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Brief Reviews

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Innate Immune Memory and the Host Response to Infection

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Unlike the adaptive immune system, the innate immune system has classically been characterized as being devoid of memory functions. However, recent research shows that innate myeloid and lymphoid cells have the ability to retain memory of prior pathogen exposure and become primed to elicit a robust, broad-spectrum response to subsequent infection. This phenomenon has been termed innate immune memory or trained immunity. Innate immune memory is induced via activation of pattern recognition receptors and the actions of cytokines on hematopoietic progenitors and stem cells in bone marrow and innate leukocytes in the periphery. The trained phenotype is induced and sustained via epigenetic modifications that reprogram transcriptional patterns and metabolism. These modifications augment antimicrobial functions, such as leukocyte expansion, chemotaxis, phagocytosis, and microbial killing, to facilitate an augmented host response to infection. Alternatively, innate immune memory may contribute to the pathogenesis of chronic diseases, such as atherosclerosis and Alzheimer's disease. *The Journal of Immunology*, 2022, 208: 785–792.

Immunological memory is a hallmark of the adaptive immune system of vertebrates and the basis for modern vaccines (1, 2). B and T lymphocytes express a diverse repertoire of highly specific Ag receptors that are generated via gene rearrangement during lymphocyte development (3). Ag recognition by naive, Ag-specific lymphocytes elicits clonal expansion and generation of memory cells that persist for years and are poised to react quickly and robustly to future encounters with the same Ag (3, 4). In contrast, the innate immune system is classically characterized as being nonspecific, generally devoid of memory functions, and serving to provide a mechanism to rapidly respond to diverse pathogens and facilitate early containment of infection (5, 6). However, investigators recognized decades ago that ligands that activate the immune system independently of Ag receptors (i.e., Igs, TCR) have the capacity to elicit a memory response (7–10). More recent research shows that innate myeloid and lymphoid cells, as well as nonimmune cells, such as epithelial and endothelial cells, have the ability to retain memory of prior exposure to microbes and inflammatory mediators and become primed to elicit a heightened, broad-spectrum response to subsequent infection (11, 12) (Fig. 1). This phenomenon has been termed innate immune memory or trained immunity and is particularly crucial to the survival of organisms that lack an adaptive immune system (i.e., invertebrates and plants) but is also functional in the complex immune system of vertebrates (13, 14).

Innate immune memory is induced by activation of pattern recognition receptors (PRR) and the actions of cytokines and hematopoietic factors on innate leukocytes and bone marrow progenitors and has the capacity to persist for weeks to months (15–18). The memory response can be induced by infection or treatment with microbe-derived pathogen-associated molecular patterns (PAMPs) and is not specific to the inciting organism or PAMP. For example, treatment with the TLR4 ligands LPS or monophosphoryl lipid A (MPLA), derived from Gram-negative bacteria, confers resistance against Gram-negative (*P. aeruginosa*), Gram-positive (*S. aureus*), and fungal (*C. albicans*) pathogens, as well as polymicrobial sepsis caused by cecal ligation and puncture (19–22). Peptidoglycan, a TLR2 ligand derived primarily from Gram-positive bacteria, induces resistance to infection with Gram-negative and Gram-positive pathogens (23, 24). β-Glucan, a fungal cell wall constituent that activates dectin-1 and TLR2, induces resistance to

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Abbreviations used in this article: BCG, bacillus Calmette-Guérin; HIF-1α, hypoxia-inducible factor 1α; H3K27ac, H3K27 acetylation; MPLA, monophosphoryl lipid A; mTOR, mammalian target of rapamycin; ODN, oligodeoxynucleotide; oxLDL, oxidized low density lipoprotein; PAMP, pathogen-associated molecular pattern; PRR, pattern recognition receptor; SAM, *S*-adenosylmethionine; TCA, tricarboxylic acid.

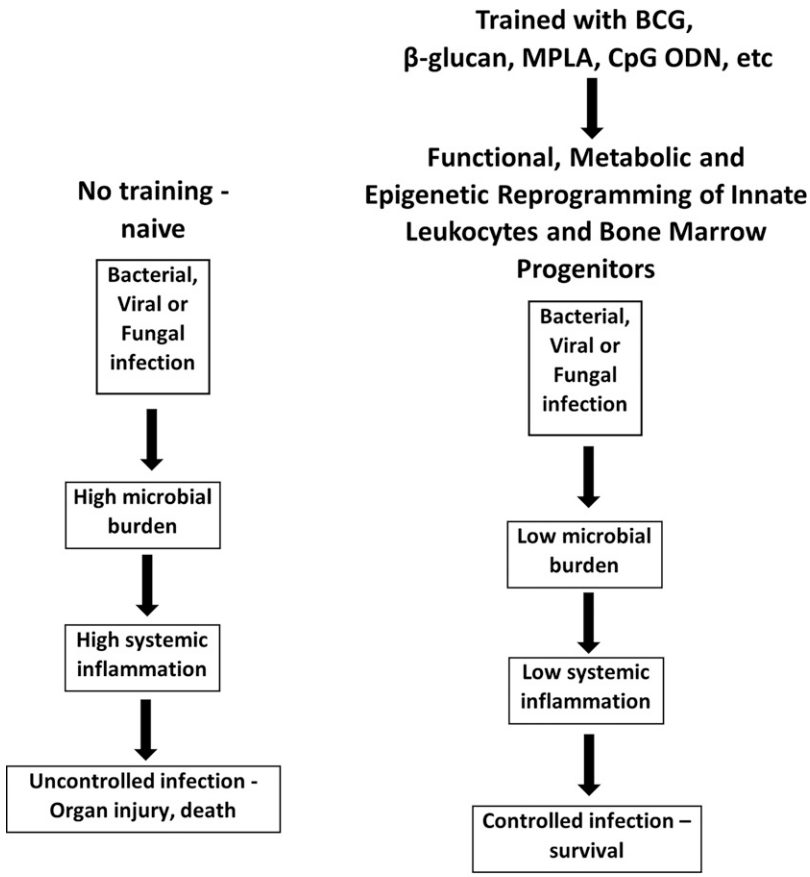

FIGURE 1. The biological basis of innate immune memory. Treatment with PAMPs, such as β-glucan, MPLA, or CpG ODN, induces epigenetic, metabolic, and functional reprogramming of the innate immune system resulting in augmented resistance to local and systemic infection.

infection with Gram-negative and Gram-positive bacterial and fungal pathogens (10, 16, 25).

The broad and nonspecific nature of innate immune memory could have benefits in the clinical setting. Innate immune training agents such as MPLA and CpG oligodeoxynucleotide (ODN) are already used clinically as vaccine adjuvants and are a major focus of current vaccine research (26–28). However, a multitude of organisms cause hospital- and community-acquired infections, and it is impossible to predict which pathogen will infect any given individual. Thus, the broad-spectrum protection provided by innate immune training reagents may have application to treat or prevent opportunistic infections in critically ill, hospitalized, and immunosuppressed patients. Vaccination of children with bacillus Calmette-Guérin (BCG) not only provides targeted protection from infection with *M. tuberculosis* but protects from other respiratory pathogens and neonatal sepsis (29, 30). There is great interest in whether applying this strategy in other vulnerable populations could decrease the burden of infection. Recent commentaries have lauded the potential benefits of harnessing innate immune memory as a bridging strategy during pandemics, such as the current SARS-Cov-2 pandemic, to provide resistance to infection before development of vaccines (31). Innate immune training agents may also have benefit in the treatment of cancer as standalone drugs or in combination with other cancer therapies (32).

Trained immunity may play a role in the pathogenesis of some chronic diseases, such as atherosclerosis and Alzheimer's disease (33, 34). Bekkering et al. (35) showed that treatment of human monocytes with oxidized low-density lipoprotein (oxLDL) induced foam cell formation. Later work by Keating et al. (36) showed that training of human monocyte-derived macrophages with oxLDL induced increased glycolysis and oxidative metabolism and enabled a proinflammatory phenotype. A link between innate immune training and Alzheimer's disease has also been demonstrated, a phenomenon that may be mediated by training of microglia (37).

Most early work in the field of innate immune memory was performed using monocytes and macrophages. Evidence indicates that activation of innate myeloid cells with PAMPs induces epigenetic and metabolic reprogramming that facilitates a phenotype characterized by augmented antimicrobial functions, such as chemotaxis, phagocytosis, and microbial killing. Expansion and reprogramming of myeloid progenitors, including neutrophil precursors, in the bone marrow is also crucial for inducing and sustaining the trained phenotype (15, 38). This brief review provides an overview of the cellular and molecular alterations that initiate and sustain innate immune memory.

The cellular biology of innate immune memory

Trained immunity can be induced in a multitude of innate leukocytes and in nonleukocyte populations (Fig. 2). Early work on trained immunity focused on mature peripheral blood monocytes, which have a circulating life span of 1–7 d, depending on subset (39–41). Isolated monocytes were incubated with training agents, such as β-glucan or BCG, ex vivo for 24 h and allowed to rest for 5–7 d to induce innate immune memory. Trained monocytes developed functional, epigenetic, and metabolic alterations that are hallmarks of the trained phenotype (40–42). However, given the short life span of monocytes, questions arose as to how these findings translated to the

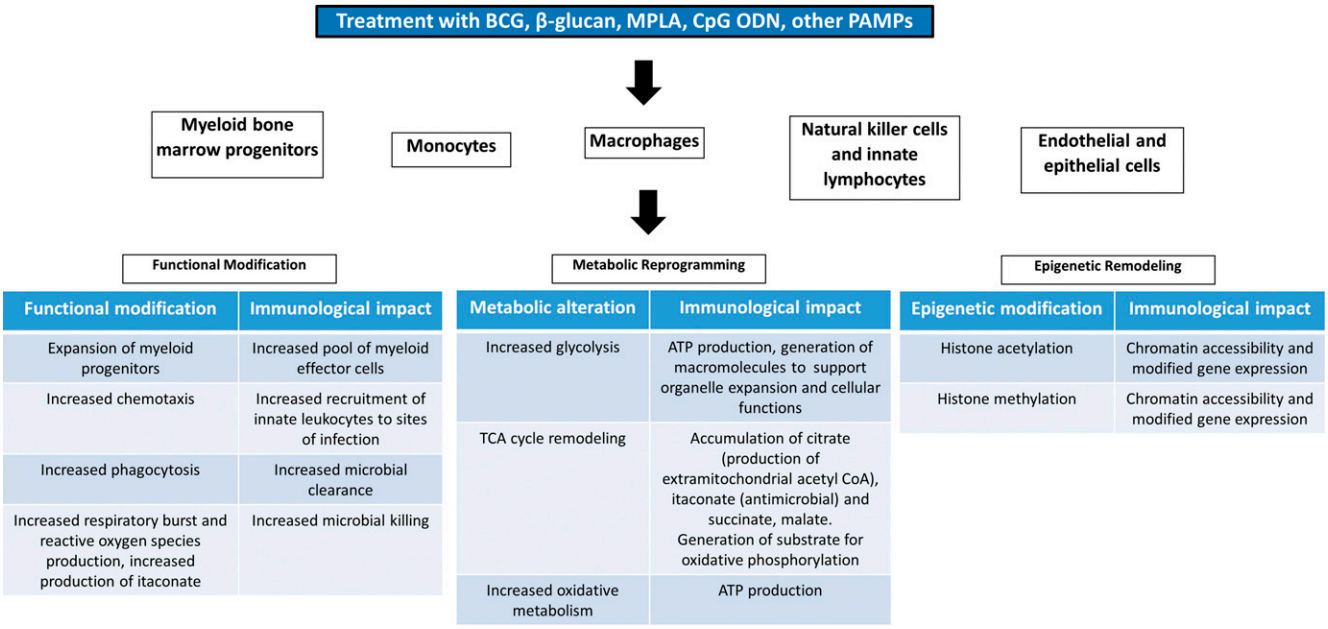

FIGURE 2. Functional, metabolic, and epigenetic alterations driving innate immune memory. Training of innate leukocyte and nonleukocyte populations induces functional alterations that facilitate innate leukocyte progenitor expansion, leukocyte recruitment, phagocytosis, and microbial killing. These alterations are enabled, in part, by epigenetic remodeling and metabolic reprogramming.

in vivo setting where trained immunity persists for weeks to months. One possibility is that trained circulating monocytes migrate to sites of infection or distant organs in vivo, where they differentiate into macrophages, which have a longer life span consistent with that of trained immunity (43). However, there is no published evidence to indicate that this occurs. In fact, work by Fensterheim et al. (21) showed that innate immune memory can be fully induced in $CCR2^{-/-}$ mice, which sequester monocytes in the bone marrow and prevent their migration to sites of infection or inflammation. Those findings suggest that migration of trained monocytes to tissues and subsequent differentiation into macrophages does not contribute to trained immunity *in vivo*. However, further work is needed to fully evaluate this cellular mechanism.

Later work provided evidence that myeloid-biased hematopoietic stem cells in the bone marrow can be trained and sustain the innate immune memory phenotype in vivo by providing a persistent supply of trained mature myeloid cells. Mitroulis et al. (44) demonstrated that β-glucan induces a sustained increase in myeloid-biased hematopoietic progenitors that confers a protective response to subsequent inflammation- or chemotherapy-induced myeloablation. The observed myelopoietic response was associated with increased IL-1β and GM-CSF signaling and adaptations in glucose and cholesterol metabolism. Expansion of the bone marrow compartment by BCG vaccination has been reported by Cirovic et al. (17). Progenitor expansion was associated with a specific epigenetic and transcriptional program that was transferred to peripheral blood monocytes up to 3 mo after BCG treatment. Kalafati et al. (15) reported that β-glucan induces transcriptomic and epigenetic rewiring of granulopoiesis with associated augmentation of antitumor immunity, a process that was dependent on generation of reactive oxygen species. They further showed that the antitumor effect was conferred by transplantation of trained bone marrow progenitors into naive mice. Likewise, Bohannon et al. (38) showed that the TLR4 agonist MPLA induces expansion of myeloid progenitors in bone marrow resulting in augmented recruitment of neutrophils to sites of infection and concomitant enhancement of microbial clearance. The effect was ablated by G-CSF neutralization or neutrophil ablation. These findings are consistent with other studies showing that training with β-glucan or MPLA augments neutrophil and monocyte recruitment to sites of infection and enhances their phagocytic, respiratory burst, and killing functions (16, 45).

Immune training of differentiated macrophages provides an alternative or complementary cellular mechanism driving trained immunity. Macrophages prominently express PRR and serve to initiate and orchestrate the host response to infection (46). Evidence indicates that a memory phenotype can be induced in tissue-resident macrophages, which have a life span of months to years and the capacity to self-renew (47). Fensterheim et al. (21) showed that treatment with MPLA induces macrophage expansion at sites of infection, and that ablation of macrophages reverses the trained phenotype in vivo. The expansion of macrophages was independent of monocyte migration because the trained phenotype and macrophage expansion was observed in CCR2-deficient mice. Further studies by Stothers et al. (16) show that adoptive transfer of differentiated macrophages trained with β-glucan confers a level of resistance to infection with *P. aeruginosa* that mimics that of mice treated with β-glucan alone. Yao et al. (48) showed that memory is induced in alveolar macrophages via prior pathogen exposure, a response that required local T cell help. Sherwood et al. (49) showed that training of splenic, hepatic, and peritoneal macrophages with β-glucan confers innate memory and an antitumor phenotype.

Taken together, research indicates that innate immune memory is mediated through training of myeloid precursors in the bone marrow and differentiated macrophages. However, innate lymphoid cells (i.e., NK cells and innate lymphoid cells), as well as nonimmune cells (i.e., endothelial cells, epithelial cells, and

fibroblasts) also have the capacity to develop memory under varying conditions (50–52). Many of the modifications induced in monocytes and macrophages are also likely to be induced in dendritic cells. Treatment of dendritic cells with training agents such as MPLA or CpG ODN augments Ag presentation and proinflammatory cytokine production and facilitates their effectiveness as vaccine adjuvants (53). Training of NK cells by prior viral exposure induces an antiviral phenotype that provides broad resistance to subsequent viral infection (51). Recent work by Larsen et al. (52) shows that epidermal stem cells have the capacity to recall prior encounters with inflammatory mediators, a process that contributes to tissue homeostasis. Hato et al. (54) demonstrated that training with low-dose LPS protects against sepsis-induced acute kidney injury, a process in which kidney proximal tubular cells and kidney-resident macrophages play important protective roles. That study underscores the importance of leukocyte and epithelial cell cross-talk as a potential mechanism mediating organ protection after innate immune training.

Induction of innate immune memory: PRRs and signaling

Innate myeloid cells recognize pathogens via PRRs, including TLRs, nucleotide-binding and oligomerization domain–like receptors, and C-type lectin receptors, including dectin-1, the β-glucan receptor (55–57). Activation of PRR triggers downstream signaling pathways leading to gene transcription and mobilization of cellular metabolism and antimicrobial functions (21, 39, 58). Numerous PAMPs, including microbe-derived proteins, carbohydrates, lipids, and nucleic acids, serve as ligands for PRRs, and many are known to induce innate immune memory. In the 1950s, Landy and Pillemer (7) noted that animals treated with the TLR4 ligand LPS had augmented resistance to subsequent infection. Further work by Di Luzio, Williams, and colleagues (10, 25, 59) established that treatment with β-glucan, a carbohydrate component of the fungal cell wall recognized by dectin-1, boosted host resistance to infection with a broad array of fungal and bacterial pathogens. Since then, a multitude of PAMPs have been recognized for their ability to induce innate immune memory and facilitate broad resistance to subsequent infection.

In addition to PAMPs, other mechanisms have been observed to induce innate immune memory. Weavers and colleagues (60) showed that phagocytosis of apoptotic cells, or efferocytosis, by macrophages induces innate immune memory and a more effective response to subsequent infection or injury. However, other investigators have reported that efferocytosis triggers a proresolving phenotype in macrophages that facilitates tissue repair and resolution of inflammation (61). Larsen et al. (52) showed that induction of skin inflammation with imiquimod induces a memory phenotype in epidermal stem cells that is similar to that induced in leukocytes by PAMPs. Several investigators showed that oxLDL induces a trained phenotype in endothelial cells and macrophages, with important implications in the pathogenesis of atherosclerosis (35, 62).

Numerous downstream signaling pathways are induced by activation of PRR. TLRs initiate downstream signaling by recruiting the adaptor proteins MyD88 and/or TRIF (55). Activation of the MyD88-dependent pathway leads to downstream mobilization of the NF-κB, MAPK, and PI3K pathways (56, 63, 64). The transcription factor IRF3 is mobilized via activation of the TRIF-dependent pathway (65). Activation of nod-like receptors leads to mobilization of NF-κB and MAPK signaling and has varying impact on the PI3K/Akt pathway (66). Activation of dectin-1 and/or TLR2 by β-glucan induces NF-κB, MAPK, and PI3K/Akt signaling (57). Of these signaling pathways, PI3K/Akt has been most extensively studied in the context of innate immune memory. Early work by Williams et al. (67) showed that activation of PI3K/Akt signaling by β-glucan reduced morbidity and mortality caused by subsequent sepsis and ischemia/reperfusion injury. Later work by Cheng et al. (68) tied PI3K/Akt/mTOR (mammalian target of rapamycin)/HIF-1α (hypoxia-inducible factor 1α) signaling to metabolic and epigenetic changes that are hallmarks of innate immune memory. Several other investigators have demonstrated that PI3K/Akt/mTOR/HIF-1α signaling is activated during acute inflammation, and blockade of components of this pathway attenuates induction of the memory phenotype (45, 69–71). Based on these findings, PI3K/Akt/mTOR/HIF-1α signaling is considered an underlying mechanism driving innate immune memory, likely caused by activation and orchestration of metabolic alterations that support the phenotype.

Recent research by Larsen et al. (52) showed that the coordinated activities of STAT3 and AP-1 regulate chromatin accessibility in a model of chronic skin inflammation that mimics trained immunity. They further demonstrated that numerous cell types exposed to inflammatory mediators showed enrichment for AP-1 footprints at memory domains and postulated that AP-1 serves as a universal mediator of innate immune memory. Work by Balic et al. (72) also implicated STAT3 as a factor mediating metabolic reprogramming during acute inflammation induced by TLR4 activation. These findings identify STAT3 and AP-1 as potential transcriptional regulators of the memory phenotype and open an intriguing new area of research.

Cytokines regulate the induction and maintenance of innate immune memory. Several studies have shown the ability of type I and II IFNs to induce trained immunity independently or to augment the trained phenotype induced by PAMPs (73–76). Type I IFNs have primarily been shown to possess the capacity to facilitate training in the hematopoietic compartment, whereas IFN-γ acts on differentiated macrophages and other myeloid cells in the periphery (48, 74, 76, 77). Studies have also demonstrated contributions of IL-1β, GM-CSF, and G-CSF to inducing hematopoietic stem cell expansion and memory in response to training agents, such as BCG, β-glucan, and MPLA (38, 78). In addition to direct virus recognition via Ly49 proteins and CD49, IL-12/15/18 play an important role in facilitating memory in NK cells (79). Cytokines, particularly those of the IL-1 family, also have the capacity to downregulate the memory response. Cavalli et al. (80) reported that the anti-inflammatory cytokine IL-37 abrogates immunometabolic and epigenetic changes in trained myeloid cells and reverses protection from *Candida* infection conferred by β-glucan. De Graaf et al. (81) showed that IL-38 prevents trained immunity induced by β-glucan via its capacity to inhibit mTOR signaling.

Innate immune memory and epigenetics

Gene expression is regulated by the accessibility of transcription factors, enhancers, repressors, and RNA polymerase to promoter, enhancer, and transcription start regions of the genome (82, 83). This accessibility is modulated by chromatin structure and under the control of epigenetic modifications, including

histone acetylation and methylation (84, 85). Epigenetic modifications associated with prior pathogen exposure have been described in plants and mammalian myeloid cells, and evidence supports their role in sustaining the trained phenotype (86) (Fig. 2). Kalafati et al. (15) reported increased chromatin accessibility in myeloid progenitors from mice trained with β-glucan at sites regulating granulocyte activation pathways. Similarly, Cirovic et al. (17) described changes in chromatin accessibility in human peripheral blood monocytes at 90 d after BCG vaccination with inflammation-associated loci being preferentially impacted. H3K27 acetylation (H3K27ac) at promoter sites and distal enhancer regions has been reported as the most dynamic epigenetic mark in monocytes trained with β-glucan, and the location of the observed H3K27ac modifications correlated with transcriptional changes that characterize macrophage differentiation and training (40). Saeed et al. (40) further defined H3K4me1 as a memory mark associated with a faster and more robust response to restimulation. Likewise, H3K27ac and H3K4Me3 marks at promoter sites of genes regulating metabolism and inflammation have been described as prominent features of trained human monocytes (39, 68). Novakovic et al. (87) further described dynamic H3K27ac modifications in macrophages trained with β-glucan at gene clusters associated with leukocyte differentiation, activation, metabolism, and phagocytosis and described replacement of repressive H3K4me3 marks with memory H3K4me1 marks. Later work by Rasid et al. (88) showed H3K4me1 to be an important memory mark in NK cells trained with LPS. Taken together, research indicates that H3KMe1 and H3K27ac marks are deposited during the early inflammatory response and are retained at memory domains in trained leukocytes.

Early in vitro studies showed that *pan*-methyltransferase inhibitors attenuate the trained phenotype induced by β-glucan or *C. albicans*, an observation that has been confirmed in later studies using a variety of training ligands and cell types (39, 62, 68). Keating et al. (89) reported that the Set7 lysine methyltransferase facilitates the induction of trained immunity in human peripheral blood monocytes and mouse bone marrow–derived macrophages by regulating expression of genes that control metabolic and inflammatory pathways, most notably H3K4Me1-mediated plasticity of genes regulating oxidative phosphorylation. Mourits et al. (90) reported that histone methyltransferase G9a is a negative regulator of trained immunity that is downregulated in monocytes treated with BCG and accompanied by decreased H3K9me2 at proinflammatory gene promoters. G9a inhibition facilitated the induction of trained immunity by BCG, LPS, and oxLDL. Research performed by Arts et al. (91) showed that accumulation of fumarate in trained monocytes induces epigenetic reprogramming by inhibiting KDM5 histone demethylases, which upregulates trimethylation of H3K4 in the promoter regions of genes regulating the inflammatory response. Less work has been done to determine the contributions of specific histone acetyltransferases and deacetylases to generation of trained immunity. However, Sun et al. (92) reported that chronic activation of NOD2 on monocyte-derived macrophages induced activation of histone deacetylases 1 and 3 in a Twist1- and Twist2-dependent manner to facilitate trained immunity. Further work is needed in this area.

Metabolic alterations that facilitate the availability of methyl and acetyl group donors are another mechanism mediating epigenetic regulation. Lauterbach et al. (93) showed that LPS induces metabolic reprogramming in macrophages characterized by increased tricarboxylic acid (TCA) cycle flux, ATP-citrate lyase activity, and extramitochondrial acetyl CoA generation. Induction of ATP-citrate lyase and accumulation of extramitochondrial acetyl CoA, a major intracellular acetyl group donor, was associated with LPS-induced histone acetylation and early gene expression. Work by Yu et al. (94) showed that LPS stimulates the pentose phosphate and serine synthesis pathways and one carbon metabolism to facilitate increased production of the methyl group donor *S*-adenosylmethionine (SAM). Increased SAM production was associated with histone methylation and expression of proinflammatory gene products. Although increased production of extracellular acetyl CoA and SAM appear to facilitate early gene expression after LPS exposure, it is unclear whether these alterations facilitate the epigenetic and gene expression changes that drive trained immunity. Other epigenetic mechanisms that could facilitate innate immune memory include histone succinylation and lactylation. Zhang and colleagues (95) demonstrated that LPS induces 28 distinct histone lactylation sites in macrophages that direct proinflammatory gene expression. However, the roles of histone succinylation and lactylation in trained immunity require further investigation.

Metabolic basis of innate immune memory

Reprogramming of cellular metabolism has been a consistent feature of the memory phenotype, most notably in monocytes and macrophages (Fig. 2). Innate leukocytes respond to infection by mobilizing glycolysis to rapidly meet emerging energy requirements and to generate essential precursors for amino acids, nucleotides, and fatty acids that are needed to mediate antimicrobial functions, such as phagocytosis and killing (96, 97). Classically, this metabolic phenotype is characteristic of proinflammatory M1 macrophages. Alternatively, M2 macrophages, which facilitate tissue repair and homeostasis, predominantly use oxidative metabolism to sustain their ongoing functions (96). Cheng et al. (68) reported that training of human monocytes with β-glucan for 7 d induced a metabolic phenotype characterized by increased glucose consumption and glycolysis in parallel with decreased oxidative phosphorylation, a metabolic signature commonly referred to as the Warburg effect and characteristic of M1 macrophages. Other investigators have described the same metabolic shift in monocytes trained with BCG or oxLDL (98). Like monocytes, trained macrophages show a sustained increase in glycolysis (99). Yet, oxidative metabolism is also augmented in trained macrophages (98). The increase in oxidative metabolism is paralleled by increased TCA cycle flux, mitochondrial mass, and mitochondrial membrane potential. Similarly, Groh et al. (100) showed that monocytes trained with oxLDL developed a metabolic phenotype characterized by increased mitochondrial mass and membrane potential, TCA cycle flux, and oxidative metabolism. Pharmacologic interference with mitochondrial function and oxidative metabolism alleviated key features of trained immunity induced by oxLDL, MPLA, or β-glucan (99, 101).

Reprogramming of the TCA cycle is a common feature of trained innate leukocytes. Trained macrophages show increased flux of glucose through the TCA cycle and enhanced accumulation of TCA cycle intermediates, especially citrate, itaconate, and succinate (21, 100). Fensterheim et al. (99) showed a break in

the TCA cycle distal to citrate with reestablishment of TCA cycle flux at α-ketoglutarate in trained macrophages. The break at citrate was associated with increased production of itaconate and evidence of citrate transport out of the mitochondria with subsequent conversion to extramitochondrial acetyl CoA. Extramitochondrial acetyl CoA serves as a major acetyl group donor, and its enhanced production in trained leukocytes likely contributes to histone acetylation (93). Reestablishment of the TCA cycle distal to isocitrate was dependent on glutamine anaplerosis. Arts et al. (91) showed that glutaminolysis is essential for sustaining the trained phenotype, a finding that further supports the contribution of glutamine for sustaining TCA cycle reprogramming in innate leukocytes. Itaconate is a TCA cycle metabolite derived from *cis*-aconitate that is not part of the energy-generating functions of the cycle (102). Several functions have been attributed to itaconate, including inhibition of succinate dehydrogenase, attenuation of cytokine production, and direct antimicrobial functions (102–104). The contribution of itaconate to trained immunity remains to be fully established. However, Domínguez-Andrés et al. (105) reported that itaconate contributes to the development of immune tolerance, and that training of monocytes with β-glucan inhibits Irg1, the enzyme catalyzing itaconate biosynthesis, to facilitate the induction of trained immunity. Other than citrate and itaconate, concentrations of succinate, malate, and fumarate are increased in trained innate leukocytes (91, 99). Succinate and fumarate can stabilize HIF-1α and may play a role in stabilizing the metabolic features that are a hallmark of trained immunity (106). Fumarate has been shown to inhibit the activity of KDM5 histone demethylases and contribute to trained immunity by regulating epigenetic modifications (91). Succinate may also play a role in regulating the inflammatory response during innate immune training because succinate accumulation in innate leukocytes fuels a proinflammatory phenotype via succinate-induced stabilization of HIF-1α, augmentation of mitochondrial reactive oxygen species production, and protein succinylation (107).

Alterations in cholesterol metabolism have also been reported in trained innate leukocytes (108). Inhibition of cholesterol biosynthesis using statins inhibited induction of innate immune memory by BCG, β-glucan, and oxLDL in monocytes (109). Further analysis identified mevalonate accumulation as an important factor driving trained immunity. Changes in fatty acid metabolism may also contribute to the induction and maintenance of innate immune memory. Although inhibition of fatty acid biosynthesis during the training process did not impair the induction of innate immune memory, it did blunt the trained phenotype during restimulation, suggesting that fatty acid biosynthesis plays a role in the innate memory response (110).

Conclusions

Innate immune memory can be defined as a set of sustained alterations in innate leukocyte function that supports a more robust response to downstream infections. This process is crucial for host defense in nonvertebrate organisms that depend on the innate immune system but is also functional in vertebrates. Recent research has identified cellular and molecular mechanisms that define and mediate innate immune memory. Functional, metabolic, and epigenetic alterations have been described, but further work is needed to fully understand the factors that induce and sustain innate immune memory. From a clinical perspective, understanding and application of innate immune memory has significant potential for preventing or treating infections in vulnerable populations and improving vaccine adjuvant development. In contrast, a better understanding of the deleterious impact of innate immune memory may allow for novel treatment options for chronic inflammatory diseases, such as atherosclerosis and Alzheimer's disease.

Disclosures

The authors have no financial conflicts of interest.

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