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Flu infection reveals many paths to immune response

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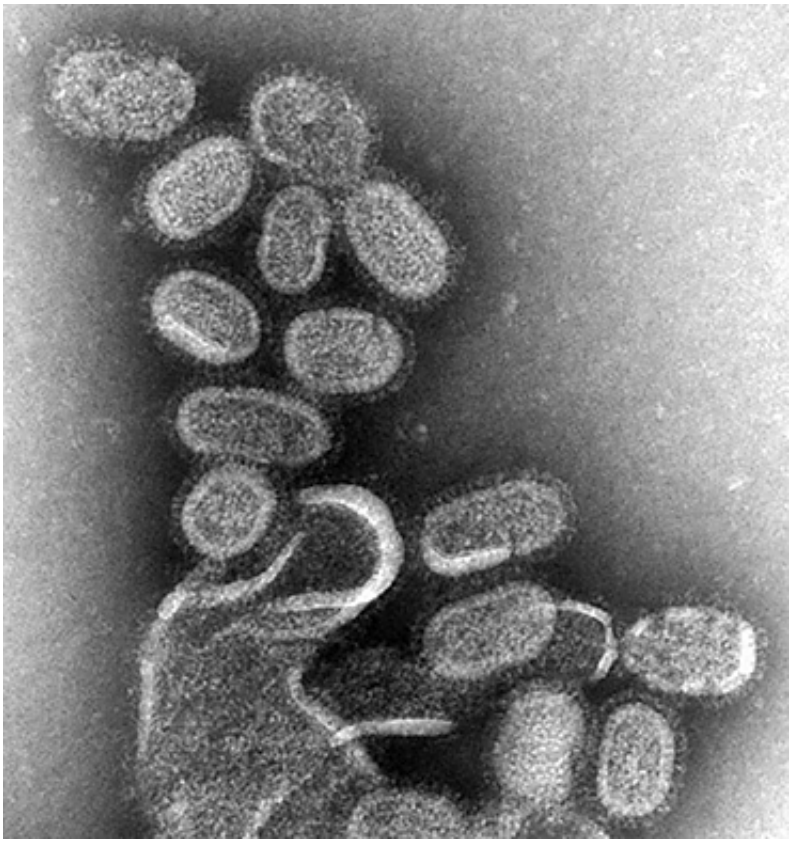

Electron microscopy of influenza virus. Credit: CDC

A new study of influenza infection in an animal model broadens understanding of how the immune system responds to flu virus, showing that the process is more dynamic than usually described, engaging a broader array of biological pathways. The researchers say their findings

may offer key insights for designing more effective vaccines in general.

"During infection, viral proteins are present throughout the cell, not just in the limited compartments that have been the focus of attention in classical immunology," said study leader Laurence C. Eisenlohr, Ph.D., a viral immunologist in the Department of Pathology and Laboratory Medicine at The Children's Hospital of Philadelphia (CHOP). "By investigating how active infections interact with mechanisms deep inside immune cells, we can design vaccines with broader protection against invading pathogens."

The study appears online today in *Nature Medicine*. Before recently arriving at CHOP, Eisenlohr led this research at Thomas Jefferson University.

Conventional textbook approaches, said Eisenlohr, rely on laboratory studies of "nominal" antigens, usually in the form of purified proteins introduced into cell cultures. An antigen-presenting cell (APC) takes up the proteins and delivers them to a compartment inside itself called the endosome, where the proteins are digested ("processed") into peptides. Those peptides, displayed at the cell surface, stimulate CD4+ T cells, which are vitally important in the body's defense against most infectious agents.

Eisenlohr and colleagues showed in their current study that live influenza virus follows a more complicated path. "During active infection, viral proteins are delivered to regions in the antigen-presenting cell well beyond the endosome, and are consequently subjected to diverse types of processing machinery. As a result, peptides are produced in greater amounts and broader variety compared to the conventional model," he said.

The classical model is said to rely on an exogenous process—in which

the antigens are introduced into the APC from outside the cell. The current study, Eisenlohr said, revealed the potency of the endogenous process—in which the virus infects the APC and the APC processes, through a variety of mechanisms, viral proteins that are being produced inside the cell. These processing pathways generate more diverse peptides, which in turn elicit a more robust antiviral response from CD4+ T cells.

Eisenlohr said the study results have implications for designing more effective vaccines, against both influenza and other viruses. "Live vaccines are generally more effective than inactivated vaccines," he said. "That supports the concept that natural infection elicits a larger, more comprehensive immune response than a killed virus. Therefore, if safety concerns preclude use of a live vaccine, we may need to modify inert vaccines to better mimic natural infection—accessing a broader variety of peptides and thus generating a more protective immune response."

He added that "more rational vaccine design will need to consider specific details of each pathogen, to better access those peptides, but the extra work will likely be worth it."

More information: "Endogenous antigen processing drives the primary CD4+ T cell response to influenza," *Nature Medicine*, published online Sept. 28, 2015. doi.org/10.1038/nm.3958

Provided by Children's Hospital of Philadelphia

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