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Stifling danger signals in rheumatoid arthritis

Blocking an inflammatory pathway may offer a new way to treat autoimmune disease.

By Eric Bender | Aug 17, 2016

Like hybrid cars, your cells can choose between two sources of energy. There's an efficient aerobic source and a less-efficient, albeit rapid source known as glycolysis, which can work without oxygen and is triggered under inflammatory stress.

Novartis Institutes for Biomedical Research (NIBR) scientists now have revealed details about how an acid called succinate gets exported from cells when they switch to glycolysis, and how this can amplify the autoimmune response that drives rheumatoid arthritis. Additionally, the researchers have found a promising molecular target—the succinate receptor GPR91—for dampening this response and treating the disease, which manifests as a chronic condition of the joints.

When macrophages (immune cells) in joint fluid are exposed to inflammatory stress, they ramp up the glycolysis pathway and begin releasing succinate around them, says Amanda Littlewood-Evans, an investigator in NIBR's Autoimmunity Transplantation and Inflammation group in Basel, Switzerland. Her group has shown that this exported succinate binds to GPR91, which is expressed on macrophages. That action then kicks off an amplified release of an immune signaling protein called IL-1beta, further driving a cascade of inflammation.

If these macrophages sitting in your joints "suddenly receive a hint that something's amiss, they become activated and release succinate as a danger signal that prepares their neighbors for imminent peril," sums up Littlewood-Evans, lead author on a **paper** recently published online in the *Journal of Experimental Medicine*.

The team's work suggests that GPR91 blockers may be promising candidates for the treatment of rheumatoid arthritis, a common chronic illness associated with pain, physical disability and increased mortality risk. Scientists don't understand what initially launches the autoimmune attack in rheumatoid arthritis. The disease's severity and symptoms differ widely among patients, and various drugs treat the symptoms with varying degrees and periods of effectiveness.

"It's a really complex disease," says Littlewood-Evans. "We need to unravel the underlying mechanisms and search for new drug targets."

Making joint progress

Her team's research builds on studies by José Carballido, an executive director in the Autoimmunity Transplantation and Inflammation group, and senior author on the paper. In a 2008 **Nature Medicine paper**, Carballido and his colleagues showed that human and mouse dendritic cells (immune cells) had high expression of GPR91. They also found evidence in humans and mice suggesting that GPR91 can raise an alarm for immunological danger.

Littlewood-Evans followed up on clues linking GPR91 and succinate to rheumatoid arthritis. For one thing, GPR91 is expressed in macrophages, and macrophages are major drivers of rheumatoid arthritis. Moreover, other research groups found high levels of succinate in the joint fluids of patients with the disease.

Beginning their study in mouse models of rheumatoid arthritis, Littlewood-Evans and her colleagues found that GPR91 was abundantly expressed on macrophages, which also release plenty of succinate under inflammatory conditions.

Additionally, when the researchers incubated such mouse macrophages with joint fluid from patients with rheumatoid arthritis, they saw that the macrophages released cytokines such as IL-1beta. “The more succinate in the joint fluid, the more pro-inflammatory cytokines are produced, so you can almost think of succinate as a biomarker for the disease,” she says. The scientists also found that in mouse models of arthritis, mice that lacked GPR91 expression showed diminished symptoms.

Overall, she says, “activated macrophages export succinate as a danger signal, and that released succinate binds to GPR91 on other macrophages and then enhances the production of pro-inflammatory mediators such as IL-1beta, which make the disease even worse.”

A potential drug target and biomarker

Mice lacking GPR91 expression appear normal in every way, one early suggestion that side effects from a GPR91 inhibitor may be acceptable, she adds.

Succinate may be a good biomarker for indicating which patients with arthritis might benefit from GPR91 inhibition, says Tobias Junt, senior co-author on the paper and investigator in the Autoimmunity Transplantation and Inflammation group. However, Junt notes, it may not be practical to tap into human joints to take a sample. “If succinate isn’t accessible in joints or found in high concentrations in the blood, an alternative biomarker in the blood indicating pathway activity could be helpful for patient stratification,” he says.

Several organs besides joints show elevated expression of GPR91, the scientists note, and they speculate that GPR91 inhibitors might help to address other illnesses driven by macrophage inflammation. “GPR91 may be an excellent target for other autoimmune diseases, particularly those with a relapsing pattern, like multiple sclerosis,” suggests Carballido.

Main image: Scientist Amanda Littlewood-Evans and her group have discovered a promising new target to treat rheumatoid arthritis. Photo by Marta Sanchez-Oro.

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