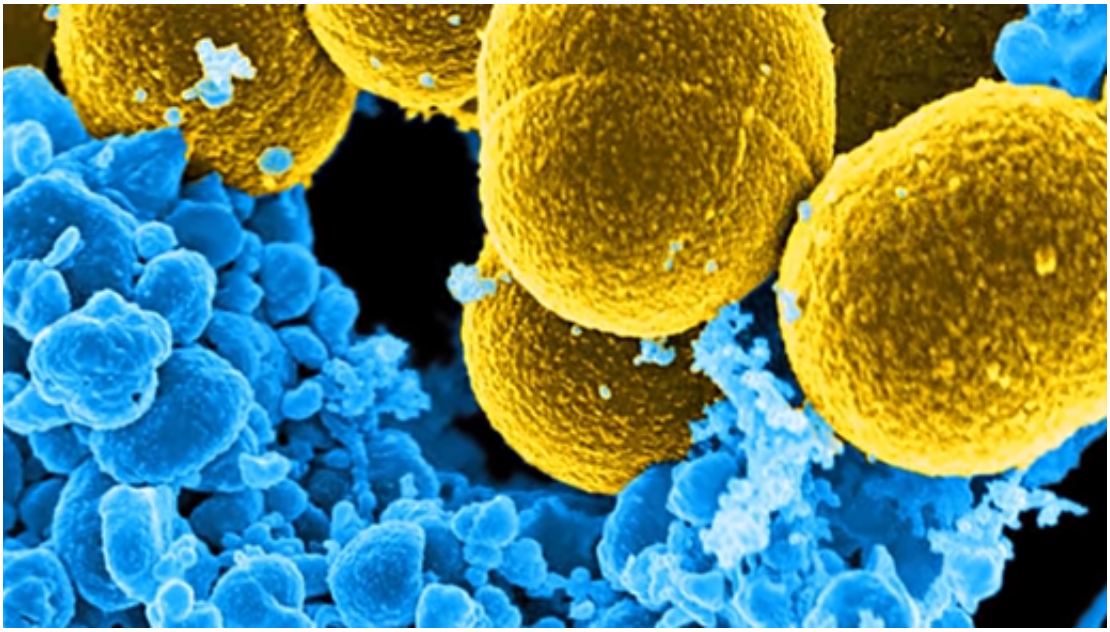
MedicalXpress

Researchers decode lupus using DNA clues

November 4 2015, by Quinn Eastman



People with systemic lupus erythematosus can experience a variety of symptoms, such as fatigue, joint pain, skin rashes and kidney problems. Often the symptoms come and go in episodes called flares. In lupus, the immune system goes haywire and produces antibodies that are directed against the body itself.

A team of Emory scientists has been investigating some fundamental questions about lupus: where do the cells that produce the self-reactive antibodies come from? Are they all the same?

In the accompanying video, Kelli Williams, who helps study the disease and has lupus herself, describes what a flare feels like. In addition, Emory researchers Iñaki Sanz, MD and Chris Tipton, PhD explain their findings, which were published this summer in *Nature Immunology*.

Sanz is a Georgia Research Alliance Eminent Scholar, director of the Lowance Center for Human Immunology and head of the Rheumatology division in the Department of Medicine at Emory University School of Medicine. Tipton is assistant professor of medicine at Emory University School of Medicine.

While the researchers did not directly investigate the effects of drugs used to treat lupus, their findings could guide drug development, because they precisely define the subsets of antibody-producing cells that cause patients the most trouble.

The immune system can produce many types of antibodies, directed against infectious viruses (good) or against human proteins as in lupus (harmful). Each antibody-secreting cell carries DNA rearrangements that reflect the makeup of its antibody product. With next-generation sequencing technology, scientists can use the DNA to identify and track that cell, like reading a bar code on an item in a supermarket.

Tipton and Sanz and their colleagues have been using these DNA bar codes to deepen our understanding of immune responses in lupus. They obtained blood samples from eight patients experiencing lupus flares and compared them to eight healthy people who had recently been vaccinated against influenza or tetanus.

When the immune system is responding to something it's seen before, such as when someone receives a booster vaccine, the bar codes of the antibody-producing cells look quite similar to each other. A set of just a few antibody-producing cells multiply and expand. In contrast, the

researchers found that in lupus, many different cells are producing antibodies.

"We expected to see an expansion of the cells that produce autoantibodies, but instead we saw a very broad expansion of cells with all types of specificities," Tipton says.

This is a difference from another autoimmune disease, multiple sclerosis, in which the autoantibody-producing cells attack a limited set of proteins found in the nervous system. Another key finding of the Nature Immunology paper was that some of the autoantibody-producing cells grow out of a pool of "activated naïve" B cells. This is a paradoxical term, since once B cells are activated, they are not naïve anymore. But it refers to the molecules seen on the cells' surfaces.

In a booster vaccine response against flu or tetantus, the few clones that expand are already highly trained; they have undergone a process of hypermutation that fine-tunes the antibodies that they produce. In lupus, the activated naïve cells are, in effect, untrained; they jump into producing antibodies without mutations. In the video, Sanz explains some signs that these activated naïve cells may be persisting in the body for several months.

More information: Christopher M Tipton et al. Diversity, cellular origin and autoreactivity of antibody-secreting cell population expansions in acute systemic lupus erythematosus, *Nature Immunology* (2015). DOI: 10.1038/ni.3175

Provided by Emory University