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Scientists find potential new targets for anti-inflammatory therapies

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A team led by scientists at The Scripps Research Institute (TSRI) has identified key signaling proteins in the inflammation process that contribute to the development of inflammatory diseases such as rheumatoid arthritis, psoriasis, sepsis and inflammatory bowel diseases. The finding highlights possible new ways of treating these inflammation disorders, which sicken or kill millions of people around the world each year.

"We hope our approach will lead to the development of drugs that augment current anti-inflammatory strategies," said TSRI Assistant Professor Young Jun Kang, who was the principal investigator for the new study, which was reported recently in the journal *Science Signaling*.

The inflammatory signaling pathway in question is an ancient one that can be found in a range of evolutionarily disparate species, from fruit flies to humans. Working as a primary defense system against bacteria and other intruders, it is triggered by a special set of receptors on white blood cells called Toll-like receptors (TLRs), which recognize molecular patterns associated with common microbes.

When they have detected a foe in this way, TLRs switch on the production, within their host cells, of a variety of inflammatory and anti-microbial compounds. These include the inflammatory protein TNF-? (tumor necrosis factor alpha), a cause of fever and malaise in systemic infections, and also a contributor—when produced for too long—to inflammatory disorders such as rheumatoid arthritis, psoriasis and

inflammatory bowel disease.

TNF-? also features heavily in the condition called sepsis, a runaway process of inflammation in the bloodstream that can end up damaging vital organs, lowering blood pressure to life-threatening levels (septic shock) and causing blood to coagulate within vessels throughout the body. Sepsis as a result of bacterial infection kills a quarter of a million people in the U.S. each year.

As Kang and other investigators have shown, this type of inflammation typically has an early, acute phase and a late, sustained phase, the two phases being driven by distinct clusters of signaling molecules. Ideally, to treat or prevent inflammatory disorders, one would want to suppress the late phase while leaving the early phase intact to fight ordinary infections—and this has been Kang's aim for most of the past decade. In a study published in 2007 when he was a postdoctoral fellow at TSRI, Kang identified an immune cell protein called 4-1BBL as a critical factor in the late phase of a common type of inflammation triggered by the receptor TLR4.

In the new study, Kang and his colleagues examined 4-1BBL and its signaling partners in more detail to better understand the pathway and to find suitable drug targets.

In a series of experiments with cultured cells, Kang's colleagues Research Associates Jianhui Ma and Bo-Ram Bang were able to show that in late-phase, TLR4-triggered inflammation, 4-1BBL depends heavily on two other key proteins, TIRAP and IRAK2.

TIRAP appeared to be particularly important. Blocking its interaction with 4-1BBL by removing its gene from cells or by applying a specific chemical inhibitor, reduced late-phase inflammation—as shown by a big drop in TNF-? production. In mice with TLR4-triggered sepsis,

inhibiting TIRAP again worked to reduce TNF-? levels and extended the animals' survival.

Kang and his laboratory now plan to test anti-inflammation therapeutic strategies, such as small chemicals and recombinant proteins that target the TIRAP-4-1BBL interaction, with the hope of eventually being able to develop a new class of anti-inflammatory therapy.

As Kang notes, current anti-inflammatory therapies typically aim to reduce TNF-? activity, for example with antibodies, after the protein has already been produced. His strategy has the potential advantage that it targets an earlier part of the process and thereby suppresses TNF-? production—nipping it in the bud, so to speak.

"We think that this will at least complement the current strategy," Kang said.

More information: "The Tumor Necrosis Family Member 4-1BBL Sustains Inflammation by Interacting with TLR Signaling Components During Late-Phase Activation," stke.sciencemag.org/cgi/conten … /abstract/6/295/ra87

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