Fragments of cell powerhouse trigger immune response that leads to kidney damage, failure after trauma

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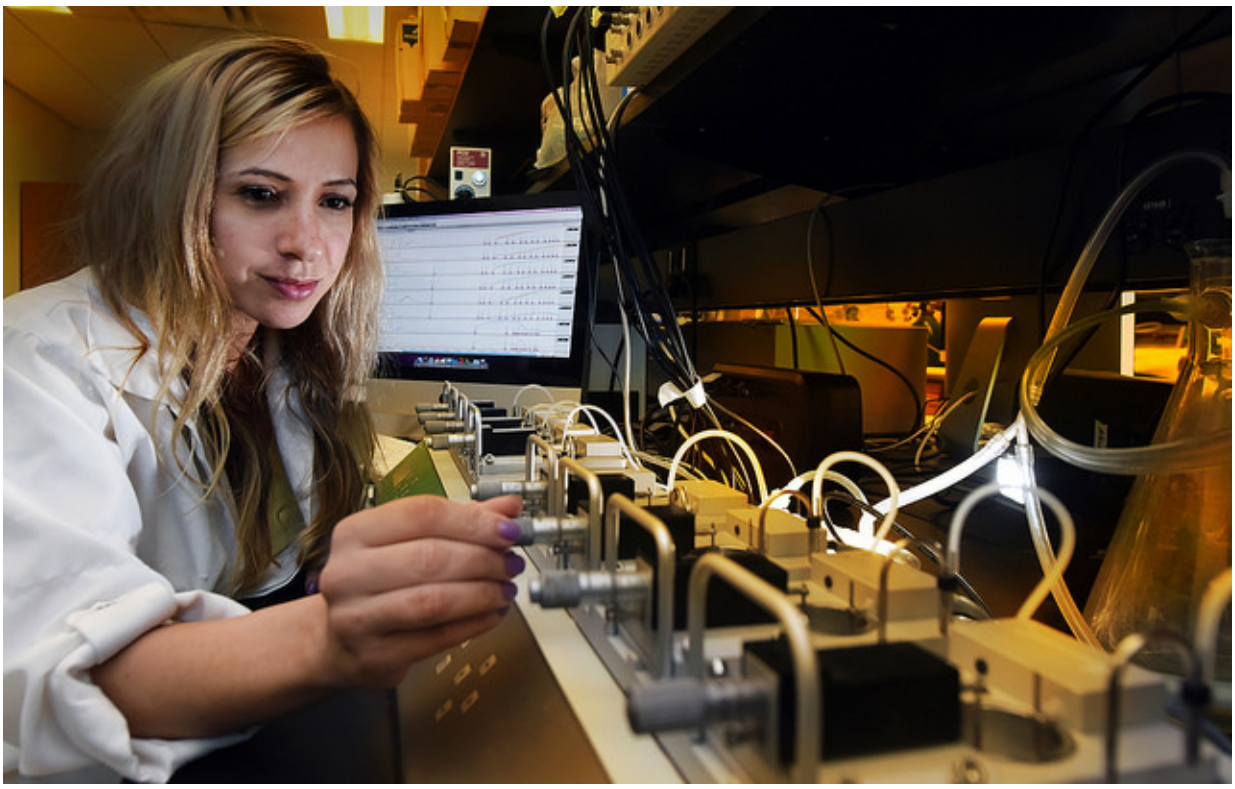

Dr. Camilla Ferreira Wenceslau, cardiovascular physiologist and postdoctoral fellow in the Department of Physiology at the Medical College of Georgia at Augusta University. Credit: Phil Jones

Following major trauma like a car crash, debris from the powerhouses of

damaged cells appear to make their way to an immune system outpost in the kidneys, setting in motion events that can permanently damage or destroy the organs.

The interesting theory backed up by early scientific evidence has caught the imagination of a young investigator wanting to prevent the kidney damage and death that occurs in a high percentage of trauma patients.

"My question is why does the kidney die or have damage," said Dr. Camilla Ferreira Wenceslau, cardiovascular physiologist and postdoctoral fellow in the Department of Physiology at the Medical College of Georgia at Augusta University.

A new $1 million Pathway to Independence Award from the National Institute of General Medical Sciences is helping her find answers that appear to go back to the biological irony that mitochondria, or cell powerhouses, while essential to every cell's function, have their own distinctive DNA. That distinction, which scientists believe dates back to the days when mitochondria were bacteria, makes them look like an invader to the immune system when trauma, for example, causes cell contents to get dumped into the body's circulation.

"Dying cells start releasing their mitochondria and other inflammatory substances," Wenceslau said. While cell death may be common, the huge volume that can occur with major trauma can quickly become problematic throughout the body. While mitochondria also can't survive outside a cell, their dying fragments can cause an extensive immune stir.

These fragments have been shown to contribute to bodywide inflammation called systemic inflammatory response syndrome, or SIRS as well as sepsis, widespread infection, which typically has a clear bacterial basis. SIRS and sepsis are the major causes of death of trauma patients in the United States. Part of the resulting havoc is a major, rapid

dilation of blood vessels, likely to ensure easy access by immune system workers such as macrophages that need to clean up the mess. But the result is also a dramatic drop in blood pressure, reduced perfusion of the body as well as organs like the kidney that are very vascular and leaky blood vessels that prompt swelling and further compromise blood flow.

While the immune system, which is largely housed in the gut, is clearly a player, Wenceslau is among the investigators putting together how immune system outposts, called formyl peptide receptors, in the heart, blood vessels, kidneys, and likely elsewhere, also get activated by the circulating mitochondrial debris, called N-formyl peptides, and help sound the alarm.

Curious why the receptors were present in the vascular system she studies, Wenceslau has already watched the scenario play out in the lab in the cardiovascular system, as she infused mitochondrial fragments into rats, watched receptors get activated and saw a rapid decline in blood pressure, much as if she had inserted a foreign bacteria. When she blocked the receptors, it blocked the reaction.

"These receptors recognize bacteria like the immune system, but we didn't understand their function in the cardiovascular system," she said. "We thought maybe the receptor in the cardiovascular system contributes to the hypotension (very low blood pressure) that can kill."

Now Wenceslau wants to know more about the odd presence and function of the formyl peptide receptors in the kidneys. They have some evidence trauma releases the mitochondrial fragments in humans with SIRS and that kidney dysfunction is a consequence. The new grant will enable them to learn more about how the kidney damage occurs. They propose that high levels of this mitochondrial debris make its way through the wide-open blood vessels to the kidneys, activate the immune system substation Wenceslau found there, and the result is arterial

dysfunction and, ultimately, acute kidney injury. She hopes that piecing together this puzzle will ultimately lead to therapies that protect the kidney from damage or destruction.

She's looking both in human arteries from the kidney - procured by her collaborator Dr. Olaf Grisk in the Department of Physiology at Germany's University of Greifswald - as well as an animal model of acute kidney injury she is developing. To suppress the formyl peptide receptor, Wenceslau is using several drugs related to the immunosuppressive drug cyclosporine, which is used to help patients avoid rejection of a transplanted organ.

Wenceslau, her mentor Dr. R. Clinton Webb, chairman of the MCG Department of Physiology, and others reported in 2013 the hypothesis that trauma released the mitochondrial fragments that activate the formyl peptide receptors in the arteries, triggering vascular collapse and inflammation and setting the stage for sepsis. Webb and Dr. Paul O'Connor, renal physiologist at MCG, are her mentors for the new NIH-funded project.

Other hallmarks of SIRS include a rapid heart rate and breathing, and a plunging body temperature and high white blood cell count, a sign of infection, while no obvious bacterial infection is detected.

Provided by Medical College of Georgia at Augusta University