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New insight may lead to better detection and treatment of autoimmune disorder Sjögren's syndrome

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The autoimmune disorder Sjögren's syndrome is often overlooked or misdiagnosed because the symptoms are similar to other conditions. Its characteristic symptoms are dry eyes and dry mouth, and reduced tear production is used as part of the diagnosis. However, researchers from the University of Southern California (USC) Roski Eye Institute believe that distinct changes in the composition of tears may occur before tear production lessens. They found a protein called cathepsin S present only in the tears of patients with Sjögren's syndrome, and in a new study in *American Journal of Physiology—Cell Physiology*, link its presence to proteins involved in tear secretion.

Sjögren's syndrome affects an estimated four million people in the U.S and nine out of 10 patients are women. The disease is caused by immune cells attacking the mucous membrane and fluid-secreting glands. Although its characteristic symptoms are in the eyes and mouth, the disease is systemic—it affects the entire body—and can damage other organs including kidney, liver and brain. Patients with Sjögren's syndrome also have a higher risk of developing lymphoma. Despite the prevalence of the disease, how the disease starts and develops is not well-understood, says Sarah Hamm-Alvarez, PhD, vice chair of basic research and professor of ophthalmology at the USC Roski Eye Institute and lead investigator of this study. No therapies specific to Sjögren's exist, and current treatments only manage the symptoms. "Earlier detection and treatment would offer the potential to prevent some of

these serious systemic effects and the opportunity to prevent serious damage and loss of glandular tissue beyond repair," Hamm-Alvarez says.

A previous study from Hamm-Alvarez's group found that the tears of patients with Sjögren's syndrome had higher amounts of cathepsin S—a protein that breaks down other proteins and helps cells get rid of waste—while patients with dry eyes not due to Sjögren's did not have cathepsin S in their tears. "We think that the large increase in tear cathepsin S is a fairly robust biomarker for Sjögren's syndrome-mediated dry eye," Hamm-Alvarez says.

In this new study, Hamm-Alvarez and her research team sought more evidence to understand the abnormal secretion of cathepsin S. They focused on proteins involved in the tear secretion process, Rab3D and Rab27. Using genetically modified mice, the researchers saw that mice missing Rab3D had more cathepsin S in their tears while mice lacking Rab27 had less cathepsin in their tears. Rab3D and Rab27 counteracted each other, and loss of Rab3D may increase the influence of Rab27, contributing to the release of cathepsin S in the tears of patients with Sjögren's syndrome, the researchers wrote.

To help develop better therapies for Sjögren's syndrome, the research team is currently exploring how cathepsin S interacts with the tear production process and the eye surface. It is also investigating Rab3D's molecular pathway to find drug targets that can restore tear production.

More information: Zhen Meng et al. , *American Journal of Physiology - Cell Physiology* (2016). DOI: 10.1152/ajpcell.00275.2015

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