



Genes Linked to Autoimmune Diseases

Scientists link 30 genes to multiple sclerosis and other autoimmune diseases.

WEB EXCLUSIVE

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Jan. 21, 2007 - The immune system is what keeps most people's bodies healthy and free of disease, but for as many as 23 million Americans, it is a cause of disease, too. In autoimmune disorders, the system goes haywire, mistaking the body's own tissues for foreign invaders and destroying them. Drugs for these conditions, which include type 1 diabetes, multiple sclerosis and lupus, have been elusive. But on Sunday, scientists are reporting in the journal *Nature* that they have found a set of 30 genes that go awry in autoimmune disorders—and that could be potential targets for cures. NEWSWEEK's Mary Carmichael spoke with two of the discoverers, Richard Young, a biologist at the Massachusetts Institute of Technology's Whitehead Institute, and Alexander Marson, an M.D./Ph.D. student in Young's lab. Excerpts:

NEWSWEEK: What do these 30 genes normally do in a healthy person's body?

Richard Young: There was a very, very important discovery made about a decade ago, which was that a specialized class of "regulatory T cells" was controlling the immune system's arms of attack. Now, the million-dollar question is why this wonderful system that keeps you healthy might turn against you and begin to attack your own body. And it turns out that in these autoimmune disorders, there are genetic defects in the regulatory T cells, which would otherwise be a check on the rest of the immune system.

These regulatory T cells can't keep the system in line, and it starts attacking things it shouldn't?

Alexander Marson: Yes. In mice, if you remove all the regulatory T cells, what you see is a massive, multiorgan autoimmune disease. In some common human autoimmune disorders, like multiple sclerosis, there's not a total lack of these cells, but there's a subtler dysfunction. The regulatory T cells are present, but they don't work as well at turning off the other immune cells and preventing them from attacking the body.

What exactly is wrong with the genes in these regulatory T cells? What are they doing that they shouldn't be doing?

Young: In autoimmune disorders, most of these genes are less active than they normally would be. What Alex and his colleagues discovered is that this turns the regulatory T cells' activities down, so they're not as aggressive or powerful as they normally would be. Now, it was only three years ago that scientists discovered the "brain" of the regulatory T cells, or the gene that tells them how to do their job. This is a gene called *Foxp3*.

So *Foxp3* is the immune system's big boss, and the 30 genes you've found inside the regulatory T cells are the middle managers?

Young: Right. Until now, it was not known exactly how *Foxp3* was giving these T cells directions—which genes it was controlling in order to do that.

And these are the 30 genes, the ones that aren't following the proper directions. So you think this dysfunction is the basis not just for one disorder, but a whole host of autoimmune diseases?

Marson: Yes, regulatory T cells appear to be key in preventing type 1 diabetes, lupus, multiple sclerosis, rheumatoid arthritis, and inflammatory bowel disease, as well as autoimmune thyroid disorders. Dysregulation of the genes controlling those cells could contribute to a wide range of autoimmune conditions.

That's a huge number of people—the pharmaceutical industry must be very excited about this discovery.

Young: The imperative in the pharmaceutical industry, when you're thinking about investing nearly a billion dollars in a program, is to have deep knowledge of the molecular pathways you're going to be focused on.

There's this sea of noise that's hard to get through when you're looking for drug targets, unless you have a very small group of genes to look at. Here, we have that—we have the opportunity to take many, many, many autoimmune diseases and search more quickly because we've narrowed down the genes that are involved. Considering what drives the industry, this gives them a real leg up on developing cures.

What if you narrowed it down further? Could a drug for all of these disorders be aimed at Foxp3, the master controller of these 30 genes?

Young: It's an option. If you find some secret sauce that will modify Foxp3's activities and you've shown that this is critical to a broad spectrum of disorders, that's going to be a great thing. Let's say for the sake of speculation that in one of these diseases, Foxp3 itself is not working at adequate levels or is slightly defective. That would make it a single target we could go after and see if we could tune it up. On the other hand, it could turn out—as it usually does—that life's more complex than that. For each one of the diseases, there may be some subset of the 30 target genes that aren't working right, and we'd have to use another, more specific approach in each disorder.

Marson: One of the key next steps is to take each of these 30 genes and figure out what they're doing within the T cells. There's evidence that they play important roles, but the molecular underpinning of that is really still unknown. The other thing will be to look for chemicals that mimic the function of Foxp3. There may be some that are already known, but hopefully there will be more to be discovered in the future.

Could you also manipulate these genes in healthy people to suppress the immune system if you needed to, the way doctors do now in organ transplantations?

Young: Sure. In the same vein that you can imagine the loss of function of these genes, you can think of situations where you'd like to turn down the immune response, like in transplantation. There are already drugs that do that, of course, but the best evidence we have so far is that those drugs are working in a different way, on different genes than the ones we've discovered. Then again, sometimes if you discover new genes and then you go and test what the known drugs are doing, you're often surprised that they're doing multiple things and are involved in pathways you didn't anticipate.

Marson: One of the major drugs that's used to suppress the immune system now is cyclosporin, which inhibits a protein called NFAT. We and others have evidence that Foxp3 is also inhibiting that protein.

Young: Many of these genes are operating together with others, collaborating in the control of regulatory T-cell function. They're like drinking buddies. So it may turn out that the connection is a whole lot closer than we've imagined.

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