REVIEW ARTICLE

Trained Immunity and its Role in Health and Diseases: A Review

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Received on: 22 June 2024; *Accepted on:* 18 October 2024; *Published on:* 20 December 2024

Abstract

The term immunity mostly refers to adaptive immunity, even though innate immunity also plays a crucial role. Immunological memory is the key feature distinguishing adaptive immunity from innate immunity. Adaptive immunity features observed in innate cells, i.e., the immunological memory to past insults, has given an entirely new perspective to immunity. This is called trained immunity. Innate cells, after recognition of the pathogens, mount an exaggerated inflammatory response if challenged again. These responses protect not only against the target pathogen but also against other pathogens. This heterologous response of trained immunity is a unique property with a lot of therapeutic promise.

Metabolic and epigenetic reprogramming of innate cells are the central mechanisms of trained immunity. This reprogramming, evoked by endogenous and exogenous stimuli, result in trained immunity which is now considered to be evolutionally conserved. It protects the organism in the same way as the adaptive immune memory. Though trained immunity is beneficial, maladaptation at times may lead to hyper-inflammatory state with detrimental effects.

Trained immunity has found its applications in understanding many clinical conditions and possibly new therapeutic potential. In this review, a brief account of trained immunity, its mechanistic undercurrents and therapeutic exploitations are described.

Keywords: Amplified vaccines, Immune gene priming IncRNAs (long noncoding RNAs), Innate immune memory, Innate lymphoid cells, Lactylation, Trained immunity.

Indian Journal of Medical Biochemistry (2025): 10.5005/jp-journals-10054-0247

Introduction

Our immune system operates through innate and adaptive arms, which are separate but interact. Immunological memory is one of the key features which distinguishes adaptive immunity from innate immunity.

Innate immune cells have pathogen recognition receptors (PRRs) which recognize pathogens and damaged tissues through their molecular structures called pathogen-or damage-associated molecular patterns (PAMPs and DAMPs).[1] This recognition activates many nonspecific and innate processes like phagocytosis, inflammation, cytokine secretion, etc., to kill and remove the pathogen. This also stimulates T and B lymphocyte dependent highly specific adaptive immune response for the complete elimination of the pathogen and development of immunological memory for future protection.[2] According to present understanding, there is no such memory development in the innate immune system.

Trained immunity describes the immune memory developed in response to past immune challenges by the innate system. Signaling in the innate cells after the engagement of their PRRs by PAMPs and DAMPs induces trained immunity.[3] Inflammatory cytokines are the main effector molecules for this trained immunity.[4] It is often short-lived and less specific than adaptive memory. It produces a rapid and stronger secondary response for the improved survival of the organism as in adaptive immunity.

This review aims to focus on this new horizon of the immunology and briefly outline the emergence and concept of trained immunity, the various cells involved, and the underlying mechanisms, involving metabolic and epigenetic changes, for its development. Its role in several clinical conditions, based on the available evidence, is highlighted along with possible therapeutic implications.

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How to cite this article: Gupta SK. Trained Immunity and its Role in Health and Diseases: A Review. Indian J Med Biochem 2025;29(1): 36–44.

Source of support: Nil

Conflict of interest: Dr SK Gupta is associated as the National Advisory Board member of this journal and this manuscript was subjected to this journal's standard review procedures, with this peer review handled independently of this editorial board member and his research group.

Trained Immunity

In 2003, a minute crustacean, lacking T and B cells, showed immunological memory which prevented reinfection with a tapeworm.[5] This memory was associated with innate immune system. It was then observed in other invertebrates and vertebrates, including humans. Innate memory is now considered ubiquitous and evolutionally conserved.[6]

Following many animal studies, trained immunity has also been documented in humans.[7–9] Many live vaccines such as smallpox, Bacillus Calmette-Guérin (BCG), measles, and oral polio, produce trained immunity along with nonspecific protection, leading to reduced mortality and better survival.[10–12] Augmented proinflammatory cytokine response of monocytes is seen after BCG vaccination induced cross protection against yellow fever and malaria.[13,14] The antitumor immune response of the BCG vaccine

is well documented against cancer of the bladder, melanoma, leukemia, and lymphoma.[15–17] These effects are likely due to trained immunity induced by the BCG vaccine through the monocytes and macrophages. Thus, a large body of evidence points to the trained immunity in humans as well.

The term trained immunity was first introduced in 2011 to describe the development of an exaggerated response to past immune challenges. Following initial exposure to some immunological stimuli, innate immune cells can adjust their response to subsequent insults, resulting in an enhanced response to previously encountered infectious agents.[18]

Inducers of Trained Immunity

Most studies of PAMPs and DAMPs as inducers of trained immunity are based on Candida albicans and BCG vaccine.[3,4,9,19] However, monocytes also acquire innate memory on infection with viruses and parasites and exposure to many other molecules such as oxidized low-density lipoproteins (oxLDLs), catecholamines, heme, and uric acid.[4,20–24] All these may be important in the development of atherosclerosis, gout and other diseases.

The timing and dose of inducer is critical for the trained immune response. It is known that lipopolysaccharides (LPS) induce trained immunity at very low doses but are also capable of inducing immune tolerance at relatively higher doses.[25]

Cells Involved in Trained Immunity

A diverse variety of immune and nonimmune cells are involved in trained immunity including microglia, endothelial, urothelial, epithelial and vascular smooth muscle cells.

Monocytes and Macrophages

Trained immunity was initially described in monocytes and macrophages.[3,4] Exposure of these cells to *β-glucan,* BCG vaccine, and Candida albicans have resulted in trained immunity with enhanced secondary response even against microbes with different PRRs.[7,9,19] Experiments show that the monocyte-derived macrophages acquire trained immunity phenotypes and produce increased proinflammatory cytokines like TNF-α, IL-6, and IL-1β upon secondary stimulation.[26, 27] Markers of trained immunity are also noted in the chromatin of these cells.

Natural Killer (NK) Cells

In the past decade, several studies have shown trained immunity responses in natural killer (NK) cells. In mice studies, NK cells show 10 fold clonal expansion following cytomegalovirus (CMV) infection with a rapid secondary response including cytokines degranulation.[4,28] Human NK cells show similar response to a human CMV encoded glycoprotein through the NKG2C receptor presented by nonclassical HLA-E molecules This response is independent of the recombinase activating gene (RAG) mediated antigen receptor gene rearrangement.[29,30]

Innate Lymphoid Cells (ILCs)

Innate lymphoid cells are a recently described family of lymphoid cells that have a role in inflammations, host defense, tissue remodeling, and trained immunity.[31] In contrast to typical T and B lymphocytes, ILCs do not possess antigen-specific receptors and still rapidly respond to signals from the tissues and other cells. Natural killer cells are founding members of this group and are cytotoxic like the $CD8^+$ T cells. Other ILCs are not cytotoxic.

Based on their cytokine secretions and requirement of transcription signals for their development, they are divided into many groups.[31] Innate lymphoid cell show plasticity, a large degree of heterogeneity, and variable effector functions dependent on tissue microenvironments. Innate lymphoid cell showed transcriptional, epigenetic, and phenotypic changes of trained immunity and enhanced protective response on secondary infection.

Dendritic Cells (DCs)

Conventionally, DCs are cells of the innate immune system but play a crucial role in adaptive immunity.[2] Recently, they are also shown to develop trained immunity. Dendritic cells from mouse infected with the fungus *Cryptococcus neoformans*, displayed enhanced proinflammatory cytokine secretion like IFN-γ and TNF-α on secondary stimulation. These effects were dependent on epigenetic changes like DNA histone methylation, since specific enzyme inhibitors abrogated these effects.[32]

Stromal and Epithelial Cells

Trained immunity is also exhibited by stromal and epithelial cells which are crucial in cellular regeneration and homeostasis. Epithelial stem cells residing in distinct niches in bone marrow provide unique signals responsible for their future behavior and functions. Events like inflammation, infections, etc., influence these signals and overrides the normal function. Enduring epigenetic memory is developed in these cells on encountering PAMPs and DAMPS.

Stem cells possess receptors to sense the breach of barriers and initiate processes to limit and repair the damage.[33] For example, skin stem cells recruit specific immune cells. Then, through two-way communications with the immune cells, stem cells receive signals to proliferate and plug the breach. This coordination is established to achieve maximal repair response.

Smooth Muscle Cells (SMCs) and Fibroblasts

Smooth muscle cells form the inner lining of hollow organs like lungs, arteries, intestines, and bladders to regulate vascular tone and diameter because of their elastic phenotype. Endothelial cells and vascular SMCs have roles in vascular inflammation, atherosclerosis, and fibrous cap formation.[34] They are capable of undergoing memory phenotype on exposure to oxLDL or BCG in *in vitro* experiments. They show enhanced cytokine production upon secondary stimulation.

Fibroblasts can also acquire the trained immunity phenotype, initiate inflammation, and produce cytokines and antimicrobial peptides in the presence of invading microorganisms. Synovial fibroblasts in RA are capable of persistent activation after initial stimulation with stable epigenetic changes and prolonged inflammatory memory leading to joint destruction. Further, in periodontal disease, human gingival fibroblasts also mount an inflammatory memory response regulated via epigenetic changes.[35,36]

Central and Peripheral Trained Immunity

It is now believed that the trained immunity occurs both as the peripheral and central trained immunity mediated by peripheral blood myeloid cells and hemopoietic progenitor stem cells in the bone marrow, respectively. The bone marrow stem cells are long-lived cells and undergo continual divisions to generate mature peripheral blood cells. Recent studies in mouse show that the BCG

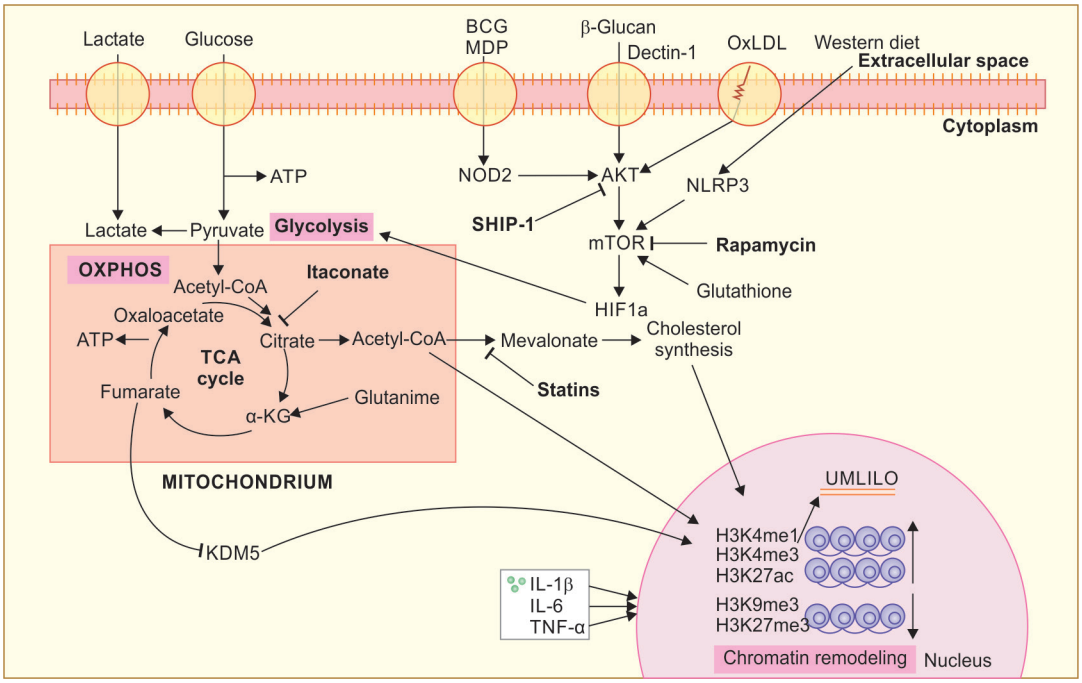

Fig. 1: Mechanism of trained immunity

vaccine induces myelopoiesis in hemopoietic progenitor cells in bone marrow in an IFN -γ dependent manner, resulting in trained immunity.[37] Similar results are reported with β-glucan also. Further, epithelial stem cells contribute to the persistence of diseases by acting as repositories of memories of allergic insults in humans with nasal polyps.[38]

Mechanism of Trained Immunity

Following sensing of inducers through various PRRs, several epigenetic and metabolic changes occur in myeloid cells and hemopoietic stem progenitor cells (HSPCs) leading to the development of trained immunity as shown below in Figure 1.

Metabolic Reprogramming

Energy and nutritional demand are increased in cells undergoing trained immunity as compared to resting cells. Hence, several changes occur in metabolic pathways to meet these demands, such as aerobic glycolysis, glutaminolysis, enhanced fatty acid, and cholesterol synthesis.

Increased glycolysis was demonstrated in oxLDL-induced trained immune cells.[39] In 2014, high glucose consumption, lactate formation, and the nicotinamide adenine dinucleotide (NAD^+)/NADH ratio were reported in β-glucan-trained-human monocytes. This shift from oxidative phosphorylation to aerobic glycolysis (Warburg Effect) was mediated by mammalian target of rapamycin (mTOR) activation dependent signaling through AKT-HIF1α pathway. Rapamycin inhibited the glycolysis activation in a dose dependent manner (Fig. 1).[40]

Reduced glutathione generation was observed to compromise mTOR activation as well as proinflammatory cytokines secretion and protection induced by β glucan against heterologous secondary challenges.[41] Inhibition of SHIP-1 (SH2 domain containing inositol phosphatase) or its deficiency in macrophages promoted AKT phosphorylation, resulting in activation of glycolysis and enhanced trained immunity. Further inhibition of mTOR pathway-dependent glycolytic efflux by rapamycin inhibited the monocyte training, but the inhibition of the oxidative branch of the HMP pathway by 6-amino-nicotinamide (6-AN) had no effect.[42] This indicates the dependence of glycolysis on AKT-mTOR-HIF1α pathway during the development of trained immunity.

Other metabolic changes reported are enhanced cholesterol synthesis in HSPCs in β-glucan-induced trained immunity. Mevalonate induced trained immunity occurs in monocytes through IGF-1 receptor activation and mTOR signaling. It is inhibited by statins; these observations are strengthened by the presence of constitutively trained monocytes in hyperimmunoglobulin D syndrome patients, in whom there is mevalonate accumulation due to a lack of the enzyme mevalonate kinase. These patients often experience sterile inflammatory attacks, which are likely due to the trained monocytes with microbial protection.[43]

Immunometabolic Interactions

Many studies show that the different metabolites derived from these enzymatic processes act as cofactors and integrate the metabolic and epigenetic reprogramming. Some examples are mentioned below:

Acetyl CoA is a substrate for acetylation and its synthesis is augmented by the activation of the enzyme adenosine tri phosphate (ATP) citrate lyase and redirection of glucose metabolites towards its synthesis in immune cells.[44,45] α-ketoglutarate is a coenzyme for dioxygenases enzymes such as TET (ten eleven translocation) methylcytosine dioxygenase enzymes, lysine-specific demethylase enzymes (KDM) and JumonJi C domain (JMJD) containing enzymes.[46] These enzymes catalyze the demethylation, using dioxygen. Succinate and fumarate act as the competitive inhibitors and reduce the activity of KDM5.[47]

S-adenosyl methionine (SAM), a methyl group donor participates in DNA and histone methylations. Its low concentration

restricts histone 3 lysine 4 trimethylation (H3K4m3) and influences gene expression and trained immunity development.[48,49]

Lactate in cells, undergoing trained immunity modifies histones by binding to their lysine, residues leading to histone lactylation. This promotes homeostasis and an anti-inflammatory cytokines state. Histone lactylation is inversely related to and counterbalances histone acetylation.[50]

Nicotinamide adenine dinucleotide is a coenzyme for histone deacetylase enzymes belonging to the sirtuin1 family silent mating information regulation 2 homologue (SIRT1).[51] High NAD^+/NADH ratio and lactate in aerobic glycolysis influence histone deacetylation and gene expression by interacting with NF-κB and enhance cell apoptosis, and decrease the proinflammatory response to TNF-α dependent trained immunity. Silent mating information regulation 2 homologue 2 -/- mice have enhanced proinflammatory response in a colitis model.[52]

Butyrate, derived from the gut dietary fibers, is also linked with epigenetic modifications as an inhibitor of the histones deacetylases (HDAC) leading to inhibition of trained immunity development.[53] Butyrate inhibits the development of trained immunity in gout patients. Similar results are seen in cells pretreated with butyrate and trained ex-vivo with monosodium urate and on dietary supplementation with butyrate.[54,55] The abundance of these metabolites allow the cell to sense their energetic state and then act as rheostats to regulate the activity of epigenetic enzymes.[56]

Epigenetic Reprogramming

In the resting state, proinflammatory gene loci remain repressed and are not accessible to the transcription machinery. Epigenetic changes promote chromatin modification which regulates their accessibility for transcription. Of these changes, histone methylation and acetylation are the key modifications, especially the histone methylation which is tightly regulated**.**

Studies have pointed out that the primary stimulation of the immune cells leaves a stable epigenetic mark in the regulatory elements of the stimulated genes. These genes then show altered transcription on subsequent stimulation manifesting as trained immunity.[57,58]

Different states of methylation and acetylation at specific lysine residues of histone proteins act as activators or repressors of transcriptions. For example, in the activated genes, mono-methylation of histone 3 lysine residue 4 (H3K4me1) is seen in distal enhancers, while its trimethylation is seen in promoters. Similarly, histone 3 lysine 27 acetylation (H3K27ac) is seen in enhancers and promotor regions of the active genes. The trimethylation of H3K9 and H3K27 are reduced during the induction of trained immunity.[4,19,26]

Long noncoding RNAs (lncRNAs) also modulate trained immunity.[59] Studies on chromosomal interactions reveal that many classes of innate immune system genes are brought into particular topology-associated domains (TADs) which then interact with a specific class of long noncoding RNAs (lncRNA) called "immune gene priming lncRNA" (IPLs). These IPLs, with the help of preformed 3D loop contacts, bring the H3K4me3 histone-modifying complex close to the promoters of highly responsive innate immune genes for transcription. During the induction of trained immunity in human monocytes by β-glucan, increased levels of H3K4me3 were seen bound to UMLILO (upstream master of lncRNA of inflammatory chemokines locus), which is a lncRNA-regulated immune gene promoter. The functional significance of IPLs in H3K27ac has been demonstrated in β-glucan-induced phenotypes.[59]

How the H3K27ac occurs at specific sites in activated genes is not fully known. Data from the HSPCs exposed to BCG vaccine indicate that this acetylation leads to the opening of specific TADs. It then persists, at least partially, into the fully differentiated cells. It may be possible that this mark (H3K27ac) in the differentiated cells may undergo a gain or loss in response to LPS tolerization or β-glucan stimulation for trained immunity.[37]

New studies suggest different DNA methylation patterns in responders (showing enhanced macrophage antitubercular activity and IL-β secretion) than non-responders following BCG vaccination. Responders displayed loss of DNA methylation in the promoters of many genes of immune pathways than the non-responders.[60] These genes may have predictive value for trained immunity.

Reprogramming of HSPCs

The lasting of trained immunity one year after BCG vaccination indicated the probable reprogramming of HSPCs in bone marrow.[61] Two groups independently showed it in the chimeric mice model as well as by adoptive cell transfer study. Kauffman et al.[37] demonstrated that BCG-induced reprogramming of the HSPCs generated epigenetically modified macrophages which provided heterologous protection. Mitroulis[62] showed that β-glucan-induced expansion of HSPCs utilized glucose and cholesterol synthesis to provide heterologous protection against secondary LPS challenge and protection from chemotherapy-induced myelosuppression. In healthy volunteers, intradermal BCG vaccination led to the trained immunity with persistent bias towards myelogenesis through transcriptional alterations resulting in $CD14^+$ monocytes.[63] These long-lasting effects of trained immunity are likely due to the resultant cells generated from the reprogramming of HSPCs.

Trained Immunity Antagonists

As outlined above, most studies have focused on the induction of the trained immunity than its regulation. However, some observations do point to a few antagonistic molecules. For example, IL-37 reversed the metabolic and epigenetic modifications in trained monocytes and abrogated the host defense against infections by reducing proinflammatory cytokines.[64] Similarly, IL-38 acted as an antagonist against β-glucan-induced trained immunity.[65] Hydroxyquinine prevented the epigenetic modifications needed for trained immunity.[66] These studies point to the possible regulatory circuits of trained immunity, but full details are yet to be outlined.

Inheritance of Trained Immunity

Recently, animal studies have indicated the possibility of inheritance of the trained immunity. Offsprings of the sub-lethally infected male mouse with *C. albicans* showed features suggestive of trained immunity against heterologous infections, along with transcriptional and epigenetic changes in HSPCs.[67] These studies and the stable long-lasting programming of the HSPCs indicate the possible inheritable nature of trained immunity.

The Beneficial Effects of Trained Immunity

Neonatal Protection

Neonates are protected immediately after birth through their innate immune system and by the antibodies received from the

mother. Subsequently, the vaccinations also play a role in it. Trained immunity provides both target and heterologous protection.[7–9] Environmental exposure of candidiasis and vaccinations like smallpox and BCG, measles, and oral polio, initiate this specific and nonspecific protection.[10–12] Overall, there is accelerated clearance of pathogens by the innate immune system.

COVID-19 and Innate Immune System

During the COVID-19 pandemic, several studies indicated the association of the BCG vaccine with decreased risk of COVID-19. Retrospective observational studies indicated that the history of BCG vaccination was associated with low seropositivity, a decrease in clinical symptoms and severity of COVID in a cohort of healthcare workers.[68] These effects were attributed to the trained immunity induced by the BCG vaccine. Another study in COVID-19 recovered patients, revealed that the S-protein of the SARS-COVID-19 virus itself induced a proinflammatory response.[69]

Antitumor Effects of BCG Vaccine

Bacillus Calmette-Guérin vaccine's role is well known in cancer.[70] In bladder cancer, it is used as an adjunct therapy and leads to an intratumor cellular inflammation resulting in the shrinkage of the tumor.[15] This immunotherapy was the first of its kind for solid tumors resulting in a decrease in recurrence rates. Currently, BCG vaccine is considered the gold standard treatment for noninvasive high- and medium-risk bladder muscle tumors. It is known to have antitumor effects in other malignancies such as melanoma, leukemia, and lymphoma.[16,17]

The Pathological Effects of Trained Immunity

These are usually due to the hyperinflammatory state of trained immunity which may have a significant role in some inflammatory diseases.

Rheumatoid Arthritis (RA)

Rheumatoid arthritis is a chronic inflammatory disease. Synovial fibroblasts from RA patients are chronically activated releasing proinflammatory cytokines, which lead to joint inflammation and destruction. Eventually these cells are epigenetically modified and become independent of the activating stimuli leading to a hyper-inflammatory state.[71] Inhibition of glycolysis and trained immunity have shown a decrease in inflammation and disease severity.[72]

Atherosclerosis

Chronic inflammation of the arteries by the oxLDL is one of the causes of atherosclerosis. Oxidized low-density lipoproteins also induces trained immunity.[21] Monocytes from atherosclerosis patients show trained immunity phenotype with enhanced inflammation and increased glycolysis than the healthy controls.[39] Further, progesterone is found to suppress oxLDL induced trained immunity in macrophages with beneficial effects.[73]

Neurodegenerative Diseases

Under normal physiological conditions, microglia, the resident brain macrophages, are tightly regulated by the local microenvironment. In neurodegenerative disorders with accumulated misfolded proteins, microglia are seen in an active and proinflammatory state. This phenomenon is called microglial priming and is considered an equivalent of trained immunity.[74] Recently, rapamycin has been shown to suppress the microglial priming and trained immunity with beneficial effect and a possible therapeutic target.[73,75]

Allergy

Allergy is a consequence of hypersensitivity of the immune system to common allergens in the environment. Compared to the healthy children, monocytes from the allergic children show enhanced response to toll like receptor (TLR) ligands.[76] Another study indicated higher secretion of IL-6, IL-1β, and TNF-α in cord blood monocytes of those children who subsequently developed food allergies in response to LPS.[77] Thus, an enhanced state of trained immunity is seen in food allergy. Large randomized clinical trials are underway to test the beneficial role of BCG vaccination in neonates.[78]

Organ Transplantation and Rejection

Though tissue rejection following transplantation is an adaptive immune response, the role of trained immunity is highlighted in macrophages which have a critical role in both arms of immunity. The trained macrophages have been proposed with upregulated expression of costimulatory molecules and proinflammatory cytokines to potentiate the graft rejection.[79] This could be exploited to reduce the graft rejection with the development of nanobiologicals, based on this new understanding as explained below.

Therapeutic Implications of Trained Immunity

Though trained immunity is a stable and relatively long-lasting process, but it is not permanent. This offers the possibility of its manipulation for therapeutic purpose as mentioned below.[80]

Nano-immunotherapy

Several studies point to the use of nanoparticles containing active therapeutic agents, based on trained immunity, as medicine in several clinical conditions.

In a heart transplant mouse model, a nanomolecule targeting mTOR inhibitor blocked the development of trained macrophages. Instead, it led to the expression of regulatory tolerogenic $CD4^+$ T cells and prevented the development of alloreactive $CD8^+$ T regulatory cells. So overall the survival of graft was enhanced.[81]

A similar approach is being explored in atherosclerosis. A statin molecule, incorporated into a synthetic nanoparticle resembling high-density lipoprotein (HDL) as an inducer of trained immunity is found to reduce the atherosclerotic plaques.[82]

A nanoparticle named MTP10-HDL, containing muramyl tripeptide phosphatidyl ethanolamine as inducer of trained immunity in a synthetic HDL particle labeled with zirconium, inhibited tumor growth and activated HSPCs. These effects are due to trained immunity induced myelopoiesis caused by epigenetic reprogramming of HSPCs in bone marrow.[83,84] Based on such evidence, muramyl dipeptide and other nanobiologicals are being explored for their therapeutic potential.

Antibody Immunotherapy

Since cytokines mediate trained immunity, corresponding monoclonal antibodies (mABs) as antagonists are likely to offer therapeutic benefits.

Neutralizing mABs targeting IL–1β had been tried in many inflammatory diseases, even before the emergence of trained immunity, such as in type 2 DM, RA, and cerebral stroke.[85] In a recent

study, canakinumab (anti-IL-1β mAB) showed a significantly reduced rate of recurrent cardio vascular system (CVS) events in a double-blind placebo-controlled randomized phase III clinical trial.[86] Likewise, monoclonal against GM-CSF have also shown promising results in studies on patients with RA, psoriasis, and asthma.[87]

Vaccines Based on Trained Immunity

The vaccines are usually developed for long-term protection against a specific target pathogen. They involve the adaptive arm of the immunity, though the innate cells, especially the macrophages and dendritic cells, recognize and present the antigen to the T-cells. They also provide the crucial costimulatory signal and cytokines for the T-cell activation.

We know, by now, that the trained immunity can be induced to provide heterologous protection also, besides the target pathogen. Consequently, it is possible to design vaccines based on trained immunity to suitably modify the innate immune response to the pathogen. Alternatively, trained immunity-based vaccines may be co-delivered to provide adjunct support besides the specific adaptive immune protection. An example is available from the studies of the BCG vaccine in bladder cancer.

A recombinant BCG vaccine, expressing detoxified pertussis toxin, produced many-fold higher trained immunity response in human leukocytes *in-vitro*, indicated by higher IL-6 secretion. It also prolonged the survival by several folds, in bladder cancer patients.[88] Another recombinant BCG vaccine expressing a stimulator of interferon genes (STING) produced higher antitumor protection by enhancing trained immunity and remodeling.[89] In another study, a squalene-based adjuvant containing α-tocopherol, ASO3, when given with an influenza virus vaccine, produced a robust trained immune response against heterologous pathogens.[90] Recent developments on the front of nanotherapeutics, indicate the possibility of specifically targeting the epigenetic and metabolic reprograming of the innate cells to deliver a tailor-made trained immune response.

Summary and Future Perspective

Trained immunity is a newly described property of innate immune cells. It has opened an entirely new field of intense research in immunology. The trained innate cells, after an initial insult, respond with an enhanced proinflammatory response to secondary challenges. This augments the protection not only against the target pathogen, but also against other pathogens. This has opened a wide area of its applications as immunotherapy in infections, inflammatory diseases, cancers, organ transplantation, etc.

The metabolic and epigenetic reprogramming of the trained cells is the underlying mechanism. In trained immunity development, inducers like β-glucan, BCG, muramyl dipeptide (MDP), oxLDL, etc., enter the cell through diverse receptors, then activate the AKT-mTOR-HIF1α axis. This modulates metabolic reprogramming of various pathways like glycolysis, oxidative phosphorylation, TCA cycle, cholesterol synthesis, etc. Several metabolites of these pathways then regulate the epigenetic reprogramming resulting in trained immunity.

The metabolic and epigenetic reprogramming of the trained cells, though firmly footed, is being unfolded in greater details to fill the gaps in the cellular, metabolic, and epigenetic understanding in the development of trained immunity. Even though, many transcriptional signatures of trained immunity are identified at the single cell resolution and integrative genomics has delineated several gene loci involved in this, more studies are needed to exploit it fully for its therapeutic potential. The regulatory aspects of trained immunity are the least explored. Though some antagonists are known, wide availability of epigenetic modifiers will go a long way in appropriate application of the inflammatory response therapeutically. Proteins with bromodomain and extra-terminal domain have shown promise as inflammatory target gene modifiers by interfering in histone acetylation. The likely availability of a larger pool of nanobiologicals, in due course to induce and modify the trained immunity response suitably, will enable the wider clinical application. Other important questions which need to be answered in this regard are: (I) if the short-term modification of trained immunity by its inducers and/or inhibitors is sufficient for clinical applications. (II) Are there any concerns for long term writing or removal of epigenetic marks.

Neutralizing antibodies are already being used in many conditions. Availability of a wider pool based on deeper understanding of the various aspects of trained immunity will enhance their use in many diseases, especially, the inflammatory diseases.

The emerging idea of amplified vaccines is an exciting opportunity. These vaccines are combinations of classical vaccines with suitable modifies of trained immunity. Overall, they generate an appropriately amplified immune response which making them more efficient than the traditional vaccines.

Another interesting possibility of its application is in the treatment of genetic diseases. The possibility of intergenerational inheritance of trained immunity indicated by many studies, if established and understood in greater details, can be exploited towards this goal.

Overall, the potential of a suitably modified inflammatory response can be of immense therapeutic use.

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