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Vaccine boosts innate immunity in people with dormant immune cells

Bacillus Calmette-Guérin (BCG) is one of the world's oldest and most widely used vaccines. It was developed in the early 20th century to provide protection from tuberculosis. Surprisingly, this vaccine protects not only against tuberculosis but also reduces the risk for various other infections, through a mechanism called trained immunity. A new study led by Christoph Bock and Mihai Netea found that epigenetic cell states predict whether or not an individual profits from the "wake-up call" to the innate immune system that is provided by the BCG vaccine. This discovery contributes to the development of future therapeutics that induce protective trained immunity.

Humans are protected by two branches of the immune system. Innate immunity provides built-in defense against widespread characteristics of bacteria and viruses, while adaptive immunity memorizes individual pathogens that a person has already encountered. Vaccines teach the adaptive immune system about new pathogens without having to go through an actual infection. This has greatly contributed to human health, but requires a specific vaccine for each major pathogen.

Some vaccines not only teach the adaptive immune system about a specific pathogen, but also increase the overall vigilance of our body's innate immune cells. The BCG vaccine, which teaches our adaptive immune system to fight tuberculosis bacteria, has been shown to reduce infant mortality independent of its protection against tuberculosis. This observation can be explained by the concept of "trained immunity" – the idea that innate immune cells can switch between dormant and vigilant states, and are more effective at fighting infection when in their vigilant state.

Not every immune cell needs training

Inducing trained immunity by drugs or vaccines could confer protection in times of high infection risk, for example following a major surgery or during future pandemics before tailored vaccines become available. However, trained immunity is highly variable between individuals, and it is not well understood who may profit from inducing trained immunity.

To investigate this issue, a team led by Mihai Netea (Radboud University Medical Center) and Christoph Bock (CeMM & Medical University of Vienna) vaccinated 323 healthy volunteers with BCG and analyzed the effects on the immune system. They found that the induction of trained immunity was most effective in individuals with dormant innate immunity, which was reflected in a characteristic epigenetic cell state that predicted the vaccine response (Moorlag SJCFM, Folkman L, ter Horst R, Krausgruber T, et al. *Immunity.* 2024).

The team identified 213 individuals as trained immunity responders and 78 as non-responders, based on whether or not their production of inflammatory mediators had increased at day 90 after BCG vaccination – at a point when the acute response has subsided, but trained immunity is expected to persist. Trained immunity responders produced fewer mediators before vaccination and started with more dormant innate immune cells than non-responders. In other words, the non-responders already had the higher immune vigilance that the BCG vaccine induced in the responders.

Epigenetic regulation of immune balance

Both genetic and environmental factors contributed to this variability, but the most interesting differences were observed in the epigenetic states of the immune cells. Epigenetic cell states, implemented through changes in chromatin accessibility that make genes easier or harder to activate, reflect the regulatory plasticity of a cell and its ability to respond rapidly to changes in its environment, making them strong candidates for regulating trained immunity.

Indeed, in response to BCG vaccination, trained immunity responders gained open chromatin at genes involved in innate immunity, while non-responders carried such open chromatin independent of BCG vaccination, with no further increase following the vaccination. This finding explains how epigenetics allows immune cells to switch between different levels of immune vigilance, which contributes to the need to balance immune activity to provide protection against pathogens while avoiding unnecessary and harmful immune responses.

The study also clarifies a previously observed association between scar development at the site of BCG vaccination on the skin and lower child mortality. Previously, scar formation at the vaccine injection site was interpreted as a sign of a strong immune response to the vaccine. However, the team's analyses offer an alternative explanation: it seems that scar formation reflects strong immunity prior to vaccination, and these individuals may be better protected against infections independent of BCG vaccination.

Enhancing immune vigilance

These results not only provide new insights into immune biology and the role of epigenetics, but also guide the development of future therapeutics. "We can envision a new class of drugs that deliberately wake up a dormant immune system," Netea says. "Elderly people could receive a boost of their immune system prior to a planned hospital stay, and it may be possible to reactivate the suppressed immune system in patients with cancer. Several pharmaceutical companies are already pursuing ways to induce trained immunity without having to rely on the BCG vaccine."

The new study provides important guidance for such endeavors. First, a better understanding of the biological pathways underlying trained immunity may uncover novel therapeutic targets. Second, the study shows that such therapeutics are only likely to benefit individuals with dormant innate immunity, who can be identified through chromatin profiling or functional immune assays. Third, no overshooting immune responses were observed in individuals with high innate immunity prior to vaccination, which bodes well for the safety of future trained immunity inducing drugs.

Bock summarizes: "Our study highlights the close connection between epigenetic cell states and trained immunity, allowing the human body to switch between vigilant and dormant innate immunity. This process is variable across individuals and may be exploited with precision medicine."

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Pictures attached

Picture 1: Artistic rendering of the BCG vaccine's effect on trained immunity (© Rob ter Horst). The illustration shows "trained" cells of the innate immune system
Picture 2: Graphical abstract of the BCG vaccine trained immunity study (© Immunity)
Picture 3: Photo of the CeMM team who led the data analysis (© CeMM)

The study "Multi-omics analysis of innate and adaptive responses to BCG vaccination reveals epigenetic cell states that predict trained immunity" was published in *Immunity* on January 9, 2024. DOI: 10.1016/j.immuni.2023.12.005

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Christoph Bock is a Principal Investigator at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences and Professor of [Bio]Medical Informatics at the Medical University of Vienna. He is also the scientific coordinator of the Biomedical Sequencing Facility at CeMM, member of the Human Cell Atlas Organizing Committee, fellow of the European Lab for Learning and Intelligent Systems (ELLIS), and co-founder of a Vienna-based start-up company (Myllia Biotechnology). He has received major research awards, including an ERC Starting Grant (2016-2021), an ERC Consolidator Grant (2021-2026), the Otto Hahn Medal of the Max Planck Society (2009), the Overton Prize of the International Society for Computational Biology (2017), and the Erwin Schrödinger Prize of the Austrian Academy of Sciences (2022).

Mihai Netea heads the division of Experimental Medicine, Department of Internal Medicine, Radboud University Medical Center in Nijmegen. He is scientific founder of the biotech start-up companies Trained Therapeutix Discovery and Lemba, and of the biotech incubator Biotrip. He is mainly interested in understanding the memory traits of innate immunity (trained immunity) and has received major grants such as ERC Consolidator (2012-2017) and ERC Advanced (2019-2024). He is elected fellow of the Infectious Diseases Society of America, recipient of the van Loghem Award of the Netherlands Society of Immunology, and of the Spinoza Prize (2016). Since 2016 he is a member of the Netherlands Royal Academy of Sciences (KNAW).

The **CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences** is an international, independent and interdisciplinary research institution for molecular medicine under the scientific direction of Giulio Superti-Furga. CeMM is oriented towards medical needs and integrates basic research and clinical expertise to develop innovative diagnostic and therapeutic approaches for precision medicine. Research focuses on cancer, inflammation, metabolic and immune disorders, and rare diseases. The Institute's research building is located on the campus of the Medical University and the Vienna General Hospital.
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www.meduniwien.ac.at

The **Radboud University Medical Center** is one of seven academic medical centers in the Netherlands. With ~11,100 employees it provides patient care, teaching (BSc and MSc medical and biomedical sciences, and postgraduate courses) and research. The center's mission in scientific research is to advance human knowledge by conducting biomedical, translational and clinical research in order to improve wellbeing. Its key strength is medical life sciences and clinical practice, with an infrastructure comprising of state-of-the-art technology platforms and (translational) research facilities.
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