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Geisel researchers contribute to study of trained immunity

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A study published in the journal *science* provides support for a new—and still controversial—understanding of the immune system. the research was conducted by collaborators in the U.S. and Europe, including Robert Cramer, PhD, an assistant professor of microbiology and immunology at the Geisel School of Medicine and member of the Dartmouth Lung Biology Center, and Kelly Shepherdson, PhD, at the time a graduate student in Cramer's lab.

Typically, scientists divide the immune system into two categories: the innate immune response and the adaptive immune response. The adaptive immune response is familiar to most people because of its role in providing long-term protection against disease, as when a vaccine triggers the immune system to "remember" a specific threat and mount a robust response if challenged by that pathogen later in life.

The innate immune system is older in evolutionary terms and usually thought of as responding to immediate threats from pathogens or other foreign entities. But over the past few years, informed by studies in plants and invertebrates, scientists have begun to suspect that the innate response has a form of "memory" as well, complicating the division of the immune system into two neat categories. "The innate immune system is typically thought of as a quick, generally non-specific broad response to an initial infection that lacks immunological memory," says Cramer. "But studies of trained immunity suggest that maybe that's not the case, and that is not only paradigm shifting but potentially directly relevant to the treatment and prevention of many diseases."

In 2011, researchers in the Netherlands, including Mihai Netea, MD, PhD, the senior author on the new paper in *Science*, coined the term "trained immunity" to refer to immune responses that involve immunological memory deriving from cells associated with the innate immune system. Trained immunity is capable of providing non-specific protection from secondary infections. However, the mechanisms of how trained immunity is initiated and maintained remain unclear. Recent research has found that epigenetic changes occurred in innate immune cells when exposed to certain pathogens or their antigens and are an important feature of trained immunity. But the specific genes and biochemical pathways associated with trained cells were unknown.

In the *Science* paper, the researchers report that changes in metabolism are a critical driving force behind the trained immunity phenotype. Epigenetic profiling experiments identified genes involved in glucose metabolism as being critical for trained immunity. Cramer and Shepherdson became involved in the research because of their work on HIF1α and the innate immune response to fungi. HIF1α is a protein that acts as a transcription factor for genes involved in metabolism, among other genes.

Using mice in which the HIF1α gene was deleted from cells of the innate immune system, Cramer and Shepherdson tested the hypothesis that changes in metabolism, mediated in part through the HIF1α pathway, were critical for trained immunity. They first exposed the mice to a fungal polysaccharide antigen, beta glucan, that induces a trained immune response and then challenged the mice with a bacterial pathogen that can cause sepsis. The normal mice were protected against the pathogen by the trained immune response, but the mice without HIF1α were not protected, indicating that the lack of HIF1α prevented the trained immune response and protection against secondary infection. "This was a critical set of experiments for the research as they were conducted in vivo in a whole animal that lacked HIF1α in the key

effector cells of trained immunity," Cramer says.

These findings have potential implications both for the prevention and treatment of inflammatory diseases and for bolstering the immune response to pathogens in situations where the immune system is not functioning properly. A next step in this line of research, Cramer says, is to identify genes downstream of HIF1α critical for the trained phenotype that may make viable specific targets for therapeutic development. "If we can figure out these underlying mechanisms, we might be able to enhance the efficacy of vaccines," he says. And, he adds, it might also be time to rethink the traditional understanding of the immune system.

More information: www.sciencemag.org/content/345 … 38-bb40-e1ce78e38410

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