Antibody selection method could mean better drugs

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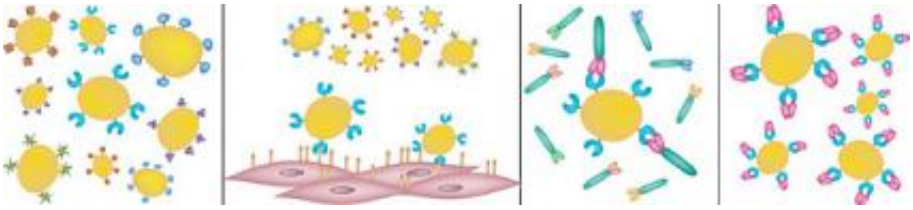

The illustration shows the streamlined antibody selection strategy. From left, random mutants of Mac-1 integrins are expressed on yeast cells. The yeast cells are screened against a sample tissue that expresses receptors identical to those that Mac-1 integrins would bind to in the body. Remaining yeast cells, now expressing only active Mac-1 integrins, are exposed to fluorescently tagged antibodies. Final selection of specific antibodies is made.

(PhysOrg.com) -- Biomedical engineering researchers have made antibodies that block only specific immune cells that cause inflammation, but not the ones the body normally uses to fight infections.

Drugs that target chronic inflammation -- associated with everything from rheumatoid arthritis to cancer -- without suppressing the entire immune system could be the payoff of new Cornell research on lab-created antibodies.

Researchers led by Moonsoo Jin, assistant professor of biomedical

engineering, made antibodies that block only specific immune cells that cause inflammation, but not the ones the body normally uses to fight infections.

The research was published online March 22 in Proceedings of the National Academy of Sciences (In print April 6, Vol. 107 no. 14).

The key to the experiments are integrins, which are proteins expressed by the body's immune cells -- in this case, cells called neutrophils -- that allow the cells to travel to a cut, infection or other source of inflammation.

Integrins are receptor molecules located on the cell surface that are like velcro that can be turned on and off. When they are chemically signaled to activate, they subtly change shape, called conformation, thereby exposing binding sites allowing them to firmly attach to receptors around them. This enables the neutrophils to stick to the inside of a blood vessel and invade into the surrounding tissue to a site of inflammation or infection.

"Integrins have these amazing, very dramatic conformational changes," said graduate student Sungkwon Kang.

Inflammatory diseases like rheumatoid arthritis occur because the immune system has shifted into overdrive, with the body essentially attacking itself. Immune cells, which normally fight infection, flock to an area and cause painful swelling. Drugs now in clinical trials that block this immune response are indiscriminate, suppressing even those immune cells that are involved in healthy immune responses. That's why these drugs can make patients weak and susceptible to infections.

The researchers' antibodies block a specific integrin called Mac-1, but only in its active state -- that is, in its conformation that allows it to bind

to and move through tissue. The new antibodies leave alone the cells with integrins in a resting state -- those that are just waiting to be needed for an immune response. This would greatly cut down on the side effects associated with immunosuppressive drugs.

The researchers used a novel screening method that eventually isolated only these specific antibodies. They started by growing random mutations of Mac-1 integrins on the surfaces of yeast cells. They screened the yeast cells against a sample tissue that expresses receptors identical to those that Mac-1 integrins would normally bind to in the body. After an extensive washing of the remaining yeast cells, they exposed them, now expressing only active Mac-1 integrins, to fluorescently tagged antibodies to discern which antibodies bound to the remaining integrins. The strategy allowed quick, error-proof examination of antibody binding.

Therapies and treatments that could result from this research are numerous, said research associate and first author Xuebo Hu. Mac-1 activation is known to cause inflammation that can lead to some cancers, for example. Also, the antibodies could be fluorescently tagged to image, for example, inflammation or metastasized tumors.

"Blocking Mac-1 or using the active Mac-1 for diagnosis or treatment of patients could be pretty significant," Kang said.

Provided by Cornell University

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