

Team's Discovery Links Statins to Immune System Reaction, Muscle Damage

With momentum generated by sharp observation, creative thinking and plain old hard work, scientists in the Myositis Center have discovered a rare, potentially dangerous side effect of statins, drugs used to lower cholesterol for millions of people.

Myositis is inflammation of the muscles; it can have many causes and can range from mild to severe. The immune system is often involved – which means that the body is mounting a defense to something it perceives as an enemy – but even this response differs from person to person, at the most basic levels. That's why, at the Myositis Center at Johns Hopkins Bayview, every patient who walks through the door has a blood test for antibodies. Think of it as a biochemical pat-down, a frisking for potential weapons the body may be using to fight off invaders – which, themselves, may be making things worse.

"Some people have well-known antibodies, some have antibodies which were not previously recognized, and others don't seem to have antibodies," explains Antony Rosen, M.D., Director of Rheumatology. The antibody analysis measures particular proteins that the antibodies react to; the proteins are labeled on the basis of their size. Last year, scientists in the Myositis Center noticed that the same distinct pattern of proteins, labeled 100-kd and 200-kd, kept cropping up on these analyses. And the patients who had this new and unusual pattern also had some unique clinical features: very high blood levels of muscle enzymes called CK (creatinine kinase), and significant muscle damage on their biopsy specimens; in fact, they had necrotic (dead or dying) muscle cells, plus some nasty-looking, infiltrating inflammatory cells. Clearly, their muscles were under attack and the body was calling out the immune system's cavalry; but what was causing this?

The 100-/200-kd antibody pattern was present in about half of the biopsy samples of patients who had necrotizing myopathy. Of these, it turns out, 63 percent had taken statins – drugs that are known to cause muscle damage in a small percentage of people who take them (see side story). All of the patients got better when their immune systems were suppressed, and many experienced a relapse of muscle weakness when doctors tried to taper off the medication, although over time, they eventually "quieten down," as the body stops fighting itself, Rosen says. The scientists' work on this unusual immune-mediated myopathy and its treatment was published in the journal, *Arthritis & Rheumatism* in September 2010.



The researchers, with more questions than answers, then worked to identify the antigen, the "invader" that triggered the antibody response. The Center's co-directors, Lisa Christopher-Stine, M.D., M.P.H., and Andrew Mammen, M.D., Ph.D., and colleagues including investigator Livia Casciola-Rosen, Ph.D., set out to come up with a better test, as opposed to the very general, open-ended analysis they had been using. What they had, in effect, was a wide net, like shrimp trawlers use; they needed something more like a baited hook.

They Lower Cholesterol, But in a Few People, They Cause Muscle Trouble

“They did a very simple experiment,” explains Rosen, who collaborated with them in further work, published in the March 2011 issue of *Arthritis & Rheumatism*. “They said, ‘We know that it seems to be associated with statin use. If you treated cells with statins and used these antibodies, could you detect the antigen in higher amounts? It was a home run.’” And this, Rosen adds, led to what he describes as a “thought experiment.” Some scientists, ranging from senior investigators to graduate students, were sitting around, brainstorming. Someone noted that one of the major targets of statins, a protein with a string of names that’s abbreviated HMG CoA reductase, becomes more powerful after statin exposure; the body becomes

There’s a drawback to statins, drugs taken by millions of people worldwide. They’re great at lowering cholesterol, but not always so friendly to the muscles. In fact, muscle problems – ranging from pains and an increased likelihood of muscle injury, to inflammation, weakness, and permanent tissue damage – are known, though not terribly common, complications of statins, and most of these go away when you stop taking the drugs. Some people aren’t so lucky, and their bodies develop an immune response.

Regenerating muscle cells also churn out high levels of HMG CoA reductase, Rosen says, which explains why in these patients, symptoms persisted even after they stopped taking the statins. Suppressing the immune system, in effect, allowed the body to recover because it shut off the expression of HMG CoA reductase. In these studies, the scientists demonstrated the link between an environmental trigger (taking the statins) and the development of a sustained autoimmune response.

Among the many lessons learned by this work, Rosen says, is “that even in this day and age, luck is an important part of discovery, and your ability to harness luck is really proportional to how many people with diverse knowledge and skills you have in the room. The more diverse the representation of knowledge, the more likely you are to make a discovery without doing an experiment. That moment of saying, ‘I think the antigen is HMG CoA reductase’ – everybody resonated around the same concept at the same time. It was a most amazing event.”

This research has sparked many more questions, and more research. “Everybody who’s working on it can write a grant,” Rosen says, “because they’re all working on different aspects.” One question is, what caused this response in the patients who had not taken statins? Other environmental factors may be to blame, Rosen suspects. Are there genes that make someone more susceptible to statins? Exploring these issues may help scientists be able to predict in advance who should avoid using these cholesterol-lowering drugs. ■

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more susceptible to it. Someone else noted that the molecular weight of this protein is 100k; it joins up with another molecule to form a dimer (basically, a set of identical twins), whose molecular weight is 200k. Coincidence? No way. In further, painstaking lab work, the scientists confirmed that “what’s causing the problem in these patients is the very enzyme that the statins target.” The scientists devised an ELISA assay – a test easily translatable to more general use – and proved that they could diagnose this condition using a simple test.