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Induction of innate immune memory: the role of cellular metabolism

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The paradigm that only adaptive immunity can develop immunological memory has recently been challenged by studies showing that cells from the innate immune system can undergo functional reprogramming, facilitating a faster and enhanced response to secondary infections. This improved secondary response is not always specific, as it can also protect from infections caused by non-related pathogens. This has been termed innate immune memory or *trained immunity*. Trained immunity not only involves rewiring the intracellular immune signaling of innate immune cells, but also induces profound changes in cellular metabolic pathways such as glycolysis, oxidative phosphorylation, fatty acid and amino acid metabolism, increasing the capacity of the innate immune cells to respond to a secondary stimulation. The understanding of these intracellular processes opens new therapeutic possibilities for the modulation of the innate immune responses during infections and inflammatory diseases.

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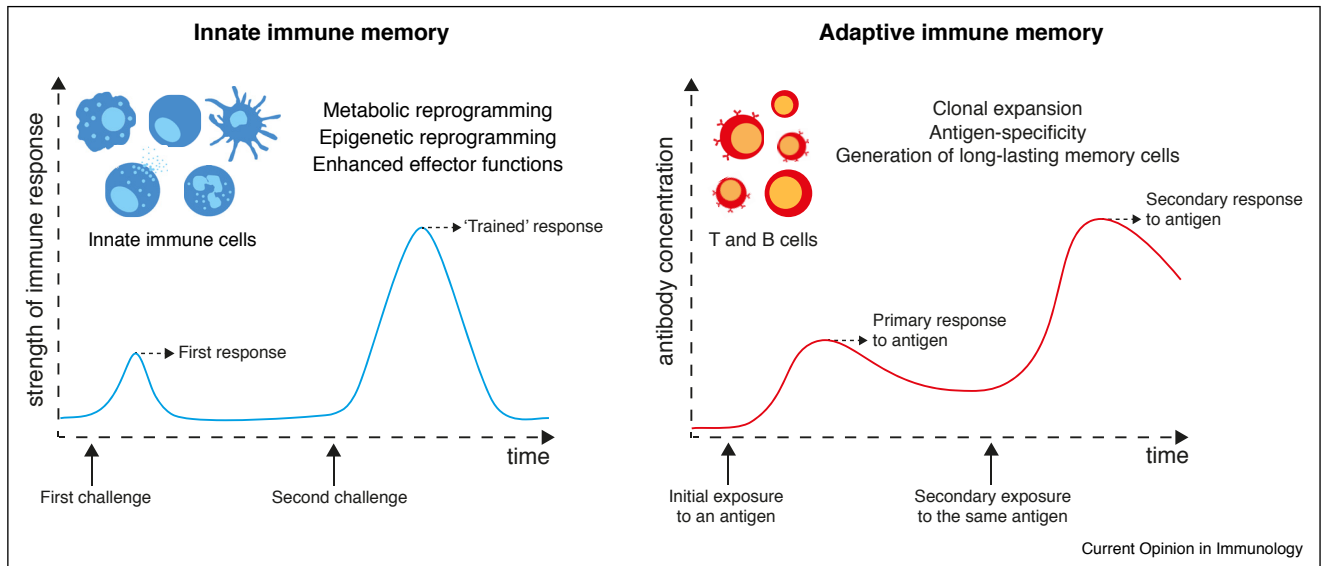
Introduction

For a long time, it was thought that only adaptive immunity had the ability to develop immunological memory. Naive B and T lymphocytes first proliferate, and then develop antigen-specific, long-lasting memory cells after their first encounter with a pathogen,

providing effective and specific protection against re-infection by the same microorganism [1]. The paradigm of memory within the adaptive immune system is essentially the result of somatic genetic re-arrangements and clonal selection, while the innate immune system is a germline-encoded system that is not capable of carrying genetic memory through cell division. As a result, innate immune system functions were considered to be only associated with the nonspecific acute elimination of pathogens either by cellular mechanisms such as phagocytosis, or humoral processes such as the complement system. However, in the last years, a series of discoveries have proven that cells from the innate immune system are also able to undergo long-term adaptation and acquire enhanced capability to respond to certain stimuli, a process that has been termed innate immune memory or trained immunity [2], which is based on the long-term reprogramming that the cells of the innate immune system such as monocytes, macrophages and NK cells undergo after infection or vaccination [3]. This long-term innate immune response does not have an antigen-specific character, thus it does not rely on a particular infectious organism or stimulant (Figure 1). For example, training with β -glucan, a component of fungal cell walls, induces increased protection against bacterial infections caused by *Staphylococcus aureus* [4]. Similarly, muramyl dipeptide (MDP), a component of bacterial cell wall peptidoglycan [5], can induce protection against toxoplasmosis, while CpG dinucleotides provide protection against *Escherichia coli* infections [6].

Furthermore, a growing body of evidence illustrates that the development of trained immunity is not always beneficial for the organism, and sterile inflammatory insults, such as oxLDL (oxidized low-density lipoprotein) and urate crystals can trigger strong proinflammatory responses that can potentially contribute to development of atherosclerosis or gout [7,8]. Increasing evidence links trained immunity to epigenetic and metabolic regulation that involve a number of central cellular metabolic pathways such as glycolysis, oxidative phosphorylation (OXPHOS), glutaminolysis, as well as fatty acids and cholesterol-synthesis pathways. In this review we will focus on the most recent and relevant advances provide novel insights into mechanisms centered on the immunometabolic reprogramming that induces trained immunity (Table 1).

Figure 1



Immunological memory is not exclusive of T and B lymphocytes.

Cells from the innate immune system, such as monocytes, macrophages, DCs and NK cells are also influenced by the contact with different antigens, undergoing metabolic and epigenetic reprogramming and facilitating an enhanced response to future threats. While the responses driven by T and B lymphocytes are antigen-specific, secondary responses involving innate cells can be triggered by a wide variety of stimuli.

Metabolic pathways in innate immune memory

Glycolysis

Aerobic respiration is the main source of ATP in most human cells. However, glycolysis, an alternative form of glucose metabolism, plays a central role in both immunity and disease states [9]. Several cell subsets require the upregulation of glycolysis during immune cell activation: activated T cells show increased rates of glycolysis and so do proinflammatory macrophages [10,11], resulting in an increased rate of glucose consumption with higher lactate production [12]. After stimulation of macrophages, pyruvate produced from glucose is transformed into lactate

that is subsequently released from the cell, instead of entering the mitochondria to undergo oxidation [13]. Although less efficient in generating ATP than OXPHOS, glycolysis can be upregulated to a greater extent resulting in a faster production of ATP. As a result of this, innate immune cells can use this metabolic adaptation to provide energy and building blocks needed for activation in a timely fashion.

Cheng *et al.* showed that glucose consumption is increased in β -glucan-trained macrophages [14]. In a follow-up study, Arts *et al.* proved that glucose was converted into lactate in β -glucan-trained monocytes, validating the upregulation of glycolysis with concomitant lactate production in β -glucan-trained monocytes [15^{**}]. For its part, pro-inflammatory macrophages are highly glycolytic, but anti-inflammatory macrophages rely mainly on OXPHOS and fatty acid oxidation [16]. High rates of glycolytic metabolism and the accumulation of intermediate metabolites of the TCA cycle such as fumarate and succinate, control the methylation and acetylation of histones, forming the metabolic basis for trained immunity [15^{**}]. Several metabolites from glycolysis and the TCA cycle have been shown to act as cofactors for DNA and histone methyltransferases and demethylases [17]. After priming of monocytes with β -glucan, genes involved in glycolysis, such as those encoding for the rate-limiting enzymes of glucose metabolism hexokinase and pyruvate kinase, were epigenetically upregulated one week later [14]. This metabolic rewiring is also present in

Table 1

Overview of pathologies in which a positive or a negative role for innate immune memory mechanisms have been reported

Positive effects mediated by trained immunity-mediated mechanisms

Reversal of immunoparalysis in sepsis patients	[44 [*] ,48]
Improved hematopoiesis under chemotherapy treatment	[18 ^{**}]
Non-specific protective effects of vaccinations	[19,49]
Protection from neonatal sepsis	[43 [*]]

Negative effects mediated by trained immunity-mediated mechanisms

Atherosclerosis and systemic inflammation	[32 [*] ,47]
Hyper immunoglobulin D syndrome	[7 [*]]
Diabetes	[45]
Alzheimer disease	[46]
Autoimmune disorders	Reviewed in Ref. [50]

bone marrow progenitors, where β -glucan administration involves a global increase in energy metabolism, being glycolysis one of the most enriched pathways one week after β -glucan injection in mice [18**]. Of note, the induction of glycolysis has recently been proven to be crucial for the induction of trained immunity following BCG vaccination of human volunteers, leading to reduction of yellow fever viremia [19].

TCA cycle and OXPHOS

The tricarboxylic acid (TCA) cycle captures the energy stored in the chemical bonds of acetyl-CoA in a series of reactions, trapping it in high-energy chemical bonds contained in intermediate molecules. This energy is then transferred to OXPHOS, where electrons transported by molecules such as NAD⁺ and FADH generate a gradient that will be used to synthesize ATP. Induction of trained immunity by fungal components such as β -glucan leads to a shift of cellular metabolism from OXPHOS towards aerobic glycolysis via the mTOR/HIF1 α /Akt pathway, which is essential for the induction of trained immunity by β -glucan [14]. However, OXPHOS is not shut down, and other metabolites can compensate the drift of glucose from the TCA cycle towards the enhanced glycolytic pathways. In this regard, Arts *et al.* recently showed that glutamine replenishment of the TCA cycle leads to an increase in the intracellular concentration of fumarate, whose accumulation turns to be crucial for the induction of trained immunity. The immunomodulatory effects of fumarate are mediated by inhibition of the histone demethylases from the KDM5 family, leading to a subsequent increase in histone methylation and open chromatin, favoring the expression of proinflammatory genes (see also below) [15**].

The variation in the levels of the different TCA cycle intermediates also has an impact in the function of other enzymes involved in giving shape to the epigenetic scenario of the innate immune cells. According to this, DNA/histone methyltransferases require S-adenosyl methionine for their proper functioning, while the actions of Ten-eleven translocation (TET) proteins, involved in DNA demethylation in hematopoietic cells, rely on the availability of the TCA cycle intermediate α -ketoglutarate [20]. Histone lysine demethylases of the JmjC and JmjD family need α -ketoglutarate as a cofactor for the demethylation process [21]. Other TCA cycle intermediates, such as succinate, citrate or acetyl-CoA can play a fundamental role in the regulation of inflammatory responses. Succinate accumulates and stabilizes HIF1 α by inhibiting its hydroxylation, promoting IL-1 β transcription in inflammatory macrophages [22]. Citrate levels are elevated in pro-inflammatory macrophages, being important for the production of different proinflammatory factors such as prostaglandins, reactive oxygen species, and nitric oxide [23]. Trained cells undergo increased histone acetylation in proinflammatory genes, increasing

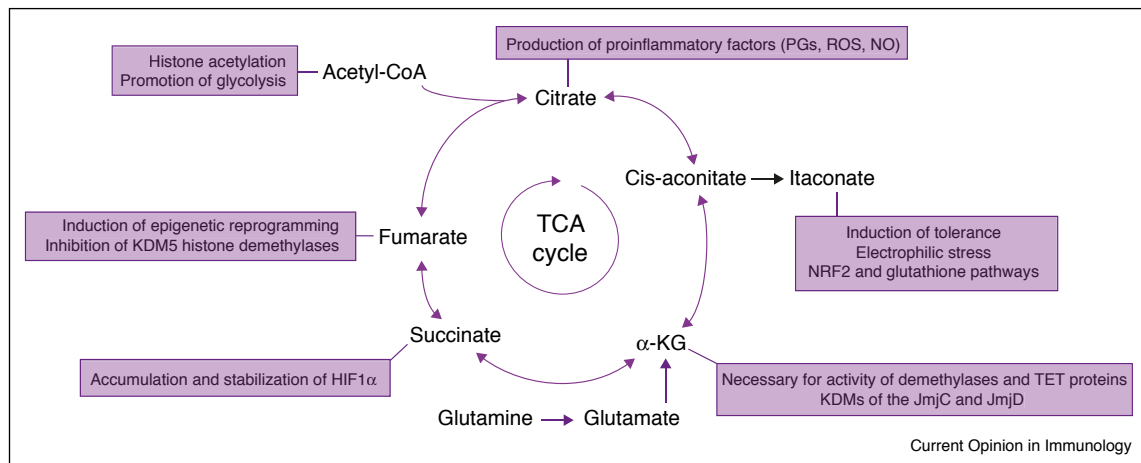
the accessibility to these genes for transcription factors upon secondary stimulation. Acetylation of histones by histone acetyl transferases (HATs) requires acetyl-CoA from the TCA cycle, which is supplied via the export of mitochondrial citrate [24]. Moreover, it has been shown that acetyl-CoA derived from both glycolysis and glutamine induces histone acetylation of genes encoding for glycolytic enzymes, such as hexokinase 2, phosphofructokinase, and lactate dehydrogenase [25], therefore promoting glycolysis. Other TCA cycle metabolites, such as itaconate [26**,27] and 2-hydroxyglutarate [28] have shown great potential in the modulation of the inflammatory response. In this regard, itaconate has been pointed out as one of the most promising endogenous molecules with an immunomodulatory potential through the induction of electrophilic stress, reacting with glutathione and subsequently regulating pathways such as the I κ B ζ -ATF3 inflammatory axis [26**] or the KEAP1-Nrf2 system [27], leading to the induction of immune tolerance and having been related with the prevention of immunopathology during *Mycobacterium tuberculosis* infection [29]. With all this in mind, further research linking TCA cycle products with trained immunity or tolerance is warranted (Figure 2).

Lipid metabolism

During induction of trained immunity, β -glucan trained macrophages display an increased activity of the cholesterol synthesis pathway [30], while trained monocytes/macrophages display a proatherogenic phenotype [31]. In line with this, a growing body of evidence has shown that trained immunity might play a central role in the pathogenesis of atherosclerosis. A recent study proved that metabolites of the cholesterol synthesis pathway are crucial for establishing innate immune memory in human macrophages after priming with β -glucan, oxLDL, or BCG. Moreover, Christ *et al.* have shown that the exposure of mice to high-fat diet for a limited period induces long-term transcriptional and functional reprogramming of hematopoietic precursors, leading to consistent increase in systemic inflammation and persistent enhanced secondary responses by a mechanism-dependent of NLRP3 and IL-1 β [32*]. Interestingly, mevalonate, a metabolite of the cholesterol synthesis pathway, is able to amplify the induction of trained immunity through an IGF1R-mediated pathway [7*]. Moreover, hyper immunoglobulin D syndrome patients who accumulate mevalonate have a constitutive trained immunity phenotype with increased cytokine production, which is likely central to the attacks of sterile inflammation in this disease [7*].

Fatty acids synthesis is generally associated with a pro-inflammatory macrophage phenotype [33]. Fatty acids can induce a state of intracellular stress and activation innate immune pathways [34], while its oxidation plays an important role in regulating the inflammatory

Figure 2



The metabolic–epigenetic interplay during induction of trained immunity. Overview of the influence of different TCA cycle intermediates in epigenetic mechanisms involved in the induction and development of innate immune memory.

signature of macrophages. Increased intracellular levels of unsaturated fatty acids (oleic acid, linoleic acid, and arachidonic acid) stimulated a pro-inflammatory phenotype by upregulating IL-1 α production by uncoupling mitochondrial respiration [35^{*}], and endogenously derived triacylglycerides are catabolized by β -oxidation in the mitochondria to generate acetyl-CoA to fuel OXPHOS [36]. Lachmandas *et al.* hypothesized that the nuclear receptor PPAR- γ , whose activation is thought to be associated with the establishment of training cell phenotypes in atherosclerosis [37], may be upregulated as a consequence of the higher levels of polyunsaturated fatty acids found in monocytes stimulated with Pam3Cys compared to LPS [38]. The relevance of these pathways was recently demonstrated in an *in vivo* model of trained immunity, in which Mitroulis *et al.* recently showed that lipid changes accompany trained-immunity-associated effects on hematopoietic progenitors. β -Glucan injection causes a reduction in metabolites involved in linoleic and arachidonic acid metabolism, compared to PBS injection [18^{**}]. In this line, cells from β -glucan-trained mice contained lipids with shorter and more saturated acyl chains, while cells from the PBS-treated control group contained lipids with longer acyl chains and increased levels of polyunsaturated fatty acids [18^{**}]. All together, the results derived from these studies suggest that inflammation-mediated products, such as IL-1 α and IL-1 β , are likely to be central regulatory nodes regulating the mechanisms behind the induction of trained immunity. Of note, monocytes from patients suffering from sepsis-induced immunoparalysis, the functional program opposing the induction of trained immunity in infectious disease scenarios, show lower pro-

inflammatory cytokine production accompanied by an impaired defective capacity to mount glycolysis and also β -oxidation [14], highlighting the importance of lipid metabolism in this context.

Amino acid metabolism

Amino acids are the basic chemical building blocks during biogenesis, but they also act as precursors of different metabolites necessary for the correct induction of innate immune memory. Different studies have shown that glutamine metabolism into glutamate, α -ketoglutarate and succinate semialdehyde can act as a central source of fumarate and succinate for the TCA cycle [15^{**},39]. As pointed out before, glutamine replenishment of the TCA cycle is important for the induction of trained immunity by means of fumarate accumulation [15^{**}]. Inhibition of glutaminolysis in mice downregulated the induction of pro-inflammatory cytokine production in human monocytes exposed to *C. albicans* [12] and also impaired the enhancement of trained immunity triggered by β -glucan [15^{**}]. 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 [40]. In the context of atherosclerosis, glycine, cysteine, alanine and leucine decreased triglyceride levels while glutamate and glutamine caused an increased triglyceride accumulation in macrophages [41]. The synthesis of nitric oxide from arginine is of crucial importance in early stages of the disease [42].

Conclusions and future directions

Trained immunity induces long-term reprogramming in innate immune cells, allowing a robust innate host

response to a secondary stimulus. The mechanisms mediating the induction and upkeep of innate immune memory should be elucidated at the level of the interplay between the different cell subsets involved, and also at the level of the epigenetic, and metabolic processes involved. As described here, metabolic rewiring is a crucial step for the induction of trained immunity, but many questions remain; which of the other metabolic pathways are involved (e.g. the role of pentose phosphate pathway or reactive oxygen species metabolism), which are the specificities of these effects in various cell types, what are the metabolic imbalances in immune cells in autoinflammatory and autoimmune diseases.

The characterization of the differential metabolic responses of the different cells involved in each process depending on the type of stimulus, cell subset, or tissue microenvironment will represent a fundamental step to unravel the functional consequences for the responses involved in each of the pathological scenarios here discussed. Enhancement of trained immunity could be beneficial in immunocompromised individuals, such as newborn infants [43^{*}], patients undergoing anticancer therapy [18^{**}] or those suffering from immunodeficiencies or sepsis-related immunoparalysis [44^{*}]. However, the therapeutic modulation of this responses must be carefully handled since a maintained induction of innate immune memory mechanisms might lead to development of chronic inflammatory conditions such as arthritis or atherosclerosis in the long term [32^{*},37]. Alternatively, inhibition of trained immunity could be used to counteract the excessive inflammation implicated in the pathogenesis of several diseases with an inflammatory component, such as diabetes [45], Alzheimer disease [46] or atherosclerosis [47]. In this regard, the development and use of the latest epigenetics-technology and metabolomics-technology platforms warrants further progress in this field, opening new therapeutic strategies to modulate the potential of trained immunity.

Conflict of interest statement

Nothing declared.

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- of special interest
- of outstanding interest

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