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Scientists Spot Key Autoimmune Disease Genes

By Jeffrey Perkel
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MONDAY, Jan. 22 (HealthDay News) -- The identification by U.S. scientists of genes thought to be key to autoimmune disorders could be a big step toward new treatments for these illnesses, which include lupus, rheumatoid arthritis and type 1 diabetes.

Cells called regulatory T-cells are supposed to help keep the immune system in check, but in autoimmune disease, these mechanisms can fail.

Now, researchers reporting this week in the journal *Nature* have identified a set of genes closely linked to regulatory T-cell function. The finding could have important implications for research into autoimmune disease and even cancer, experts say.

"This is certainly important in trying to understand how these regulatory T-cells work," said Dr. Noel Rose, director of the Johns Hopkins Center for Autoimmune Disease Research in Baltimore. "Whether this will have important functional implications, only time will tell," said Rose, who was not involved in the study.

Though it is meant to shield our bodies from all pathogens foreign and domestic, the immune system can be frustratingly temperamental. For example, when presented with cancer, the system basically shrugs. In other cases, the cell's defense department can sometimes go into overdrive, leading to autoimmune disorders like systemic lupus erythematosus and Graves' disease, where the body attacks its own cells.

Both of these situations are linked to the immune system's fundamental purpose: to distinguish the body's own cells (and related entities) from foreign invaders. So, cancer cells are ignored by the immune system because they are determined to be the body's own cells. Autoimmune disorders arise when the immune system gets confused and attacks healthy tissues.

In this study, researchers from Harvard Medical School, the Dana-Farber Cancer Institute, the Massachusetts Institute of Technology, and the Whitehead Institute for Biomedical Research focused on genes that help direct these processes via regulatory T-cells.

They focused on a protein that is found only in regulatory T-cells, called Foxp3. Foxp3 is a transcription factor -- that is, it dials up or down the production of other genes. Its significance in controlling the immune system is underscored by the fact that people with mutant Foxp3 genes develop IPEX, a syndrome marked by massive autoimmune disorders and early mortality.

Using sophisticated gene microarray technology, the team scanned the entire T-cell genome. "We identified a set of roughly 30 genes that are clearly regulated by Foxp3 and, surprisingly, a lot of them

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are suppressed by Foxp3," said study lead author Alexander Marson, a graduate student at Harvard Medical School and MIT.

These targets, "are probably essential to give regulatory T-cells their unique function," and include genes that have previously been implicated in immune regulation, Marson said. Mutation in one of these down-regulated genes, Ptpn22, is associated with a number of autoimmune disorders.

Marson said the work has at least two significant implications for research. "One is that we've identified this core set of genes that are probably likely to play key roles in preventing autoimmune disease," he said. "The second implication, which is maybe more long-term, is that we hope that identifying these targets will allow us to screen for drugs to mimic the function of Foxp3 and thus treat autoimmune disease."

According to Rose, treating autoimmune disorders will require enhancing either the number or effectiveness of regulatory T-cells.

"There are some tricks we might be able to use for both of those," he said. Rose also sees applications in transplant medicine and in the fight against cancer.

"Interestingly, people interested in tumor immunology are also interested in regulatory T-cells, because if you can get them out of the way, you can get rid of the tumor," he said.

Rose stressed that it remains to be seen which, if any, of these genes would make good drug targets. But he expressed confidence in the clinical potential of regulatory T-cells. "They have enormous implications, if we can figure out how to make them do what we want them to do."

More information

For more on how the immune system works, head to the [American College of Rheumatology](#).

SOURCES: Alexander Marson, graduate student, Whitehead Institute of Biomedical Research and Massachusetts Institute of Technology, Cambridge, Mass.; Noel R. Rose, M.D., Ph.D., professor, pathology and molecular microbiology and immunology, and director, Johns Hopkins Center for Autoimmune Disease Research, Baltimore, Md; Jan. 21, 2007, online edition, Nature

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