“In biology, the ability to turn something on is always coupled with a mechanism to turn it off. In the absence of this regulation, a biological system is akin to the ‘Sorcerer’s Apprentice,’ who set in motion a chain of events over which he had no control. TAM receptors play this role in the immune system: They regulate the innate immune responses to bacteria, viruses and other pathogens, ensuring that it is strong enough to defeat these threats, but not so strong that it endangers the host.”

Antigen-presenting cells or APCs, which provide the body’s first line of defense against disease-causing bacteria and viruses, are constantly on the prowl in search of pathogens. When they encounter foreign invaders, they unleash a “cytokine storm”—a wave of chemical messengers that jumpstart the T and B cell response. When the invaders have been successfully vanquished, the APCs need to shut down; otherwise, chronic inflammation ensues, overwhelming the regulatory mechanisms that normally distinguish “self” from “non-self,” leading to autoimmune diseases such as lupus and rheumatoid arthritis.

Lemke and his team explored how the so-called TAM receptors (Tyro3, Axl, Mer) in mice stop the immune system from mounting an out-of-control, destructive inflammatory response against invading pathogens. When receptors studded on the surface of patrolling APCs encounter a pathogen, the cells release an initial burst of cytokines, which is then amplified in a second stage through cytokine receptors. But this same activation pathway trips the fuse that is designed to prevent the inflammatory response from spiraling out of control.

The researchers found that a stimulator of inflammation—the type 1 interferon receptor (IFNAR)—turns on the expression of Axl, a TAM receptor. Axl and IFNAR then physically bind together and activate SOCS genes, whose products are potent inhibitors of pro-inflammatory signaling pathways. Without TAM receptors, they discovered, the APCs never shut down after their initial activation, but remain in a state of red alert.

Knowing how important TAM receptors are to the control of inflammation in mice will not only aid our understanding of human immune system disorders but might enable researchers to manipulate the switch in ways that could be clinically beneficial. For example, a drug that inhibited TAMs in the short term could be given along with a therapeutic vaccine in order to help the body mount a better immune response. Conversely, it may be possible to engage the TAMs early in an immune reaction to treat chronic autoimmune diseases such as lupus.

For more information, please visit www.salk.edu/faculty/lemke

From left to right: Becky Hensley, Anna Zagórska, Paqui Gonzalez, Tomas Vacik, Patrick Burrola, Greg Lemke, Jennifer Oh, Ian Dransfield, Lawrence Fourageaud, Erin Lew, Joseph Hash