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New model tracks the immune response to pathogens

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Using T cells primed for the infectious disease toxoplasmosis, Whitehead Institute researchers have created novel mouse models of the immune system that more accurately reflect how immune cells actually respond to pathogens in their presence.

"These models have a lot of potential," says Oktay Kirak, who is a postdoctoral researcher in the labs of Whitehead Members Hidde Ploegh and Rudolf Jaenisch. "It allows us to study both the biology of T cells as well as their role in toxoplasmosis."

Toxoplasma gondii, the single-celled parasite that causes toxoplasmosis with more than 30% of humans infected, the symptoms are generally minor, although toxoplasmosis can have serious or fatal effects for an immunocompromised person or a fetus, if the mother is infected during pregnancy.

In the April 9 issue of *Science*, Kirak and his colleagues describe how he used somatic cell nuclear transfer (SCNT) to create mice from single T cells that recognize the *Toxoplasma gondii* parasite.

In SCNT, a cell's nucleus is inserted into a de-nucleated, unfertilized egg cell to generate embryonic stem cells and animals with the same genetic code. In this study, Kirak, who is first author of the Science paper, transferred the nucleus of a T cell primed for toxoplasmosis into an enucleated, unfertilized mouse egg to create mice.

Kirak used T cells—a class of white blood cells that include several types of cells including cytotoxic or so-called killer T cells—because they have been difficult to study in current immune system models. Each cytotoxic T cell has its genetic material rearranged, so that it produces properly activated a receptor that can identify an antigen. An antigen is a particular part of an infectious agent, such as a virus, bacterium, or parasite, that the immune system can recognize. Once properly activated by the relevant antigen, the cytotoxic T cell will then kill any cell that is infected with that pathogen.

Many T cells may respond to a particular infectious agent, such as *Toxoplasma gondii* and they all may recognize different antigens on the parasite's surface. This multiple-pronged attack, though highly beneficial in eliminating infectious agents, complicates the study of specific T cell's interactions with the antigen and infectious agent. Kirak's method solves this problem by creating a mouse with identical T cells and activating them in the course of infection.

"Kirak's work was a really imaginative application of the nuclear transfer technique: to create a mouse with defined and predictable immunological properties, which will be useful for studying infectious diseases," says Jaenisch, who is also a professor at MIT.

This is a unique approach for immune system models. Some earlier models rely on transgenic mice in a process that leaves indelible marks created by the experiment itself and depend on a researcher subjectively choosing the mouse with the "best" immune response. Other models trick the infectious agent into producing a surrogate protein, not usually produced by that pathogen, like a protein found in egg whites. A researcher then documents how immune cells that recognize the egg white protein "respond" to the infectious agent. This model has serious drawbacks because T cells can respond at different times to different antigens during a natural infection.

In contrast to these models, SCNT generates T cell mouse models, with minimal tampering by the researcher and that depend entirely on the natural course of events. And that is an important advance for immune system models.

"The opportunity to look at true pathogen-derived antigens in the course of a natural infection provides us with a new window on how the immune system operates," says Ploegh, who is also a professor at MIT. "There's no current model that even comes close to this, by my reckoning."

More information: "Transnuclear mice with predefined T-cell receptor specificities against Toxoplasma gondii obtained via SCNT", Science, February 9, 2010.

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