

Scientists Uncover a Key Mechanism of Adrenal Damage in Addison's Disease

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Scientists at the Institute of Molecular Genetics of the Czech Academy of Sciences have developed a new experimental model of autoimmune Addison's disease, allowing them to uncover one of the key mechanisms by which the immune system damages the adrenal glands. Their findings point to a crucial role for CD4+ T cells that mistakenly target the body's own tissues. Through the signalling molecule interferon gamma (IFN- γ), these cells trigger and sustain inflammation – much like a security system sounding the alarm against someone who poses no actual threat. Blocking this signal could one day pave the way for treatments that target the underlying mechanism of adrenal damage rather than simply replacing the hormones the glands can no longer produce. The study, led by Ondřej Štěpánek and Aleš Neuwirth, was published in *JCI Insight*.

When the Immune System Turns Against the Adrenal Glands

Addison's disease affects approximately one in 10,000 people. It is a rare but serious condition in which the immune system gradually damages the adrenal cortex. As a result, the adrenal glands lose their ability to produce steroid hormones that are essential for functions including the body's response to stress and the regulation of metabolism and blood pressure.

Patients therefore require lifelong hormone replacement therapy. However, current treatment cannot fully mimic the body's natural hormone production or adjust it precisely to changing physiological needs. Patients consequently remain at risk of potentially life-threatening adrenal crises.

Efforts to develop treatments capable of stopping the autoimmune damage itself have so far been hampered by the lack of a suitable experimental model. Research directly in patients is also highly limited: obtaining adrenal tissue is invasive, and the disease itself is rare. As a result, much has remained unknown about what happens inside the affected adrenal gland and which immune cells are responsible for the damage.

A New Model Reveals a Key Driver of the Autoimmune Attack

The research team developed a mouse model of experimental autoimmune adrenalitis that reproduces important features of human Addison's disease. In the model, the researchers directed the immune response against CYP11A1, a protein naturally found in cells of the adrenal cortex. This

allowed them to track which immune cells infiltrated the adrenal glands and how they affected the glands' structure and ability to produce hormones.

Autoreactive CD4+ T cells emerged as key players. The researchers demonstrated that these cells alone can trigger adrenal inflammation and impair hormone production. Interferon gamma (IFN- γ) proved to be crucial to this process. When the researchers used T cells unable to produce IFN- γ , the mice did not develop adrenal insufficiency and formed substantially fewer inflammatory lesions.

The results therefore identify IFN- γ produced by autoreactive CD4+ T cells as one of the key mechanisms driving adrenal gland damage in this experimental model.

A New Tool for Research and the Search for Future Treatments

The new model makes it possible to follow how the disease develops and progresses and could also be used to test potential therapeutic approaches in preclinical studies. Although it does not reproduce every aspect of human Addison's disease, it captures important processes leading to autoimmune damage and impaired adrenal function.

"One of the major challenges in Addison's disease research has been the lack of a suitable experimental model that would allow us to observe what actually happens in the adrenal glands as the disease develops. Our new model enables us to study the individual stages of autoimmune damage in detail while also providing a platform for testing potential therapeutic interventions," says Aleš Neuwirth.

The findings also point to a mechanism that could potentially be targeted therapeutically in the future. Suppressing autoreactive T-cell activity or IFN- γ signalling could interfere directly with the process that damages the adrenal glands and potentially help preserve their natural hormone-producing function. However, this possibility will require further investigation, as the current findings are based on an experimental model.

"We knew that in Addison's disease the immune system attacks the body's own adrenal glands, but it was not clear which mechanisms are critical for causing the damage. Our results suggest that autoreactive CD4+ T cells and the interferon gamma they produce may play a central role. This signalling pathway could therefore represent an interesting target in the search for future treatment options," explains Ondřej Štěpánek.

The study brought together researchers from the Czech Republic, Germany, Switzerland and Norway, representing the Institute of Molecular Genetics of the Czech Academy of Sciences and Charles University, TU Dresden, the University of Lausanne and the University of Bergen. The study's first author is Arina Andreyeva from the Laboratory of Adaptive Immunity at the Institute of Molecular Genetics, with Ondřej Štěpánek and Aleš Neuwirth as corresponding authors.

The study was published in [JCI Insight](#) and selected by the journal's editors as one of the highlighted articles in the current issue. Artwork created by the study's authors was also featured on the journal's cover.

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