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Study describes new tool in the fight against autoimmune diseases, blood cancers

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A study led by a Scripps Research Institute scientist describes a new, highly pragmatic approach to the identification of molecules that prevent a specific type of immune cells from attacking their host. The findings add a powerful new tool to the ongoing search for potential treatments for autoimmune diseases, such as multiple sclerosis (MS), as well as blood cancers, such as myeloid leukemia.

The study by Thomas Kodadek, a professor in the Chemistry and Cancer Biology Departments at Scripps Florida, and colleagues was published in the November 25, 2009 issue (Volume 16, issue 11) of the journal *Chemistry & Biology*.

In the new study, Kodadek and his colleagues used samples from an animal model of multiple sclerosis to screen for T cells—a type of white blood cell that plays a central role in the immune system—with a heightened presence in the disease. The screen also identified molecules that interfere with these T cells' "autoreactivity," in other words, their attack on the body itself rather than a foreign invader such as virus or bacteria.

"Our technique simultaneously uncovers and isolates autoreactive T cells as well as inhibitors to them," Kodadek said. "It's a double whammy. At the heart of this is a comparative screening process of normal T cells versus disease-causing T cells. While the process is technically complicated and difficult, the thinking behind it is not. We wanted to simplify the process of identifying compounds that could inhibit

autoreactive T cells with exceptional specificity, and we succeeded."

The scientists used a model of MS, an autoimmune inflammatory disease affecting the brain and spinal cord, for the study. In MS, the immune system attacks the myelin sheath covering and protecting nerve cells, leading to a variety of symptoms depending on which part of the nervous system is affected. Common symptoms of the condition include fatigue; numbness; walking, balance, and coordination problems; bladder and bowel dysfunction; vision problems; dizziness and vertigo; sexual dysfunction; pain; cognitive problems; emotional changes; and spasticity.

Simplifying the Process

In setting up the new method to shed light on such autoimmune diseases and other disorders, Kodadek and his colleagues created a large collection of peptoids—molecules related to, but more stable than, the peptides that make up proteins. By arranging thousands of peptoids on a microscope slide, the pattern of binding antibodies (a type of immune molecule) and peptoids can be visualized. By looking at samples from animal models of a known disease like MS, peptoids that bind to antibodies closely associated with that disease can be easily recognized.

Better still, peptoids that bind to autoreactive T cells can be identified without knowledge of the specific antigen (molecule triggering the immune attack), providing an unbiased method with which to search for potentially useful compounds.

Most autoimmune research has focused on finding the disease-causing antigens first, Kodadek said, a Quixote-like quest that has lasted more than four decades with little success to show for it.

"With our process, it doesn't really matter what the antigen is," said Kodadek, a 2006 recipient of the National Institutes of Health Director's

Pioneer Award, which is designed to support individual scientists of exceptional creativity. "That was really the breakthrough. We're setting up a system that recognizes T cell receptors that are very abundant in a sick animal and at low levels in a healthy animal. Why the abundance? Because that's what making them sick."

Potential for Therapeutic Discovery

The new process creates new potential for therapeutic discovery. Molecules that target autoreactive T cells directly, while ignoring those T cells that recognize foreign antigens, could serve as the foundation for a novel drug development program aimed at eradicating autoreactive cells without affecting the normal function of the immune system.

"Almost without exception, drugs currently used to treat autoimmune conditions either inhibit something downstream of the autoimmune response itself, like inflammation, or they moderate the immune system non-selectively and that results in significant side effects," Kodadek said.

However, the new study isn't the final answer, according to Kodadek. He noted that the recent study used a model of MS triggered by a single antigen. In humans, there could be two—or two dozen—antigens triggering an autoimmune disease such as MS. This calls for further research. The method may be more easily applied to blood cancers, though, since the disease-causing T cells have been fully characterized and there are very few of them.

Source: The Scripps Research Institute (news : web)

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