A new 'on' signal for inflammation

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(Medical Xpress)—Inflammation is an important response in the body - it helps you to kill off invaders such bacteria that could cause a harmful infection. But if it's chronic or uncontrolled, inflammation can also cause trouble in conditions including rheumatoid arthritis, inflammatory bowel disease and a potentially fatal immune reaction to infection called sepsis.

A new study involving UCD researchers has discovered a signal that appears to trigger inflammation when the threat of a bacterial infection looms, and the experiments have also been able to block the signal in lab models, pointing to possible new approaches to treating inflammatory diseases.

The study, which was published in *Nature* and led by Trinity College Dublin, found that in the presence of a potential bacterial threat, immune cells called macrophages change how they burn energy. This switch in burning eventually leads to the build-up of a molecule called succinate in the cells, and this in turn triggers a chain of biochemical events that encourage inflammation.

One link in that chain is a molecule called hypoxia-induced factor 1a (HIF-1a). HIF-1a is best known for its role in helping you adapt to conditions of low oxygen, such as when you climb a high mountain and the ambient oxygen levels dip, explains Conway Fellow, Professor Cormac Taylor from UCD School of Medicine & Medical Science.

"When you go to high altitude, this factor gets expressed in cells and that helps to increase the number of red blood cells in your blood, so you can

adapt to the lower oxygen," he explains.

But that's not the only place that HIF-1a has a job to do. "At time of stress including inflammation you also experience an activation of this HIF pathway," says Prof Taylor. "And previous work in our lab has looked at this in models of inflammatory bowel disease."

In the new study, which was led by Prof Luke O'Neill at Trinity, Prof Taylor and Research Fellow Dr Eoin Cummins from UCD helped to work out that in macrophages sensing a bacterial threat, the build-up of succinate seems to 'tell' HIF-1a to switch on an inflammatory gene.

"In this case, HIF drives a gene called interleukin-1, which is a potent pro-inflammatory gene," explains Prof Taylor. "And that will contribute to the inflammatory process."

The new study makes an important link between energy burning processes in the immune system and an 'on' signal for inflammation, according to Prof Taylor. The research also showed that a drug usually used for epilepsy was able to tone down this succinate/HIf-1a pathway in a lab model of sepsis, and this could point to new approaches to intervening when inflammation is running out of control, he adds.

"It's a big emerging area, the links between metabolism, or energy burning, and inflammation in disease," says Prof Taylor. "And in the future we could be targeting these metabolic pathways for beneficial purposes in inflammation."

Provided by University College Dublin