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Original Article

Immunopharmacology of Trained Immunity in Infectious and Non-Infectious Diseases: A Review

Pratiksha Vyavahare*, Kranti Akhare, Dr. N. P. Sawadadkar, Dr. N. R. Kayande

Department of Pharmacy, Dr. R. N. Lahoti Institute of Pharmaceutical Education and Research Center, Sultanpur, Dist: - Buldhana

ABSTRACT

Trained immunity is a newly recognized facet of the innate immune system in which prior exposure to certain stimuli (such as vaccines, microbial components, or endogenous danger signals) induces long-lasting functional adaptations in innate immune cells. These adaptations are characterized by epigenetic and metabolic reprogramming, leading to enhanced responsiveness against subsequent challenges. Unlike adaptive immunity, trained immunity is non-specific, broad-spectrum, and involves monocytes, macrophages natural killer (NK) cells, and their progenitors. This review explores the immunopharmacological mechanisms that underlie trained immunity, examines how pharmacological manipulation of these pathways can influence host defense, and discusses implications in both infectious and non-infectious diseases. While induction of trained immunity can enhance protection against pathogens, inappropriate or excessive training may contribute to chronic inflammation and autoimmunity. Therapeutic strategies targeting trained immunity offer potential in vaccine development, infection control, cancer immunotherapy, and treatment of chronic inflammatory diseases.

Keywords: Immunopharmacology, Infectious and Non-Infectious Diseases, Trained immunity

INTRODUCTION

Historically, immunological memory was considered unique to adaptive immunity (T and B lymphocytes). However, innate immune cells such as monocytes and macrophages also exhibit enhanced functional responses upon re-exposure to stimuli, a phenomenon termed trained immunity. Trained immunity is defined as a long-term functional reprogramming of innate cells that enhances responsiveness upon re-challenge, mediated through epigenetic modifications and metabolic changes rather than antigen-specific receptor rearrangement. This provides a new understanding of innate host defense and opens new therapeutic possibilities. [1]

2. Mechanisms of Trained Immunity

2.1 Epigenetic Reprogramming

Epigenetic alterations in innate cells play a central role in trained immunity. Training stimuli induce changes in histone marks — such as increased trimethylation of histone H3 lysine 4 (H3K4me3) and acetylation of H3K27 — at promoter and enhancer regions of pro-inflammatory and antimicrobial genes, making chromatin more accessible and enabling quicker, amplified transcription upon secondary challenge. These modifications persist and prime cells for enhanced responses. [1]

2.2 Metabolic Rewiring

Metabolic shifts are closely linked with epigenetic changes. Trained cells show increased glycolysis, altered tricarboxylic acid (TCA) cycle metabolites, and lipid metabolism changes. Key metabolic regulators like Akt/mTOR and HIF-1α integrate nutrient and danger signals, and metabolites such as fumarate and acetyl-CoA support epigenetic enzymes. [2]

2.3 Signaling Pathways

Pathogen-associated molecular patterns (PAMPs) and endogenous stimuli activate pattern recognition receptors (PRRs) like dectin-1 (for β-glucan) and NOD2 (for BCG), triggering downstream pathways

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that modulate metabolism and chromatin states. This leads to enhanced cytokine production (e.g., IL-1β, TNF-α, IL-6) upon re-stimulation. [3]

3. Pharmacological Modulation of Trained Immunity

3.1 Inducers

a) BCG Vaccine: The Bacille Calmette-Guérin (BCG) vaccine, beyond its role in tuberculosis prevention, induces trained immunity through engagement of PRRs and hematopoietic progenitor reprogramming, promoting non-specific defense against various pathogens. [illegible] MDPI +1

b) β-Glucan: A fungal cell wall polysaccharide recognized by dectin-1, β-glucan is one of the most studied trained immunity inducers. It increases expression of co-stimulatory markers and enhances cytokine production upon secondary exposure, improving innate and adaptive responses. [4] These inducers reveal how microbial and vaccine-derived agents can pharmacologically empower host defense mechanisms.

3.2 Modulators and Inhibitors

Pharmacological agents can also modulate trained immunity to prevent excessive inflammation:

Metabolic inhibitors (like mTOR inhibitors) can reduce glycolytic rewiring. Epigenetic modifiers (e.g., histone deacetylase inhibitors) may reverse maladaptive chromatin states. Cytokine blockers can temper exaggerated pro-inflammatory responses. These modulators offer a means to balance trained immunity effects in clinical settings. [5]

4. Trained Immunity in Infectious Diseases

4.1 Enhanced Protection Against Pathogens

Trained immunity contributes to broad protection against bacteria, viruses, and fungi. For example, β-glucan training has been shown to protect against Mycobacterium tuberculosis infection by enhancing monocyte cytokine responses and inhibiting pathogen growth. [illegible] Mice trained pharmacologically also exhibit improved control of bacterial dissemination and better myelopoiesis due to IL-1 signaling support. [4][5]

4.2 Vaccine Enhancement and Cross-Protection

Trained immunity can reinforce vaccine responses, providing heterologous protection beyond specific adaptive immunity. This phenomenon supports the development of trained immunity-based vaccines (TIbVs) that induce broad innate priming, potentially benefitting immunocompromised populations and emerging infections. [6]

5. Trained Immunity in Non-Infectious Diseases

5.1 Chronic Inflammation and Autoimmunity

While beneficial against infections, trained immunity may contribute negatively when inappropriately activated. Persistent metabolic and epigenetic activation enhances pro-inflammatory cytokine production, which can exacerbate chronic inflammatory disorders such as atherosclerosis, autoimmune diseases like systemic lupus erythematosus, and other conditions with maladaptive inflammation. [7]

5.2 Cancer Immunotherapy

Pharmacological induction of trained immunity has been explored in cancer models, where trained innate cells enhance anti-tumor responses and complement adaptive immunotherapies. BCG is a classic example used in bladder cancer therapy and trained immunity agonists (like dectin-1 ligands) have been tested with tumor vaccines to improve outcomes. [8]

6. Clinical and Therapeutic Perspectives

Targeting trained immunity pharmacologically offers ways to:

Boost host defenses in immunocompromised or vulnerable populations. Improve vaccine efficacy by inducing broad innate priming. Counteract chronic inflammation through inhibitors and regulators. Enhance cancer immunotherapies by combining adaptive and trained responses. However, careful balancing is essential because overactivation contributes to inflammation-related pathology.

CONCLUSION

Trained immunity extends the classical view of host defense by demonstrating that innate immune cells can acquire memory-like features via epigenetic and metabolic programming. Immunopharmacological manipulation of trained immunity offers promising strategies to protect against infectious diseases, enhance vaccine responses, and improve outcomes in chronic inflammatory and cancer conditions. Continued research is essential to optimize therapeutic approaches, including identifying precise pharmacological targets and balancing beneficial versus harmful responses.

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