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REVIEW

Long-term reprogramming of the innate immune system

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Abstract

During the last few years, a growing body of evidence has shown that immunological memory is not an exclusive trait of lymphocytes, as many inflammatory insults can alter the functionality and the responsiveness of the innate immune system in the long term. Innate immune cells, such as monocytes, macrophages, dendritic cells, and NK cells can be influenced by the encounters with inflammatory stimuli, undergoing functional reprogramming and developing changed responses to subsequent chellenges. The long-term reprogramming depends on the rewiring of cell metabolism and epigenetic processes, and they stay at the basis of induction of both innate immune memory (also termed trained immunity) and innate immune tolerance. Here, we review the central role that the effects of this long-term reprogramming of innate immune cells plays in a number of clinically relevant conditions such as vaccination, atherosclerosis, sepsis, and cancer.

KEYWORDS

Innate immune system, trained immunity, metabolism, epigenetics, reprogramming, inflammation, vaccination, atherosclerosis, sepsis, cancer

1 | INTRODUCTION

The immune system is constantly challenged by external and internal stimuli since the day we are born. Every encounter between our immune cells and a stimulus leaves a footprint, shaping the originally naive immune system, which will progressively learn to differentiate between harmless stimuli and potentially pathogenic threats. Immunological memory has been clasically described for the adaptive immune system, in which naive B and T lymphocytes develop antigen-specific, long-lasting memory cells after encountering a new antigen.[1] However, in the last years, a series of disoveries have demostrated that immunological memory is not an exclusive trait of lymphocytes. The function of cells from the innate immune system, such as monocytes, macrophages, dendritic cells (DCs), and NK cells, is also influenced by the contact with different stimuli, undergoing functional reprogramming, and facilitating a faster and enhanced response to future threats.[2–4] Nevertheless, while the responses driven by T and B lymphocytes are antigen-specific, secondary responses involving innate cells are nonspecific and can be triggered by a wide variety of stimuli. The innate immunological memory in response to non-specific stimuli has beed termed systemic acquired resistance in plants,[5] and trained immunity in vertebrates.[6,7]

Long-term shaping of the immune responses requires that the reprogramming induced by the first contact with the antigen is maintained long enough to enhance an active secondary response after a subsequent encounter with a pathogen. It has been widely described that memory lymphocytes can survive or self-renew for long periods of time.[8,9] However, the mechanisms through which long-term innate immune memory is induced are still a matter of extensive research. Trained immunity involves profound reprogramming at metabolic, epigenetic, and transcriptional levels.[10–12] In this review we summarize and discuss relevant contributions to the understanding of the processes involved in the functional reprogramming of the innate immune cells.

2 | TRAINED IMMUNITY AND TOLERANCE

A growing body of evidence has shown that the long-term epigenetic and metabolic reprogramming of innate immune cells plays a central role in a high number of clinically relevant conditions, such as vaccination, atherosclerosis, sepsis, or cancer.[13–16] Anti-pathogenic responses of the innate cells are triggered after the involvement of pattern recognition receptors such as TLRs, nucleotide-binding oligomerization

Abbreviations: Akt, protein kinase B; BCG, bacillus Calmette-Guérin; DCs, dendritic cells; DTP, vaccine against diphtheria, tetanus, and polio; EGFR, epidermal growth factor receptor; EgIN, hypoxia-inducible factor prolyl hydroxylase 2; H3K27ac, acetylation of histone 3 lysine 27; H3K4, histone 3 lysine 4; H3K4me3, trimethylation of histone 3 lysine 4; HIF1α, hypoxia-inducible factor 1α; JmjC, jumonji C domain; MCV, measles-containing vaccines; mTOR, mammalian target of rapamycin; NLR, nucleotide-binding oligomerization domain-like receptors; OXPHOS, oxidative phosphorylation pathway; ROS, Reactive Oxygen Species; SDH, succinate dehydrogenase; Srepb, Sterol regulatory element-binding transcription factor 1; TET, ten-eleven translocation enzymes

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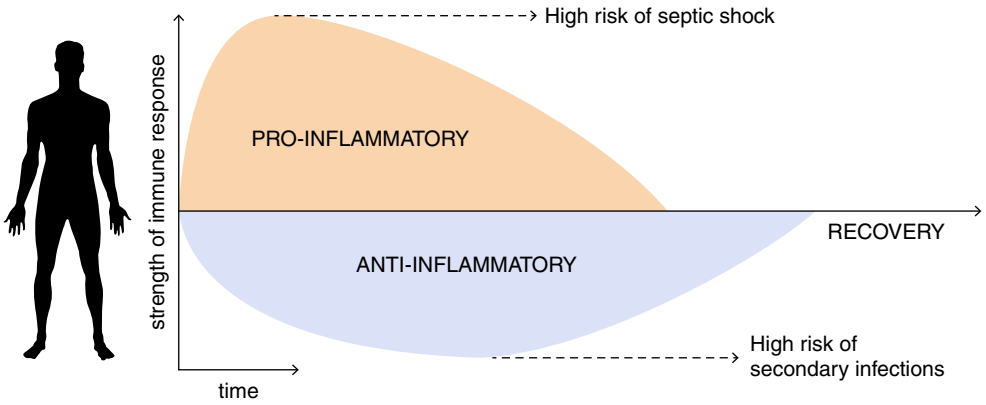

FIGURE 1 State of immune activation in patients with sepsis. The immune response during the acute phase of sepsis is characterized by exacerbated inflammation and the activation of immune effector mechanisms. Simultaneously, the immune system initiates anti-inflammatory mechanisms to reduce inflammation and promote tissue repair. The exaggerated systemic release of cytokines in the acute phase can lead to septic shock, with tissue damage, hypotension, cardiovascular dysfunction, and multiorgan failure. The disease activation of modulatory pathways may induce excessive tolerance and immunoparalysis, with the subsequent risk of secondary infections

domain-like receptors (NLR), or C-type lectins.[17,18] However, these receptors also recognize nonpathogenic signals and induce sterile inflammation.[19] In situations with excessive inflammation, tolerance acts as a mechanism that dampens the inflammatory response of the host to maintain homeostasis and prevent tissue damage and organ failure.[20–22] Nevertheless, long lasting inhibitory effects in the immune function can also lead to a state of immunosuppression associated with a higher risk of secondary infections and a poorer outcome.[23] Trained immunity and tolerance are the scales of a balance in which pro- and anti-inflammatory responses must be compensated to avoid either chronic inflammation or immune paralysis[2] (Fig. 1). Tolerance also plays a crucial role in the regulation of physiological processes, as our immune system should not react against harmless stimuli, such as food antigens, inhaled allergens, or the gut microbiota.[24]

Trained immunity can be considered the opposite of the immune tolerance. Trained immunity involves an increase of the metabolic and epigenetic activity of the cell leading to an enhanced responsiveness to secondary stimulation.[6] Tolerance is accompanied by a downregulation of the overall metabolic activities of the cell and a lack of accumulation of active histone marks at promoters and enhancers of genes related with immune functions.[20] Subsequently, overly strong or long-lasting activation of tolerance mechanisms can subsequently lead to a de facto immune paralysis with deleterious effects due to an increased susceptibility to secondary infections.[24]

Since the cells of the innate immune system have a short lifespan in circulation,[25] there was an open question regarding how reprogramming of cells from this system could exert such long-lasting effects in the organism. Recent studies have shown that some stimuli induce systemic effects that have consequences several months after the first contact by altering hematopoiesis and triggering long-term reprogramming of progenitors in the bone marrow.[26–28] Mitroulis et al. showed that β-glucan, the prototypical trained immunity-inducing agonist,[29] modulates hematopoietic stem and progenitor cells, influencing the behavior and responsiveness of peripheral myeloid cells,[28] and similar observation was made by Kaufmann et al. after bacillus Calmette-Guérin (BCG) vaccination.[27] Western-type diet-induced systemic inflammation led to prolonged enhancement of hematopoiesis and granulocyte-monocyte progenitor cell reprogramming in an IL-1 pathway-dependent fashion in an atherosclerosis mouse model.[26] The long-term reprogramming of the cells of the innate immune system takes place at different levels, namely cell metabolism and epigenetic markers.

3 | METABOLIC REPROGRAMMING IN INNATE IMMUNE CELLS

The basal metabolism of innate immune cells greatly differs in function of the subset studied (Fig. 2). Overall, quiescent cells have low biosynthetic demands, and metabolic pathways are skewed toward metabolizing glucose through glycolysis coupled to oxidative phosphorylation.[30] Upon activation, there is an increase in glucose uptake and glucose transformation into lactate through aerobic glycolysis, providing the cells with the precursors essential for the synthesis of nucleotides, amino acids, and lipids.[31] Resting circulating monocytes mainly rely on the TCA cycle, whose products are employed as biosynthetic products for different molecules or as fuel for oxidative phosphorylation.[32] Induction of trained immunity by fungal components such as β-glucan leads to a shift of cellular metabolism from oxidative phosphorylation toward aerobic glycolysis.[10,11] This is a process mediated through the protein kinase B (Akt)/mammalian target of rapamycin (mTOR)/hypoxia-inducible factor 1α (HIF1α) pathway, which is crucial for an effective induction of trained immunity.[10,11] This increased activity of the cell leads to an enhanced metabolic flux toward oxidative phosphorylation pathway (OXPHOS), where electrons transported by molecules, such as NAD+ and FADH, generate a gradient that will be used to synthesize ATP.[33] In addition, the enhancement of the metabolic activity leads to the generation of considerable quantities of metabolites with immunomodulatory functions, such as fumarate,[12] succinate,[34] or itaconate,[35,36] that also play a central role in the induction of long-term reprogramming of the cells of the innate immune system.

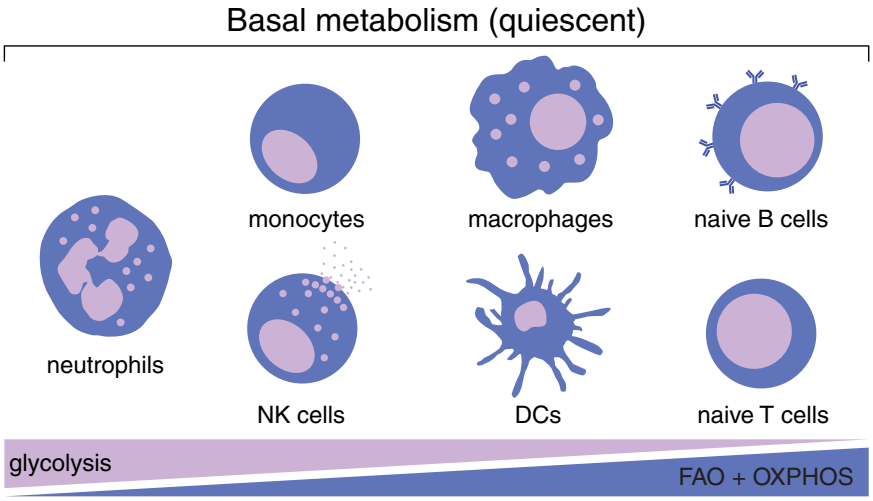

FIGURE 2 Classification of leukocytes in function of their basal metabolism in the quiescent state. Cells in the steady state have generally low biosynthetic demands and their basal metabolism is skewed toward metabolizing glucose through glycolysis coupled to oxidative phosphorylation. In this figure, cells are sorted from left to right, from more glycolysis-based metabolism to more OXPHOS and fatty acid oxidation-based basal metabolism. Left to right, resting neutrophils; resting myeloid cells (monocytes, macrophages, and dendritic cells) and NK cells; and naïve lymphocytes (T and B cells)

The process of monocyte differentiation into macrophages is also associated with rewiring of cellular metabolism. Activated proinflammatory macrophages consume large quantities of glucose in order to fuel glycolysis and OXPHOS, both necessary to produce great amounts of proinflammatory cytokines and reactive oxygen species (ROS).[37] Conversely, the metabolism of antiinflammatory macrophages is mainly mitochondrial and characterized by a blockade of glycolysis.[31] In turn, neutrophils are highly reactive, short-lived cells, in which an active glycolytic metabolism allows to quickly induce oxidative burst, ROS, and the extrusion of neutrophil extracellular traps, while the functionality of their mitocondria are mainly oriented to maintain membrane potential through electron fluxes.[38,39] The metabolism of dendritic cells changes during the different stages of development or activation. Development of DCs from precursors is associated with mitocondrial biogenesis, mainly driven by peroxisome proliferator-activated receptor γ, co-activator 1α (PGC1α), and mTOR.[40,41] The basal metabolism of immature DCs relies on OXPHOS and fatty acid synthesis,[42] while fully mature, activated DCs become highly glycolytic.[43]

In addition to myeloid cells, NK cells are lymphoid cells with innate caharcteristics that are very important for host defense, especially against virus infections. NK cells experience metabolic shifts upon activation in a stimulus-specific way. The rapid production of IFN-γ in response to cytokines in an early activation phase requires functional oxidative phosphorylation while long-term adaptation relies both in enhanced glycolysis and oxidative phosphorylation.[44,45] Granzyme B production or degranulation were independent of metabolic changes.[46] A recent study also showed that activated NK cells require the action of Srepb transcription factors to promote a metabolic pathway configuration in which glucose was metabolized to cytosolic citrate via the citrate–malate shuttle.[47]

The majority of studies on innate cell metabolism are focused on glycolysis and oxidative phosphorylation (Fig. 3). Beyond those, a number of recently released reports have shown that glucose-independent pathways also play a central role in cellular reprogramming after cell activation. Analysis of transcriptional data from macrophages stimulated with β-glucan revealed that the cholesterol synthesis pathway is highly up-regulated in trained immunity.[10] A follow-up of this study showed that the activation of the cholesterol synthesis pathway, but not its synthesis itself, is crucial for innate memory and that statins prevent the induction of trained immunity by blocking mevalonate production.[14] In agreement with this, the inhibition of cholesterol synthesis in mice reduced the induction of trained immunity by β-glucan.[48] Fatty acids are the main constituents of triglycerides and phospholipids, which form cell membranes. The synthesis of fatty acids is closely related with glucose metabolism as it employs products of glycolysis, TCA cycle, OXPHOS, and the pentose phosphate pathway.[49] Fatty acids can induce cellullar stress and activate innate immune pathways. Bone marrow-derived DCs and memory NK cells are characterized by fueling OXPHOS due to fatty acid oxidation.[42,50] In LPS stimulated monocytes, the increase in NAD+/NADH ratio activates sirtuin 1 and 6, coordinating a switch to an anti-inflammatory state with increased fatty acid oxidation.[51] Amino acids are the basic chemical building blocks during biogenesis, so they are of crucial importance in immune activity requiring cell division, cytokine, and chemokine production, but they can also act as precursors of different metabolites. Glutamine can be transformed into glutamate, and be subsequently transformed into α-ketoglutarate, that can act as a source of succinate, fumarate, and citrate, which can replenish the TCA cycle.[52] Glutamine replenishment of the TCA cycle leads to fumarate accummulation, inducing monocyte metabolic and epigenetic reprogramming by inhibiting KDM5 histone demehylases leading to enhanced secondary responses.[12]

4 | EPIGENETIC REPROGRAMMING

Together with the metabolic changes, stimuli-induced epigenetic reprogramming is the cornerstone of the induction and regulation of the innate immunological memory. Various epigenetic modifications are closely integrated with metabolic processes, as histone-modifying enzymes require metabolites as substrates or cofactors. DNA/histone methyltransferases require S-adenosyl methionine for their proper functioning; demethylases and ten-eleven translocation enzyme (TET) proteins are α-ketoglutarate-dependent dioxygenases.[53,54] HDACs and sirtuin SIRTs are NAD-dependent enzymes.[55] Acetyl-CoA is the

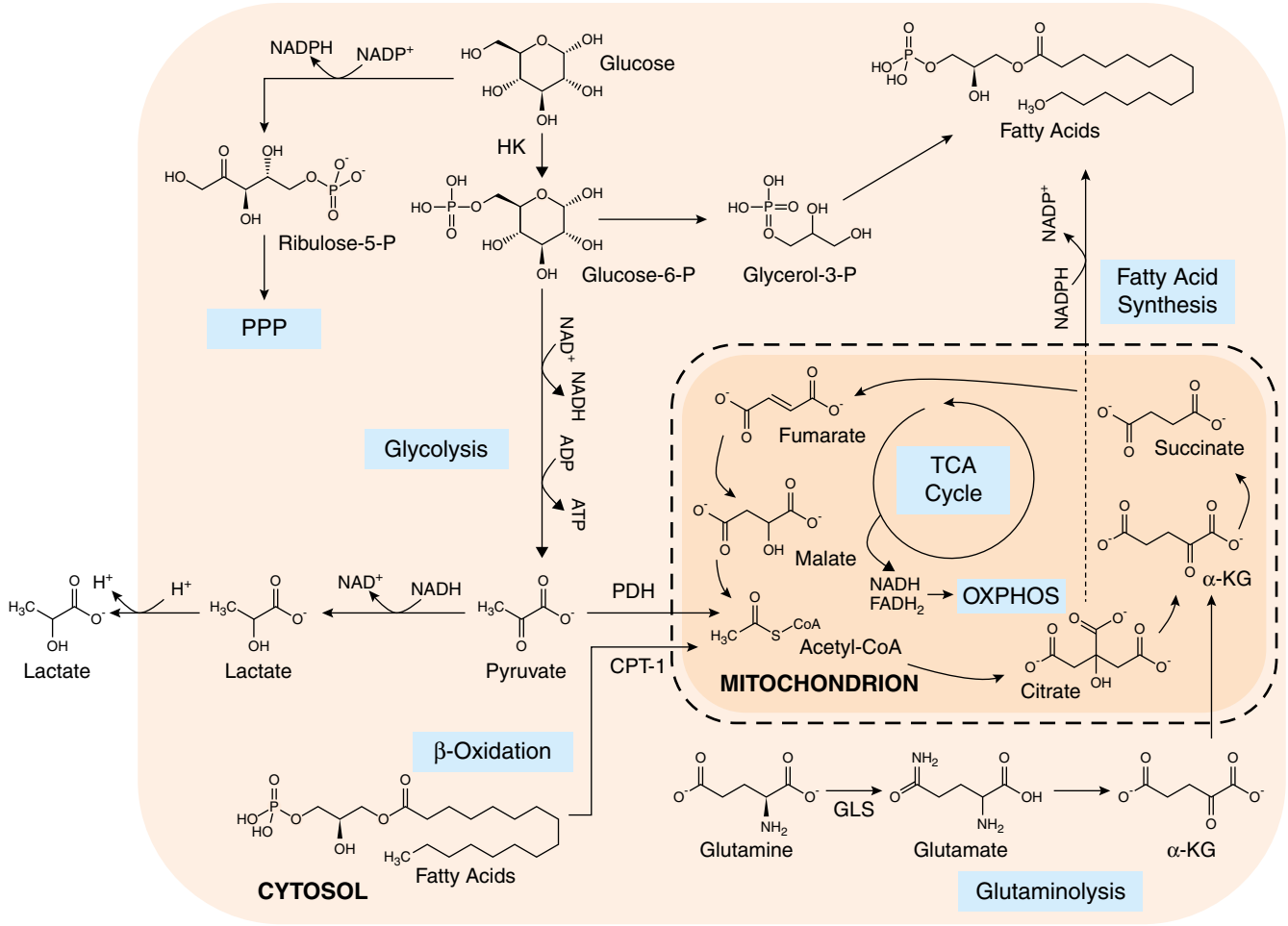

FIGURE 3 **Overview of the principal intracellular metabolic pathways in innate immune cell metabolism and the main enzymes involved.** Adapted from[119]

substrate used by histone acetyl transferase.[56,57] β-hydroxybutyrate is able to induce enrichment of histone acetylation and sustain a protective epigenetic state by inhibiting the activities of HDACs.[58] Other α-ketoglutarate-dependent dioxygenases, such as the EgIN prolyl hydroxylases, mark HIF transcription factor for destruction.[59] HIF1a synthesis is controlled by the PI3K-AKT-mTOR axis, which senses nutrients such as glucose and amino acids, while its degradation is under control of EgIN prolyl hydroxylases, which respond to changes in oxygen and TCA cycle intermediates. Inhibition of succinate dehydrogenase (SDH) dysregulates histone modification in mammalian cells.[60] Hydroxyglutarate, succinate, and fumarate are able to inhibit α-ketoglutarate dependent dioxygenases, including the jumonji C domain histone demethylases and TET proteins.[61–64]

Terminally differentiated cells, such as monocytes and macrophages, modify their histone acetylation and methylation marks upon pathogen exposure, affecting their gene expression patterns upon subsequent stimulation.[10,11] LPS induces histone modifications that lead to repressed proinflammatory gene expression after secondary stimulation, a feature of immunological tolerance.[65] Many of the pathogen-induced epigenetic changes in macrophages persist after withdrawal of the stimulus and the removal of the transcription factors responsable for the initial deposition, namely mono-methylation of lysine(K)-4 on histone 3.[66] *Candida albicans*- and β-glucan-induced functional reprogramming induced stable changes in histone trimethylation at H3K4 in human cells, showing functional relevance in a mouse in vivo model of infection.[6] A follow-up of this study showed that β-glucan-induced changes in trimethylation of histone 3 lysine 4 (H3K4me3) and acetylation of histone 3 lysine 27 (H3K27ac) in human monocytes 7 days after the first stimulation in vitro were associated with a switch to glycolysis, suggesting a deep, long lasting reprogramming of the cells.[11] Saeed et al. showed a strong correlation between H3K27ac and H3K4me3 changes during trained immunity, being H3K27ac the most dynamic mark in human cells in vitro.[10] Among the genes displaying increased H3K27ac, there was an enrichment in genes encoding for proteins involved in cellular signaling and inflammation: cytokines and chemokines, epidermal growth factor receptor and vascular endothelial growth factor pathways. The PI3K/AKT pathway was also shown to be up-regulated, fact supported by studies demonstrating the central role of this pathway in the induction of trained immunity by both BCG and β-glucan.[11,48] Arts et al. showed in human monocytes in vitro and ex vivo that the epigenetic changes observed in BCG-trained monocytes are dependent on the induction of the metabolic pathways: if glycolysis or glutaminolysis is inhibited, changes in H3K4me3 and H3K9me3 at

promoter sites of *IL6* and *TNFA* are reversed, showing a link between these two regulatory cellular processes.[12,48] The epigenetic profile induced by different stimuli shows close similarities among them, suggesting that there is a core trained immunity response induced by different stimuli.

5 | CLINICALLY RELEVANT CONDITIONS OF LONG-TERM INNATE IMMUNE REPROGRAMMING

5.1 | Vaccination

The WHO defines a vaccine as a biological preparation that improves immunity to a particular disease. In line with this definition, the concept of vaccination has clasically been linked to specificity, and therefore, to adaptive immunity. Nevertheless, the beneficial effects of multiple vaccines go far beyond the specific effects against the targeted diseases, but they can also increase resistance to other pathogens. The unspecific protective effects of vaccines were described as soon as the smallpox vaccination was introduced in the 19th century, as physicians related how people treated with the attenuated Vaccinia virus were also protected against other diseases.[67] This protective effects are generally related with live attenuated vaccines, such as BCG and measles, and possible smallpox. The mecanisms for these nonspecific effects are still a matter of discussion, but its beneficial effects have been extensively utilized, being BCG the most explored of all. The protective effects of BCG vaccination have been proved in murine models of nonmycobacterial infections[68] and different studies have shown that BGG vaccination at birth is able to reduce mortality in children by means of reducing lower respiratory tract infections and neonatal sepsis.[69] Intravesical BCG is the first option for the treatment of bladder cancer and other studies have associated BCG with protection against leishmaniasis or asthma.[70,71]

With regard to these nonspecific effects, there is a growing body of evidence that BCG is one of the most powerful agents capable of the induction of trained immunity in human monocytes, causing an strong enhancement of glycolysis, glutamine metabolism, and histone methylation marks.[48] The relevance of these mechanisms was further validated by a recently published study that showed that BCG vaccination of human volunteers reduced yellow fever viremia through the induction of epigenetic reprogramming of their monocytes and the production of IL-1β that acts as a key mediator of the development of trained immunity.[72] Kleinnijenhuis et al. showed that BCG vaccination of healthy volunteers led to the production of significantly higher levels of IFN-γ and enhanced release of monocyte-derived cytokines, such as TNF and IL-1β, in response to unrelated bacterial and fungal pathogens. These immunostimulatory effects were maintained up to 3 months after the initial vaccination.[73] Higgins et al. reviewed the results from 34 birth cohorts and analyzed the association of BCG, DTP, and measles-containing vaccines (MCV) with childhood mortality concluding that the administration of BCG and MCV reduced overall mortality by more than what would be expected just through their direct effects on the diseases they prevent.[74] Berendsen et al. found a time-dependent pattern of nonspecific effects of vaccination with BCG, DTP, and measles, and stunting, with positive associations for vaccinations given early in human life and negative associations for vaccinations given later in infancy.[75]

5.2 | Sepsis

According to recent reports, sepsis affects between 20 and 30 million people worldwide every year, remaining a leading cause of death.[76] The induction of hyporesponsiveness, or tolerance, acts a defense mechanism that decreases the response to inflammation maintaining homeostasis of the host. However, in many cases the immune system is unable to recover from this self-induced suppression, falling into an immunoparalysis state in which the host is unable to stop the progression of the infectious disease.[24] In the last years, a growing number of studies have shown how long-term reprogramming of cells after exposure to pathogens are of great importance for early cytokine production and for the induction of immunoparalysis and the establishment of disease tolerance.[15] Monocytes from patients suffering from sepsis-induced immunoparalysis show reduced proinflammatory cytokine production with a defective capacity to mount glycolysis and β-oxidation.[2] High levels of lactate and a low clearance rate can help predicting poor outcomes of septic states.[77]

However, the line between the development of tolerance or the induction of training is very thin. The development of immunoparalysis or the induction of trained immunity involves opposing regulation of common pathways[20] and the blockade of a single step in oxidative phosphorylation switches the potential of LPS-stimulated macrophages from proinflammatory to anti-inflammatory.[34] Tolerance and training are manifestations of the similar reprogramming processes, but with opposite consequences. Immune status in patients with sepsis or noninfectious systemic inflammatory response síndrome is altered.[78] It has been known for long that IFN-γ and GM-CSF can restore the responsiveness of monocytes from septic patients.[79,80] Cheng et al. demonstrated that the immunostimulant effects of IFN-γ in these patients partially relied in the restoration of the metabolic defects of innate immunotolerance by promoting glycolysis.[2] Administration of β-glucan to mice induced proliferation of the progenitors of the myeloid lineage, which was associated with enhanced signaling by IL-1β and GM-CSF, and with adaptations in glucose metabolism and cholesterol biosynthesis, improving responses to secondary LPS challenge and protecing from myeloid-induced immunosuppression in mice.[28] The intravenous injection of bone marrow stromal cells improved survival and organ function after cecal ligation and puncture in mice.[81]

5.3 | Cancer

The immune system exerts potent antitumor effects when it is efficiently activated. However, besides fighting cancer, the immune system seems to be involved in the development and progression of many cancer types. A unifying feature of cancer is long-term inflammation. The tumor environment fuctionally reprograms the immune cells to counteract the antitumor effects and promote inflammation, which is often associated with a progression of the disease.[82] Since innate cells infíltrate the area around a tumor, they become part of a complex

tumor microenvironment. The presence of inflammatory cells in the tumor microenvironment often promotes tumor progression instead of destruction, as they can promote tissue remodeling, angiogenesis, and fibrosis, which are beneficial for tumor growth and increase resistance to pharmacological treatments.[83] Much of the work done in immunotherapy during the last years has addressed the ways to revert this reprogramming of cells and recover the antitumor properties. Cancer cells promote the differentiation of monocytes into anti-inflammatory macrophages, characterized by the production of high amounts of anti-inflammatory cytokines and proangiogenic factors, impairing immune response and promoting tumor growth.[84,85]

There is strong evidence that some types of infections and vaccinations might be related with a protective response against solid tumors.[86] In this regard, the greatest success of treatment of cancer with stimuli that can induce reprogramming at the innate immunity level, is the utilization of intravesical BCG as the first option for the treatment of superficial, nonmuscle-invasive bladder cancer.[87] The antitumor effects of BCG is known since 1929, when a report of necropsies from tuberculosis patients described that the incidence of neoplastic malignancies in tuberculosis patients was significantly lower than in the control group.[88] The mechanism of action of BCG in this therapy is still a matter of controversy, but relies on a complex immune response which involves the recruitment, activation, and production of proinflammatory cytokines by monocytes, neutrophils, NK cells, and T lymphocytes.[89,90] An efficient long-term cell reprogramming is necessary to warrant the efficacy of the treatments, as shown by the failure to develop durable responses after treatment with checkpoint inhibitors in cancer patients due to epigenetic stability of exhausted T cells.[91,92] The transcription factor HIF1α, which plays a central role in the metabolic switch to glycolysis in activated monocytes, has also been implicated in the regulation of many of the genes responsable for metabolic reprogramming in cancer cells.[93] Mutations affecting SDH complex subunits,that lead to the accummulation of succinate have been identified in familiar paragangliomas.[94]

5.4 | Inflammatory diseases

The incidence of chronic and degenerative diseases with an inflammatory or auto-immune basis has augmented over the last years, especially in societies with higher socio-economic development. These diseases have flourished in the last decades as an epidemic outbreak and its incidence has increased together with the degree of industrialization.[95,96] These diseases are mainly metabolic, cardiovascular, digestive, neurologic, and allergic.[97,98] Chronic inflammation is the common feature of these diseases. Several studies have demonstrated that reprogramming of the innate immune system represents one of the central features involved in the outbreak and upkeep of chronic inflammation.[14,26]

Progression of atherosclerosis has been mechanistically linked with activation and recruitment of monocyte-derived macrophages.[99] Accummulation of cholesterol crystals triggers a number of inflammatory pathways that drive cardiovascular diseases. There is evidence that the activation of the cholesterol pathway through the action of the intermediate compound mevalonate, triggers epigenetic reprogramming and is essential for the induction of trained immunity.[14] In this regard, hyper immunoglobulin D syndrome patients, who accummulate mevalonate, have a constitutive trained imunity phenotype with higher cytokine production.[14] Western diet influences myelopoiesis and induces transcriptional and functional reprogramming of myeloid precursors, leading to long-term systemic inflammation and enhanced responses to LPS that persisted after shifting back to chow diet, by a mechanism dependent of NLRP3 and the IL-1 pathway.[26] The influence of diet also influences the activity of the sirtuin family of deacetylase enzymes. The levels of expression of NAD+ and sirtuin enzymes can adapt to metabolic state. SIRT1-mediated acetylation of PGC1α activates transcription of genes important to adaptation to starvation.[100] In obesity, macrophages accummulate in the adipose tissue and drive chronic inflammation, promoting insulin resistance.[101] Metabolic activation, including fatty acid oxidation, glycolysis, and glutaminolysis in obese individuals was associated with diabetes outcome.[102] Hypoglycemia has been linked to increased leukocyte counts and cytokine levels, leading to chronic systemic inflammation.[103,104]

Microbiota plays a central role in the development and function of the gut innate immune system, as germ-free and gnotobiotic animals show large defect in the development and maturation of Peyer's patches, mesenteric lymph nodes, and lymphoid follicles.[105] Perturbations of gut microbiota affect the interplay between microbiota and host cells resulting in an increased pathogenesis of inflammatory diseases, such as inflammatory bowel disease,[106] in which pathogenic intestinal bacteria perpetuate inflammation of the gut through disruption of tolerance. In Crohn's disease, the interactions between the bacterial flora and the mucosal immune system are facilitated by a decreased bacterial clearance by macrophages with a defective secretion of proinflammatory cytokines.[107] The interaction between the immune system and microbiota induces long-term reprogramming at local and systemic levels, inducing suppression of inflammatory responses to food and orally ingested antigens in order to limit tissue inflammation and microbial translocation.[108,109] Gut bacteria regulate the activity of intestinal phagocytes, such as macrophages and neutrophils, through continuous priming of resident macrophages to release large amounts of IL-10, what promotes the induction of tolerance to intestinal bacteria and prevents the development os systemic inflammation.[110,111] Microbiota has also been shown to trigger systemic training by inducing long-term reprogramming of bone marrow dendritic cells provoding IL-17A-dependent protection against protozoal colitis in a mouse model of this disease.[112] Of note, stromal cells of the intestine of inflammatory bowel disease patients also exhibit stable functional long-term alterations as a result of chronic exposure to an inflammatory environment,[113,114] which are likely to be mediated by epigenetic and/or metabolic reprogramming.[115]

6 | CONCLUDING REMARKS

Preservation of homeostasis is achieved not only through containment or erradication of pathogens, but also through adaptations that prepare the host for a secondary challenge. In this regard, innate immune

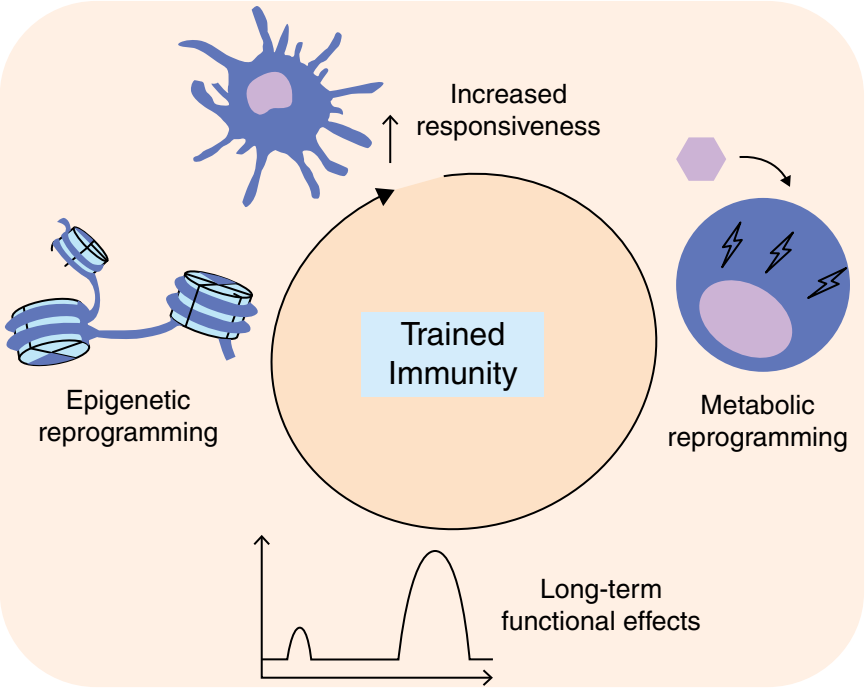

FIGURE 4 Overview of the hallmarks of trained immunity. Trained immunity involves deep changes in metabolic pathways and in the epigenetic landscape of the cell, inducing long-term reprogramming and increasing the capacity of the innate immune cells to respond to secondary stimulation

training causes long-term alterations in mature innate immune cells, enabling a robust innate host response to a secondary stimulus (Fig. 4). The evidence reviewed here demonstrates that long-term reprogramming of the innate immune system (trained immunity) is a fundamental property for host defense, being a fundamental complement for the antigen-specific immunological memory mediated by lymphocytes. Trained immunity mediates an increase in the responsiveness of the cells, as shown by the amplification of both pro- and anti-inflammatory cytokine production, ROS production, and metabolic activation.[29] Further research is required to elucidate the duration of innate immune memory and its effect on the innate immune cell precursors in the bone marrow and tissue macrophage populations. The progress of proteomics, metabolomics, transcriptomics, and epigenomics will permit the identification of the potential novel features of trained immunity and how the different genetic hallmarks of the individuals affect the quality and the range of the reprogramming.

The modulation of cellular reprogramming is also believed to have great potential as a therapeutic tool in immune-mediated diseases. By elucidating the potential role of trained immunity in these diseases, new steps can be made in better understanding their pathophysiology and potentially lead to new clinical approaches. In inflammatory diseases in which monocytes and macrophages are skewed toward a proinflammatory profile, inhibition of certain metabolic or epigenetic pathways involved in cellular reprogramming may represent a valid approach to target. Induction of metabolic pathways important for trained immunity can be used be attempted to restore immune function during sepsis-induced immune paralysis. Inducers of cellular reprogramming such as β-glucan or muramyl dipeptide have shown potential as a treatment or adjuvant for osteosarcoma,[116] influenza,[117] or skin lesions,[118] among others. The actions of innate immune memory in precursor cells of the innate immune system in the bone marrow can be therapeutically exploited to counteract the adverse effects of chemotherapy induced myelosuppression.[28] Cellular metabolic pathways for the targeting of reprogramming may also represent a novel therapeutic approach in immunodeficiencies as well as for the modulation of the potentially deleterious consequences of trained immunity in autoinflammatory diseases. All these observations provide new insights for the development of novel therapeutic strategies to reverse the pathological conditons associated with the long-term reprogramming of the innate immune system.

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AUTHORSHIP

J.D.-A. wrote the first draft and M.N. made revisions.

DISCLOSURE

The authors declare no competing interests.

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