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Review

Immunometabolic circuits in trained immunity

Rob J.W. Arts, Leo A.B. Joosten, Mihai G. Netea*

Department of Internal Medicine and Radboud Center for Infectious Diseases (RCI), Radboud University Medical Center, Nijmegen, The Netherlands

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ABSTRACT

The classical view that only adaptive immunity can build immunological memory has recently been challenged. Both in organisms lacking adaptive immunity as well as in mammals, the innate immune system can adapt to mount an increased resistance to reinfection, a *de facto* innate immune memory termed *trained immunity*. Recent studies have revealed that rewiring of cellular metabolism induced by different immunological signals is a crucial step for determining the epigenetic changes underlying trained immunity. Processes such as a shift of glucose metabolism from oxidative phosphorylation to aerobic glycolysis, increased glutamine metabolism and cholesterol synthesis, play a crucial role in these processes. The discovery of trained immunity opens the door for the design of novel generations of vaccines, for new therapeutic strategies for the treatment of immune deficiency states, and for modulation of exaggerated inflammation in autoinflammatory diseases.

Contents

1. Introduction

Classically, the immune system can be divided into innate and adaptive immunity, with monocytes, macrophages, neutrophils, and NK cells as the main cellular effectors of innate immune responses, while T- and B-lymphocytes mediate adaptive immunity. Until recently it was assumed only the adaptive immune system possesses the capacity to mount a memory response and therefore improve the immunological reaction to a second infection. However, an increasing amount of evidence accumulates, suggesting that also the innate immune system possesses adaptive characteristics. In plants and non-vertebrates, both lacking an

Abbreviations: Ac, acetylation; ATP, adenosine triphosphate; BCG, Bacillus Calmette Guerin; CIC, citrate carrier; GABA, γ-aminobutyric acid; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; H3K, histone 3 lysine; Hif, hypoxia inducible factor; HDAC, histone deacetylase; LDH, lactate dehydrogenase; me3, trimethylation; NAD(P), nicotinamide adenine dinucleotide (phosphate); OxPhos, oxidative phosphorylation; PDH, pyruvate dehydrogenase; PKM, pyruvate kinase; PPP, pentose phosphate pathway; TCA, tricarboxylic acid cycle.

* Corresponding author at: Department of Internal Medicine (463), Radboud University Nijmegen Medical Centre, Geert Grooteplein Zuid 8, 6525 GA, Nijmegen, The Netherlands.

E-mail addresses: rob.jw.arts@radboudumc.nl (R.J.W. Arts), leo.joosten@radboudumc.nl (L.A.B. Joosten), mihai.netea@radboudumc.nl (M.G. Netea).

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adaptive immune system, it has already been know for several decades that a memory response could be build that would protect from a secondary infection [1,2]. Interestingly, this improved secondary response is not always strictly specific, as infection with one pathogen can sometimes also protect from infections with non-related pathogens [3]. This process has been shown to be epigenetically regulated [4]. In retrospect, this (non-specific) memory, mediated by the innate immune system, was also seen in mice strains with known deficiencies in adaptive immune responses [3,5].

More recently, this same process of innate immune memory was also been shown to occur in human monocytes and macrophages. β-glucan, a major component of the *C. albicans* cell wall, was shown to *ex vivo* enhance cytokine production to a second unrelated stimulus, a process that was also epigenetically regulated [6,7]. Also in mice, an *in vivo* challenge with β-glucan protected from subsequent *C. albicans* or *S. aureus* infection [6,8], and infection with cytomegalovirus induced improved effector function of NK cells after the infection [9]. In humans, vaccination with Bacillus Calmette-Guérin (BCG) showed non-specific protection from all-cause mortality, mainly a result of reduced mortality from infections, in low-weight birth children in West-Africa [10,11]. In a vaccination study in healthy adult volunteers, BCG markedly increased *ex vivo* cytokine responses by inducing epigenetic reprogramming in myeloid cells [12]. These studies demonstrate that the innate immune system can adapt after a previous challenge through functional and epigenetic reprogramming, a process that has been termed *trained immunity* or *innate immune memory* [13,14]. On the one hand, trained immunity is likely an important host defense mechanism contributing to the maturation of the innate immune system of infants and mediating protection after certain infections or vaccinations. On the other hand, when induced inappropriately by endogenous stimuli, trained immunity may play a role in the pathogenesis of autoinflammatory and/or autoimmune diseases [14,15]. Therefore, better understanding of the molecular mechanisms of trained immunity is crucial for developing new ways of immunotherapy and targeting inflammatory disorders [14].

In the last years an increasing amount of evidence has been accumulated in support of the concept that cellular metabolism is correlated with the functional state of immune cells [16]. Some of the first observations reported that different subsets of lymphocytes had distinctly different cellular metabolic states. Activated T lymphocytes have high rates of both glycolysis and oxidative phosphorylation (OxPhos) and metabolize glucose to lactate [17,18], whereas memory T-lymphocytes are more dependent on lipid synthesis via mitochondrial citrate production. These lipids can be used to produce triacyglycerides (TAGs) which are being degraded by β-oxidation to fuel OxPhos via acetyl-CoA production [19]. In contrast, regulatory T-cells fuel β-oxidation and OxPhos through exogenously derived fatty acids [20]. This shows that the phenotype of lymphocytes highly correlates with the source of energy that they use [21,22]. Subsequent studies showed that different phenotypes of macrophages retrieve energy from very distinct metabolic pathways: the more inflammatory (M(IFNγ) or formerly M1) macrophages depend largely on glycolysis and show impaired OxPhos and disruption of the Tricarboxylic acid (TCA) cycle [23,24], while in the more anti-inflammatory (M(IL-4) or formerly M2) macrophages the Krebs cycle is intact as they rely on OxPhos [25,26] and furthermore show increased β-oxidation as a result of fatty acid uptake [27].

In this review we will focus on the metabolic pathways induced by innate immune training. We will discuss glycolysis, TCA cycle, glutamine, and cholesterol metabolism and discuss their (potential) effect on epigenetics and how these clues could be used as therapeutic targets.

2. Metabolic pathways in trained immunity

2.1. Glycolysis

A metabolic switch from oxidative phosphorylation to glycolysis resulting in more lactate production has been described in the highly metabolically active cancer cells already in the beginning of the last century by Otto Warburg, called thus the 'Warburg effect' [28]. Glycolysis is often increased during immune cell activation: activated T cells show increased rates of glycolysis [17,18] and proinflammatory macrophages increase glucose metabolism resulting in increased lactate production [24]. This switch is assumed to be important as glycolysis, although being less efficient in generating adenosine triphosphate (ATP), can be upregulated multiple folds and therefore results in a faster production of ATP compared to oxidative phosphorylation [28].

A similar switch is seen in β-glucan trained monocytes [29] (Fig. 1). Transcriptional and epigenetic (H3K4me3 and H3K27ac) analysis of β-glucan induced trained immunity in monocytes revealed that genes in the mTOR signalling pathway and several metabolic pathways, especially glycolysis, were highly induced [7,29]. When human monocytes are stimulated *in vitro* with β-glucan for 24 h and let to rest for 6 subsequent days, the amounts of glucose consumption and lactate production increased over time. In contrast, oxygen consumption 6 days after β-glucan training is significantly decreased compared to control macrophages [29]. These effects of β-glucan-induced training were mediated by activation of the Akt/mTOR/Hif1α pathway. Inhibiting this pathway at several levels, or making use of myeloid cell specific Hif1α knockout mice, abrogated induction of trained immunity both at cytokine and epigenetic level [29] (Fig. 1).

Induction of glycolysis results in higher ratios of NAD^+/NADH ratio, which was also the case in β-glucan trained monocytes/macrophages [29]. In LPS stimulated monocytes the vast increase in NAD^+/NADH ratio has been shown to activate sirtuin 1 and 6, supporting a switch from a proinflammatory state with high rates of glycolysis to a more anti-inflammatory state with increased fatty acid oxidation [30]. Interestingly, in β-glucan trained monocytes, sirtuin 1 expression appeared to be decreased and activation of sirtuin 1 by resveratrol inhibited training [29]. This suggests that decreased expression of sirtuin 1 might play a role in the significant increase of H3K27ac induced by monocyte training by β-glucan. However, apart from the classical role as histone deacetylases, sirtuins were also shown to deacetylate nonhistone structutes, such as NF-κB or Hif1α [31], and this should be taken into consideration too. Moreover, lactate, the end product of anaerobic glycolysis, is also able to inhibit histone deacetylase (HDAC) activity and therefore cause increased gene accessibility [32].

In addition to its direct role in energy production, induction of glycolysis might also play a role in posttranslational modification of effector molecules. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH), one of the enzymes in glycolysis can bind the 3′ UTR of *ifng* RNA and therefore decreasing IFNγ production. In activated T cells GAPDH is used in glycolysis and therefore more IFNγ can be produced. Also decreasing GAPDH expression by RNA interference increased IFNγ production [33]. A similar mechanism has been reported in murine and human monocytes and macrophages in relation to TNF mRNA induction. GADPH can posttranscriptionally repress TNF mRNA in monocytes in low glycolysis state, e.g. immunotolerant monocytes as seen in sepsis [34] (Fig. 2). Whether reversal of such effects plays a role in trained immunity remains to be elucidated.

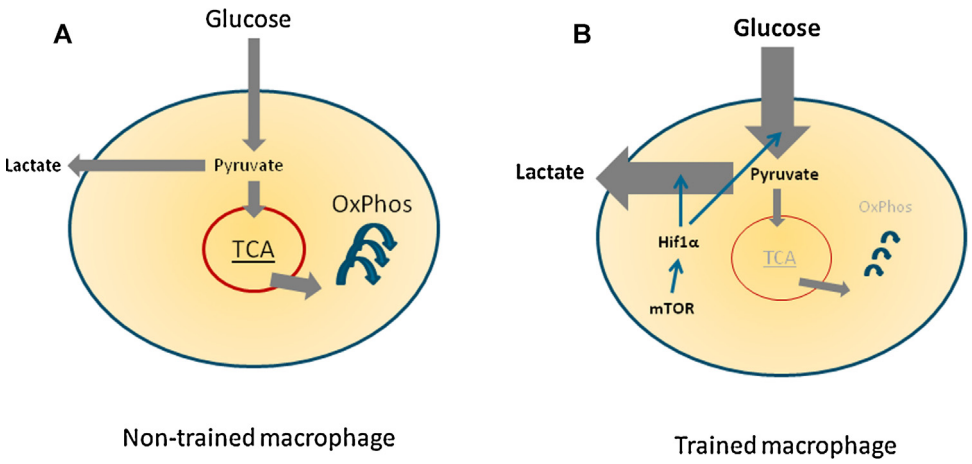

Fig. 1. Glucose metabolism in trained immunity. Induction of trained immunity by β-glucan causes activation of the mTOR pathway, effect mediated through signalling via the dectin-1 receptor, which results in an increase of Hif1α activity, a central regulating transcription factor of glycolysis-related genes. This results in an upregulation of glycolysis. Pyruvate, the end product of glycolysis, can be used to fuel the TCA cycle to produce NADH or $FADH_2$, metabolic components that could be used in the electron transport chain for oxidative phosphorylation (OxPhos). In β-glucan trained monocytes pyruvate is converted into lactate, which although less efficient than OxPhos, results in more ATP production, as it can be upregulated to a great extent.

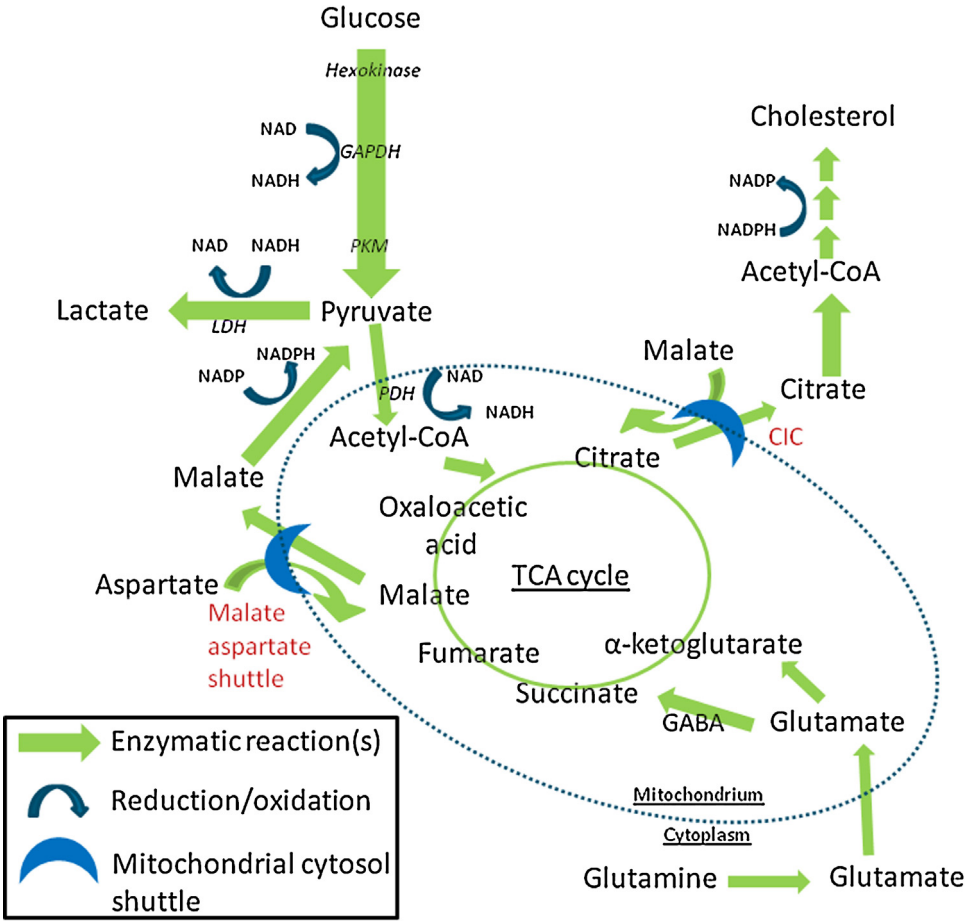

Fig. 2. Overview of the complex metabolic pathways that could play a role in trained immunity. Induction of glycolysis resulting in lactate production is one of the central hallmarks in trained immunity metabolism. In addition, glutamine metabolism, which fuels the TCA cycle and results in accumulation of certain TCA cycle metabolites, such as fumarate, is also important for induction of trained immunity. Aspartate consumption from the medium is also increased in trained monocytes and macrophages, while the cholesterol synthesis pathway appears to be an essential metabolic pathway as well, as shown by inhibition of trained immunity by statins. Several metabolites that accumulate in trained monocytes and macrophages could play a role in the induction of epigenetic modulators, such as succinate and fumarate for antagonizing histone or DNA demethylation, and acetyl-CoA as an essential substrate for acetylating processes.

2.2. Tricarboxylic acid cycle

A crucial pathway of energy metabolism in the cell is represented by the TCA cycle, leading to oxidation of various substrates, including pyruvate coming from glycolysis. After induction of trained immunity by β-glucan, trained macrophages display a decreased basal and maximum oxygen consumption, suggestive for a decrease in use of OxPhos [29]. However, although OxPhos is decreased, the TCA cycle is not completely shut down, with concentrations of several metabolites in the TCA cycle such as citrate, succinate and fumarate being increased compared to non-trained macrophages. Increased citrate concentrations might serve as a source for fatty acid synthesis, as citrate was shown to inhibit glycolysis and TCA cycle metabolism, whereas gluconeogenesis and lipid and sterol synthesis were induced [35–41]. Citrate can either be produced from glycolysis via pyruvate, or it can be derived from other metabolites, such as glutamine, which can be converted into α-ketoglutarate and enter the TCA cycle [35,42]. The latter pathway is especially important in conditions where the mTORC1 pathway is active which results in Hif1α induction (e.g. trained immunity) [43], as Hif1α inhibits pyruvate dehydrogenase (PDH) and therefore carbon incorporation of glycolysis into the TCA cycle [43,44] (Fig. 2). When citrate is being used as a source for lipid or sterol synthesis, it first should be transported from the mitochondrion into the cytosol by the citrate carrier (CIC) where it can be converted into acetyl-CoA by ATP citrate lyase [45] (Fig. 2). Acetyl-CoA is a acetyl donor for histone acetylation (a histone mark that facilitates transcription) [46]. Moreover, it has been shown that acetyl-CoA derived from both glycolysis and glutamine induces histone acetylation of genes of glycolytic enzymes, such as hexokinase 2, phosphofructokinase, and lactate dehydrogenase (LDH) [47], therefore promoting glycolysis. Inhibition of, or mutations in, CIC limit histone acetylation, showing the importance of citrate in histone acetylation [48].

Succinate and fumarate concentrations are also higher in β-glucan trained monocytes and macrophages and both have been shown to play an important role in inflammation [49]. Accumulation of succinate and fumarate has been shown to have a stabilizing effect on Hif-1α (by inhibiting Prolyl hydroxylases), and thus lead to an increase in glycolysis and IL-1β transcription [23,50,51]. Apart from the effect on Hif-1α, succinate also signals through the succinate receptor, which in dendritic cells results in intracellular calcium mobilization and synergism with Toll-like receptor 3 (TLR3) and TLR7 and promote their activity [52,53]. Succinate also results in succinylation of several proteins, e.g. GAPDH, malate dehydrogenase, LDH and the glutamate carrier 1. However, how this posttranslational modification affects the activity of these proteins remains to be elucidated [23]. Lastly, succinate and fumarate can act as an antagonist of histone and DNA demethylases. Lysine demethylases (KDMs) of the JmjC family need α-ketoglutarate as a cofactor for the demethylation process [54] and succinate and fumarate are known to serve as antagonizing factors [54,55]. For fumarate it has also been shown that it can inhibit activity of KDM5 demethylases [12,56].

2-hydroxyglutarate concentrations are also higher in trained monocytes, and this also has antagonizing effects on α-ketoglutarate-dependent demethylases [57]. Hence, 2-hydroxyglutarate could also serve as an additional factor in modulating epigenetic marks induced by β-glucan.

3. Future directions to study immunometabolism in trained immunity

3.1. Glutamine metabolism

The metabolite glutamine has been shown to be an essential source of succinate and fumarate by glutamine anaplerosis and the GABA shunt [23], and also for citrate via the reverse TCA cycle route [35]. It should therefore also be determined whether glutamine metabolism is an important component of trained immunity as well (Fig. 2). In addition, other effects of glutamine metabolism may influence cell activation during trained immunity. Firstly, glutamate could be used for ATP production, as well as NADPH by conversion of cytosolic malate to pyruvate. Therefore, mitochondrial malate needs to be transported into the cytosol by the malate shuttle. In addition, cytosolic pyruvate could also be used to maintain the NADH redox balance by conversion to lactate. Secondly, glutamate could be used to produce acetyl CoA, which acts as a substrate for histone acetyltransferases [58]; notably, H3K27Ac is an important histone mark accompanying active promoters in trained monocytes [7]. Thirdly, in a glioblastoma cell line, glutamine has been shown to contribute to the production of cholesterol and fatty acids, two pathways that were significantly upregulated in trained monocytes [7]. Glutamine enters the TCA cycle via α-ketoglutarate or succinate and is metabolized to citrate (or goes in the reverse direction [59]) that can be converted into cytosolic acetyl CoA, which can be used as a direct fuel for cholesterol and fatty acid synthesis. Fourthly, glutamine could be used to produce malate, which can be used for fueling the malate-aspartate shuttle. In this way the reducing equivalents of mitochondrial NADH can be transported to the cytoplasm for NADPH production, where it might serve as a cofactor in the cholesterol synthesis pathway, which is highly induced in β-glucan-induced trained immunity (Fig. 2). Finally, inhibition of glutamine uptake in breast cancer cell lines has been strongly correlated with reduction of H3K4me3 of essential genes, modulated by reduced expression of the methyltransferases SETD1 and ASH2L [60].

3.2. Aspartate metabolism

When consumption of amino acids from the medium of non-trained and β-glucan-trained human macrophages was compared, consumption of aspartate was shown to be highly induced in trained macrophages. Metabolism of aspartic acid serves several roles, as it is part of the urea cycle, gluconeogenesis, and the malate-aspartate shuttle, it is important for inosine formation in purine metabolism, and is a precursor for several amino acids, including methionine [61]. Aspartate could therefore contribute in several ways to the induction of trained immunity. Firstly, aspartate might act by upregulating the malate-aspartate shuttle, which would result in a transition of the reducing equivalents of mitochondrial NADH to NADPH production in the cytoplasm, where it might serve as an essential metabolite for upregulated cholesterol synthesis (Fig. 2). Secondly, aspartate might serve as fuel for purine production, which is upregulated in β-glucan-trained cells via the penthose phosphate pathway (PPP) [62]. Thirdly, aspartate can be used as a source, via transamination of oxaloacetic acid, which together with acetyl-CoA forms citrate [35] (Fig. 2). Finally, aspartate might serve for the production of essential amino acids such as methionine, which also serves, just as other metabolic pathways, such as folate and choline metabolism, as an essential cofactor for DNA and histone methyltransferases [63,64].

3.3. Cholesterol synthesis

Analysis of transcriptome data of β-glucan trained macrophages revealed that also the cholesterol synthesis pathway was also highly induced [7]. How the cholesterol synthesis pathway contributes to the phenotype of trained immunity is still to be elucidated. However, a plausible hypothesis for this effect is that cholesterol remodels the cell membrane of trained cells, which could mediate increased signal transduction upon restimulation,

for example by disrupting cholesterol and sphingolipid raft formation [65].

4. Future directions to target disease

Immunometabolism is a field that has gained more interest the last several years, and has been shown to be involved in immune activation in several diseases such as infections [66,67], autoinflammatory disorders and cardiovascular diseases [68]. Moreover, in post-sepsis immunoparalysis, we have shown that the cellular metabolism of monocytes had broad defects and that reversing these defects could at least partially restore the immunological function of these cells [8,69]. Therefore, modulation of cellular metabolism has great potential as a therapeutic in immune-mediated diseases. In autoinflammatory diseases, atherosclerosis or insulin resistance and diabetes in which monocytes and macrophages are thought to be skewed towards a proinflammatory profile, inhibition of certain metabolic pathways may represent a valid approach to target disease activity [14,68,70–73]. Moreover, the role played by cellular metabolic pathways for the induction of trained immunity may also represent a novel therapeutic approach in immunodeficiencies. Induction of metabolic pathways important for trained immunity should be attempted to restore immune function during sepsis-induced immunoparalysis. In addition, these approaches could also be used to improve the immune responsiveness in vulnerable groups such as elderly and infants that have decreased immune function and are more prone to infectious diseases [74,75].

In conclusion, boosting or inhibiting the innate immune system has several potential beneficial effects in different kinds of medical settings and modulating cellular metabolism of immune cells is a promising new approach to reach this goal.

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