UNLOCKING THE SECRET OF TRAINED IMMUNITY: A NEW PARADIGM FOR IMMUNE REGULATION

Prashant Prajapati[1]*, Dr. Daljeet Kaur Chhabra[1], Dr. Rakhi Gangil[1], Dr. Rakesh Sharda[1], Dr. Joycee Jogi[1] and Dr. Ravi Sikrodia[1]

[1]Department of Veterinary Microbiology, College of Veterinary Science & A.H., MHOW, N.D.V.S.U, Jabalpur (M.P.)- 453446, India.

Corresponding author: prajapatiprashant018@gmail.com

DOI: https://doi.org/10.5281/zenodo.15014368

ABSTRACT

The potential of innate immune cells to acquire a type of memory, leading to improved and sustained reactivity to subsequent stimuli, is known as "trained immunity," a revolutionary idea in immunology. Trained immunity is mediated by the epigenetic and metabolic reprogramming of innate immune cells, including monocytes, macrophages, and natural killer cells, in contrast to adaptive immunity, which depends on antigen-specific memory T and B cells. Histone alterations, DNA methylation, and metabolic changes specifically those influencing glycolysis and oxidative phosphorylation are the processes behind conditioned immunity. The development of vaccines, antibiotic resistance, cancer immunotherapy, and inflammatory illnesses are all significantly impacted by these phenomena. Beyond traditional immunological paradigms, new opportunities for improving immune protection may arise from an understanding of and ability to use trained immunity.

Keywords: Epigenetic, Innate immune cell, Immunological, Metabolic reprogramming, Trained immunity

I. INTRODUCTION

There has been a recent challenge to the widely held belief that immunological memory can only be developed via adaptive immunity. The innate immune system can develop resistance to reinfection in both mammals and organisms lacking adaptive immunity; this process is known as trained immunity or innate immune memory. Epigenetic reprogramming, which is broadly defined as long-term modifications to gene expression and cell physiology without involving permanent genetic alterations like mutations and recombination which are necessary for adaptive immunity is the mastermind behind trained immunity. The identification of trained immunity could lead to the development of new vaccines, innovative therapeutic approaches for immune deficiency states, and the ability to control exaggerated inflammation in auto-inflammatory diseases.

There are several traits that distinguish trained immunity. First of all, it involves a subset of cells that are distinct from those involved in classical immunological memory, including myeloid cells, natural killer (NK) cells, and innate lymphoid cells (ILCs), as well as encoded recognition and effectors molecules like cytokines and pattern recognition receptors. Second, trained immunity is mediated by signals influencing transcription factors and epigenetic reprogramming, and it is not pathogen-specific. These are broadly described as long-term, non-permanent genetic alterations like mutations and recombination-induced changes in cell physiology brought about by sustained modifications in transcription programs via epigenetic rewiring. Trained immunity depends on a modified functional state of innate immune cells that endures for weeks to months as opposed to years following the removal of the original stimulus. On the other hand, innate immune cells exhibit chromatin profile alterations that are specific

to genes or loci during trained immunity, which are brought on by prior stimulation. However, these modifications enable the cells to respond more strongly to restimulation using both the same and distinct PRRs. It is more challenging to distinguish between immune cell differentiation and trained immunity, and to some extent the distinction is even semantic: one could contend that trained immunity also includes macrophage differentiation. However, trained immunity is defined as a response to an external stumli, whereas immune cell differentiation can occur during homeostatic conditions.

II. INVERTEBRATE ANIMALS AND PLANTS WITH IMMUNOLOGICAL MEMORY

Numerous studies on plant immunity provide preliminary evidence that the innate immune system can develop a memory from previous exposure. When taken as a whole, they offer strong proof of the ability to react to reinfection more effectively, a phenomenon known as systemic acquired resistance (SAR). The majority of the molecular pathways and biochemical mediators involved in SAR are understood, with host defense rewiring based on epigenetic. Furthermore, a growing body of research indicates that memory traits are displayed by innate immunity in both plants and invertebrate animals.

In these models, the organism is protected against re-encountering the pathogen by an improved clearance of the infection. For instance, it has been demonstrated that the microbiota can induce innate immune memory to protect mosquitoes against *Plasmodium*; the social insect *Bombusterrestris* displays innate immune memory against three different pathogens; and the tapeworm *Schistocephalus solidus* can induce memory in copepod crustaceans. Thus, it makes sense to conclude that plants and lower animals, in addition to vertebrates, also possess immunological memory.

Innate immune memory in invertebrates has been explained by a number of mechanisms, including the persistent up-regulation of immune regulatory pathways, such as the bacterial peptidoglycan recognition molecules and lectins, or the Toll and Imd receptors on haematocytes, as well as quantitative and phenotypic alterations in immune cell populations.

III. INNATE IMMUNE MEMORY IN VERTEBRATES

It is possible that vertebrates also possess innate immune memory because various plant and animal lineages exhibit memory traits in their innate host defense. Experimental studies in mice that demonstrate that priming (or training) of mice with microbial ligands of pattern recognition receptors (PRR) can protect against a subsequent lethal infection provide important clues that vertebrate innate immunity also has adaptive characteristics.

For instance, β-glucan, a polysaccharide found primarily in fungal cell walls, stimulates trained immunity that protects against Staphylococcus aureus infection. Comparably, prophylactic treatment with TLR9 agonists, such as oligodeoxynucleotides containing unmethylated CpG dinucleotides, three days prior to the infection protects against sepsis and *Escherichia coli* meningitis. The peptidoglycan component muramyl dipeptide also induces protection against *Toxoplasma.* Additionally, flagellin can produce protection against *S. pneumonia* and *Rotavirus*, the latter of which is induced by interleukin (IL)-18 derived from dendritic cells, which in turn stimulates the production of IL-22 by epithelial cells, even in the absence of adaptive immunity. Apart from microbial ligands, there is proof that specific proinflammatory cytokines can also lead to trained immunity. For example, injecting mice with a single dose of recombinant IL-1 three days prior to *Pseudomonas aeruginosa* infection shielded them against death. A classical immunological memory effect is refuted by the nonspecific nature of trained immunity, which points instead to the

activation of nonspecific innate immune mechanisms.

IV. MAIN MECHANISMS INVOLVED IN TRAINED IMMUNE MEMORY

Modified PRR expression

Enhanced pathogen recognition and elevated PRR expression on the cell surface are phenotypic variations of innate immune cells with memory capabilities.

Metabolic reprogramming

A metabolic change involving "Warburg metabolism" is necessary for innate immune memory. Lactate is produced, which shifts the metabolism of glucose toward increased glycolysis and decreased oxidative phosphorylation.

Epigenetic reprogramming

Proinflammatory genes that are specifically activated by β-glucan-dependent memory are marked by trimethylation of H3 at lysine 4 (H3K4me3).

Modified release of cytokines

Enhanced protective inflammatory reactions are a hallmark of trained memory responses. As suggested for brain responses and shown in plants, the various patterns of cytokine release may play a role in the systemic establishment of a memory phenotype, reaching remote or isolated anatomical sites.

V. TRAINED IMMUNITY: A MODIFIED STEADY-STATE OF INNATE IMMUNITY AFTER INFECTION

Long-term memory effects in monocytes and macrophages have been shown in in vitro studies to last days, whereas effects in experimental studies have been reported to last weeks. Vaccines like BCG or measles have been shown in epidemiological studies to have non-specific effects on susceptibility to infections for months or even years. However, it is highly unlikely that this protection will last as long as classical immunological memory.

Proof-of-principle studies confirming the presence of trained immunity effects on circulating monocytes of volunteers for up to a year following BCG vaccination provide support for these data. As previously mentioned, this would also imply effects of vaccination on bone marrow progenitors. To elucidate the duration of trained immunity effects following infection and vaccination, more research is necessary.

VI. CONCLUSION

The aforementioned arguments imply that a basic characteristic of host defense in the mammalian immune response is trained immunity. Trained immunity, or innate immune memory, is non-specific and mediated by epigenetic reprogramming in myeloid cells or natural killer (NK) cells. In contrast, classical immunological memory, which is mediated by T and B lymphocytes, is specific and antigen-dependent, with antigen specificity being mediated by gene rearrangement in particular lymphocyte clones that undergo expansion and contraction. The duration of the effects is another significant distinction between trained immunity and classical immunological memory: trained immunity memory lasts less time than classical adaptive immune memory.

VII. REFERENCES

Bekkering, S., Domínguez-Andrés, J., Joosten, L.A., Riksen, N.P., & Netea, M.G. (2021). Trained immunity: reprogramming innate immunity in health and disease. *Annual review of immunology*, *39*(1), 667-693.

Gourbal, B., Pinaud, S., Beckers, G.J., Van Der Meer, J.W., Conrath, U., & Netea, M.G. (2018). Innate immune memory: An evolutionary perspective. *Immunological reviews, 283*(1), 21-40.

Ochando, J., Mulder, W.J., Madsen, J.C., Netea, M.G., & Duivenvoorden, R. (2023). Trained

immunity—basic concepts and contributions to immunopathology. *Nature Reviews Nephrology*, *19*(1), pp.23-37.

Netea, M.G., Domínguez-Andrés, J., Barreiro, L.B., Chavakis, T., Divangahi, M., Fuchs, E., Joosten, L.A., van der Meer, J.W., Mhlanga, M.M., Mulder, W.J., & Riksen, N.P. (2020). Defining trained immunity and its role in health and disease. *Nature Reviews Immunology*, *20*(6), 375-388.

Netea, M.G., Quintin, J., & Van Der Meer, J.W. (2011). Trained immunity: a memory for innate host defense. *Cell host & microbe*, *9*(5), 355-361.

Netea, M.G.,Van & Crevel, R. (2014). BCG-induced protection: effects on innate immune memory. In *Seminars in immunology 25*(6), 512-517.

Netea, M.G., Joosten, L.A., Latz, E., Mills, K.H., Natoli, G., Stunnenberg, H.G., O'Neill, L.A., & Xavier, R.J.(2016). Trained immunity: a program of innate immune memory in health and disease. *Science*, *352*(6284), 1098.

Cite this article

Prashant Prajapati, Dr. Daljeet Kaur Chhabra,Dr. Rakhi Gangil,. (2025). Unlocking the secret of trained immunity: a new paradigm for immune regulation. Vet Farm Frontier, 02(02), 70–73. https://doi.org/10.5281/zenodo.15014368