Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Immunology

Induction of innate immune memory: the role of cellular metabolism

Jorge Domínguez-Andrés[1], Leo AB Joosten[1,2] and Mihai G Netea[1,3,4]

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.

Addresses
[1] Department of Internal Medicine and Radboud Center for Infectious Diseases (RCI), Radboud University Nijmegen Medical Centre, Geert Grooteplein Zuid 8, 6525GA Nijmegen, The Netherlands
[2] Department of Medical Genetics, Iuliu Hatieganu University of Medicine and Pharmacy, 400349 Cluj-Napoca, Romania
[3] Department for Genomics & Immunoregulation, Life and Medical Sciences Institute (LIMES), University of Bonn, 53115 Bonn, Germany
[4] Human Genomics Laboratory, Craiova University of Medicine and Pharmacy, Craiova, Romania

Corresponding author: Netea, Mihai G (mihai.netea@radboudumc.nl)

Current Opinion in Immunology 2019, **56**:10–16

This review comes from a themed issue on **Innate immunity**

Edited by **Nicolas Manel** and **James Di Santo**

For a complete overview see the Issue and the Editorial

Available online 19th September 2018

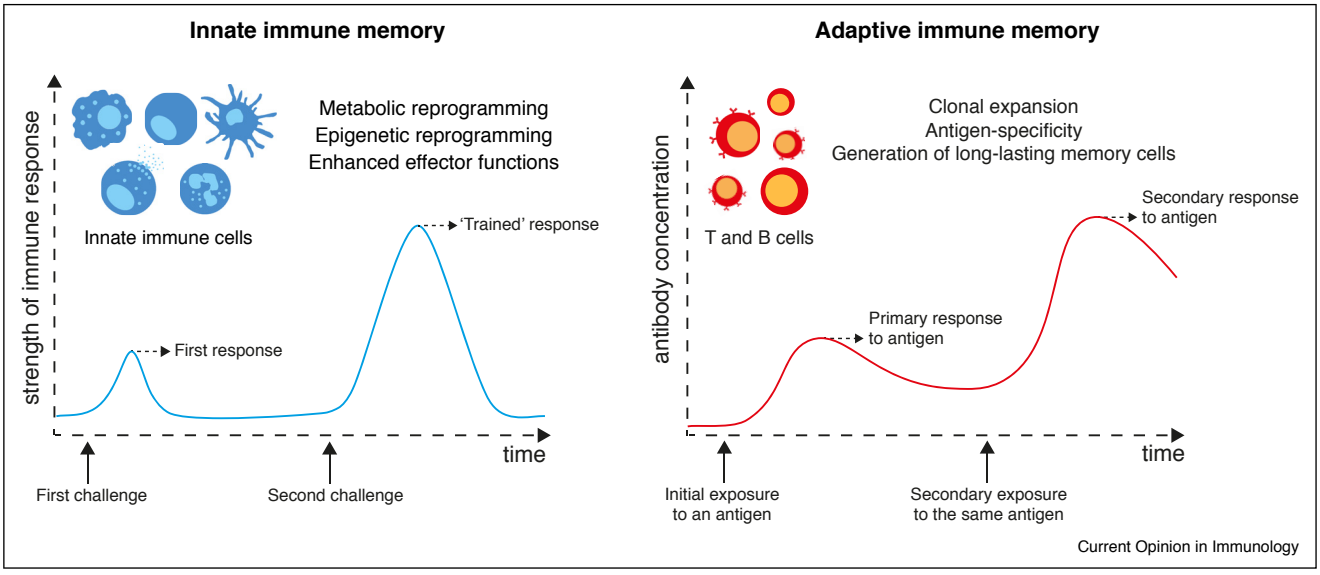
https://doi.org/10.1016/j.coi.2018.09.001

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.

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]

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 as well as histone acetyltransferases and deacetylases [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

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 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/HIF1α/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••].

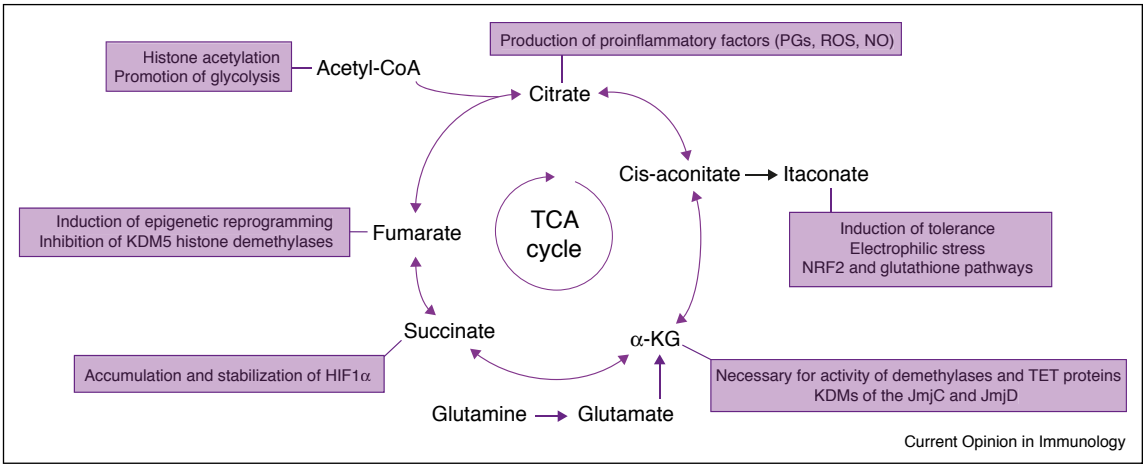
The variation in the levels of the different TCA cycle intermediates also has an impact in the function of other enzymes involved in giving shape to the epigenetic scenario of the innate immune cells. According to this, DNA/histone methyltransferases require S-adenosyl methionine for their proper functioning, 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 HIF1α by inhibiting its hydroxylation, promoting IL-1β 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 IκBζ–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-1β [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 proinflammatory 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-1α 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 inflammasome-mediated products, such as IL-1α and IL-1β, 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 immunodeficiences 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.

Acknowledgements

MGN is supported by an ERC Consolidator Grant (#310372) and by a Spinoza Grant of the Netherlands Organization for Scientific Research. LABJ is supported by a Competitiveness Operational Programme grant of the Romanian Ministry of European Funds (P_37_762). The authors apologize to those colleagues whose work was not cited due to space restrictions.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as

- • of special interest
- •• of outstanding interest

1. McHeyzer-Williams LJ, McHeyzer-Williams MG: **Antigen-specific memory B cell development**. *Annu Rev Immunol* 2005, **23**:487-513.

2. Netea MG, Quintin J, Van Der Meer JWM: **Trained immunity: a memory for innate host defense**. *Cell Host Microbe* 2011, **9**:355-361.

3. Dominguez-Andres J, Netea MG: **Long-term reprogramming of the innate immune system**. *J Leukoc Biol* 2018 http://dx.doi.org/10.1002/JLB.MR0318-104R.

4. Marakalala MJ, Williams DL, Hoving JC, Engstad R, Netea MG, Brown GD: **Dectin-1 plays a redundant role in the immunomodulatory activities of β-glucan-rich ligands in vivo**. *Microbes Infect* 2013, **15**:511-515.

5. Krahenbuhl JL, Sharma SD, Ferraresi RW, Remington JS: **Effects of muramyl dipeptide treatment on resistance to infection with Toxoplasma gondii in mice**. *Infect Immun* 1981, **31**:716-722.

6. Ribes S, Meister T, Ott M, Redlich S, Janova H, Hanisch U-K, Nessler S, Nau R: **Intraperitoneal prophylaxis with CpG oligodeoxynucleotides protects neutropenic mice against intracerebral Escherichia coli K1 infection**. *J Neuroinflammation* 2014, **11**:14.

7. • Bekkering S, Arts RJW, Novakovic B, Kourtzelis I, van der Heijden CDCC, Li Y, Popa CD, ter Horst R, van Tuijl J, Netea-Maier RT *et al.*: **Metabolic induction of trained immunity through the mevalonate pathway**. *Cell* 2018, **172**:135-146.e9.
Mevalonate mediates the induction of innate immune memory via activation of IGF1R and mTOR and subsequent histone modifications in inflammatory pathways.

8. Crişan TO, Cleophas MCP, Novakovic B, Erler K, van de Veerdonk FL, Stunnenberg HG, Netea MG, Dinarello CA, Joosten LAB: **Uric acid priming in human monocytes is driven by the AKT–PRAS40 autophagy pathway**. *Proc Natl Acad Sci U S A* 2017, **114**:5485-5490.

9. Van den Bossche J, Baardman J, Otto NA, van der Velden S, Neele AE, van den Berg SM, Luque-Martin R, Chen H-J, Boshuizen MCS, Ahmed M *et al.*: **Mitochondrial dysfunction prevents repolarization of inflammatory macrophages**. *Cell Rep* 2016, **17**:684-696.

10. Wang T, Liu H, Lian G, Zhang S-Y, Wang X, Jiang C: **HIF1α-induced glycolysis metabolism is essential to the activation of inflammatory macrophages**. *Mediators Inflamm* 2017, **2017**9029327.

11. Ashley Menk AV, Scharping NE, Moreci RS, Young HA, Gelhaus Wendell S, Delgoffe Correspondence GM, Menk AV, Zeng X, Guy C, Salvatore S *et al.*: **Early TCR signaling induces rapid aerobic glycolysis enabling distinct acute T cell effector functions**. *Cell Rep* 2018, **22**:1509-1521.

12. Domínguez-Andrés J, Arts RJW, ter Horst R, Gresnigt MS, Smeekens SP, Ratter JM, Lachmandas E, Boutens L, van de Veerdonk FL, Joosten LAB *et al.*: **Rewiring monocyte glucose metabolism via C-type lectin signaling protects against disseminated candidiasis**. *PLOS Pathog* 2017, **13**e1006632.

13. Appari M, Channon KM, McNeill E: **Metabolic regulation of adipose tissue macrophage function in obesity and diabetes**. *Antioxid Redox Signal* 2017, **29**:297-312 http://dx.doi.org/10.1089/ars.2017.7060.

14. Cheng S-C, Quintin J, Cramer RA, Shepardson KM, Saeed S, Kumar V, Giamarellos-Bourboulis EJ, Martens JH, Rao NA, Aghajanirefah A *et al.*: **mTOR- and HIF-1-mediated aerobic glycolysis as metabolic basis for trained immunity**. *Science (80-)* 2014, **345**:1250684.

15. •• Arts RJW, Novakovic B, ter Horst R, Carvalho A, Bekkering S, Lachmandas E, Rodrigues F, Silvestre R, Cheng S-C, Wang S-Y *et al.*: **Glutaminolysis and fumarate accumulation integrate immunometabolic and epigenetic programs in trained immunity**. *Cell Metab* 2016, **24(6)**:807-819 http://dx.doi.org/10.1016/j.cmet.2016.10.008.
Glycolysis, glutaminolysis, and the cholesterol synthesis pathway are essential for the induction of trained immunity by β-glucan in monocytes.

16. O'Neill LAJ, Kishton RJ, Rathmell J: **A guide to immunometabolism for immunologists**. *Nat Rev Immunol* 2016, **16**:553-565.

17. Etchegaray J-P, Mostoslavsky R: **Interplay between metabolism and epigenetics: a nuclear adaptation to environmental changes**. *Mol Cell* 2016, **62**:695-711.

18. •• Mitroulis I, Ruppova K, Wang B, Chen L-S, Grzybek M, Grinenko T, Eugster A, Troullinaki M, Palladini A, Kourtzelis I *et al.*: **Modulation of myelopoiesis progenitors is an integral component of trained immunity**. *Cell* 2018, **172**:147-161.e12.
Induction of trained immunity modulates metabolism of hematopoietic progenitors in the bone marrow and increases myelopoiesis.

19. Arts RJW, Moorlag SJCFM, Novakovic B, Li Y, Wang S-Y, Oosting M, Kumar V, Xavier RJ, Wijmenga C, Joosten LAB *et al.*: **BCG vaccination protects against experimental viral infection in humans through the induction of cytokines associated with trained immunity**. *Cell Host Microbe* 2018, **23**:89-100.e5.

20. Xu W, Yang H, Liu Y, Yang Y, Wang P, Kim S-H, Ito S, Yang C, Wang P, Xiao M-T *et al.*: **Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of α-ketoglutarate-dependent dioxygenases**. *Cancer Cell* 2011, **19**:17-30.

21. Xiao M, Yang H, Xu W, Ma S, Lin H, Zhu H, Liu L, Liu Y, Yang C, Xu Y *et al.*: **Inhibition of α-KG-dependent histone and DNA demethylases by fumarate and succinate that are accumulated in mutations of FH and SDH tumor suppressors**. *Genes Dev* 2012, **26**:1326-1338.

22. Tannahill GM, Curtis AM, Adamik J, Palsson-McDermott EM, McGettrick AF, Goel G, Frezza C, Bernard NJ, Kelly B, Foley NH *et al.*: **Succinate is an inflammatory signal that induces IL-1β through HIF-1α**. *Nature* 2013, **496**:238-242.

23. Williams NC, O'Neill LAJ: **A role for the Krebs cycle Intermediate citrate in metabolic reprogramming in innate immunity and inflammation**. *Front Immunol* 2018, **9**:141.

24. Friedmann DR, Marmorstein R: **Structure and mechanism of non-histone protein acetyltransferase enzymes**. *FEBS J* 2013, **280**:5570-5581.

25. Wellen KE, Hatzivassiliou G, Sachdeva UM, Bui TV, Cross JR, Thompson CB: **ATP-citrate lyase links cellular metabolism to histone acetylation**. *Science (80-)* 2009, **324**:1076-1080.

26. •• Bambouskova M, Gorvel L, Lampropoulou V, Sergushichev A, Loginicheva E, Johnson K, Korenfeld D, Mathyer ME, Kim H, Huang L-H *et al.*: **Electrophilic properties of itaconate and derivatives regulate the IκBζ–ATF3 inflammatory axis**. *Nature* 2018, **556**:501-504 http://dx.doi.org/10.1038/s41586-018-0052-z.
Itaconate induces LPS-induced hyporesponsiveness by cysteine alkylation of KEAP1, leading to enhanced activity of the antiinflammatory factor Nrf2 in a type I IFN dependent fashion.

27. Mills EL, Ryan DG, Prag HA, Dikovskaya D, Menon D, Zaslona Z, Jedrychowski MP, Costa ASH, Higgins M, Hams E *et al.*: **Itaconate is an anti-inflammatory metabolite that activates Nrf2 via alkylation of KEAP1**. *Nature* 2018, **556**:113-117 http://dx.doi.org/10.1038/nature25986.

28. Han J, Jackson D, Holm J, Turner K, Ashcraft P, Wang X, Cook B, Arning E, Genta RM, Venuprasad K *et al.*: **Elevated d-2-hydroxyglutarate during colitis drives progression to colorectal cancer**. *Proc Natl Acad Sci U S A* 2018, **115**:1057-1062.

29. Nair S, Huynh JP, Lampropoulou V, Loginicheva E, Esaulova E, Gounder AP, Boon ACM, Schwarzkopf EA, Bradstreet TR, Edelson BT *et al.*: **Irg1 expression in myeloid cells prevents immunopathology during M. tuberculosis infection**. *J Exp Med* 2018, **215**:1035-1045.

30. Saeed S, Quintin J, Kerstens HHD, Rao NA, Aghajanirefah A, Matarese F, Cheng S-C, Ratter J, Berentsen K, van der Ent MA *et al.*: **Epigenetic programming of monocyte-to-macrophage differentiation and trained innate immunity**. *Science (80-)* 2014, **345**:1251086.

31. de Bruin RG, Shiue L, Prins J, de Boer HC, Singh A, Fagg WS, van Gils JM, Duijs JMGJ, Katzman S, Kraaijeveld AO *et al.*: **Quaking promotes monocyte differentiation into pro-atherogenic macrophages by controlling pre-mRNA splicing and gene expression**. *Nat Commun* 2016, **7**:10846.

32. • Christ A, Günther P, Lauterbach MAR, Duewell P, Biswas D, Pelka K, Scholz CJ, Oosting M, Haendler K, Baßler K *et al.*: **Western diet triggers NLRP3-dependent innate immune reprogramming**. *Cell* 2018, **172**:162-175.e14.
High-fat diet induces long-lasting functional reprogramming immunity in myeloid cells that remain after shifting back to chow diet.

33. Posokhova EN, Khoshchenko OM, Chasovskikh MI, Pivovarova EN, Dushkin MI: **Lipid synthesis in macrophages during inflammation in vivo: effect of agonists of peroxisome proliferator activated receptors alpha and gamma and of retinoid X receptors**. *Biochemistry (Mosc)* 2008, **73**:296-304.

34. Sheedy FJ, Grebe A, Rayner KJ, Kalantari P, Ramkhelawon B, Carpenter SB, Becker CE, Ediriweera HN, Mullick AE, Golenbock DT *et al.*: **CD36 coordinates NLRP3 inflammasome activation by facilitating intracellular nucleation of soluble ligands into particulate ligands in sterile inflammation**. *Nat Immunol* 2013, **14**:812-820.

35. • Freigang S, Ampenberger F, Weiss A, Kanneganti T-D, Iwakura Y, Hersberger M, Kopf M: **Fatty acid-induced mitochondrial uncoupling elicits inflammasome-independent IL-1α and sterile vascular inflammation in atherosclerosis**. *Nat Immunol* 2013, **14**:1045-1053.
Fatty acids induce vascular inflammation by an IL-1α-dependent mechanism, leading to the development of atherosclerosis.

36. Cui G, Staron MM, Gray SM, Ho P-C, Amezquita RA, Wu J, Kaech SM: **IL-7-induced glycerol transport and TAG synthesis promotes memory CD8+ T cell longevity**. *Cell* 2015, **161**:750-761.

37. Christ A, Bekkering S, Latz E, Riksen NP: **Long-term activation of the innate immune system in atherosclerosis**. *Semin Immunol* 2016, **28**:384-393.

38. Lachmandas E, Boutens L, Ratter JM, Hijmans A, Hooiveld GJ, Joosten LAB, Rodenburg RJ, Fransen JAM, Houtkooper RH, van Crevel R *et al.*: **Microbial stimulation of different Toll-like receptor signalling pathways induces diverse metabolic programmes in human monocytes**. *Nat Microbiol* 2016, **2**:16246.

39. Le A, Lane AN, Hamaker M, Bose S, Gouw A, Barbi J, Tsukamoto T, Rojas CJ, Slusher BS, Zhang H *et al.*: **Glucose-independent glutamine metabolism via TCA cycling for proliferation and survival in B cells**. *Cell Metab* 2012, **15**:110-121.

40. O'Neill LAJ, Pearce EJ, O'Neill LAJ, Pearce EJ: **Immunometabolism governs dendritic cell and macrophage function**. *J Exp Med* 2015, **213**:15-23.

41. Rom O, Grajeda-Iglesias C, Najjar M, Abu-Saleh N, Volkova N, Dar DE, Hayek T, Aviram M: **Atherogenicity of amino acids in the lipid-laden macrophage model system in vitro and in atherosclerotic mice: a key role for triglyceride metabolism**. *J Nutr Biochem* 2017, **45**:24-38.

42. Loscalzo J: **Adverse effects of supplemental L-arginine in atherosclerosis: consequences of methylation stress in a complex catabolism?** *Arterioscler Thromb Vasc Biol* 2003, **23**:3-5.

43. • Ulas T, Pirr S, Fehlhaber B, Bickes MS, Loof TG, Vogl T, Mellinger L, Heinemann AS, Burgmann J, Schöning J *et al.*: **S100-alarmin-induced innate immune programming protects newborn infants from sepsis**. *Nat Immunol* 2017, **18**:622-632.
Neonates present an inmunological tolerance status that prevents excessive inflammation caused by pathogens in the first weeks of life, while allowing for sufficient immunological protection.

44. • Novakovic B, Habibi E, Wang S-Y, Arts RJW, Davar R, Megchelenbrink W, Kim B, Kuznetsova T, Kox M, Zwaag J *et al.*: **β-Glucan reverses the epigenetic state of LPS-induced immunological tolerance**. *Cell* 2016, **167**:1354-1368.e14.
Shows that the epigenetic and transcriptional landscape of human macrophage LPS-induced tolerance and characterizes the potential of β-glucan to reverse it.

45. Boutens L, Hooiveld GJ, Dhingra S, Cramer RA, Netea MG, Stienstra R: **Unique metabolic activation of adipose tissue**

macrophages in obesity promotes inflammatory responses. *Diabetologia* 2018, **61**:942-953.

46. Wendeln A-C, Degenhardt K, Kaurani L, Gertig M, Ulas T, Jain G, Wagner J, Häsler LM, Wild K, Skodras A *et al.*: **Innate immune memory in the brain shapes neurological disease hallmarks**. *Nature* 2018, **556**:332-338 http://dx.doi.org/10.1038/s41586-018-0023-4.

47. Bekkering S, Quintin J, Joosten LAB, van der Meer JWM, Netea MG, Riksen NP: **Oxidized low-density lipoprotein induces long-term proinflammatory cytokine production and foam cell formation via epigenetic reprogramming of monocytes**. *Arterioscler Thromb Vasc Biol* 2014, **34**:1731-1738.

48. Cheng S-C, Scicluna BP, Arts RJW, Gresnigt MS, Lachmandas E, Giamarellos-Bourboulis EJ, Kox M, Manjeri GR, Wagenaars JAL, Cremer OL *et al.*: **Broad defects in the energy metabolism of leukocytes underlie immunoparalysis in sepsis**. *Nat Immunol* 2016, **17**:406-413.

49. Kaufmann E, Sanz J, Dunn JL, Khan N, Mendonça LE, Pacis A, Tzelepis F, Pernet E, Dumaine A, Grenier J-C *et al.*: **BCG educates hematopoietic stem cells to generate protective innate immunity against tuberculosis**. *Cell* 2018, **172**:176-190.e19.

50. Arts RJW, Joosten LAB, Netea MG: **The potential role of trained immunity in autoimmune and autoinflammatory disorders**. *Front Immunol* 2018, **9**:298.