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First 'live' imaging of specialized immune system cells reveals new clues about body's security system

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To keep the body safe, the immune system enlists more than one form of protection. A circulating task force of immune system cells monitors the body's periphery, and sends information back to field command centers — the lymph nodes — located at pivotal traffic points.

But scientists are learning that another, little known team of security experts enhances the body's safety from a fixed location.

Rockefeller University scientists, working in collaboration with researchers at New York University, provide the scientific community's first view, in real time, of the live actions of a network of dendritic cells, specialized components of the immune system, that spend their entire lifespan inside the body's lymph nodes. Their findings are published in December's *Nature Immunology*.

Confirming the existence of this network and studying its activities in a living organism's lymph nodes may add another important layer of explanation for how the body prevents its powerful immune system from turning against "self," or the body's own cells.

Dendritic cells, which were discovered by Rockefeller scientist Ralph Steinman in 1973, already are known to play a special role in protecting the body from microbes and other foreign invaders, or antigens.

The dendritic cells' long, spindly arms extend and retract in order to detect antigens. Once antigens are detected, dendritic cells migrating throughout the body typically travel to the lymph nodes to use those same spindly arms, called processes, to inform other immune cells, the white blood cells called T and B cells, to take action against the invader.

"It surprised us to see that this entirely different population of dendritic cells inside lymph nodes form what looks like a stationary network," says first author Randall Lindquist, a Rockefeller University graduate student in the Laboratory of Molecular Immunology, headed by Professor Michel Nussenzweig.

"The network dendritic cells are just sitting there waving their processes. They're not migrating." Lindquist added.

To visualize the dendritic cells found tucked deep inside the lymph nodes alongside the body's nascent B and T cells, the Rockefeller part of the research team created laboratory mice genetically modified so that their immature dendritic cells release a yellow fluorescent protein. The protein, coupled with a microscopic imaging technique that excites the fluorescent molecules with infrared light, creates perfect conditions for studying molecular activity in living systems.

"This imaging study has never been done before," says first author Randall Lindquist, "All of the other live microscopy experiments looking at dendritic cells in lymph nodes used cells that came from other sources and that were labeled with fluorescent dye." Lindquist and his colleagues' imaging technique preserves the immune system's natural conditions to the fullest extent possible, and most closely represents how the immune system really works.

Dendritic cells, when mature, spur B and T cells to seek and destroy foreign invaders, usually microbes. Dendritic cells in the non-migrating

network are a combination of mature and immature. However, Rockefeller scientists believe that this colony of dendritic cells specializes in informing T and B cells what the body's own tissues look like so that they are safe in the case of a real immune system emergency. This immature but informative activity of dendritic cells is part of what immunologists call the "steady-state" of the immune system.

The much-studied mobile population of dendritic cells seems to interact with the stationary population, says Lindquist. In a related set of experiments, the researchers showed that transiting, mature dendritic cells can and do join the network, and they likely share their information across the network.

"Being able to watch dendritic cells in the steady state is valuable," says Lindquist. If this network is teaching other immune cells to recognize, or tolerate, the body's own tissues significant medical advances in the treatment of cancer and autoimmune diseases such as lupus may follow.

"Specific tolerance is what we've been looking for since the immune system was discovered," says Nussenzweig.

Already other research teams around the country are following in the Rockefeller-NYU team's footsteps. Nussenzweig predicts many new dendritic cell insights based on non-invasive live imaging techniques in mice, such as the system he and his colleagues have developed.

Lindquist, Nussenzweig and their colleagues, too, are pursuing many new experiments based on what they've already learned. "The next thing we'd like to confirm," says Lindquist, "is how the network dendritic cells interact with T cells under conditions that induce tolerance or active immunity."

Provided by Rockefeller University