Location, location, location: Immunization delivery site matters

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Credit: National Cancer Institute

In vaccination, a certain subpopulation of dendritic cells is vital to triggering the body's adaptive immune system, report researchers at The Jackson Laboratory (JAX), Yale University and Astra-Zeneca.

Their findings have important implications for vaccine delivery, as the usual method, intramuscular injection, is likely not the most effective

way to target those dendritic cells.

Vaccines train the immune system to fight a given pathogen (e.g., bacteria or virus), known generally as an antigen, by simulating a natural infection. When an antigen is detected, a dendritic cell, which has the job of processing and transporting antigens, carries it to a lymph node. There it "presents" the antigen to a specialized T cell, known as a T follicular helper (Tfh) cell, activating it. Through signaling the Tfh cells stimulate B cells, which in turn produce antibodies specific to the antigen.

So for a vaccine to work at its best, it needs to be delivered where it's most accessible to dendritic cells. However, there are many different kinds of dendritic cells, and they're not distributed uniformly throughout the body.

In a paper published in *Science Immunology*, the team, led by senior co-authors JAX Assistant Professor Adam Williams, Ph.D. and Stephanie Eisenbarth, M.D. Ph.D., of Yale, showed that dendritic cells known as cDC2s (for CD11b+ migratory type 2 conventional DCs) are both necessary and sufficient for robust Tfh cell induction. Working with mice that lack a protein needed for cDC2 mobility, the team demonstrated that Tfh cells were not induced and antibodies not produced following vaccination, even in the presence of other, functional dendritic cells.

The authors used inhalants for their research and show that multiple types of DCs access antigens through this delivery form. In particular, cDC2s deliver inhaled antigens to lung-draining lymph nodes, and there induce a potent Tfh response.

In contrast, the usual method of vaccination through intramuscular injection delivers antigen to where cDC2s are relatively scarce. Based on

older epidemiological data and a similar repertoire of cDC2s in the superficial layer of the skin, the researchers speculate that intradermal injections may be far more efficient in driving antibody production.

Moreover, more efficient delivery of vaccines could mean that smaller doses could be administered, expanding the number of people who could be vaccinated during a pandemic or when a given vaccine is in short supply.

Williams notes that the work also underscored the importance of using an animal model system rather than in vitro cell lines. "Not only are dendritic cell types concentrated in different areas of the body, they also migrate to specialized areas within the lymph node. This fundamental aspect of immune architecture is lost in vitro," says Williams. "Having mouse models in which specific dendritic cells were disabled or deleted was essential for this work."

More information: J.K. Krishnaswamy el al., "Migratory CD11b+ conventional dendritic cells induce T follicular helper cell dependent antibody responses," *Science Immunology* (2017). immunology.sciencemag.org/look … 6/sciimmunol.aam9169

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