists, more work is needed to successfully apply the method to humans.

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