Molecular 'trip switch' shuts down inflammatory response

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Like a circuit breaker that prevents electrical wiring from overheating and bringing down the house, a tiny family of three molecules stops the immune system from mounting an out-of-control, destructive inflammatory response against invading pathogens, researchers at the Salk Institute for Biological Studies have found.

Without these critical molecules — known as TAM receptor tyrosine kinases — patrolling immune cells on the look-out for danger would never cease activating the body's defense system once they find an alien microbe, and the body would suffer, say the Salk investigators, whose findings appear in the Dec. 14 issue of the journal *Cell*.

"A truism in biology is that if you turn something on, you have to be able to turn it off, and we have found an essential switch that controls immune inflammation," said the study's senior investigator, Greg Lemke, Ph.D., a professor in the Molecular Neurobiology Laboratory. "The TAM signaling network represents a previously unknown, yet powerful and broadly acting, pathway for the inhibition of inflammation."

The findings suggest that researchers might be able to manipulate the switch in ways that would be clinically beneficial, said Carla V. Rothlin, Ph.D., a postdoctoral researcher in the Lemke lab and the study's lead author. "For example, a drug that inhibited TAMs in the short term could be given along with a therapeutic vaccine, be it one against infectious microorganisms such as anthrax or against cancer cells, in

order to help the body mount a better immune response," she said.

"Conversely, it may be possible to engage the TAMs early in an immune reaction in order to treat chronic autoimmune diseases such as lupus," Rothlin said. "Knowing how important TAM receptors are to the control of inflammation in mice will aid our understanding of human immune system disorders."

The findings are the culmination of a decade of study on TAM receptors by Dr. Lemke's laboratory. He and his colleagues have discovered that the three TAM genes (Tyro3, Axl, Mer), also known as the Tyro3 family, produce cell surface molecules known as receptor tyrosine kinases, which regulate diverse cellular processes. When the Lemke lab produced mice that lack all three TAM receptors, the animals developed a severe autoimmune reaction, due to a malfunction in a subclass of antigen-presenting cells, or APCs, which provide the body's first line of defense against disease-causing bacteria and viruses.

APCs constantly patrol the body's peripheral tissues (such as the skin and lining of the gut) 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 battled, the APCs go off duty and lymphocyte numbers and activity taper off.

Without TAM receptors, however, the APCs never shut down after their initial activation, but remain in a state of red-alert. Over time, the ensuing chronic inflammation overwhelms the regulatory mechanisms that normally distinguish "self" from "non-self", leading to autoimmune diseases such as lupus and rheumatoid arthritis.

In his latest study, supported by the Lupus Research Institute, Lemke and his team explored how TAM receptors give the "all clear" signal to

recall the emergency crews and discovered a self-limiting cycle of inflammation in dendritic cells (DCs) - APCs that play a key role in the immune response.

Patrolling DCs use toll-like receptors (TLRs) studded on their surface to "see" pathogens by recognizing their distinctive DNA patterns and configurations of cell surface proteins and sugars. Activation of TLRs leads to an initial burst of cytokines, which is then amplified in a second stage via a feed-forward loop working through cytokine receptors. In other words, TLRs turn on genes inside dendritic cells that then activate more cytokines on the cell surface.

But this same activation pathway also sows the seeds for the later inhibition of both cytokine receptor and TLR signaling. An essential stimulator of inflammation — the type 1 interferon receptor (IFNAR) — and its associated transcription factor, STAT1, turn on expression of Axl, a TAM receptor. Axl and IFNAR then physically bind together and induce the transcription of SOCS genes, whose products are potent inhibitors of both cytokine receptor and TLR signaling pathways.

This is the physical switch, the fuse that is tripped to shut down the inflammatory response, Lemke said. "It's a cool thing. TAM receptors can't work without binding to the interferon receptors, so that means that a pro-inflammatory signaling system is co-opted and re-directed to drive the expression of genes that will shut it down."

"Everything we have tested that stimulates DCs engages this circuit breaker," Rothlin says. "It's an essential switch that keeps the immune response in balance."

Source: Salk Institute