5 years ago

#science

#medicine

#autoimmune disease

#tregs

#immunology

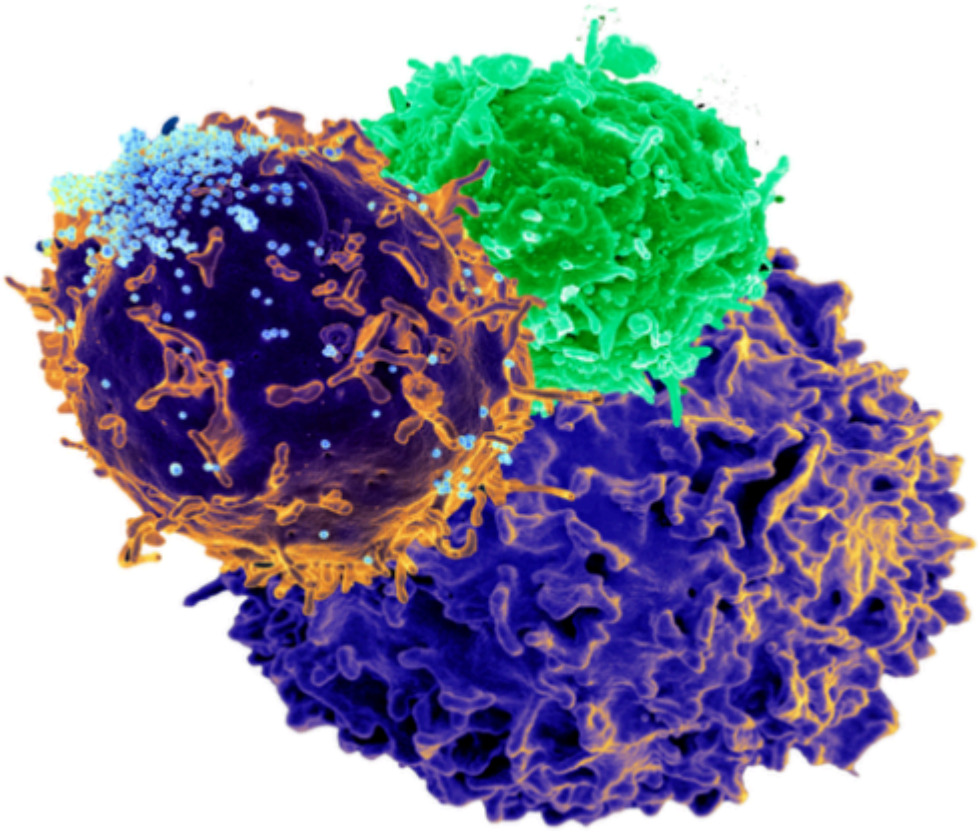
JUST THE FAQs: Potential New Approach to Treating Autoimmune Diseases

Autoimmune diseases — such as type 1 diabetes, rheumatoid arthritis or multiple sclerosis — all have one thing in common: they occur when the body's own immune system attacks itself. One culprit is effector T cells, immune cells that are supposed to stimulate inflammation and help get rid of cells infected with viruses. Their cousins, regulatory T cells (Tregs), act like a brake, keeping some of those effector T cells in check. Tregs inhibit inflammation and prevent autoimmune diseases.

But sometimes, Tregs don't do a very good job, the immune system gets out of hand and healthy cells and tissues suffer as collateral damage.

John T. Chang, MD, associate professor at UC San Diego School of Medicine, and his research team study T cells and how they develop and function. They recently discovered that a family of molecules called integrins helps Tregs to function properly — in other words, integrins can help apply the brake on pro-inflammatory T cells.

In this installment of JUST THE FAQs, Chang discusses their latest findings, published June 15 in the *Journal of Immunology*, and their potential implications for treating autoimmune diseases.



A regulatory T cell (Treg) is shown in green interacting with a CD4 T cell on the bottom and virus on the left. Source: Wikimedia

What are integrins?
Integrins are proteins embedded in the membranes of most cells. They're most famous for their adhesive properties — integrins help cells stick to one another and their surrounding tissues — but they also play roles in cellular communication, molecular signaling and trafficking.

What's new about integrins?
We wondered whether the activation state of integrins is important for Treg function. So we dove in and looked at this question in a rigorous way. We did that by deleting a gene in mice that encodes talin, an activator of beta-integrins. And we did that specifically in Tregs, not other cell types.

Then we looked at what happened to the mice. Those lacking talin (and therefore lacking activated beta-integrins in their Tregs) developed spontaneous autoimmunity. We took this a step further and looked at mice that had a mutated version of talin that specifically could not activate integrins. These mice also developed spontaneous autoimmunity. We also looked at the Tregs in these mice and found that they're defective in multiple ways — the pattern of genes they express is dramatically altered and they're no longer able to suppress inflammation.

That told us that integrin activation is crucial for Treg function.

What surprised you?
We were surprised at how severe the disease was in the mice that lacked talin in their Tregs. Even shortly after birth, they clearly looked sick. They had skin disease, didn't gain weight and their fur didn't grow well. They developed spontaneous, lethal disease within two to three months.

Why is this important?
Since our findings implied that integrin activation is needed for Tregs to function properly, it made us wonder … can you manipulate that pathway to boost Treg function? That might be useful in a variety of autoimmune diseases in which Tregs aren't working properly and other T cells are allowed to run amok.

Integrins toggle between activated and inactivated states, and there are antibodies that lock the integrins in activated conformations. So we treated talin-deficient mice with one of these antibodies and found that it improved their inflammation.

We think manipulating integrins to boost Tregs could be a new approach to treating autoimmune diseases.

What's next?
Next we want to test the integrin-activating antibodies on human cells and in animal models of autoimmunity to see if they can reverse or prevent disease. There are good mouse models for many autoimmune diseases, including type 1 diabetes, inflammatory bowel disease, rheumatoid arthritis and multiple sclerosis. They're not perfect replacements for humans, of course, but it's a starting point to test our hypotheses and unravel the mechanisms at play.

What challenges remain?
A major challenge in moving this approach along to human clinical trials is the fact that integrins are found in every cell in the body. So manipulating them could have adverse effects. We're looking for ways to target our intervention only to Tregs. But, there is a chance that won't be necessary. Lots of drugs target all cells, but the therapeutic dosage minimizes toxicity. For example, proteasome inhibitors are used to treat multiple myeloma. Every cell needs its proteasomes, but the dose is such that it doesn't affect every cell and preferentially involves diseased cells. We've done some testing and found that our integrin-activating antibody doesn't affect other T cells, at least in terms of their ability to expand, but we need to do more rigorous testing.

Previous Next post