New anti-inflammatory agents silence overactive immune response

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A new way to fight inflammation uses molecules called polymers to mop up the debris of damaged cells before the immune system becomes abnormally active, researchers at Duke University Medical Center report.

The discovery, published Monday in the journal Proceedings of the National Academy of Sciences, offers a promising new approach to treat inflammatory auto-immune disorders such as lupus and multiple sclerosis, which are marked by an overactive immune response.

"Depending on the disease, cells that are damaged drive or perpetuate the immune response," said Bruce A. Sullenger, Ph.D., director of the Duke Translational Research Institute and senior author of the study. "We have shown that we can inhibit that process."

Sullenger said the idea for the new approach stems from earlier findings by Duke scientists and others that dying and diseased cells spill nucleic acids - the building blocks of life that include DNA and RNA - that then circulate at high levels in the bloodstream.

While DNA and RNA inside the cell regulate important functions such as growth and division, outside of cells in the blood, these nucleic acids serve as powerful signals to the immune system that something is amiss. Once activated, the immune system launches an attack to fight whatever caused the cell damage, whether an infection or toxic substance. Under normal circumstances, this inflammatory response eventually restores order.

In some cases, however, the inflammatory response becomes persistent and out of control, leading to tissue damage and causing symptoms such as fever and pain. Chronic inflammation has been implicated in lupus, multiple sclerosis, obesity, psoriasis, irritable bowel syndrome, arthritis and numerous other maladies.

The Duke scientists, working to interrupt this cycle, focused on a set of molecules called nucleic acid binding polymers that were designed to infiltrate the nucleic acid inside of cells and deactivate specific immune triggers.

"Then we had a 'eureka moment,'" Sullenger said. "Because the inflammatory nucleic acids are outside of cells, whereas DNA and RNA normally function inside cells, we realized that the polymers could bind to the external nucleic acids without disrupting intracellular functions of DNA and RNA."

It was a simple mop-up approach, and it worked as planned in experiments on mice: "We could use the polymers as molecular scavengers - sponges to go around and soak up and neutralize those inflammatory nucleic acids so the immune system doesn't recognize them and go into the overdrive of inflammation," Sullenger said.

David S. Pisetsky, M.D., Ph.D., a rheumatologist at Duke and co-author of the study, said the anti-inflammatory approach has numerous potential applications, not only for auto-immune disorders, but also for the acute tissue damage of severe bacterial and viral infections, shock and injuries.

"One setting to test the effects of the polymers involves acute events such as injuries, where it may be easier to measure the presence of the nucleic acids in the blood and the effects of polymer binding," Pisetsky said, adding that the long-term safety of the new anti-inflammatory approach in humans remains unknown.

Sullenger said patents have been filed on the finding, and the team is pressing ahead to develop therapies. "At some level we've opened up this huge treasure chest of opportunities and now we have to figure out which way to go," he said.

Provided by Duke University Medical Center