Can we hypercharge vaccines? Tapping a chemical we already make could enhance T-cell production

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Credit: National Cancer Institute

Researchers at Boston Children's Hospital report that a fatty chemical naturally found in damaged tissues can induce an unexpected kind of immune response, causing immune cells to go into a "hyperactive" state that is highly effective at rallying infection-fighting T-cells. The findings, published online by *Science* on April 21, could enhance

vaccines and make them much more effective.

The researchers, led by Jonathan Kagan, PhD, got a five times greater adaptive immune response in mice when using the chemical, called oxPAPC. They believe that oxPAPC or a related synthetic compound could be used to help immunize people against a wide range of infections. "We think this could be a general means to increase response to any type of vaccine," says Kagan, also an associate professor at Harvard Medical School.

oxPAPC targets only dendritic cells—sentinels that circulate around the body searching for microbes and activating T-cells to destroy the invaders. Previously, it was thought that dendritic cells (also commonly known as antigen-presenting cells) have just two states: an inactive state, in which they can search for microbes, and an active state, in which they have encountered a microbe and gain the ability to activate T-cells.

"We identified a naturally-occurring molecule that creates a heightened, 'hyperactive' state of dendritic cell activation," says Kagan. "These hyperactive cells live for a long time and are the best activators of T-cells that we know of, so this could be a very useful tool in vaccine development."

In particular, when they gave oxPAPC to mice, they saw strong activation of memory T-cells. Memory T-cells respond more effectively to invaders than other kinds of T-cells, but are not efficiently elicited by ordinary activated dendritic cells.

Kagan's team further showed that hyperactivated dendritic cells make a critical protein, IL-1ß, that triggers memory T-cell production. Dead dendritic cells also release IL-1ß, but only for a short period of time. Hyperactivated dendritic cells produce IL-1ß for longer times, which likely explains why they are such effective stimulators of memory T-

cells.

Finally, the researchers found that oxPAPC's key target is an enzyme called caspase-11. When activated by other molecules, caspase-11 triggers cell death and inflammation. But when activated by oxPAPC, the enzyme promotes hyperactivation of dendritic cells.

"These discoveries highlight that dendritic cells and caspase-11 can have more than one activation state, which was never before known," says Kagan.

Kagan and Boston Children's Hospital's Technology and Innovation Development Office (TIDO), have filed for a patent on this work and are seeking investor interest so they can move oxPAPC or a similar compound toward a clinical trial.

More information: "An endogenous caspase-11 ligand elicits interleukin-1 release from living dendritic cells" *Science*, DOI: 10.1126/science.aaf3036

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