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Organs are not just bystanders, may be active participants in fighting autoimmune disease

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Organs affected by autoimmune disease could be fighting back by "exhausting" immune cells that cause damage using methods similar to those used by cancer cells to escape detection, according to a study by researchers at the University of Pittsburgh School of Medicine published today in the *Journal of Clinical Investigation*.

The conclusions, based on studies in mouse models of systemic lupus erythematous (SLE) - referred to as lupus—could explain why autoimmune diseases may take a long time to cause significant organ damage. They could also explain how widely used cancer immunotherapy drugs can have deleterious autoimmune side effects on normal organs.

"These findings really turn our current understanding of autoimmune tissue damage on its head and suggest that we could more effectively treat these diseases if we can develop targeted methods to enhance the body's natural ability to tune down the immune system," said senior author Mark Shlomchik, M.D., Ph.D., UPMC endowed professor and chair, Department of Immunology, Pitt School of Medicine, and an investigator at the UPMC Immune Transplant and Therapy Center.

In autoimmune diseases like lupus, immune cells that normally protect against invaders, such as bacteria or cancer cells, instead begin to recognize the body's own cells as foreign and attack them. In lupus nephritis, a kidney disease associated with SLE, a large number of these autoreactive cells—called kidney infiltrating T cells (KITs) - were

thought to be activated, causing damage over time.

Wondering how exactly these cells cause kidney damage, Jeremy Tilstra, M.D., Ph.D., an assistant professor of medicine at Pitt and a researcher in Shlomchik's lab, began to study them in three different mouse models of lupus nephritis.

As the researchers expected, there were millions of KITs in the kidney, but surprisingly, they were not highly active as had previously been thought.

"The T cells were there, but they weren't aggressively active, in fact, it was the exact opposite," said Tilstra. "They were sluggish, ineffective killers and didn't divide very well, which was completely unexpected."

Experiments showed that these KITs did not respond to stimulation like normal T cells—they neither released characteristic inflammatory proteins, nor did they reproduce very well. The cells also took up and used much less energy, displaying signs of metabolic exhaustion.

Interestingly, the exhausted KITs were quite similar to T cells found inside tumors. The affected kidney cells also resembled tumor cells in certain ways, as they expressed higher levels of a protein called PD-L1, which cancer cells use to suppress T cells that enter the tumor.

"Our findings suggest that the body is capable of actively fighting back against autoimmune diseases, not sitting idly by. The similarity between T cells in lupus-affected kidneys and in tumors has important implications," noted Shlomchik. "It suggests that the ability to suppress T cells is not an abnormal mechanism that cancer cells have somehow developed to defeat the immune system, rather it's an existing natural mechanism against autoimmune disease that tumors have adopted to their advantage."

In the future, the researchers plan to expand the study to patients with lupus to see if they can find similar exhausted T cells in urine or tissue samples.

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