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Researchers discover mechanism behind development of autoimmune hepatitis

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A gene mutation disrupts the activity of certain immune cells and causes the immune system to erroneously attack the liver, according to a new animal study from the Icahn School of Medicine at Mount Sinai. The findings, published in the *Journal of Clinical Investigation*, will provide a new model for studying drug targets and therapies for Autoimmune Hepatitis (AIH), a condition for which the only treatment options are short-acting steroids or liver transplant.

T-cells, immune cells created in an organ called the thymus, grow into healthy T-cells with the help of medullary thymic epithelial cells (mTECs). mTECs act as coaches to T-cells to teach them when to attack tissue that might be harmful and when to leave it alone. T-cells that attack healthy body tissue are programmed to die. Led by Konstantina Alexandropoulos, PhD, Associate Professor of Medicine in the Division of Clinical Immunology at Mount Sinai, the research team sought to create a model for understanding why certain immune cells called T-cells inappropriately attack healthy tissues in the body, leading to inflammation and autoimmune diseases like lupus, rheumatoid arthritis, and AIH.

Dr. Alexandropoulos and her team, consisting of Anthony Bonito, first author and PhD candidate at Mount Sinai and contributing author Costica Aloman, PhD, former Assistant Professor of Medicine in the Division of Liver Diseases at Mount Sinai, created mutations in a gene called Traf6 in a mouse model, which caused depletion of mTECs. The research team hypothesized that without mTECs to coach them, T-cells

would aberrantly attack healthy cells. Surprisingly, while the depletion of mTECs did cause an autoimmune reaction, the T-cells homed directly to the liver and attacked it rather than other healthy tissue.

"We thought that deleting Traf6 would trigger an autoimmune reaction due to a depletion of mTECs, but did not expect the autoimmune response to be specific to the liver," said Dr. Alexandropoulos. "These findings provide an exciting new animal model to study AIH. We hope that this research will pave the way for new therapies to address a significant unmet need for people with this disease."

Dr. Alexandropoulos and her team hope to identify and study compounds or proteins that prevent the depletion of mTECs using cells from humans with AIH. Mount Sinai has one of the largest cohort of patients in the country to support research on liver diseases such as AIH.

Provided by The Mount Sinai Hospital