A promising new approach to autoimmune diseases

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Researchers from Harvard Medical School and MIT have developed a new approach for identifying the "self" proteins targeted in autoimmune diseases such as multiple sclerosis, diabetes and rheumatoid arthritis.

In a paper published in Nature Biotechnology, H. Benjamin Larman and colleagues showed that errant immune responses which mistakenly target the body's own proteins rather than foreign invaders can now be examined in molecular detail. Further research could lead to new insights into the exact causes of these debilitating autoimmune disorders. The results come from the laboratory of Stephen Elledge, the Gregor Mendel Professor of Genetics and Medicine at HMS and senior author of the study.

The immune system, the body's main line of defense against disease, has a critical responsibility to distinguish self-derived proteins from those of invaders like viruses and bacteria. Autoimmune diseases arise when a person's immune system fails to make that critical distinction and mistakenly attacks a normal tissue, such as nerve, joint, or insulin-producing pancreatic cells. These disorders are usually progressive and in some cases even lead to life-threating disease. Understanding where the immune system went wrong has been a major goal for generations of biomedical researchers.

"Knowledge of the self-antigens involved in autoimmune processes is important not only for understanding disease etiology, but also for developing diagnostic tests," the authors write. "In addition, physicians

may someday use antigen-specific therapies to destroy or disable auto-reactive immune cells."

But looking through the haystack of cellular complexity for those single-needle self-antigens targeted by the immune system has proved daunting, to say the least. Ideally, scientists would be to develop some kind of biological magnet that could pull these fine needles out of the mass.

In this report, the researchers describe an approach which does just that.

Elledge and colleagues improved upon a well-established technique called phage display in which bacterial viruses, called bacteriophage, display DNA-encoded protein fragments on their surfaces. As Nicole Solimini, co-corresponding author on the paper, explained, the researchers "built a reproduction of all the proteins in the human body (collectively, the human proteome) by synthesizing the corresponding DNA fragments for expression on the surface of bacteriophage."

This new proteome library provides a physical link between the protein being studied and the gene that makes it, allowing researchers to look for and identify interactions between any human proteins, such as that between an autoantibody in a patient's blood and a self-protein that prompts an autoimmune response. In fact, this technology can be used to look for any type of interaction between human proteins, providing a powerful new tool to biomedical investigators in any discipline.

Applying their technology to autoimmune disease, the team developed a technique called phage immunoprecipitation sequencing ("PhIP-Seq"). Using cerebrospinal fluid from three patients suffering from an autoimmune disorder called paraneoplastic neurological disease, the researchers could identify known and previously unreported self-proteins targeted by patients' immune systems—that is, interactions between an autoantibody in the cerebrospinal fluid and the self-protein that drives

the autoimmune response.

According to Larman, "a small sample of blood from a diabetic patient, synovial fluid from an arthritic joint, or cerebrospinal fluid from a patient with multiple sclerosis would be mixed together with the proteomic library. The self-reactive antibodies in the patient's sample will seek out and then bind to the targeted proteins in our library. We can then separate out the antibody-bound protein fragments and determine their identity by high-throughput, next-generation DNA sequencing."

Based on six years of laboratory work at HMS, the project is directly linked to the ongoing success of the Human Genome Project, which had already made available almost all of the genes the body needs in order to build, operate and repair itself. As the end products of individual genes, the body's many individual proteins are central players in all aspects of health and disease.

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