Researchers discover new method to reduce disease-causing inflammation

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Researchers at the University of Georgia report in the *Journal of Biological Chemistry* that an enzyme known as Tumor Progression Locus 2, or Tpl2, plays a key role in directing and regulating several important components of the body's immune system. Their discovery may one day lead to new treatments for many common autoimmune diseases.

"We know that immune dysfunction plays a serious role in a number of conditions, and we need better methods for controlling chronic inflammation," said Wendy Watford, assistant professor of infectious diseases in UGA's College of Veterinary Medicine and principal investigator for the study. "Our laboratory is searching for ways to disrupt the fundamental cellular processes that cause inflammation and disease."

The human immune system is an extraordinarily complex system of cells, proteins, tissues and organs that, when everything works properly, search out and destroy disease-causing toxins and pathogens like bacteria and viruses. But sometimes it becomes confused, and the microscopic troops that normally attack only invaders turn their weapons on healthy tissues.

The resulting inflammation caused by wayward defense cells is associated with a number of autoimmune diseases and conditions, including diabetes, obesity, depression, heart disease, stroke, respiratory disease and certain cancers.

Watford and her colleagues conducted tests with genetically modified mice lacking the Tpl2 enzyme in which they stimulated the animal's immune system and observed the behavior of several proteins known as chemokine receptors.

Chemokines act like a dispatcher, alerting the immune system's army of white blood cells to potential threats and directing them to problem areas.

The researchers found activity of three chemokine receptors—known as CCR1, CCR2 and CCR5—were reduced in Tpl2 negative mice. With these proteins operating at reduced capacity, fewer of the white blood cells commonly associated with autoimmune disease are able to accumulate at inflamed tissues where they can attack healthy tissue.

While reducing Tpl2 expression may ease the burden of many painful and debilitating disorders, it also weakens the immune system, making it harder for the body to fight off bacteria, viruses, parasites and cancerous cells.

"A number of laboratories throughout the world have researched the inhibition of chemokine receptors as a potential therapy for a variety of disorders," Watford said. "We still face a number of hurdles, but we hope that this may one day serve as the foundation for a new approach to disease treatment."

The research group is planning additional tests using mouse models that mimic the symptoms of rheumatoid arthritis to see if Tpl2 inhibition will reduce inflammation and ease symptoms.

"This is an emerging field," Watford said. "We have a lot of work to do, but many of our preliminary results are promising."

Provided by University of Georgia