Research points way to 'holy grail' therapy for autoimmune diseases

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(Medical Xpress)—Scientists at the University of Kansas are working toward a potential breakthrough therapy for a host of autoimmune diseases. Long a goal of immunology, the approach targets only the handful of dangerous "self-reactive" T cells that can harm the body and leaves alone the vast majority of T cells that are vital to the human immune system.

The research team's findings recently were published in the journal *Clinical Immunology* and selected by that journal as a highlighted article. The research also was selected for recognition in Global Medical Discovery.

"T cells are controlling cells of the immune response and are designed to attack cells infected with viruses, bacteria, fungi, parasites and cancer cells," said Stephen Benedict, professor of molecular biology, who co-authored the findings. "Self-reactive T cells are T cells that mistakenly can attack normal things in our bodies. In the case of Type 1 diabetes, the target of these cells is the beta cells of the pancreas."

Benedict said that if self-reactive T cells enter the immune system they could cause multiple sclerosis, rheumatoid arthritis, psoriasis and scores of other diseases in addition to Type 1 diabetes.

"We are learning that self-reactive T cells participate in emphysema and atherosclerosis as well, so the total of 80 autoimmune diseases is expected to increase," Benedict said. "Also, this is the same process that

attacks and rejects organ transplants, so this is a crucial system in the body."

Immunology researchers have long sought an ideal therapy, one that kills only self-reactive T cells, leaving healthy millions of other T cells that guard the human body.

"However, most therapeutic approaches that target T cells do not distinguish between good and bad and just kill T cells," said Benedict. "This leaves the patient without proper defenses against infections and cancer, and patients treated in this manner are weaker in their immune response—this is called immunosuppressed."

To target only the self-reactive T cells, Benedict and his co-authors interrupt the second of two signals T cells rely upon before attacking a cell in the human body.

"Each T cell has a very specific molecule on its surface that guides the cell to attack a beta cell, for example, or a specific virus-infected cell and not to attack a normal heart cell or a different virus, or a cell in the pancreas that is not a beta cell. This is called the first signal, or signal 1," said Benedict. "But the cells must receive a second signal to tell the T cell that it is really OK to attack the target. In this case one of a few different protein molecules on the T cell surface interact with a counterpart on the surface of the target cells. If this signal 2 takes place, the T cell is given permission to attack the target. If the interaction does not take place, the T cell knows that it should not attack and either backs away or it inactivates itself, or it dies."

The team's approach blocks the second signal using peptides—small fragments of the much larger protein molecule. Mimicking the normal situation where a T cell receives the first signal that is specific to disease but does not receive the second signal that is the fail-safe signal, the

approach hinders T cells' attack.

"So peptide 'a' is taken from the contact domain of protein 'A' on the T cell, and peptide 'b' is from the contact domain of protein 'B' on the target cell," Benedict said. "Peptide 'a' binds to protein 'B,' and peptide 'b' binds to protein 'A.' These contact domains normally touch, and the cells involved realize that a signal is being sent. When we add the peptides, they bind to the counter domains of the cell-surface protein molecules and prevent the bigger proteins from touching and delivering a second signal."

The group's work was carried out using human cells in test tubes and petri dishes, then using animal models in the late stages of the research.

"We have had success with mouse models of rheumatoid arthritis, type 1 diabetes and most recently emphysema," Benedict said. "Also recently, we have extended our work to horses where we are adapting our peptide approach to treat moon blindness, also known as equine recurrent uveitis. This disease is similar to one that humans get and can cause blindness in both horses and humans."

In animal models, the researchers were able to preserve a large amount of pancreatic tissue, including beta cells, from being destroyed and to delay appearance of the aggressive symptoms of diabetes. For this, the team has garnered interest and excitement from immunologists.

"The major point of enthusiasm is that we may have inactivated the disease-specific T cells and left the major populations of T cells alone to continue to function," Benedict said. "If the concept holds up with further study, it moves us closer to selective immunotherapy where we do not suppress all 100 million T cell types in the patients and instead target only the cells involved in the disease."

Next, the scientists plan to seek funding to test the therapy in several diseases and more than one species and eventually take the therapy through the clinical trials process for use in humans.

Provided by University of Kansas