Journal of Clinical and Cellular Immunology

OPEN ACCESS Freely available online

Short commentary

Innate Memory: Trained Immunity in Infection and Vaccination

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DESCRIPTION

The immune system has traditionally been divided into two distinct arms innate and adaptive immunity. The adaptive immune system, with its highly specific T and B lymphocytes, is renowned for its ability to "remember" previous encounters with pathogens, providing long-lasting protection through memory cells. In contrast, the innate immune system comprising macrophages, dendritic cells, natural killer cells, and neutrophils was long considered a nonspecific, short-lived first line of defense, responding to pathogens without retaining any memory. However, recent research has overturned this dogma, revealing that innate immune cells can exhibit a form of memory termed "trained immunity." This discovery has profound implications for our understanding of host defense, infection control, and vaccine development.

Understanding trained immunity

Trained immunity refers to the phenomenon whereby innate immune cells undergo functional reprogramming after exposure to certain pathogens or vaccines, leading to an enhanced response upon subsequent encounters with the same or even unrelated pathogens. Unlike adaptive immunity, which relies on antigen-specific receptors, trained immunity depends on epigenetic modifications and metabolic rewiring within innate immune cells. These changes enhance the production of cytokines, chemokines, and other effector molecules, effectively "training" the immune system to respond more robustly.

The mechanism of trained immunity is rooted in epigenetic modifications, such as histone methylation and acetylation, which alter gene expression patterns in innate immune cells. For instance, exposure to Bacille Calmette Guerin (BCG) vaccine, originally developed for tuberculosis, has been shown to induce long-lasting histone modifications in monocytes, enhancing their responsiveness to secondary infections. Similarly, changes in cellular metabolism, such as increased glycolysis and cholesterol synthesis, provide the energy and substrates required for a heightened inflammatory response.

Unlike adaptive immune memory, which targets a specific pathogen, trained immunity can confer cross-protection against unrelated infections. For example, BCG vaccination has been associated with reduced mortality from infections unrelated to tuberculosis in newborns and children in high-mortality regions. These observations suggest that harnessing trained immunity could offer broad-spectrum protection, especially in populations vulnerable to emerging infectious diseases.

Implications for infection control and vaccination

The concept of trained immunity has far-reaching implications for both natural infection and vaccination strategies. In the context of infectious diseases, trained immunity can act as an immediate line of defense, reducing pathogen replication and disease severity. By priming innate immune cells to respond more vigorously, the host may achieve faster pathogen clearance, limiting the opportunity for severe disease progression. This is particularly relevant for pathogens that evade or suppress adaptive immunity, such as Mycobacterium tuberculosis, certain viruses, and fungal pathogens.

From a vaccination perspective, trained immunity provides a novel avenue to enhance vaccine efficacy. Traditional vaccines primarily aim to stimulate adaptive immune memory, but integrating strategies that also engage trained innate responses could result in faster and more robust protection. For instance, the nonspecific benefits of BCG vaccination have inspired research into its use as a potential tool against respiratory infections, including influenza and COVID-19. Similarly, adjuvants designed to induce trained immunity could be incorporated into existing vaccines to boost innate responses, particularly in populations with weaker adaptive immunity, such as the elderly.

Moreover, understanding trained immunity may guide the development of next-generation vaccines that are not limited to a single pathogen. By inducing epigenetic and metabolic reprogramming in innate cells, vaccines could provide broad protection against a spectrum of infectious agents. This approach is particularly appealing in the face of emerging infections and pandemics, rapid deployment of pathogen-specific vaccines may not be immediately feasible.

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Received: 18-Aug-2025, Manuscript No. JCCI-25-39127; **Editor assigned:** 20-Aug-2025, PreQC No. JCCI-25-39127 (PQ); **Reviewed:** 03-Sep-2025, QC No. JCCI-25-39127; **Revised:** 10-Sep-2025, Manuscript No. JCCI-25-39127 (R); **Published:** 17-Sep-2025, DOI: 10.35248/2155-9899.25.16.765

Citation: Hong A (2025). Innate Memory: Trained Immunity in Infection and Vaccination. J Clin Cell Immunol. 16:765

However, there are challenges and caveats associated with leveraging trained immunity. While enhanced innate responses can improve pathogen clearance, excessive or dysregulated activation may contribute to chronic inflammation, autoimmunity, or tissue damage. Therefore, therapeutic strategies must carefully balance the benefits of trained immunity with the risk of inflammatory pathology. Ongoing research is needed to define the optimal conditions and stimuli that elicit protective, yet controlled, innate immune memory.

Furthermore, trained immunity is not uniform across all individuals. Factors such as age, genetics, microbiome composition, and prior exposure to pathogens influence the magnitude and duration of trained responses. This variability underscores the importance of personalized approaches when considering vaccines or therapies designed to exploit trained immunity.

CONCLUSION

The discovery of trained immunity has fundamentally altered our understanding of the innate immune system, revealing that it is not merely a passive first responder but a dynamic network capable of memory and adaptation. By bridging the gap between innate and adaptive immunity, trained immunity offers new insights into host defense mechanisms, infection control, and vaccine development. Its ability to confer nonspecific protection, coupled with the potential to enhance vaccine efficacy, positions trained immunity as a promising frontier in immunology.

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