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Scientists identify potential targets for new autoimmune disease treatments

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Researchers have provided new insight into how a gene associated with autoimmunity contributes to disease in humans.

Their findings, published in the journal *eLife*, could have significant implications for the development of novel treatments for conditions where the body is attacked accidentally by the immune system.

The adaptive immune system needs to be able to eliminate all potential external threats while still maintaining tolerance towards normal tissues. Failure to do so can result in different types of autoimmune disease, which can include type 1 diabetes, rheumatoid arthritis and inflammatory bowel disease. T cells play an important role in this, as variants in human genes related to the cells' function are the most common mutations associated with such conditions. A team of US scientists are now studying how one autoimmunity-associated gene, Histone Deacetylase 7 (HDAC7), can contribute to disease.

"Our previous work has shown that interference with the normal functioning of HDAC7 can block an important process during the development of T cells, called negative selection, which is required for eliminating cells that recognise and attack self-derived tissues," says Eric Verdin, President and CEO of The Buck Institute for Research on Aging, California, and lead author of the current study.

"Defects in this process are clearly associated with autoimmunity, and we have confirmed that altering HDAC7 function in mice causes

autoimmune diseases. However, even though a particular mutation in HDAC7 allows T cells that are reactive to many different tissues to survive when they should have been eliminated, only a few tissues in the animals actually develop disease - remarkably the same ones which are affected in the diseases associated with HDAC7 variants in humans. We wanted to find the mechanism that underlies this unlikely coincidence."

To address this question, Verdin and his team altered and studied the function of HDAC7 in a combination of cell cultures and genetically modified mice. They discovered that the gene regulates both the elimination of self-reactive T cells and the development of a specialised class of T cells called invariant natural killer T (iNKT) cells. The same interference with HDAC7 function that blocks negative selection also blocks the development of these cells, which are specialised to provide rapid defense against bacterial invasion in the same tissues - namely the liver, pancreas, and the digestive system - that developed disease in the mice and also more often in humans with a mutated HDAC7 gene. "Importantly, when we restored the cells in mice, we saw that their disease symptoms were improved," Verdin adds.

"Together, our results provide evidence that HDAC7 and the network of genes surrounding it could be effective targets for interventions in human inflammatory diseases of the bowel, pancreas and liver," concludes co-author Herbert Kasler, Staff Scientist in Verdin's lab at the Buck Institute. "They also suggest that defects in cells such as iNKTs may play an underappreciated role in these diseases, which we would like to explore further.

"Additionally, our next steps will be to identify the other key genes involved in HDAC7's regulation of iNKT cell development, evaluate their targeting in mouse models of the same diseases, and search for more variants in HDAC7 and its network of genes that are associated with human disease."

More information: Herbert G Kasler et al, Histone deacetylase 7 mediates tissue-specific autoimmunity via control of innate effector function in invariant Natural Killer T-Cells, *eLife* (2018). DOI: 10.7554/eLife.32109

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