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"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,' in that it sets in motion a chain of events over which it has no control. Our work on the TAM receptors has revealed that they play this role in the immune system: They regulate the innate immuneresponses to bacteria, viruses, and other pathogens, ensuring that it is strong enough to defeat these threats, but not so strong that 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, a chronic inflammation ensues, overwhelming the regulatory mechanisms that normally distinguish "self" from "non-self," leading to autoimmune diseases such as lupus and rheumatoid arthritis.

In their latest study, 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 via a feed-forward loop working 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 an essential 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
salk.edu/faculty/lemke.html

Left to right:

Back row: Carla Rothlin, Michael Reber, Amy Blount, Nick Bevins, Asa Gardner, Patrick Burrola, Joe Hash

Front row: Thomas Vacik, Lawrence Fourgeaud, Erin Lew, Greg Lemke, Becky Hensley