Cells that make our insides slick also calm our spleens

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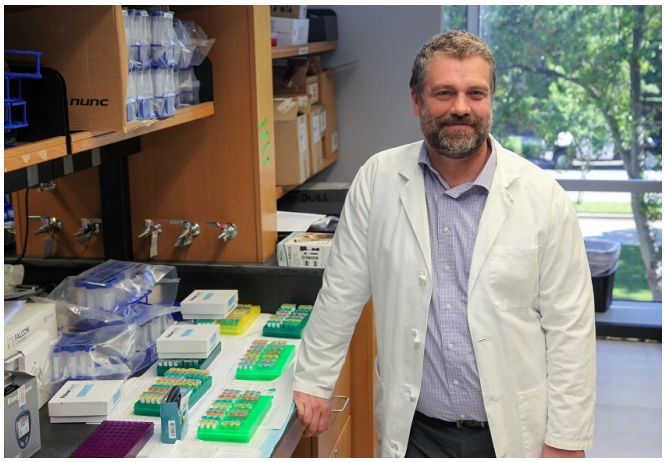

Dr. Paul O'Connor, renal physiologist in the Department of Physiology at the Medical College of Georgia Credit: Phil Jones, Senior Photographer, Augusta University

It's called icing sugar spleen, when the usually purplish organ looks like it has been dipped in unhealthy white icing, and the surface is bumpy and thick.

This inexplicable, altered look is a surprisingly common finding on autopsy. Now scientists have found that the simple act of slightly repositioning the spleen for just a few seconds—as might be needed during a surgery near the fist-sized organ that sits just above the stomach—can produce this look and alter the function of this organ known to help modulate the immune response.

The unhealthy bottom line is that even a momentarily repositioned spleen appears to stop enabling a healthy balance between inciting an immune attack when needed and keeping it from going overboard, to instead primarily promoting inflammation, says Dr. Paul O'Connor, renal physiologist in the Department of Physiology at the Medical College of Georgia at Augusta University.

The MCG scientist says the transformation likely indicates an also surprising role of the mesothelial cells surrounding the organ, which is like a big lymph node full of immune cells.

Mesothelial cells form a slippery, protective tissue that lines the inside of body cavities like the chest and abdomen, providing a slick, safe environment so our organs don't bump up against each other. More recently mesothelial cells have been found to also have a role in the immune response, and O'Connor's lab has evidence that includes a direct line of communication with immune cells in the spleen and perhaps beyond.

The more traditional way we think of the spleen being aware of a bacterial invader, for example, is when it shows up in the blood passing through it. "We think through these mesothelial cells, it's possible they are actually signaling the spleen to say 'Hey I have an infection,' before it even gets into the blood or into the spleen," O'Connor says.

He thinks this potentially overlooked role of mesothelial cells could mean breaking their connection to the spleen is bad. He also thinks the usual anti-inflammatory message the cells seem to send the spleen may be of help in controlling out-of-control immune responses like deadly sepsis, an overreaction to an invader, typically a bacterium, where instead of protection the result is organ damage, precipitous blood pressure drops, shock and death. Sepsis is a leading cause of death of hospitalized patients, effects about 1.7 million Americans annually, killing about 270,000, and it's on the rise, according to the National Institute of General Medical Sciences.

Sepsis aside, O'Connor reasons these are important answers to pursue since the spleen is often moved in surgical procedures, breaking connections now thought to have a limited role. "This would indicate it is functional, and if you break it during surgery, there are consequences that we

may not have recognized."

A two-year, $422,719 pilot grant (1R21AI150723-01) from the National Institute of Allergy and Infectious Diseases, is helping his lab further pursue both angles.

"We want to know if the mesothelium really does work like an early warning system for the spleen and, if it does, if you move the spleen, are those connections ever restored or not," O'Connor says. Without the connections, they suspect the spleen responds like there is always an invader coming its way.

They have some evidence that these mesothelial cells around the spleen essentially provide a regular dose of healthy, anti-inflammatory signals to the organ by releasing the neurotransmitter acetylcholine, which activates the alpha7 nicotinic acetylcholine receptor, or ?7nAChR, which inhibits the release of proinflammatory cytokines. In fact, it's known that deleting the receptor ?7nAChR, results in a spleen that promotes inflammation, and they suspect the physical changes to the spleen's surface are an unsuccessful effort to try and reestablish these important connections. One of the things they are looking at with the new grant is whether reconnection is ever successful.

Traditionally, neurons have been thought to have this key role in the body's reflex response to infection with the vagus nerve, which also regulates basics like heart rate and digestion, releasing acetylcholine which activates the receptor ?7nAChR which tamps down an inflammatory response in many organs. But O'Connor's team has evidence that, at least with the spleen, mesothelial cells actually take on a neuron-like function, even have little projections like neurons, called synapses, that enable neurons to communicate, and the message they send also is anti-inflammatory.

His lab came across the dynamic when studying the anti-inflammatory response to bicarbonate, and getting rid of the spleen and its anti-inflammatory role in the process. While they found the spleen does mediate the anti-inflammatory response to bicarbonate, they did find some surprises in their sham control group. In this group, they also made an incision like they were going to remove the spleen but only repositioned it for a few seconds. They found the inflammatory response was as severe as removing the spleen. They also witnessed the physical changes to the spleen itself within a couple of weeks: The surface turned grayish, hardened and thick. Others have noted similar physical changes to the spleen in the lab, but why it happens has remained elusive.

The new grant is enabling O'Connor's lab to further explore their theory that the simple disruption can result in prolonged, systemic inflammation; and they predict the receptor on mesothelial cells is key as well to the spleen's calming role in inflammation. So they also are knocking the receptor out in mesothelial cells to look at the impact and suspect it will be inflammation.

They also are disrupting these connections with surgery but this time not touching the spleen, then measuring the immune response 24 hours, 21 days and three months later in response to an infection to see if the proinflammatory state occurs and abates, if the spleen resumes its previous physical state and mesothelial cells and the spleen regain what they think is their previously unknown biological connection.

In 2018, O'Connor and his colleagues reported in The Journal of Immunology that simple baking soda encourages the spleen to promote a fairly widespread anti-inflammatory state in the body. They found sodium bicarbonate becomes a trigger for mesothelial cells all around the spleen to tell the organ that there is no need to mount an immune response, that it's more likely the remnants of a meal rather than an infection coming their way. They also saw the neuron-like behavior of mesothelial cells which appeared to be talking to the spleen with the help of the chemical messenger acetylcholine.

The receptor ?7nAChR is found in the spleen, brain and elsewhere and involved in many body processes, including long-term memory, and has a role in immunity, inflammation and neuroprotection.

Deadly sepsis, O'Connor says, is like a strong

allergic reaction: "What kills you often is the overt inflammatory response, so you don't die from the bug, you die from your own body's over-the- top inflammatory response to it. It's your immune response that kills you, not the bug."

"If you break your arm, it swells up and goes red, you get more blood flow to that area," he says as blood vessels dilate to let in more blood because you need more immune cells to fight the infection. "It turns out you can't do that to all your organs at the same time because you don't have enough blood and that is what happens in septic shock," O'Connor says. Instead your blood pressure falls and you go into potentially deadly septic shock.

Provided by Medical College of Georgia at Augusta University