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How the Immune System Avoids Attacking Itself

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A finding by University of Pennsylvania School of Medicine researchers about how immune cells "decide" to become active or inactive may have applications in fighting cancerous tumors, autoimmune diseases, and organ transplant rejection.

Pathology and Laboratory Medicine Professor Gary A. Koretzky, MD, PhD, director of the Signal Transduction Program at Penn's Abramson Family Cancer Research Institute describes, in the current issue of *Nature Immunology*, one way in which T cells may develop tolerance to host cells and proteins. Koretzky and colleagues found that small fatty acids called diacylglycerols (DAGs), and the enzymes that metabolize them, are critical players in the molecular pathway that leads to activity versus inactivity.

Immune cells called T lymphocytes recognize invaders in the body, such as viruses, bacteria, tumor cells, or allergens. Normally, T cells are activated by a complex series of signals that end with the destruction of the foreign substance. However, some T cells are not activated, in fact they are inactivated by a process called anergy or tolerance. This process helps prevent immune cells from attacking themselves and other normal cells and proteins.

“How T lymphocytes become activated or inactivated has been one of the major questions in the field of immunology,” says senior author Koretzky. “Our discovery shows that DAGs are critical for T-cell activation so these cells can respond to foreign invaders. However, when

DAGs are chemically modified by enzymes called diacylglycerol kinases, T cells become tolerant or unresponsive to foreign substances and to self."

The discovery was made by studying mice that had been engineered to lack diacylglycerol kinases (DGKs). Although T cells from these knock-out mice were normal in most respects the induction of tolerance was impaired. When DAGs could not be chemically altered because the DGKs were absent, the T cells were hyperreactive to foreign antigens and could not be made tolerant to host cells.

Hyperreactivity was shown when purified T cells from DGK knockout mice were stimulated by antigen in a culture dish. The failure of the T cells to become tolerant was demonstrated in experiments where mice were treated with a toxin from staphylococcal bacteria that should have induced unresponsiveness. Instead, the T cells produced about five times more of an immunity factor than did cells from normal mice.

The hyperreactive state, if controlled, might be beneficial to the body under some circumstances; for example, some T cells might be made more effective at eliminating tumors. The research team is continuing to study DGK knock-out mice to see if they are more resistant to tumors. If the hyper-reactive T cells in these mice recognize the tumor cell as a foreign invader, then the tumor might be eliminated or reduced.

Conversely, if the tolerant state could be induced in a controlled manner, it might benefit individuals with autoimmune disease or help prevent rejection of transplants.

Co-authors, in addition to Koretzky, are Benjamin A. Olenchock and Martha Jordan from Penn, as well as Rishu Guo, Jeffery H. Carpenter, and Xiao-Ping Zhong from Duke University Medical Center and Matthew K. Topham from the University of Utah.

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