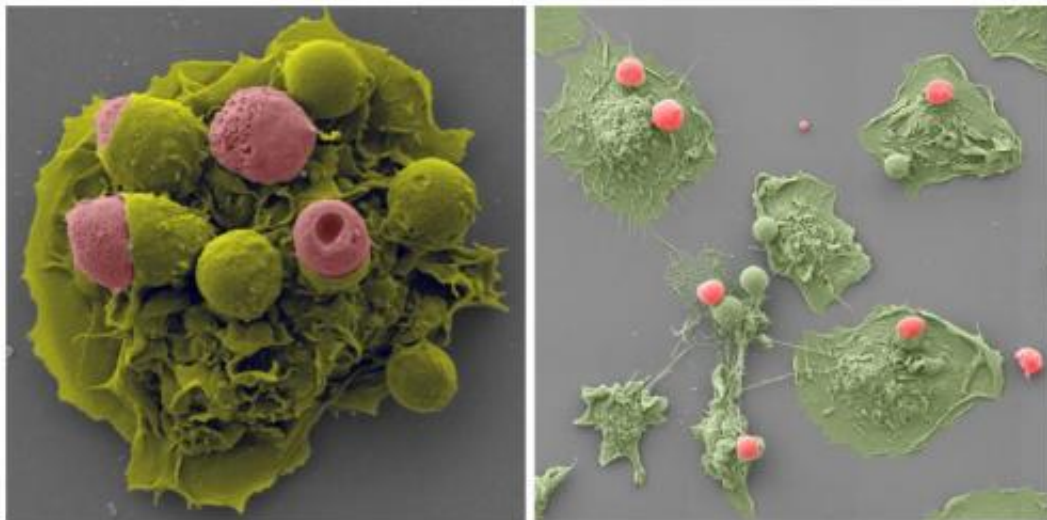


Scientists identify how immune cells use two critical receptors to clear dead cells from the body

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In an inflammatory environment (left) and normal environment (right) macrophages (green) engulf dead cells (pink). Credit: Anna Zagorska and Matt Joens, Waitt Advanced Biophotonics Center, Salk Institute

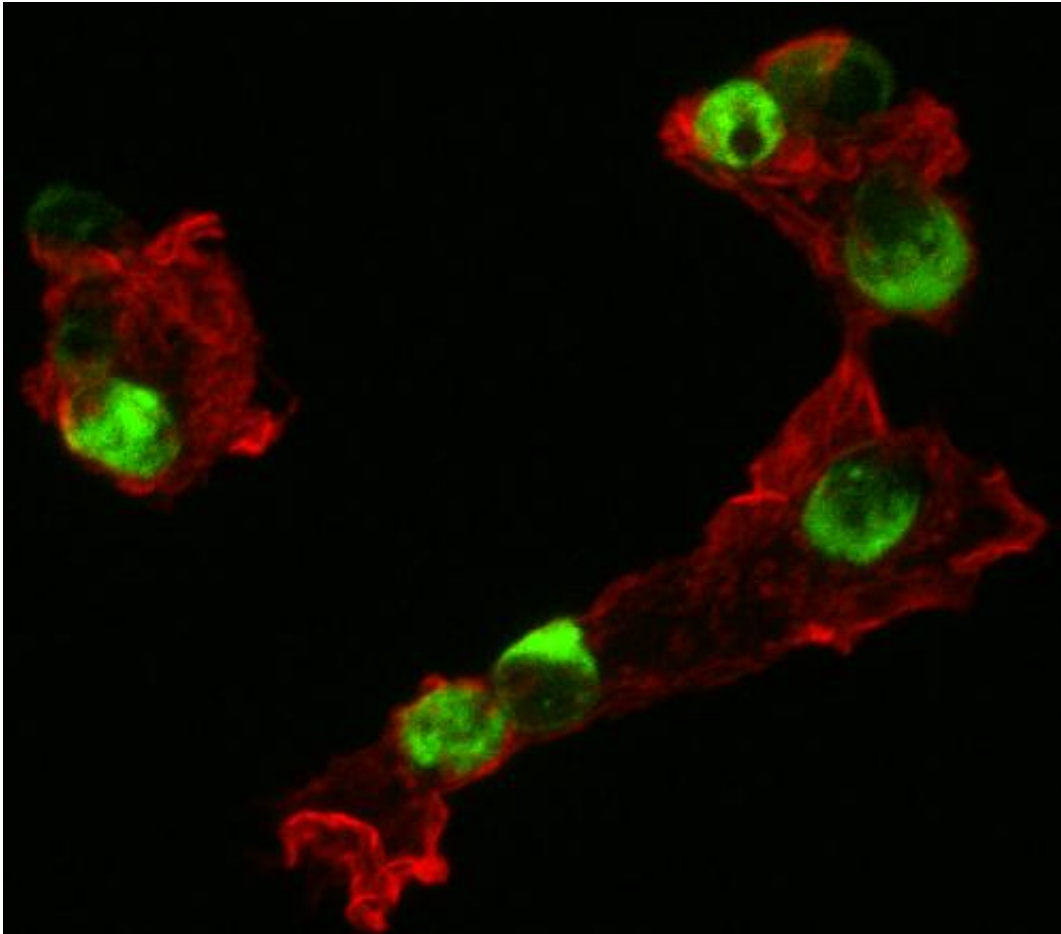
In most of the tissues of the body, specialized immune cells are entrusted with the task of engulfing the billions of dead cells that are generated every day. When these garbage disposals don't do their job, dead cells and their waste products rapidly pile up, destroying healthy tissue and leading to autoimmune diseases such as lupus and rheumatoid arthritis.

Now, Salk scientists have discovered how two critical receptors on these garbage-eating cells identify and engulf [dead cells](#) in very different environments, as detailed today in *Nature Immunology*.

"To target these receptors as treatments for autoimmune disease and cancer, it's important to know exactly which receptor is doing what. And this discovery tells us that," says senior author of the work Greg Lemke, Salk professor of molecular neurobiology and the holder of Salk's Françoise Gilot-Salk Chair.

The garbage-disposing cells, known as macrophages, have arrays of receptors on their surface, two of which—called Mer and Axl—are responsible for recognizing dead cells in normal environments and inflamed environments, respectively. Mer operates as a "steady-as-she-goes" receptor, clearing out dead cells in healthy tissues on a daily basis. Axl, in contrast, acts as an "all-hands-on-deck" receptor, kicking macrophages into action in inflammatory settings that result from infection or tissue trauma. These inflamed environments have many more dead cells.

"We thought Axl and Mer were doing the same job, and they are: they both recognize a so-called 'eat me' signal displayed on the surface of dead cells. But it turns out that they work in very different settings," says Lemke, whose lab first discovered the two receptors—which, along with a third, make up the TAM family—two decades ago. Lemke and colleagues explored the roles of TAM receptors in the brain initially, but observed that the absence of these receptors had dramatic effects on the immune system, including the development of autoimmune disease. The receptors have since become a growing focus for cancer and autoimmune research, and previous work has found that these three receptors are important in other areas, including the intestines, reproductive organs and vision.



Vast numbers of dead cells are cleared from inflammatory sites to enable the efficient resolution of inflammation. The image shows inflammatory macrophages (red) engulfing dead cells (green). Credit: Anna Zagórska, Salk Institute

"This basic research focus allowed us to discover a completely new aspect of immune regulation that no one—including any immunologist—had known about before," adds Lemke.

In the new work, the researchers found multiple critical differences between Axl and Mer. For example, the receptors use different molecules—called ligands—to be activated: Axl has a single such ligand

and, once engaged, is quickly cleaved off of the surface of the macrophage. Levels of the free-floating Axl in the blood have turned out to be an accurate, general biomarker for inflammation, quickly showing up in the circulation after tissue trauma or injury.



From left to right: Salk professor Greg Lemke, Erin Lew, Anna Zagorska, and Paqui Gonzalez. Credit: Salk Institute for Biological Studies

"We compared the behavior and regulation of the receptors, and the results were very striking," says first author Anna Zagórska. "In response to many different pro-inflammatory stimuli, Axl was upregulated and Mer was not. In contrast, immunosuppressive corticosteroids, which are widely used to suppress inflammation in people, upregulated Mer and

suppressed Axl. These differences were our entry point to the study."

Next, the researchers are looking into each receptor's activity in more detail. The team is finding that these receptors are unusual in that they have a three-step binding procedure, whereas most cell receptors bind in one step. Exploring and understanding this process will help to lead to more targeted therapeutics for cancers and other diseases in which the [receptors](#) are thought to act.

More information: Diversification of TAM receptor tyrosine kinase function, *Nature Immunology*, [dx.doi.org/10.1038/ni.2986](https://doi.org/10.1038/ni.2986)

Provided by Salk Institute

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