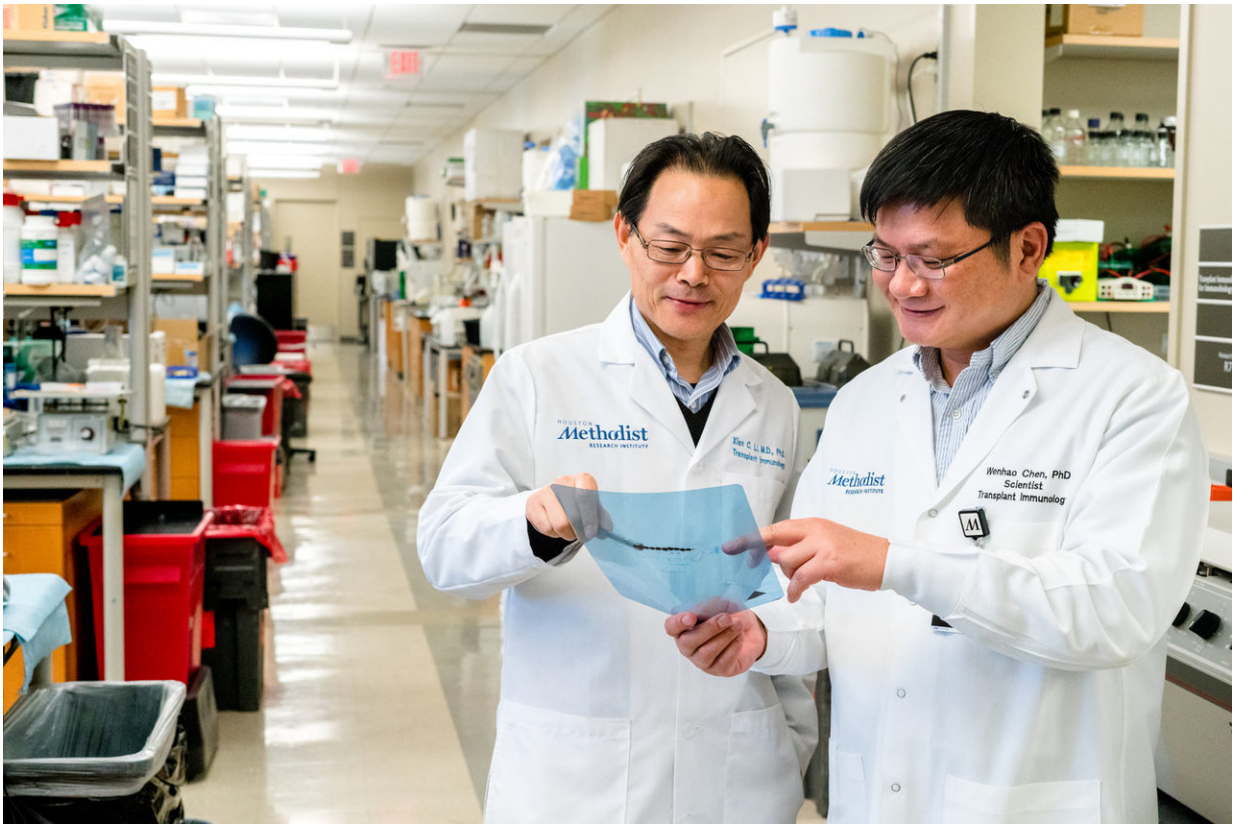
Medical Xpress

Researchers find key to making transplant rejection a thing of the past

December 21 2017



Wenhao Chen , Ph.D., (right) and Xian C. Li, Ph.D., (left) at the Houston Methodist Research Institute collaborated on a landmark study that definitively reveals targeting the IRF4 molecule in T-cells is the key to potentially unlocking the door to curing autoimmune diseases and eliminating organ transplant rejection. Credit: Humberto Jaime, Houston Methodist

Houston Methodist researchers have cracked a code in T-cells that could make autoimmune diseases and organ transplant rejection a thing of the past.

Wenhao Chen, Ph.D., a scientist in the Immunobiology and Transplant Science Center at the Houston Methodist Research Institute, and his colleagues have identified a critical switch that controls T-cell function and dysfunction and have discovered a pathway to target it.

Their findings are described in an article titled "Ablation of Transcription Factor IRF4 Promotes Transplant Acceptance by Driving Allogenic CD4+ T Cell Dysfunction" in the Dec. 19 issue of *Immunity*, a top medical journal of immunology published by Cell Press.

T-cells, which are a type of white blood cells that protect the body from infection, play a central role not only in infections, but also autoimmune diseases and transplant rejection. Understanding how T-cells work is of critical importance for treating these diseases. Chen and his team are doing this by systematically deleting different molecules in T-cells to check which ones are required for the T-cells to function.

What they have found is that one of the most critical molecules controlling gene expression in T-cells is the transcription factor IRF4, which is usually only found in the immune system and not expressed in other cells. Chen says IRF4 is what needs to be targeted to solve the problem of transplant rejection or to develop an autoimmunity cure.

"We found that IRF4 is an essential regulator of T-cell function," said Chen, who is the corresponding author on this paper. "If we delete IRF4 in T-cells they become dysfunctional. In doing so, you can solve the issue of autoimmunity and have a potential solution for organ transplant rejection. You need them functional, however, to control infection. If we can find an IRF4 inhibitor, then those issues would be solved. That's

big."

The way they will be able to do this is by only targeting active T-cells that have already been exposed to antigens, leaving the so-called naïve T-cells—those that have never seen antigens and produce no or little IRF4 - alone. These naïve T-cells produce IRF4 only when needed to fight infections. It's the activated T-cells armed with IRF4 that are responsible for organ transplant rejection and autoimmunity. These, he says, are the ones that are a potential target, thereby leaving other T cells in the immune system still armed against infection.

Their initial results were promising. By inhibiting IRF4 expression for 30 days - the usual timeframe required for transplant patients to remain infection free - the T-cells became irreversibly dysfunctional. In practice, this could mean prolonging a patient's ability to tolerate a transplanted organ.

"How to therapeutically inhibit IRF4 is the Nobel-prize winning question," Chen said. "If we can find a way to inhibit IRF4 as desired in activated T-cells, then I think most autoimmune diseases and transplant rejection will be solved."

More information: Jie Wu et al, Ablation of Transcription Factor IRF4 Promotes Transplant Acceptance by Driving Allogenic CD4 + T Cell Dysfunction, *Immunity* (2017). DOI: 10.1016/j.immuni.2017.11.003

Provided by Houston Methodist

transplant.html