There's a new 'officer' in the infection control army

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Johns Hopkins scientists have identified a previously unrecognized step in the activation of infection-fighting white blood cells, the main immunity troops in the body's war on bacteria, viruses and foreign proteins.

"It's as if we knew many of the generals, colonels and majors and now we have discovered a new officer that helps the troops carry out the right battle plan," says Joel Pomerantz, Ph.D., an assistant professor of Biological Chemistry in the Institute for Basic Biomedical Sciences and member of the Institute for Cell Engineering at Johns Hopkins.

The discovery, published in *Molecular Cell* on December 10th also presents new opportunities to develop drugs to enhance the immune system, or to slow down hyperactive immune cells in cases of autoimmunity and cancer, Pomerantz says.

Faced with infection, the body's white blood cells are commanded by a protein — CARD11 — to either make more antibodies and white blood cells that attack the invader or to stand down and abort the mission.

The new research shows that CARD11 is under the control of GAKIN, another protein that supervises the directives given to each white blood cell. Because of CARD11's importance in the decision-making process, it needs a regulator to make sure it turns off when it's no longer needed to avoid the risk of hyperactivity. If too many T or B cells, particular types of white blood cells, are made or sent to battle infection, the

consequences can be cancer or autoimmune disease, Pomerantz says.

The discovery of GAKIN's role in immune cell activation began when researchers attached the gene that codes for luciferase — a natural protein that makes fireflies glow — to a gene that CARD11 turns on in response to an infection. This allowed them to see when a CARD11-responsive gene was turned on by measuring the amount of light released from the cells. Pomerantz's group discovered that the more GAKIN protein they added to the cells, the less the cells glowed, meaning that GAKIN represses these genes' activation.

In other experiments, the researchers learned that GAKIN has multiple ways of controlling CARD11 output. CARD11 can only turn on if all of the other specific key regulatory proteins — like a tactical team — are present. When researchers labeled the CARD11 protein with a red-colored tag and watched it under a microscope inside a white blood cell, they could see that CARD11 moved away from its tactical team activators to a different location in the cell shortly after the cell was alerted of an infection. But, CARD11 hung out longer with the tactical team activators in cells that had less GAKIN. According to Pomerantz, GAKIN can control CARD11 by moving it to another location in the cell away from the proteins that are needed to turn CARD11 on.

More information: Molecular Cell: www.cell.com/molecular-cell/

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