Small molecules induce trained immunity, opening a new approach to fighting disease

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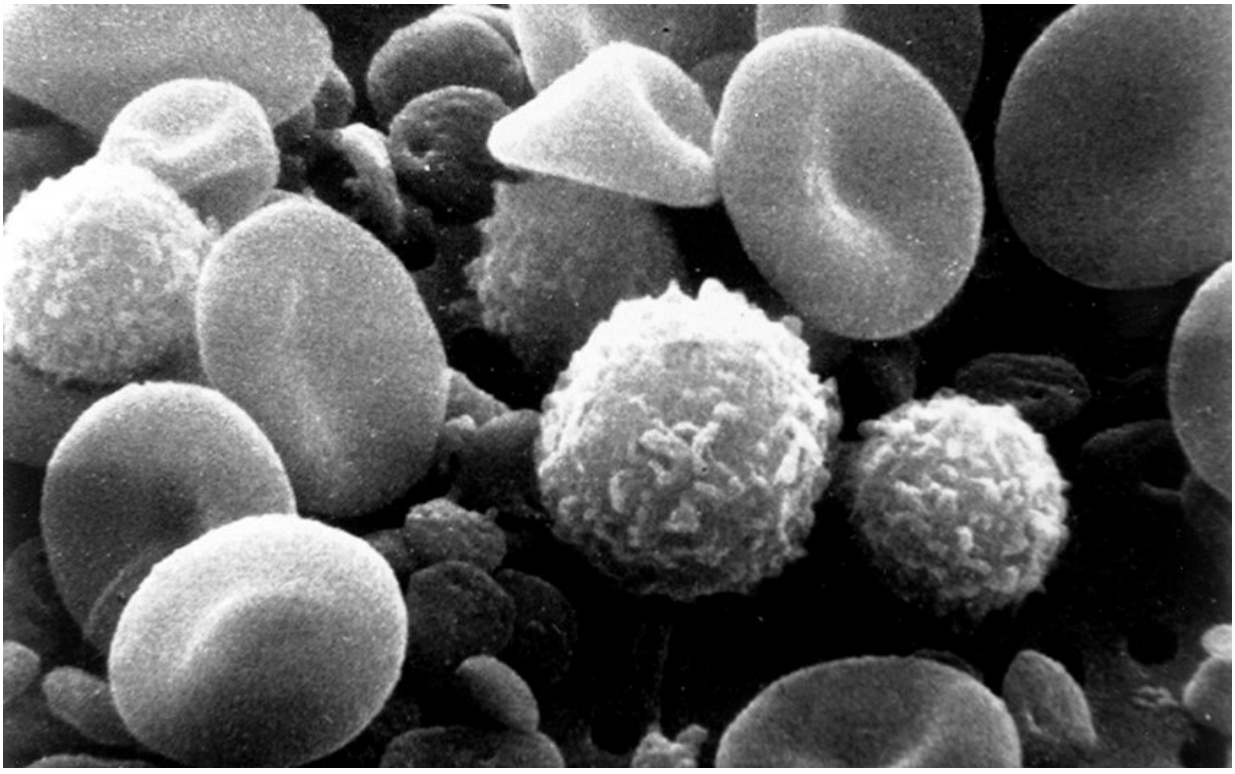

Myeloid immune cells alongside red blood cells in an electron micrograph of human blood. Credit: National Cancer Institute

Vaccines provide a front-line defense against dangerous viruses, training adaptive immune cells to identify and fight specific pathogens.

But innate immune cells—the first responders to any bodily invader—have no such specific long-term memory. Still, scientists have found that they can reprogram these cells to be even better at their jobs, potentially fighting off seasonal scourges like the common cold or even new viral diseases for which vaccines have not yet been developed.

A University of Chicago Pritzker School of Molecular Engineering (PME) team has found several small molecule candidates that induce this trained immunity without the potential side effects of other methods.

In a twist, they found that several of the top candidates were steroids, a class of drugs that is known to suppress the immune system, not boost it.

"This has opened up a whole new line of research in our lab," said Prof. Aaron Esser-Kahn, who led the research with graduate student Riley Knight. "Many of the molecules we found are already approved by the FDA for other treatments, which makes this a promising therapeutic direction."

The research was published in the journal *Proceedings of the National Academy of Sciences.*

The idea of trained immunity has been around ever since scientists found that babies who received the BCG vaccine—a live, attenuated vaccine for tuberculosis—yielded much lower mortality rates overall. Eventually, scientists figured out that the vaccine offered non-specific protection against other infections, as well, and could even prevent or treat cancers.

Trained immunity—an epigenetic and metabolic rewiring of immune cells—was born, but it was not without problems. Scientists also found that trained immunity, if left unchecked, could also lead to autoinflammatory diseases such as atherosclerosis.

A surprise set of small molecule candidates

In the Esser-Kahn lab, Knight set out to find out whether any small molecules—drugs that can easily enter cells—could also induce trained immunity. This approach would allow scientists to be more targeted and specific with training, sidestepping the need for initial immune activation.

Working with UChicago's Cellular Screening Center, Knight screened 2,000 small molecules on live cells and tested the level of cytokines produced by the immune cells. Cytokines are small proteins that--when released--signal the body's immune system to get to work.

What the team found surprised them: 13 of the top 24 small molecule compounds that produced the most cytokines were glucocorticoids, a class of steroids. Hydrocortisone and prednisolone, for example, belong to this group.

But these steroids are known to suppress certain parts of the immune system, like inflammation.

"I didn't believe it at first myself," Knight said. But when the team tested seven of the top candidates, including two steroids, in a mouse model, they found the same results. After receiving the small molecules, the mouse models were given an injection to induce inflammation. The small molecule steroids induced four to six times more cytokines than normal while also not eliciting further inflammatory response.

"It was really striking to get such an amplified response," Knight said. The team also found that this immune training is dependent on glycolysis, the process in which a cell breaks down glucose to produce energy.

A new line of research

The findings opened up several new research directions in the lab. Team members are now conducting research into how these compounds could improve responses to vaccines and prevent metastasis of cancer. Others are working to understand just how these steroids work with the immune system, and how such steroids could be delivered directly to targeted areas of the body with nanoparticles.

"We have now more than doubled the known compounds reported to induce trained immunity," Esser-Kahn said. "These are potentially new tools in our approach to treating disease."

Other authors include Ellen Ketter, Trevor Ung, Adam Weiss, Jainu Ajit, Qing Chen, Jingjing Shen, Ka Man Ip, Chun-yi Chiang, and Luis Barreiro.

More information: Hannah Riley Knight et al, High-throughput screen identifies non inflammatory small molecule inducers of trained immunity, *Proceedings of the National Academy of Sciences* (2024). DOI: 10.1073/pnas.2400413121

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