

REVIEWS

Metabolic regulation of inflammation

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Abstract | Immune cells constantly patrol the body via the bloodstream and migrate into multiple tissues where they face variable and sometimes demanding environmental conditions. Nutrient and oxygen availability can vary during homeostasis, and especially during the course of an immune response, creating a demand for immune cells that are highly metabolically dynamic. As an evolutionary response, immune cells have developed different metabolic programmes to supply them with cellular energy and biomolecules, enabling them to cope with changing and challenging metabolic conditions. In the past 5 years, it has become clear that cellular metabolism affects immune cell function and differentiation, and that disease-specific metabolic configurations might provide an explanation for the dysfunctional immune responses seen in rheumatic diseases. This Review outlines the metabolic challenges faced by immune cells in states of homeostasis and inflammation, as well as the variety of metabolic configurations utilized by immune cells during differentiation and activation. Changes in cellular metabolism that contribute towards the dysfunctional immune responses seen in rheumatic diseases are also briefly discussed.

Metabolism is the fundamental process by which energy homeostasis is maintained and cells are supplied with the building blocks required for the synthesis of macromolecules. During the past few years, it has become evident that the metabolic state of an immune cell can directly influence its ability to function and differentiate, ultimately affecting immunity, tolerance and, in the case of autoimmunity, the failure of an immune response^{1–4}.

Different immune cell subsets have different metabolic requirements and face a variety of metabolic challenges; however, they all share the need to maintain energy homeostasis to survive and function. Once homeostasis is disturbed, for example during infection or tissue damage, signals released from infected, dying or stressed cells and tissues induce the precise and timely process of inflammation⁵. Although the end point of the inflammatory response is the resolution of inflammation and the re-establishment of homeostasis, resolution can sometimes be insufficient (as in the case of immunodeficiency) or the inflammatory response exacerbated, leading to chronic inflammation or autoimmunity. In the past 5 years, it has become evident that as well as intrinsic risk factors such as a genetic predisposition to a disease, extrinsic environmental factors such as nutritional factors and a patient's microbiota or, more precisely, their microbial metabolites, contribute to the development of autoimmunity^{6–8}. Several research groups have found alterations in the metabolic configurations of cells during different autoimmune diseases

with regard to metabolic enzyme activities, metabolites and intermediates and key metabolic checkpoint molecules, which could contribute to aberrant immune cell behaviour^{4,9,10}.

In this Review, we summarize and discuss what is known to date about immunometabolism in homeostasis and its reconfiguration during inflammatory responses, as well as discussing the effects of immunometabolism upon the resolution of inflammation in different immune cell subsets. We focus particularly on the effect of metabolic enzymes, intermediates and metabolites on inflammatory responses, and on how metabolism affects immune responses in rheumatic diseases. This Review provides an overview of immunometabolism; the specific role of immunometabolism in systemic lupus erythematosus (SLE)¹¹, rheumatoid arthritis (RA)¹² and osteoarthritis¹³, as well as current knowledge on targeting metabolic pathways therapeutically¹⁴ are covered in other articles in this journal.

Cellular metabolism in homeostasis

All cells need access to sufficient and appropriate nutrients and oxygen to maintain homeostasis. Most resting immune cells (such as naive T cells, resting B cells and circulating monocytes^{1,2,15}), but also so-called long-lived cells (such as resting immature bone-marrow-derived dendritic cells (DCs), memory T cells and plasma B cells) are relatively metabolically inactive, with minimal biosynthetic demands beyond normal 'housekeeping' processes^{16–20} (FIG. 1). Resting immune cells use energy

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Key points

- Immune cells face a variety of variable and sometimes demanding environmental conditions, requiring them to display a dynamic range of metabolic adaptation processes
- Under inflammatory conditions, stimulated immune cells have an acute need to generate sufficient energy and biomolecules to support growth, proliferation and the production of proinflammatory molecules
- Metabolic reconfiguration varies between innate and adaptive immune responses, and influences both the effector phase of inflammation and the resolution of inflammation by modulating immune cell fate and function
- Metabolic enzymes, metabolites and regulators of metabolism have a direct influence on certain inflammatory responses
- Alterations of metabolic configurations of immune cells can contribute to dysfunctional immune responses, a typical feature of autoimmunity

Glycolysis

An oxygen-independent metabolic pathway that generates two molecules of pyruvate, ATP and NADH from every one molecule of glucose, supporting the tricarboxylic acid cycle and providing intermediates for the pentose phosphate pathway, glycosylation reactions and the synthesis of biomolecules (including serine, glycine, alanine and acetyl-CoA)

Tricarboxylic acid (TCA) cycle

(Also known as the Krebs cycle) A set of connected pathways in the mitochondrial matrix, which metabolize acetyl-CoA derived from glycolysis or fatty acid oxidation, producing NADH and FADH₂ for the electron transport chain and precursors for amino acid and fatty acid synthesis

Electron transport chain

A series of proteins in the inner mitochondrial membrane that transfer electrons from one to the other in a series of redox reactions, resulting in the synthesis of ATP and in the movement of protons out of the mitochondrial matrix

Oxidative phosphorylation

A metabolic pathway that produces ATP from the oxidation of acetyl-CoA and the transfer of electrons to the electron transport chain via NADH and FADH₂

Fatty acid oxidation

A metabolic process that produces ATP from the oxidation of acetyl-CoA derived from the mobilization of fatty acids

in the form of ATP, which is produced predominantly via aerobic metabolism. At low rates of glucose uptake, ATP is generated directly by glycolysis and indirectly by the oxidation of glucose-derived pyruvate to CO₂ via the mitochondrial tricarboxylic acid (TCA) cycle, which generates the reducing energy intermediates NADH and FADH₂. These reducing agents provide electrons for complexes I and II of the electron transport chain, thereby driving the process of oxidative phosphorylation. This process establishes a proton gradient across the inner mitochondrial membrane, fuelling ATP synthases and ultimately generating a maximum of 36 ATP molecules per one molecule of glucose¹. Interestingly, long-lived memory T cells, regulatory T (T_{reg}) cells and immature bone-marrow-derived DCs can also utilize fatty acid oxidation, yielding large amounts of acetyl-CoA, NADH and FADH₂ to fuel the TCA cycle and oxidative phosphorylation^{16–19} (FIG. 1). Inhibiting glycolysis can promote the formation of long-lived memory T cells²¹. Moreover, promoting oxidative phosphorylation in 'short-lived' immune cells, such as activated DCs, results in an increased cellular lifespan, whereas inhibiting fatty acid oxidation and oxidative phosphorylation reduces memory T cell formation²². These results highlight the flexibility of immune cells to adapt to different metabolic requirements.

Metabolic challenges for immune cells

Under normal conditions, most tissues are well-supplied with nutrients and oxygen by networks of blood and lymphatic vessels, so it is not surprising that most tissue-resident cells are metabolically well-adapted to these conditions. Local and systemic metabolic responses of tissue-resident cells vary with the supply of nutrients and are influenced by gut microbiota and organs such as the gut, liver and kidneys, which distribute metabolites around the body²³. Immune cells, however, traverse a broad range of tissues, travelling from their origin (for example, bone marrow) via the bloodstream to their target tissue or to a site of immune action, eventually arriving in the lymphatic drainage system. During this process, immune cells face a variety of variable and sometimes demanding environmental conditions, requiring them to display a dynamic range of metabolic adaptation processes.

By contrast, during activity, transformation, growth, development or inflammation, local microenvironmental conditions can become metabolically challenging. During inflammation, 'front-line' resident immune cells such as macrophages and DCs become activated by signals from infected or damaged tissues. As a result, blood flow to the surrounding area increases, as does the concentration of cells within the blood, promoting the active recruitment of neutrophils and other leukocytes to the site of inflammation²³. After activation, immune cells undergo substantial changes to support robust cell growth (for example, the transition from monocytes to macrophages), rapid cell proliferation (such as clonal T cell expansion) or new functions such as phagocytosis or enhanced release of inflammatory mediators. Competition for nutrients, oxygen and metabolites not only with other immune cells, but also with bacteria or parasites present in the host, can lead to substantial changes in conditions within the tissue microenvironment. These changes can switch accommodative metabolic conditions to hostile metabolic conditions. As a result, each immune cell subset has its own adaptive metabolic programmes, often set in motion by activation or differentiation, which enable them to cope with these hostile conditions and to fulfil specific functions during the inflammatory process.

Metabolic regulation of inflammation

Almost a century ago, Otto Warburg observed that immune cell activation, or conversion from a resting state into an effector mode, required an abrupt metabolic switch from oxidative phosphorylation to glycolysis (something that usually occurs in hypoxia), regardless of the availability of oxygen (termed aerobic glycolysis), providing energy in the form of ATP and biosynthetic precursors for cell proliferation and effector functions. This phenomenon was termed the Warburg effect²⁴ (FIG. 2).

Under inflammatory conditions, stimulated immune cells have an acute need to generate sufficient energy and biomolecules to support growth, proliferation and the production of proinflammatory molecules. Thus, immune cell metabolism shifts towards aerobic glycolysis. This shift funnels glucose-6-phosphate into the pentose phosphate pathway (PPP), provides 3-phosphoglycerate for the serine biosynthetic pathway (required for the synthesis of amino acids to create cytokines) and supplies pyruvate for the TCA cycle, which synthesizes citrate (an intermediate for fatty acids used in membrane assembly)¹ (FIG. 2). Moreover, metabolic reconfiguration of immune cells towards aerobic glycolysis enables these cells to better cope with metabolically restrictive inflammatory conditions, such as during the transition from normoxic to hypoxic conditions^{25,26}. Notably, efficient ATP production via oxidative phosphorylation is prevented under hypoxic conditions, such as those found in areas with active inflammatory processes^{27,28}.

Aerobic glycolysis occurs in macrophages stimulated with IFN γ or activated via Toll-like receptors (TLRs)^{29,30}, TLR-activated DCs¹⁶, phorbol 12-myristate 13-acetate-stimulated neutrophils³¹, engaged natural killer cells^{32,33}, B cells³⁴, activated effector T cells^{1,35} (such as

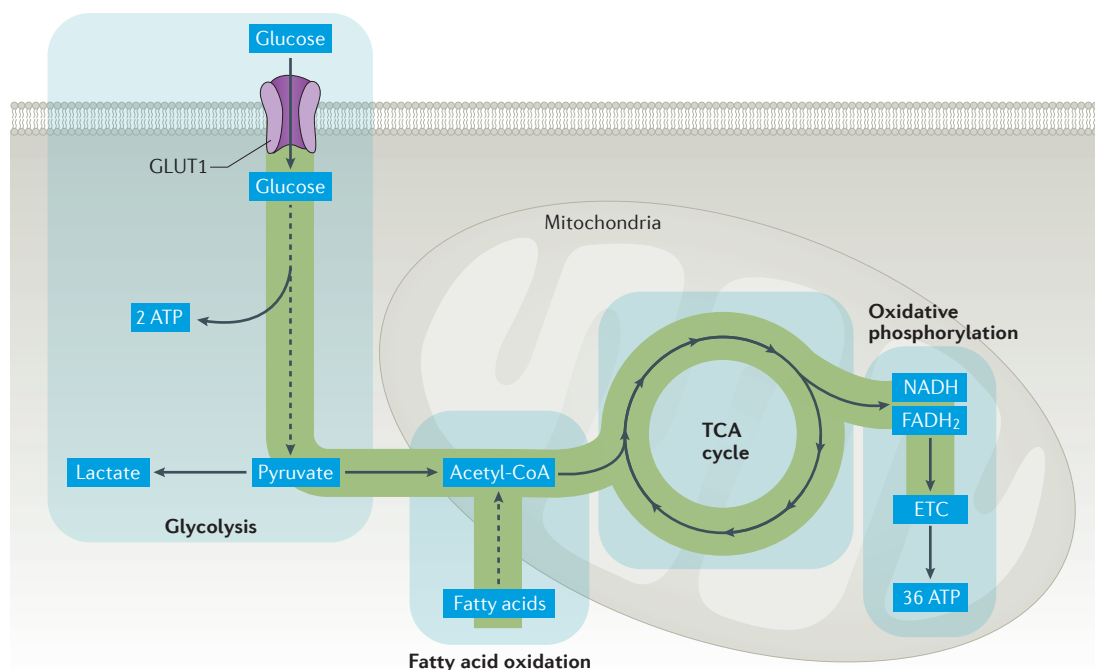


Figure 1 | Immune cell metabolism during homeostasis. Immune cells need energy in the form of ATP to survive, grow, reproduce and perform specific functions. Glucose is imported into the cytosol via glucose transporter type 1 (GLUT1), where it is converted to pyruvate over a series of enzymatic steps known as glycolysis. After transfer to the mitochondria, pyruvate is converted to the tricarboxylic acid (TCA) cycle substrate, acetyl-CoA. In resting, long-lived immune cells, such as regulatory T cells or memory T cells, acetyl-CoA is also produced by fatty acid oxidation. Pyruvate is ultimately metabolized to CO₂, generating NADH and FADH₂. These two reducing agents drive the electron transport chain (ETC) in a process called oxidative phosphorylation, by donating electrons and providing hydrogen molecules for the creation of water. This process builds a proton gradient that ultimately generates ATP through the phosphorylation of ADP.

CD4⁺ T helper (T_H) cells^{17,36}) and CD8⁺ effector T cells³⁷. Shifting immune cell metabolism towards aerobic glycolysis begins with an increased expression of the facilitators of glucose transport, such as glucose transporter type 1 (GLUT1), enabling the efficient uptake of glucose in an environment in which the supply of nutrients is restricted by inflammation³⁸. Although glucose is an essential fuel for immune cell activation, effector cells can instantly adapt to low glucose levels by increasing their uptake of glutamine and initiating glutaminolysis to keep the TCA cycle going³⁰ (FIG. 2). Moreover, effector T-cell differentiation and function are impaired when glutamine supply is abolished, shifting effector T cells from a type 1 T helper (T_H1) cell fate towards a T_{reg} cell phenotype^{39–41}. Alongside glutamine, T cells can also generate metabolic intermediates through the uptake of several other amino acids such as arginine and leucine, which are required for optimal effector T-cell function^{42,43}.

Immunometabolism during inflammation Lymphoid cells

T cells. During inflammation, professional antigen-presenting cells (such as macrophages and DCs) engage the adaptive immune system by activating metabolically quiescent naive T cells. Upon activation, naive T cells switch from oxidative phosphorylation to aerobic glycolysis, increasing their glucose uptake (for example by increasing the amount of GLUT1 at the cell surface)³⁸. Glucose is the main source of carbon for the biosynthetic

pathways producing nucleotides, amino acids and lipids that aid the massive clonal expansion of antigen-specific T cells^{38,44}, with T cells that lack GLUT1 failing to increase glycolysis, grow or proliferate following activation³⁸. This initial step of metabolic reconfiguration is mainly regulated by mechanistic target of rapamycin (mTOR), the catalytic subunit of two distinct complexes, mTOR complex 1 (mTORC1) and mTORC2. mTOR maintains levels of the transcription factor Myc proto-oncogene protein, leading to Myc-mediated expression of glycolytic genes^{42,45,46}. Subsequently, T cells differentiate into functionally distinct subsets, possessing unique metabolic configurations that are essential for their function; mTORC1 is required for differentiation of T_H1 cells and type 17 T helper (T_H17) cells, whereas mTORC2 is required for type 2 T helper (T_H2) cell differentiation⁴⁷. Furthermore, in T_{reg} cells and memory T cells, mTOR activity has to be low for the cells to switch back to an oxidative metabolic state⁴⁸. Effector T cell subsets (CD4⁺ T_H1, T_H2 and T_H17 cells and CD8⁺ cytotoxic T cells) induce the Warburg effect upon activation and rely mainly on aerobic glycolysis and the PPP with some glutaminolysis to support cellular metabolism, although still utilizing oxidative phosphorylation to fuel proliferation^{17,44,45,49}.

By contrast, T_{reg} cells are more likely than effector T cells to depend on oxidation of low levels of glucose and to fuel oxidative phosphorylation via fatty acid oxidation using exogenously derived fatty acids^{17,36,50}. Indeed, blocking glycolysis inhibits proinflammatory

Glutaminolysis

The metabolic process by which glutamine is metabolized to glutamate and then to α-ketoglutarate to replenish the tricarboxylic acid cycle

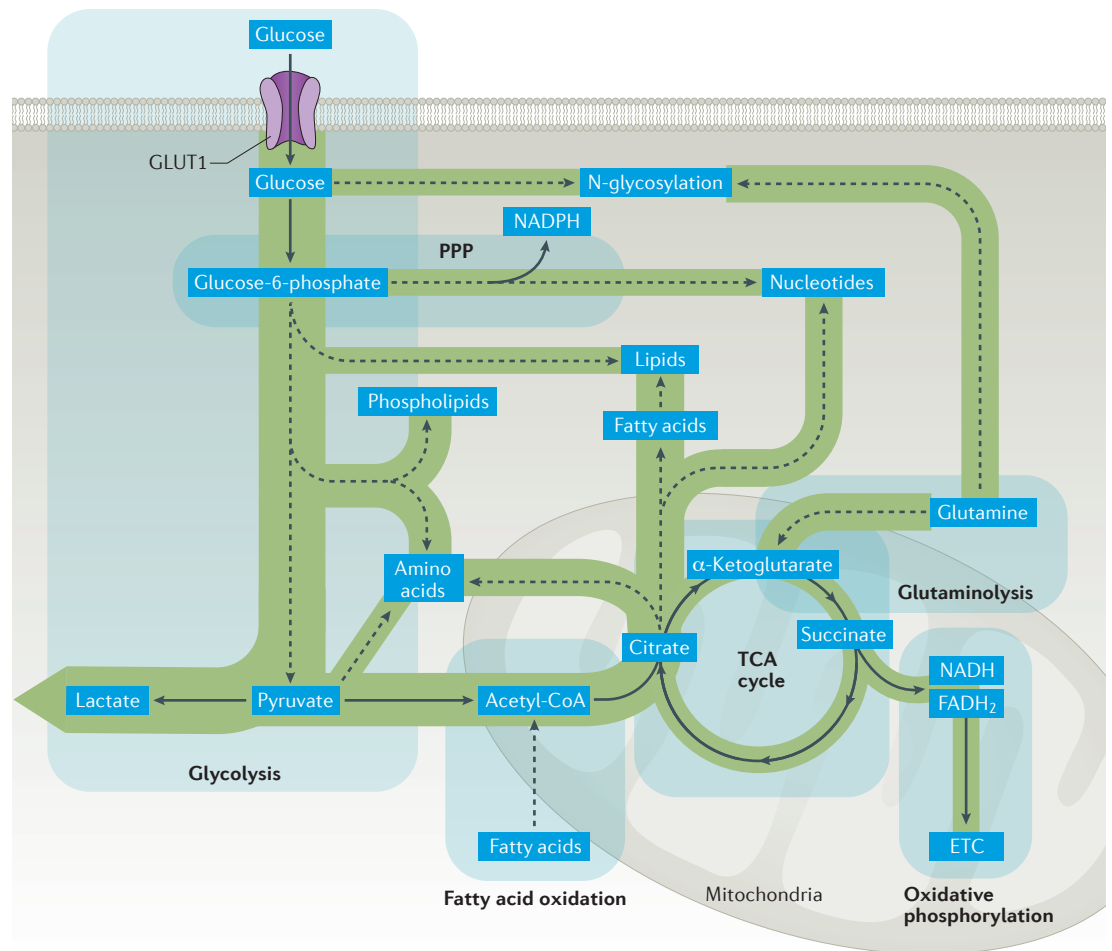


Figure 2 | Metabolic reprogramming of immune cells upon activation. During inflammation, immune cells are activated and convert from a resting state into an effector mode, reprogramming their metabolism to aerobic glycolysis. An increase in glucose transportation into the cell drives elevated glycolytic activity, causing excessive availability of glycolytic intermediates, which serve as precursor molecules for biosynthetic processes. For example, glucose 6-phosphate (generated by the first step in glycolysis) can feed into the pentose phosphate pathway (PPP), supporting nucleotide synthesis and the generation of NADPH. Another example is cytoplasmic acetyl-CoA (generated from glucose via pyruvate), which supports the production of cholesterol and fatty acids for lipid synthesis. Of note, many pyruvate molecules are converted to lactate, which is secreted from cells and can substantially affect the pH of the surrounding milieu. Although aerobic glycolysis is an inefficient way to generate ATP (creating only two molecules of ATP per molecule of glucose), high rates of flux through this pathway enables energy homeostasis to be sustained, even when mitochondrial ATP synthesis is impaired. Alternative fuels such as glutamine feed into the tricarboxylic acid (TCA) cycle and supply biomolecules for biosynthetic processes. ETC, electron transport chain; GLUT1, glucose transporter type 1.

T_H17 cell development but promotes the generation of anti-inflammatory T_{reg} cells³⁶. Moreover, T_H17 cells can utilize *de novo* fatty acid synthesis, a process also observed in classically activated macrophages^{51–54}. Inhibition of *de novo* fatty acid synthesis in T_H17 cells promotes the development of T_{reg} cells⁵¹. The proliferative and suppressive capacities of T_{reg} cells are also kept in balance by T_{reg} cell metabolism. TLR ligation-mediated increases in glycolysis, anabolic metabolism and mTORC1 activity reduced the suppressive function of T_{reg} cells, but increased their proliferation⁵⁵. Conversely, these effects were opposed by FOXP3 expression, which led to increased use of oxidative and catabolic pathways⁵⁵.

An interesting proteome-based study focusing on conventional $CD4^+$ T cells and FOXP3⁺ T_{reg} cells shed new light on T-cell metabolism in *ex vivo* and *in vitro*

cultured T cells⁵⁶. *Ex vivo* T_{reg} cells were highly glycolytic, whereas T_{reg} cells engaged both glycolysis and fatty acid oxidation to proliferate *in vitro*⁵⁶, as observed previously in other studies^{17,55,57}. By contrast, *ex vivo* conventional T cells predominantly utilized fatty acid oxidation, whereas conventional T cell proliferation mainly relied on glycolysis *in vitro*⁵⁶, again, in agreement with previous studies^{17,57}. The differences in metabolism between T cell subtypes might reflect bias caused by *in vitro* manipulation, which should be addressed by further research.

The final step in generating an adaptive memory following antigen challenge involves memory T cells undergoing further metabolic re-configuration towards oxidative metabolism, thereby downregulating glycolysis and inducing fatty acid oxidation to efficiently produce energy¹⁸. Furthermore, memory T cells also induce

mitochondrial biogenesis¹⁹. Thus, the ability to recall an immune response following a second activation — the primary principle of immune memory — is granted by the ability of memory T cells to rapidly induce aerobic glycolysis^{18,19,37}.

B cells. In contrast to the wealth of information available regarding the regulation of cellular metabolism in T cell subsets, information about B cell subsets is scarce. Like T cells, B cells also undergo metabolic reprogramming upon activation, transitioning from naive quiescent cells to activated anabolic cells. This metabolic shift results in rapid growth, proliferation and differentiation, thereby increasing not only glucose uptake and aerobic glycolysis, but also glutaminolysis and oxidative phosphorylation in equal measure^{34,58,59}.

The classical B cell response begins when antigen-experienced CD4⁺ T cells engage B cells via CD40, initiating further differentiation⁶⁰. Once activated, B cells undergo antigen-driven clonal expansion and secondary rearrangement of their immunoglobulin repertoire, a process that takes place in the germinal centre, a poorly vascularized site of intense cell activity and proliferation within lymphoid structures⁶¹. Thus, germinal centre B cells face increased metabolic demands while in a restrictive microenvironment, which inevitably leads to germinal centre hypoxia⁶². Although germinal centre hypoxia accelerates class switch recombination and plasma cell formation⁶³, sustained hypoxia or expression of hypoxia-inducible factors limits mTORC1, which is essential for B cell development and B cell clonal expansion⁶⁴. These findings suggest that a regional variation in hypoxia is essential for B cell survival and function⁶². However, germinal centre B cells can adapt their metabolic programme to respond to a hypoxic environment by increasing mitochondrial biogenesis, glucose uptake and hypoxia-inducible factor 1 α (HIF-1 α)-dependent glycolysis¹⁵. Limiting glycolysis by providing cells with the non-metabolizable glucose analogue 2-deoxy-D-glucose (2-DG)¹⁵ or by deleting *GLUT1* (REF. 58) results in decreased numbers of mature germinal centre B cells and reduced T cell-dependent IgM and IgG antibody production. Durable antibody-producing B cells (so-called long-lived plasma cells) also enhance their survival capacity by increasing their rate of glucose import²⁰. Only a small amount of this glucose is used to sustain glycolysis and mitochondrial pyruvate import (suggesting the use of oxidative phosphorylation), whereas most is required for antibody glycosylation²⁰.

Aside from classical B cell activation involving B cell receptor and CD40 engagement, a variety of stimuli such as TLR ligands and cytokines can induce the metabolic reprogramming of B cells towards aerobic glycolysis via different signalling pathways that culminate in mTORC1, Myc or signal transducer and activator of transcription 6 (STAT6) signalling^{34,58,65–68}. In a 2017 study, glycogen synthase kinase 3 was identified as a ‘metabolic checkpoint regulator’ in B cells¹⁵. Glycogen synthase kinase 3 acts via several mechanisms in anti-CD40-stimulated and IL-4-stimulated B cells, including restricting cell mass accumulation, promoting maintenance of a quiescent

state in naive recirculating B cells, repressing Myc-dependent cell growth, restricting metabolic activity, repressing proliferation and reducing reactive oxygen species (ROS)-induced apoptosis in response to nutrient stress and hypoxia¹⁵.

Myeloid cells

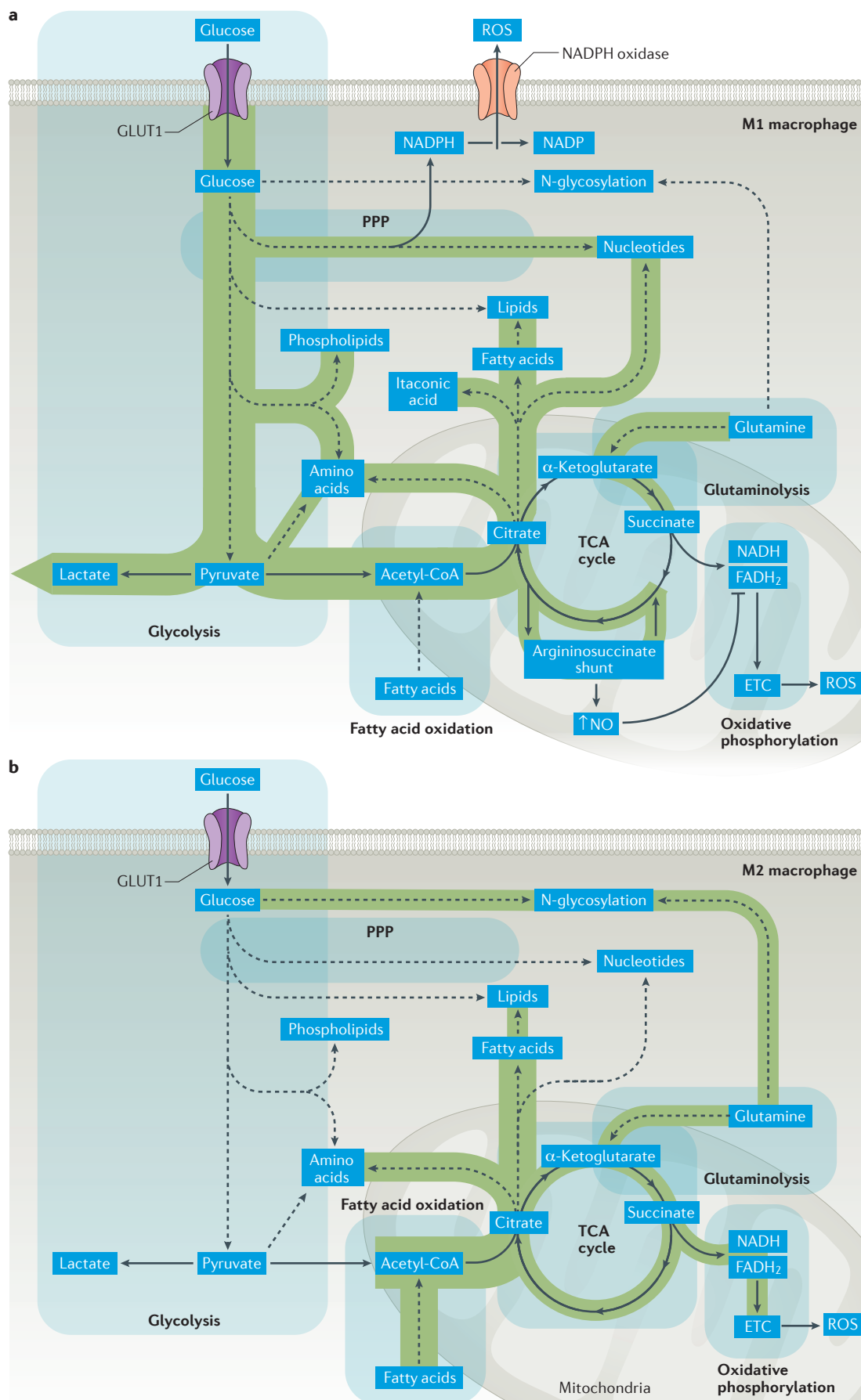
Initiation of inflammation is induced by macrophages, mast cells and DCs, which act as sentinels. Upon activation, these cells initiate well-controlled programmes to direct inflammatory processes that result in increased permeability of local blood vessels, release of chemokines and recruitment of neutrophils⁶⁹. Macrophages, DCs and neutrophils are mature, terminally differentiated myeloid cells. In contrast to lymphocytes, these cells do not tend to proliferate, but are highly phagocytic and secrete a variety of immune mediators.

M1 macrophages. Macrophages can be polarized into distinct subsets, including proinflammatory classically activated (also known as M1) macrophages and alternatively activated (also known as M2) macrophages. Monocytes differentiate into M1 macrophages upon activation via pattern-recognition receptors or proinflammatory cytokines⁷⁰. Once activated, M1 macrophages are highly microbicidal, release ROS (for example hydroxide) and reactive nitrogen species (such as nitric oxide (NO)), and secrete large amounts of proinflammatory cytokines such as TNF, IL-1 β and IL-6.

Activated M1 macrophages (and DCs) rely primarily on glycolysis, expressing high levels of the rate-limiting glycolytic activator 6-phosphofructo 2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3), but have reduced flux through the electron transport chain and almost no oxidative phosphorylation⁵² (FIG. 3a). Hypoxic conditions caused by the inflammatory process and inducible nitric oxide synthase (iNOS)-dependent NO production directly inhibit electron flux through the electron transport chain, abolishing oxidative phosphorylation⁵². As a result, the TCA cycle halts and intermediates such as citrate and succinate accumulate⁵². Citrate is exported from the mitochondria into the cytosol, where it is converted to acetyl-CoA, an important intermediate for several biosynthetic pathways such as the synthesis of fatty acids and the production of antimicrobial and proinflammatory molecules (including itaconic acid, NO, ROS and prostaglandins)^{52–54} (FIG. 3a).

Succinate is oxidized by succinate dehydrogenase, thereby elevating mitochondrial ROS levels⁷¹. The presence of succinate and its oxidation by-product, ROS, leads to the stabilization and increased activity of HIF-1 α ^{52,53,71,72}, the oxygen-sensitive α -subunit of the transcription factor HIF-1, which is stable under hypoxic conditions and following lipopolysaccharide (LPS) stimulation, and which dimerizes with the constitutively expressed HIF-1 β -subunit⁷³. Once stabilized, HIF-1 transactivates target genes that support the Warburg effect, and, in M1 macrophages, that sustain IL-1 β production^{71,72}.

One key feature of M1 macrophages is their ability to produce high levels of ROS and reactive nitrogen species, either via an inhibited or incomplete mitochondrial



◀ **Figure 3 | Metabolic configurations of M1 and M2 macrophages. a** | Classically activated M1 macrophages primarily use aerobic glycolysis to generate energy and molecules for biosynthetic processes, thereby increasing flux through the pentose phosphate pathway (PPP), leading to an increase in NADPH (an energy substrate for redox homeostasis and for the production of reactive oxygen species (ROS) by NADPH oxidases). ROS are also produced by mitochondria. Although the tricarboxylic acid (TCA) cycle is mainly fuelled by pyruvate from glycolysis and acetyl-CoA or succinyl-CoA from fatty acid oxidation, TCA intermediates removed from the mitochondria for use in biosynthetic pathways have to be replenished by glutamine in M1 macrophages due to the interruption of the TCA cycle at two positions. The first break in the TCA cycle leads to the accumulation of citrate, a substrate for the synthesis of itaconic acid and fatty acids (including the generation of prostaglandins). Anabolic synthesis of fatty acids generates NADPH and, subsequently, ROS via NADPH oxidases. The second break leads to the accumulation of succinate, which activates hypoxia-inducible factor 1 α -induced inflammatory gene expression and increases glycolysis. The argininosuccinate shunt replenishes levels of fumarate and malate, required for citrate production, thereby generating nitric oxide (NO), which inhibits succinate dehydrogenase activity. **b** | Alternatively activated M2 macrophages are characterized by increased fatty acid oxidation, low glycolysis activity and reduced flux through the PPP. Acetyl-CoA generated by fatty acid oxidation enters the intact TCA cycle for oxidative metabolism. Glutamine is mainly used for the synthesis of amino-sugars and nucleotide sugars, but also fuels the TCA cycle. ETC, electron transport chain; GLUT1, glucose transporter type 1.

electron transport chain⁷⁴, or via NADPH oxidase and iNOS during the elimination of phagocytosed pathogens⁷⁵. NADPH oxidase and iNOS utilize NADPH as a substrate, which is produced by the PPP or by the conversion of malate to pyruvate by malate dehydrogenase^{54,75,76}. Moreover, NADPH is also used by M1 macrophages for phagocytosis and for the production of the antioxidant glutathione, which protects the cell against ROS-mediated damage⁷⁶. Phagocytosis requires a large turnover of lipids for the generation of membranes, which is facilitated by the metabolic provision of citrate and NADPH, essential substrates for fatty acid synthesis⁷⁷. Thus, an increase in glycolysis, reduction in oxidative phosphorylation, inhibition of fatty acid oxidation and induction of fatty acid synthesis act together to facilitate the differentiation of proinflammatory M1 macrophages (FIG. 3a).

M2 macrophages. Alternatively activated (M2) macrophages, have an anti-inflammatory phenotype and low antigen-presentation capacity, and are associated with tissue regeneration and angiogenesis. M2 macrophages have an important role in the resolution of inflammation and differ substantially in their metabolic configuration from M1 macrophages⁷⁰.

In contrast to the relatively short-lived M1 macrophages, sustained oxidative phosphorylation, glucose deprivation and the presence of free fatty acids promote a shift from proinflammatory to anti-inflammatory macrophage functions, and towards differentiation into longer-lived M2 macrophages^{30,52,76,78–80} (FIG. 3b). M2 macrophages express low levels of PFKFB3 and high levels of PFKFB1, which has less kinase activity than PFKFB3, thereby reducing glycolytic flux²⁹. Furthermore, M2 macrophages have high levels of arginase-1 activity, which is needed to metabolize arginine to proline, a component of collagen, thus stimulating extracellular matrix synthesis, required for tissue repair and resolution of inflammation^{70,81}. Polarization of cells to an M2-like macrophage phenotype by IL-4 stimulates

mitochondrial biogenesis and fatty acid oxidation, providing fuel for the intact TCA cycle as well as for oxidative phosphorylation and preparing the cells for tissue re-oxygenation following the induction of angiogenesis⁸².

M2 macrophages utilize glutamine to generate TCA cycle intermediates (FIG. 3b), but also for protein glycosylation. Furthermore, M2 macrophages downregulate flux through the PPP by inducing carbohydrate kinase-like protein, which inhibits this pathway, resulting in reduced NADPH-mediated glutathione levels⁷⁶. Notably, M2 macrophages, FOXP3⁺ T_{reg} cells and long-lived memory T cells have metabolic features in common. FOXP3⁺ T_{reg} cells and long-lived memory T cells also both rely on oxidative metabolism with low rates of glycolysis and fuel oxidative phosphorylation by oxidation of exogenously derived fatty acids^{17–19,36,37,50}.

Dendritic cells. In the initial phase of inflammation, DCs recognize invading pathogens or endogenous danger signals by the engagement of pattern-recognition receptors such as TLRs, and activate innate and adaptive immune responses by facilitating antigen-specific T cell activation⁸³. Activation of DCs via TLR agonists increases glycolysis within minutes, but inhibits flux through the electron transport chain by increasing levels of NO⁸⁴. Thus, upregulation of glycolysis in activated DCs provides these cells with molecular building blocks, *de novo* lipid synthesis for the expansion of the Golgi apparatus and the endoplasmic reticulum, as well as cellular energy required for DC effector functions⁵².

Data from 2005 indicated that during maturation, DCs are also capable of storing large amounts of fat and glycogen⁸⁵. This finding was supported by the results of a 2016 study, which showed that carbon molecules from glycogen-derived glucose feed into the TCA cycle to support early DC maturation, a critical step for early effector responses in these cells⁸⁶. Thus, glycogen metabolism supports the activation of DCs, particularly during the period before these cells can increase their surface expression of GLUT1 (REF. 87). However, inhibition of glycolysis impairs both the survival and effector function of activated DCs, highlighting the importance of glucose as a substrate in supporting the response of DCs to TLR agonists⁵².

Other myeloid cells. In contrast to macrophages and DCs, data on the metabolic configuration of mast cells is scarce. A study on mast cell metabolism from 1967 implicated a role for both glycolysis and oxidative phosphorylation in the degranulation process, since histamine release is inhibited by 2-DG⁸⁸. In the past few years, however, research has shown that mast cell mitochondria translocate to the site of exocytosis during degranulation, suggesting an involvement of mitochondrial oxidative phosphorylation in degranulation^{89,90}, and implicating mitochondrial STAT3 in this process⁹¹. In a 2017 study, mast cell effector function, namely degranulation upon IgE and antigen stimulation through the high-affinity IgE receptor, resulted in a rapid increase in aerobic glycolysis, but not in an increase in mitochondrial respiration, although inhibition of oxidative phosphorylation drastically decreases mast cell degranulation and cytokine production⁹².

The metabolic configuration of granulocytes has been best described for neutrophils and follows the same metabolic principles as M1 macrophages and tissue-resident mature DCs⁶⁹. Primarily, neutrophils rely on glycolysis and have very low levels of oxidative phosphorylation^{31,93–95}. Neutrophil effector functions such as the formation of neutrophil extracellular traps depend on glycolysis and the PPP^{31,96,97}.

Metabolic enzymes in inflammation

Knowing that cellular metabolism influences both the effector phase of inflammation and resolution of inflammation by modulating immune cell fate and function raises the question of whether metabolic enzymes and regulators of metabolism might have a direct influence on certain inflammatory responses (FIG. 4).

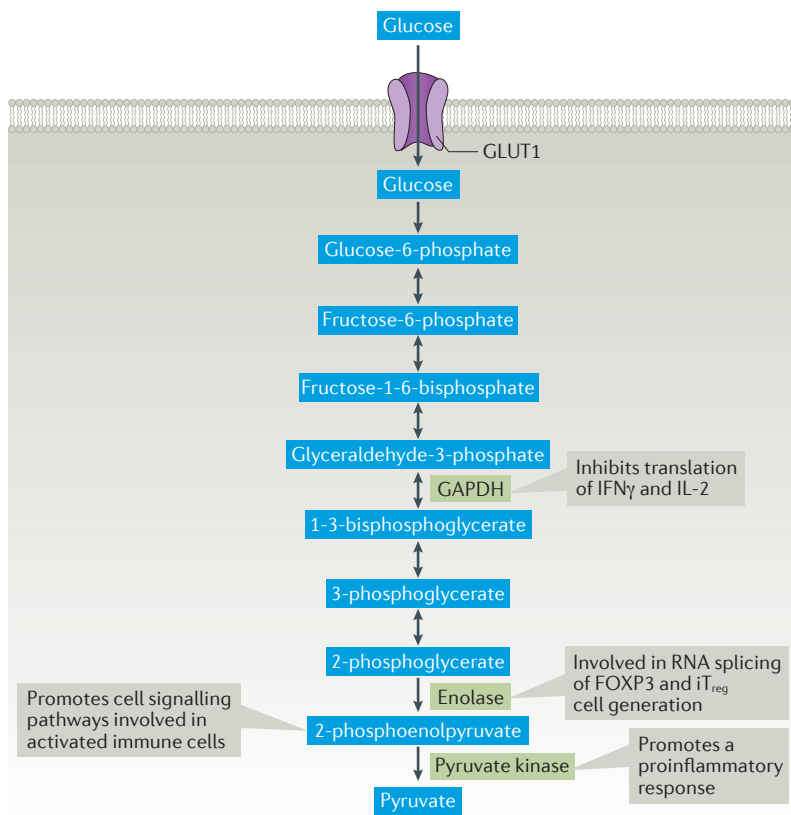


Figure 4 | Immune regulatory roles of glycolytic intermediates. Glycolytic intermediates not only influence immune function and inflammation by their role in metabolism, but also by specifically regulating various processes. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) also functions as an RNA-binding molecule that can inhibit the translation of *IFNG* and *IL2* mRNA. High glycolytic flux forces excess GAPDH into the glycolytic process, thereby relieving RNA from inhibition. Reduction of glycolytic flux releases enolase from the glycolytic pathway, upon which it enters the nucleus to aid the formation of the alternative splice variant of the transcription factor FOXP3, FOXP3-E2, generating potentially immunosuppressive induced regulatory T (iT_{reg}) cells. The glycolytic intermediate 2-phosphoenolpyruvate promotes Ca²⁺ signalling, which supports T cell activation during high rates of glycolysis. When the M2 isoenzyme of pyruvate kinase (PKM2) is activated as a tetramer, it supports flux through glycolysis into the tricarboxylic acid cycle. As a dimer, PKM2 either acts as co-activator of hypoxia-inducible factor 1 α , or it supports signal transduction by phosphorylating signal transducer and activator of transcription 3, which both support proinflammatory immune responses.

In 1995, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was discovered to directly bind to AU-rich regions of RNA, thereby inhibiting RNA translation⁹⁸. In activated CD4⁺ T cells that are provided with co-stimulation and growth factors but blocked from engaging glycolytic pathways, GAPDH also binds to the 3' untranslated regions (3'UTRs) of *IFNG* and *IL2* mRNA; as a result, the ability of these cells to produce IFN γ is markedly compromised⁹⁹. During aerobic glycolysis, GAPDH was utilized as a glycolytic enzyme, releasing *IFNG* and *IL2* mRNA for translation. Thus, modulation of GAPDH expression levels and regulation of glycolysis controlled effector cytokine production⁹⁹. In a 2016 study, GAPDH was also found to bind to the AU-rich 3'UTR of *HIF1A* mRNA in glycolytically inactive naive and memory T cells, although in effector T cells with active glycolysis and decreased GAPDH availability, HIF-1 α expression was elevated¹⁰⁰. These data suggest that glycolytic metabolism is able to regulate the translation of *HIF1A* mRNA to enable T cells to adapt to hypoxia.

By contrast, during repression of glycolysis, a translational variant of the glycolytic enzyme enolase inhibits the formation of the alternative spliced variant FOXP3-E2 in potentially anti-inflammatory induced T_{reg} (iT_{reg}) cells¹⁰¹. Pyruvate dehydrogenase (PDH) (which catalyses the conversion of cytosolic pyruvate into mitochondrial acetyl-CoA) and its inhibitor, PDH kinase 1 (PDHK1) (which promotes the glycolytic pathway), both also influence the balance between T_H17 cells and T_{reg} cells. Inhibition or knockdown of PDHK1 in mice increased the number of T_{reg} cells and diminished the number of T_H17 cells, resulting in protection against autoimmunity, owing in part to an accumulation of ROS⁵⁷.

Another glycolytic enzyme with a dual role is the M2 isoenzyme of pyruvate kinase (PKM2)¹⁰². Pyruvate kinase catalyses the conversion of 2-phosphoenolpyruvate and ADP into pyruvate and ATP during the final, rate-limiting step of glycolysis. PKM2 exists both as a dimeric enzyme and as a tetrameric enzyme. The tetrameric form is highly active in converting 2-phosphoenolpyruvate into pyruvate, and functions in a similar way to pyruvate kinase to provide pyruvate for the TCA cycle. By contrast, dimeric PKM2 is enzymatically almost inactive¹⁰². This less-active, dimeric form of PKM2 makes up the majority of cellular PKM2 and is strongly upregulated in LPS-activated macrophages, thereby supporting aerobic glycolysis and biosynthetic processes^{23,103,104}.

PKM2 also participates in non-glycolytic processes upon its translocation to the nucleus following mitogenic, oncogenic and LPS stimulation. In these non-glycolytic processes, PKM2 acts as a co-activator of HIF-1 α , helping to promote the Warburg effect¹⁰⁵. Briefly, upon LPS activation, PKM2 translocates to the nucleus where it forms a transcriptional complex with HIF-1 α , binding directly to the *IL1B* promoter and initiating *IL1B* transcription¹⁰⁶. In sepsis, PKM2 promotes the release of high mobility group box 1 (HMGB1), which acts as a potent proinflammatory cytokine, through its interaction with and activation of HIF-1 α ^{107,108}. PKM2 that has translocated to the nucleus upon LPS stimulation either binds to the *STAT3* promoter, or phosphorylates STAT3,

enhancing the transcription and subsequent activation of STAT3 and boosting the expression of IL-1 β and IL-6 (REFS 104, 109). In mast cells, PKM2 interacts with ITAM motifs on the γ -chain of the high-affinity IgE receptor, resulting in a decrease in PKM2 activity, which is essential for mast cell degranulation¹¹⁰.

PKM2 is not only a key enzyme in glycolysis, but is also important for several inflammatory processes. It is therefore not surprising that many, if not all, inflammatory disorders are associated with increased expression of PKM2 (REFS 99, 111–114).

Metabolites that control inflammation

Not only do metabolic programmes differ between immune cell populations and according to immune cell functions, they also result in different types of metabolites being produced in different amounts, which, in turn, can directly affect immune cell responses. For example, the glycolytic intermediate 2-phosphoenolpyruvate, levels of which increase during glycolysis, inhibits the re-uptake of Ca²⁺ into the endoplasmic reticulum, thereby sustaining levels of Ca²⁺ (an important second messenger) in the cytoplasm and promoting cell signalling via the transcription factor NFAT1, which is involved in T cell activation¹¹⁵ (FIG. 4).

In M1 macrophages, interruption of the TCA cycle results in a massive accumulation of TCA intermediates such as α -ketoglutarate, fumarate and succinate⁵². The metabolites α -ketoglutarate, fumarate and succinate regulate the activity of hypoxia-inducible factors by inhibiting the activity of hydroxylases^{72,116–118}. As a result of this inhibition, HIF-1 upregulates a variety of proinflammatory molecules (such as IL-1 β) and anti-inflammatory molecules (such as the microRNA miR-210 or programmed cell death 1 ligand 1) in myeloid cells^{72,119–122}.

Moreover, TCA intermediates participate in the epigenetic control of gene expression as important substrates or inhibitors for DNA-modifying and histone-modifying enzymes (FIG. 5). For example, the enzymes of the TET family (which facilitate DNA demethylation) and the JmJc-domain-containing histone demethylases both require α -ketoglutarate as a substrate and are repressed by succinate¹²³. Epigenetic modulation by methylcytosine dioxygenase TET2 affects not only T_H1 cell and T_H17 cell cytokine responses¹²⁴, but also the stability of FOXP3 expression in iT_{reg} cells¹²⁵. Lysine-specific demethylase 6B has a critical role in the regulation of CD4⁺ T cell differentiation¹²⁶, and is associated with gene expression changes in LPS-stimulated macrophages¹²⁷.

Another epigenetic modification that affects DNA structure and gene expression is the acetylation and deacetylation of histones. Acetylation of histones by histone acetyltransferases requires acetyl-CoA, which is supplied via various mechanisms such as metabolism of the TCA intermediate citrate or by enhanced lactate dehydrogenase expression or activity. The latter mechanism creates high concentrations of acetyl-CoA, resulting in increased histone acetylation and subsequent transcription of *IFNG*, thus promoting effector T cell differentiation¹²⁸. Deacetylation of histones by sirtuins is directly connected to cellular metabolism, as it is regulated by the

balance of oxidized NAD⁺ and reduced NADH¹²⁹. Sirtuins use oxidized NAD⁺ as a substrate for the deacetylation process and are inhibited by its reduced form. Sirtuins do not solely modulate histone deacetylation; they are also capable of modulating immune responses directly by deacetylating FOXP3 (thereby inhibiting T_{reg} cell responses)^{130,131}, by deacetylating the transcription factor ROR γ t (thereby promoting T_H17 cell responses)¹³², or by reducing inflammatory responses through inhibition of the transcription factor NF- κ B¹³³. Moreover, sirtuins are associated with the regulation of so-called clock genes, thus providing a direct link between immunometabolism and circadian rhythms^{134,135}.

In addition, the metabolic shift in glucose metabolism from oxidative phosphorylation to aerobic glycolysis (which leads to an increase in TCA intermediates and skews the NAD⁺:NADH ratio) provides nonspecific innate immune protection from recurrent infections, aiding the development of memory characteristics by the innate immune system (also known as trained immunity)^{129,136}.

Key regulators of immunometabolism

The majority of immune cells participating in an inflammatory reaction (such as activated M1 macrophages and T_H17 cells) shift their metabolism towards enhanced glucose uptake, aerobic glycolysis and increased activity of the PPP and fatty acid synthesis. Key regulators of these changes are mTOR and the transcription factors Myc and HIF-1 α , which oppose AMP-activated protein kinase (AMPK) in these processes⁸². mTOR activation supports cell growth, proliferation and effector function by sensing amino acids and growth factors and by upregulating mRNA translation and lipid synthesis^{48,137}. Moreover, mTOR helps to maintain cellular and nuclear levels of Myc, which induces a glycolytic gene expression profile^{42,45,46}. Thus, mTOR activation supports both the differentiation of T cells and monocytes into proinflammatory T cell subsets and M1 macrophages, respectively, and the proinflammatory effector functions of these cells^{48,137}. Interestingly, the type of mTOR complex used during glycolytic reprogramming of T cells upon activation differs depending on the differentiation state of the T cell³⁷. The induction of aerobic glycolysis in proliferating effector T cells after primary antigen challenge requires mTORC1 signalling, whereas immediate-early glycolytic reprogramming after a recall response in memory T cells needs mTORC2 signalling³⁷. By contrast, immune cells with low rates of glycolysis and high oxidative metabolism tend to be long-lived with anti-inflammatory and regulatory properties, such as M2 macrophages, T_{reg} cells and quiescent memory T cells. Thus, reduction of glycolysis by inhibition or deletion of mTOR complexes in T cell receptor (TCR)-activated T_H cells supports the development of T_{reg} cells while preventing the generation of effector T cell subpopulations^{47,138}.

In opposition to mTOR, AMPK promotes anti-inflammatory and regulatory properties in immune cells and limits effector cell responses, thereby inhibiting mTOR activity⁸². AMPK is activated by low levels of cellular energy (for example, a high AMP:ATP ratio) and during nutrient deprivation, resulting in a catabolic

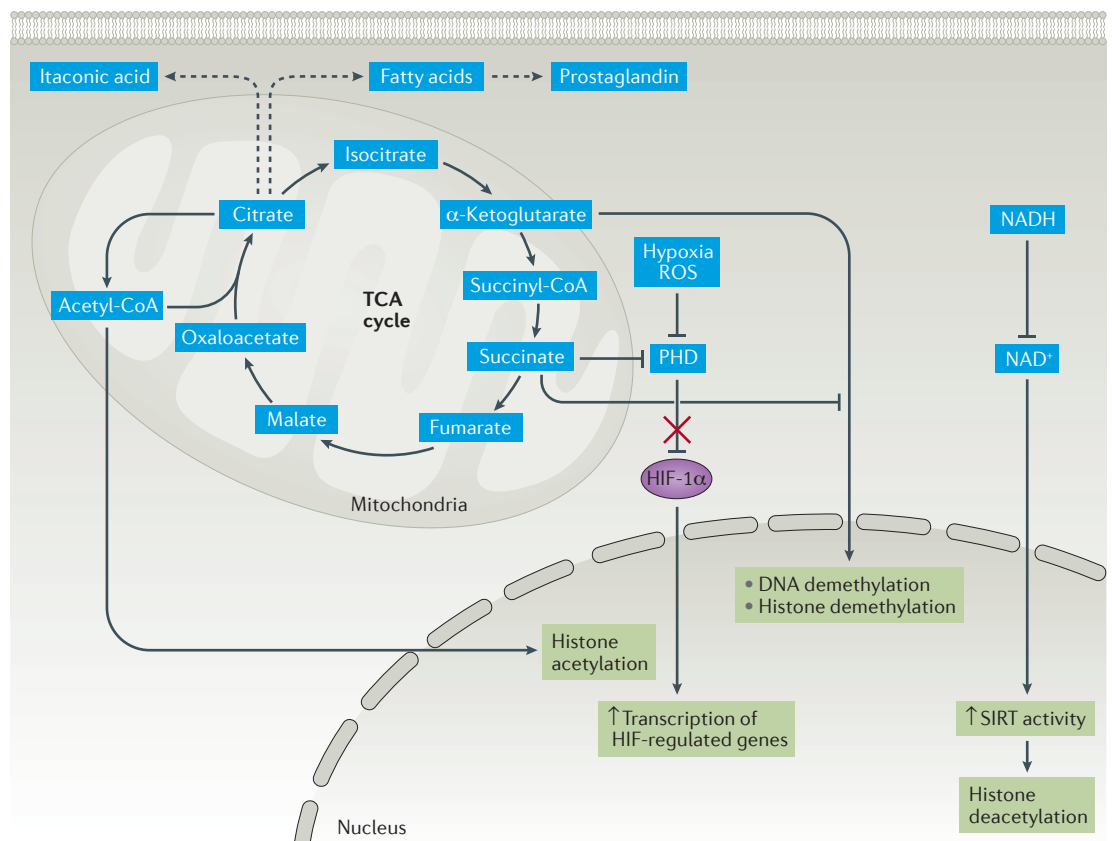


Figure 5 | Regulation of inflammation by metabolites. Citrate serves as a substrate for the antimicrobial molecule itaconic acid and is necessary for the production of prostaglandin. Accumulation of the tricarboxylic acid (TCA) cycle intermediate succinate leads to inhibition of prolyl hydroxylases (PHDs), negative regulators of hypoxia-inducible factor 1 α (HIF-1 α), thereby promoting HIF-mediated gene transcription, which enhances glycolysis and both proinflammatory and anti-inflammatory immune responses. Cellular metabolism is also critically involved in epigenetic processes. Acetyl-CoA is a key substrate for histone acetylation, whereas histone deacetylation by sirtuins (SIRT) is aided by a high ratio of NAD⁺ to NADH. Moreover, a high ratio of α -ketoglutarate to succinate promotes the demethylation of DNA and histones, thereby linking cellular metabolism to epigenetic control of immune responses. ROS, reactive oxygen species.

turnover of molecules such as fatty acids⁸². In T_{reg} cells, memory T cells and M2 macrophages, AMPK and TNF receptor-associated factor 6 support oxidative metabolism^{17,22,137,139,140}.

Glycolytic reprogramming of effector T cells and M1 macrophages requires transcriptional changes mediated by a variety of transcription factors. These changes include the activation of HIF-1 and Myc and a reduction in levels of the transcription factor BCL6, which competes with both HIF-1 α and Myc to bind to DNA in T_H1 cells, and result in the repression of glycolytic reconfiguration^{36,45,120,129}. Myc is essential for the initial metabolic switch to glycolysis, but its expression is transient and decreases after activation. Therefore, in CD8⁺ T cells, the Warburg effect is maintained by the transcription factors AP-4 and IRF4, downstream targets of Myc^{141,142}. AP-4 induces a similar glycolytic transcriptional profile to Myc, supporting aerobic glycolysis and effector function in CD8⁺ T cells¹⁴¹. IRF4 also cooperates with Myc to sustain aerobic glycolysis in a later phase of CD8⁺ T cell activation¹⁴².

Immunometabolism in rheumatic diseases

Alterations of metabolic configurations of immune cells can contribute to dysfunctional immune responses. For instance, a dysfunctional T cell response is a typical feature of autoimmunity and is associated with altered metabolic cellular configurations. Naive CD4⁺ T cells from patients with RA should immediately induce the Warburg effect following TCR engagement, but instead are characterized by low levels of ATP and lactate compared with T cells from healthy individuals¹⁰. Due to decreased expression of PFKFB3, T cells from patients with RA shunt glucose towards the PPP (a process termed the 'anti-Warburg effect'), resulting in the accumulation of NADPH and a reduced intracellular level of ROS¹⁰. Restoring intracellular ROS was able to correct the abnormal proliferative behaviour of T cells from patients with RA and to suppress synovial inflammation in a human synovium-NSG chimeric mouse model¹⁴³. In a study published in 2016, diminished expression of PFKFB3 in healthy individuals at risk of developing RA and individuals

with established RA was associated with impaired induction of tyrosine-protein phosphatase non-receptor type 22 (PTPN22)¹⁴⁴. However, further investigation is required to elucidate the reasons behind the failure of PFKFB3 and PTPN22 induction in T cells from patients with RA.

In contrast to T cells from patients with RA, glycolysis and mitochondrial oxidative metabolism are activated in T_H cells from patients with SLE and in T cells from lupus-prone mice that have concomitant mTORC1 activation^{3,9}. The high levels of glucose and oxygen consumption seen in T_H cells from patients with SLE were also detected in naive T cells, and were not a result of immune activation, suggesting an intrinsic malfunction in cells from these patients³. Interestingly, T_H cells from patients with RA and patients with SLE have different metabolic dysfunctions. T_H cells from patients with RA are characterized by reduced glycolytic flux, leading to energy deprivation, whereas T cells from patients with SLE are metabolically overactive, leading to excessive ROS production^{3,9,10,143}. For a more detailed and comprehensive view of the metabolic configuration of immune cells in SLE and RA, see the Reviews by Morel¹¹ and Weyand & Goronzy¹² in this journal.

Although the metabolic configuration of T cells is seemingly different in RA and SLE, these disorders, as well as other chronic rheumatic diseases (such as ankylosing spondylitis, systemic sclerosis and idiopathic inflammatory myopathies) have been associated with an increased risk of coronary artery disease in large epidemiological studies^{145–150}. A study published in 2016 found that the metabolic configuration of monocytes and macrophages from patients with coronary artery disease seem to be unbalanced, leading to oxidative stress and tissue inflammation¹⁰⁴. Whether a generally unbalanced metabolism in monocytes from patients with rheumatic diseases might contribute to cardiovascular comorbidities remains to be clarified.

Conclusions

Cellular metabolism is considerably varied and has dual roles in immune cells: the delivery of energy and substrates for biosynthesis and the direct regulation of immune cell function. During inflammation, alterations in the tissue microenvironment, characterized by hypoxia and competition for nutrients with high numbers of infiltrating cells, force immune cells to adapt by reprogramming their metabolism. Metabolic reconfiguration varies between innate and adaptive immune responses, and between effector and resolution phases depending on a cell's specific functional needs. These metabolic changes are not only a response to an inflammatory microenvironment; they also guide immune cell differentiation and function via several mechanisms, including the differential activities of metabolic enzymes, metabolites and metabolic intermediates and the activity of key regulators of metabolism such as HIF-1. Failure to reprogramme metabolism ultimately results in a dysregulated immune response, as seen in rheumatic diseases.

Increasing our knowledge of immune cell metabolism will, it is hoped, create numerous opportunities for the development of novel therapeutic strategies to modulate these reprogramming mechanisms by specifically targeting metabolic intermediates or molecules at metabolic checkpoints. Although several existing immunosuppressant drugs (such as methotrexate) are known to interfere with cell metabolism by directly or indirectly targeting key metabolic checkpoints, increasing our knowledge of their mechanisms of action during metabolic reprogramming in inflammation will be invaluable for developing new therapeutic strategies. For instance, combined treatment with immunosuppressive therapies and drugs that directly target cellular metabolism might increase the pharmacological efficacy and reduce the adverse effects of classic immunosuppressive drugs. Clearly, more research is needed to increase our knowledge of the biochemistry of immune cells and its effect on immune responses.

- O'Neill, L. A., Kishton, R. J. & Rathmell, J. A guide to immunometabolism for immunologists. *Nat. Rev. Immunol.* **16**, 553–565 (2016).
- Murray, P. J., Rathmell, J. & Pearce, E. SnapShot: immunometabolism. *Cell Metab.* **22**, 190–190.e1 (2015).
- Yin, Y. *et al.* Normalization of CD4⁺ T cell metabolism reverses lupus. *Sci. Transl. Med.* **7**, 274ra18 (2015).
- Yang, Z., Matteson, E. L., Goronzy, J. J. & Weyand, C. M. T-cell metabolism in autoimmune disease. *Arthritis Res. Ther.* **17**, 29 (2015).
- Yilmaz, O. *et al.* ATP-dependent activation of an inflammasome in primary gingival epithelial cells infected by *Porphyromonas gingivalis*. *Cell. Microbiol.* **12**, 188–198 (2010).
- Rooks, M. G. & Garrett, W. S. Gut microbiota, metabolites and host immunity. *Nat. Rev. Immunol.* **16**, 341–352 (2016).
- Castro, C. N., Freitag, J., Berod, L., Lochner, M. & Sparwasser, T. Microbe-associated immunomodulatory metabolites: influence on T cell fate and function. *Mol. Immunol.* **68**, 575–584 (2015).
- Yurkovetskiy, L. A., Pickard, J. M. & Chervonsky, A. V. Microbiota and autoimmunity: exploring new avenues. *Cell Host Microbe* **17**, 548–552 (2015).
- Yin, Y. *et al.* Glucose oxidation is critical for CD4⁺ T cell activation in a mouse model of systemic lupus erythematosus. *J. Immunol.* **196**, 80–90 (2016).
- Yang, Z., Fujii, H., Mohan, S. V., Goronzy, J. J. & Weyand, C. M. Phosphofructokinase deficiency impairs ATP generation, autophagy, and redox balance in rheumatoid arthritis T cells. *J. Exp. Med.* **210**, 2119–2134 (2013).
- Morel, L. Immunometabolism in systemic lupus erythematosus. *Nat. Rev. Rheumatol.* <http://dx.doi.org/10.1038/nrrheum.2017.43> (2017).
- Weyand, C. M. & Goronzy, J. J. Immunometabolism in early and late stages of rheumatoid arthritis. *Nat. Rev. Rheumatol.* <http://dx.doi.org/10.1038/nrrheum.2017.49> (2017).
- Mobasheri, A. *et al.* The role of metabolism in the pathogenesis of osteoarthritis. *Nat. Rev. Rheumatol.* <http://dx.doi.org/10.1038/nrrheum.2017.50> (2017).
- Rhoads, J. P., Major, A. S. & Rathmell, J. C. Fine tuning of immunometabolism for the treatment of rheumatic diseases. *Nat. Rev. Rheumatol.* (in press).
- Jellusova, J. *et al.* Gsk3 is a metabolic checkpoint regulator in B cells. *Nat. Immunol.* **18**, 303–312 (2017).
- Krawczyk, C. M. *et al.* Toll-like receptor-induced changes in glycolytic metabolism regulate dendritic cell activation. *Blood* **115**, 4742–4749 (2010).
- Michalek, R. D. *et al.* Cutting edge: distinct glycolytic and lipid oxidative metabolic programs are essential for effector and regulatory CD4⁺ T cell subsets. *J. Immunol.* **186**, 3299–3303 (2011).
- van der Windt, G. J. *et al.* CD8 memory T cells have a bioenergetic advantage that underlies their rapid recall ability. *Proc. Natl Acad. Sci. USA* **110**, 14336–14341 (2013).
- van der Windt, G. J. *et al.* Mitochondrial respiratory capacity is a critical regulator of CD8⁺ T cell memory development. *Immunity* **36**, 68–78 (2012).
- Lam, W. Y. *et al.* Mitochondrial pyruvate import promotes long-term survival of antibody-secreting plasma cells. *Immunity* **45**, 60–73 (2016).
- Sukumar, M. *et al.* Inhibiting glycolytic metabolism enhances CD8⁺ T cell memory and antitumor function. *J. Clin. Invest.* **123**, 4479–4488 (2013).
- Pearce, E. L. *et al.* Enhancing CD8 T-cell memory by modulating fatty acid metabolism. *Nature* **460**, 103–107 (2009).
- Kotas, M. E. & Medzhitov, R. Homeostasis, inflammation, and disease susceptibility. *Cell* **160**, 816–827 (2015).
- Warburg, O., Gawehn, K. & Geissler, A. W. Metabolism of leukocytes [German]. *Z. Naturforsch. B* **13B**, 515–516 (1958).
- Gaber, T. *et al.* Pathophysiological hypoxia affects the redox state and IL-2 signalling of human CD4⁺ T cells and concomitantly impairs survival and proliferation. *Eur. J. Immunol.* **43**, 1588–1597 (2013).
- Gaber, T. *et al.* Macrophage migration inhibitory factor counterregulates dexamethasone-mediated suppression of hypoxia-inducible factor-1 α function and differentially influences human CD4⁺ T cell proliferation under hypoxia. *J. Immunol.* **186**, 764–774 (2011).
- Fearon, U., Canavan, M., Biniecka, M. & Veale, D. J. Hypoxia, mitochondrial dysfunction and synovial invasiveness in rheumatoid arthritis. *Nat. Rev. Rheumatol.* **12**, 385–397 (2016).

28. Biniecka, M. *et al.* Dysregulated bioenergetics: a key regulator of joint inflammation. *Ann. Rheum. Dis.* **75**, 2192–2200 (2016).
29. Rodriguez-Prados, J. C. *et al.* Substrate fate in activated macrophages: a comparison between innate, classic, and alternative activation. *J. Immunol.* **185**, 605–614 (2010).
30. Assmann, N. & Finlay, D. K. Metabolic regulation of immune responses: therapeutic opportunities. *J. Clin. Invest.* **126**, 2031–2039 (2016).
31. Rodriguez-Espinosa, O., Rojas-Espinosa, O., Moreno-Altamirano, M. M., Lopez-Villegas, E. O. & Sanchez-Garcia, F. J. Metabolic requirements for neutrophil extracellular traps formation. *Immunology* **145**, 213–224 (2015).
32. Donnelly, R. P. *et al.* mTORC1-dependent metabolic reprogramming is a prerequisite for NK cell effector function. *J. Immunol.* **193**, 4477–4484 (2014).
33. Keating, S. E. *et al.* Metabolic reprogramming supports IFN- γ production by CD56^{bright} NK cells. *J. Immunol.* **196**, 2552–2560 (2016).
34. Doughty, C. A. *et al.* Antigen receptor-mediated changes in glucose metabolism in B lymphocytes: role of phosphatidylinositol 3-kinase signaling in the glycolytic control of growth. *Blood* **107**, 4458–4465 (2006).
35. Frauwrith, K. A. *et al.* The CD28 signaling pathway regulates glucose metabolism. *Immunity* **16**, 769–777 (2002).
36. Shi, L. Z. *et al.* HIF1 α -dependent glycolytic pathway orchestrates a metabolic checkpoint for the differentiation of T_H17 and T_{reg} cells. *J. Exp. Med.* **208**, 1367–1376 (2011).
37. Gubser, P. M. *et al.* Rapid effector function of memory CD8⁺ T cells requires an immediate-early glycolytic switch. *Nat. Immunol.* **14**, 1064–1072 (2013).
38. Macintyre, A. N. *et al.* The glucose transporter Glut1 is selectively essential for CD4 T cell activation and effector function. *Cell Metab.* **20**, 61–72 (2014).
39. Blagih, J. *et al.* The energy sensor AMPK regulates T cell metabolic adaptation and effector responses *in vivo*. *Immunity* **42**, 41–54 (2015).
40. Klysz, D. *et al.* Glutamine-dependent α -ketoglutarate production regulates the balance between T helper 1 cell and regulatory T cell generation. *Sci. Signal.* **8**, ra97 (2015).
41. Nakaya, M. *et al.* Inflammatory T cell responses rely on amino acid transporter ASCT2 facilitation of glutamine uptake and mTORC1 kinase activation. *Immunity* **40**, 692–705 (2014).
42. Sinclair, L. V. *et al.* Control of amino-acid transport by antigen receptors coordinates the metabolic reprogramming essential for T cell differentiation. *Nat. Immunol.* **14**, 500–508 (2013).
43. Geiger, R. *et al.* L-arginine modulates T cell metabolism and enhances survival and anti-tumor activity. *Cell* **167**, 829–842 (2016).
44. Finlay, D. K. *et al.* PDK1 regulation of mTOR and hypoxia-inducible factor 1 integrate metabolism and migration of CD8⁺ T cells. *J. Exp. Med.* **209**, 2441–2453 (2012).
45. Wang, R. *et al.* The transcription factor Myc controls metabolic reprogramming upon T lymphocyte activation. *Immunity* **35**, 871–882 (2011).
46. Ananieva, E. A., Powell, J. D. & Hutson, S. M. Leucine metabolism in T cell activation: mTOR signaling and beyond. *Adv. Nutr.* **7**, 798S–805S (2016).
47. Delgoffe, G. M. *et al.* The kinase mTOR regulates the differentiation of helper T cells through the selective activation of signaling by mTORC1 and mTORC2. *Nat. Immunol.* **12**, 295–303 (2011).
48. Pollizzi, K. N. & Powell, J. D. Regulation of T cells by mTOR: the known knowns and the known unknowns. *Trends Immunol.* **36**, 13–20 (2015).
49. Carr, E. L. *et al.* Glutamine uptake and metabolism are coordinately regulated by ERK/MAPK during T lymphocyte activation. *J. Immunol.* **185**, 1037–1044 (2010).
50. Wang, H. *et al.* Negative regulation of Hif1 α expression and T_H17 differentiation by the hypoxia-regulated microRNA miR-210. *Nat. Immunol.* **15**, 393–401 (2014).
51. Berod, L. *et al.* De novo fatty acid synthesis controls the fate between regulatory T and T helper 17 cells. *Nat. Med.* **20**, 1327–1333 (2014).
52. Jha, A. K. *et al.* Network integration of parallel metabolic and transcriptional data reveals metabolic modules that regulate macrophage polarization. *Immunity* **42**, 419–430 (2015).
53. O'Neill, L. A. A broken Krebs cycle in macrophages. *Immunity* **42**, 393–394 (2015).
54. Infantino, V. *et al.* The mitochondrial citrate carrier: a new player in inflammation. *Biochem. J.* **438**, 433–436 (2011).
55. Gerriets, V. A. *et al.* Foxp3 and Toll-like receptor signaling balance T_{reg} cell anabolic metabolism for suppression. *Nat. Immunol.* **17**, 1459–1466 (2016).
56. Procaccini, C. *et al.* The proteomic landscape of human *ex vivo* regulatory and conventional T cells reveals specific metabolic requirements. *Immunity* **44**, 406–421 (2016).
57. Gerriets, V. A. *et al.* Metabolic programming and PDHK1 control CD4⁺ T cell subsets and inflammation. *J. Clin. Invest.* **125**, 194–207 (2015).
58. Caro-Maldonado, A. *et al.* Metabolic reprogramming is required for antibody production that is suppressed in anergic but exaggerated in chronically BAFF-exposed B cells. *J. Immunol.* **192**, 3626–3636 (2014).
59. Le, A. *et al.* Glucose-independent glutamine metabolism via TCA cycling for proliferation and survival in B cells. *Cell Metab.* **15**, 110–121 (2012).
60. Vitoria, G. D. & Nussenzweig, M. C. Germinal centers. *Annu. Rev. Immunol.* **30**, 429–457 (2012).
61. Gitlin, A. D., Shulman, Z. & Nussenzweig, M. C. Clonal selection in the germinal center by regulated proliferation and hypermutation. *Nature* **509**, 637–640 (2014).
62. Cho, S. H. *et al.* Germinal centre hypoxia and regulation of antibody qualities by a hypoxia response system. *Nature* **537**, 234–238 (2016).
63. Abbott, R. K. *et al.* Germinal center hypoxia potentiates immunoglobulin class switch recombination. *J. Immunol.* **197**, 4014–4020 (2016).
64. Iwata, T. N. *et al.* Conditional disruption of raptor reveals an essential role for mTORC1 in B cell development, survival, and metabolism. *J. Immunol.* **197**, 2250–2260 (2016).
65. Heyse, S., Connolly, T., Doughty, C. & Chiles, T. The regulation and role of L-glutamine in B-lymphocyte activation [LYM7P.618] [abstract]. *J. Immunol.* **194** (Suppl. 1), 200.210 (2015).
66. Heyse, S. A., Connolly, T. & Chiles, T. C. The role of nutrients in B lymphocyte growth and survival responses [abstract]. *J. Immunol.* **196** (Suppl. 1), 204.216 (2016).
67. Dufort, F. J. *et al.* Cutting edge: IL-4-mediated protection of primary B lymphocytes from apoptosis via Stat6-dependent regulation of glycolytic metabolism. *J. Immunol.* **179**, 4953–4957 (2007).
68. Caplow, M., Shanks, J. & Brylawski, B. P. Concerning the location of the GTP hydrolysis site on microtubules. *Can. J. Biochem. Cell Biol.* **63**, 422–429 (1985).
69. Kolaczowska, E. & Kubus, P. Neutrophil recruitment and function in health and inflammation. *Nat. Rev. Immunol.* **13**, 159–175 (2013).
70. Mantovani, A., Biswas, S. K., Galdiero, M. R., Sica, A. & Locati, M. Macrophage plasticity and polarization in tissue repair and remodelling. *J. Pathol.* **229**, 176–185 (2013).
71. Mills, E. L. *et al.* Succinate dehydrogenase supports metabolic repurposing of mitochondria to drive inflammatory macrophages. *Cell* **167**, 457–470 (2016).
72. Tannahill, G. M. *et al.* Succinate is an inflammatory signal that induces IL-1 β through HIF-1 α . *Nature* **496**, 238–242 (2013).
73. Gaber, T., Dziurka, R., Tripmacher, R., Burmester, G. R. & Buttgerit, F. Hypoxia inducible factor (HIF) in rheumatology: low O₂! See what HIF can do! *Ann. Rheum. Dis.* **64**, 971–980 (2005).
74. West, A. P., Shadel, G. S. & Ghosh, S. Mitochondria in innate immune responses. *Nat. Rev. Immunol.* **11**, 389–402 (2011).
75. O'Neill, L. A. A critical role for citrate metabolism in LPS signalling. *Biochem. J.* **438**, e5–e6 (2011).
76. Haschemi, A. *et al.* The sedoheptulose kinase CARL directs macrophage polarization through control of glucose metabolism. *Cell Metab.* **15**, 813–826 (2012).
77. Ecker, J. *et al.* Induction of fatty acid synthesis is a key requirement for phagocytic differentiation of human monocytes. *Proc. Natl Acad. Sci. USA* **107**, 7817–7822 (2010).
78. Johnson, A. R. *et al.* Metabolic reprogramming through fatty acid transport protein 1 (FATP1) regulates macrophage inflammatory potential and adipose inflammation. *Mol. Metab.* **5**, 506–526 (2016).
79. Freeman, A. J. *et al.* Metabolic reprogramming of macrophages: glucose transporter 1 (GLUT1)-mediated glucose metabolism drives a proinflammatory phenotype. *J. Biol. Chem.* **289**, 7884–7896 (2014).
80. Vats, D. *et al.* Oxidative metabolism and PGC-1 β attenuate macrophage-mediated inflammation. *Cell Metab.* **4**, 13–24 (2006).
81. Gordon, S. Alternative activation of macrophages. *Nat. Rev. Immunol.* **3**, 23–35 (2003).
82. O'Neill, L. A. & Hardie, D. G. Metabolism of inflammation limited by AMPK and pseudo-starvation. *Nature* **493**, 346–355 (2013).
83. Kelly, B. & O'Neill, L. A. Metabolic reprogramming in macrophages and dendritic cells in innate immunity. *Cell Res.* **25**, 771–784 (2015).
84. Everts, B. *et al.* TLR-driven early glycolytic reprogramming via the kinases TBK1-IKK ϵ supports the anabolic demands of dendritic cell activation. *Nat. Immunol.* **15**, 323–332 (2014).
85. Maroof, A., English, N. R., Bedford, P. A., Gabrilovich, D. I. & Knight, S. C. Developing dendritic cells become 'lacy' cells packed with fat and glycogen. *Immunology* **115**, 473–483 (2005).
86. Amiel, E. & Thwe, P. M. Intracellular glycogen reserves fuel early glycolytic metabolism associated with dendritic cell maturation and immune function [abstract]. *J. Immunol.* **196** (Suppl. 1), 202.231 (2016).
87. Thwe, P. M., Beauchamp, S. & Amiel, E. Glycogen metabolism supports effector function and energy homeostasis of dendritic cells [abstract]. *J. Immunol.* **196** (Suppl. 1), 57.56 (2016).
88. Chakravarty, N. Inhibition of histamine release from rat mast cells by 2-deoxyglucose [abstract]. *Acta Pharmacol. Toxicol. (Copenh.)* **25** (Suppl. 4), 35 (1967).
89. Zhang, B. *et al.* Mitochondria distinguish granule-stored from de novo synthesized tumor necrosis factor secretion in human mast cells. *Int. Arch. Allergy Immunol.* **159**, 23–32 (2012).
90. Zhang, B. *et al.* Human mast cell degranulation and preformed TNF secretion require mitochondrial translocation to exocytosis sites: relevance to atopic dermatitis. *J. Allergy Clin. Immunol.* **127**, 1522–1531 (2011).
91. Erlich, T. H. *et al.* Mitochondrial STAT3 plays a major role in IgE-antigen-mediated mast cell exocytosis. *J. Allergy Clin. Immunol.* **134**, 460–469 (2014).
92. Phong, B., Avery, L., Menk, A. V., Delgoffe, G. M. & Kane, L. P. Cutting edge: murine mast cells rapidly modulate metabolic pathways essential for distinct effector functions. *J. Immunol.* **198**, 640–644 (2017).
93. Maisanski, N. A. *et al.* Functional characterization of mitochondria in neutrophils: a role restricted to apoptosis. *Cell Death Differ.* **11**, 143–153 (2004).
94. Borregaard, N. & Herlin, T. Energy metabolism of human neutrophils during phagocytosis. *J. Clin. Invest.* **70**, 550–557 (1982).
95. Fossati, G. *et al.* The mitochondrial network of human neutrophils: role in chemotaxis, phagocytosis, respiratory burst activation, and commitment to apoptosis. *J. Immunol.* **170**, 1964–1972 (2003).
96. Azevedo, E. P. *et al.* A metabolic shift toward pentose phosphate pathway is necessary for amyloid fibril- and phorbol 12-myristate 13-acetate-induced neutrophil extracellular trap (NET) formation. *J. Biol. Chem.* **290**, 22174–22183 (2015).
97. McInturf, A. M. *et al.* Mammalian target of rapamycin regulates neutrophil extracellular trap formation via induction of hypoxia-inducible factor 1 α . *Blood* **120**, 3118–3125 (2012).
98. Nagy, E. & Rigby, W. F. Glyceraldehyde-3-phosphate dehydrogenase selectively binds AU-rich RNA in the NAD⁺-binding region (Rossmann fold). *J. Biol. Chem.* **270**, 2755–2763 (1995).
99. Chang, C.-H. *et al.* Posttranscriptional control of T cell effector function by aerobic glycolysis. *Cell* **153**, 1239–1251 (2013).
100. Xu, Y. *et al.* Glycolysis determines dichotomous regulation of T cell subsets in hypoxia. *J. Clin. Invest.* **126**, 2678–2688 (2016).
101. De Rosa, V. *et al.* Glycolysis controls the induction of human regulatory T cells by modulating the expression of FOXP3 exon 2 splicing variants. *Nat. Immunol.* **16**, 1174–1184 (2015).
102. Alves-Filho, J. C. & Palsson-McDermott, E. M. Pyruvate kinase M2: a potential target for regulating inflammation. *Front. Immunol.* **7**, 145 (2016).
103. Palsson-McDermott, E. M. *et al.* Pyruvate kinase M2 regulates Hif-1 α activity and IL-1 β induction and is a critical determinant of the warburg effect in LPS-activated macrophages. *Cell Metab.* **21**, 65–80 (2015).
104. Shirai, T. *et al.* The glycolytic enzyme PKM2 bridges metabolic and inflammatory dysfunction in coronary artery disease. *J. Exp. Med.* **213**, 337–354 (2016).



105. Corcoran, S. E. & O'Neill, L. A. HIF1 α and metabolic reprogramming in inflammation. *J. Clin. Invest.* **126**, 3699–3707 (2016).
106. Luo, W. *et al.* Pyruvate kinase M2 is a PHD3-stimulated coactivator for hypoxia-inducible factor 1. *Cell* **145**, 732–744 (2011).
107. Yang, L. *et al.* PKM2 regulates the Warburg effect and promotes HMGB1 release in sepsis. *Nat. Commun.* **5**, 4436 (2014).
108. Andersson, U. *et al.* High mobility group 1 protein (HMG-1) stimulates proinflammatory cytokine synthesis in human monocytes. *J. Exp. Med.* **192**, 565–570 (2000).
109. Yang, P. *et al.* Pyruvate kinase M2 accelerates pro-inflammatory cytokine secretion and cell proliferation induced by lipopolysaccharide in colorectal cancer. *Cell. Signal.* **27**, 1525–1532 (2015).
110. Ryu, H. *et al.* Regulation of M₂-type pyruvate kinase mediated by the high-affinity IgE receptors is required for mast cell degranulation. *Br. J. Pharmacol.* **154**, 1035–1046 (2008).
111. Bertrand, J. *et al.* Glutamine enema regulates colonic ubiquitinated proteins but not proteasome activities during TNBS-induced colitis leading to increased mitochondrial activity. *Proteomics* **15**, 2198–2210 (2015).
112. Tang, Q. *et al.* Pyruvate kinase M2 regulates apoptosis of intestinal epithelial cells in Crohn's disease. *Dig. Dis. Sci.* **60**, 393–404 (2015).
113. Day, A. S., Judd, T., Lemberg, D. A. & Leach, S. T. Fecal M2-PK in children with Crohn's disease: a preliminary report. *Dig. Dis. Sci.* **57**, 2166–2170 (2012).
114. Chung-Faye, G. *et al.* Fecal M2-pyruvate kinase (M2-PK): a novel marker of intestinal inflammation. *Inflamm. Bowel Dis.* **13**, 1374–1378 (2007).
115. Ho, P. C. *et al.* Phosphoenolpyruvate is a metabolic checkpoint of anti-tumor T cell responses. *Cell* **162**, 1217–1228 (2015).
116. Boulahbel, H., Durán, R. V. & Gottlieb, E. Prolyl hydroxylases as regulators of cell metabolism. *Biochem. Soc. Trans.* **37**, 291 (2009).
117. Yang, M., Soga, T., Pollard, P. & Adam, J. The emerging role of fumarate as an oncometabolite. *Front. Oncol.* **2**, 85 (2012).
118. Ratcliffe, P. J. Oxygen sensing and hypoxia signalling pathways in animals: the implications of physiology for cancer. *J. Physiol.* **591**, 2027–2042 (2013).
119. Walmsley, S. R. *et al.* Hypoxia-induced neutrophil survival is mediated by HIF-1 α -dependent NF- κ B activity. *J. Exp. Med.* **201**, 105–115 (2005).
120. Cramer, T. *et al.* HIF-1 α is essential for myeloid cell-mediated inflammation. *Cell* **112**, 645–657 (2003).
121. Noman, M. Z., Janji, B., Berchem, G. & Chouaib, S. miR-210 and hypoxic microvesicles: two critical components of hypoxia involved in the regulation of killer cells function. *Cancer Lett.* **380**, 257–262 (2016).
122. Noman, M. Z. *et al.* PD-L1 is a novel direct target of HIF-1 α , and its blockade under hypoxia enhanced MDSC-mediated T cell activation. *J. Exp. Med.* **211**, 781–790 (2014).
123. Salminen, A., Kaarniranta, K., Hiltunen, M. & Kauppinen, A. Krebs cycle dysfunction shapes epigenetic landscape of chromatin: novel insights into mitochondrial regulation of aging process. *Cell. Signal.* **26**, 1598–1603 (2014).
124. Ichijima, K. *et al.* The methylcytosine dioxygenase Tet2 promotes DNA demethylation and activation of cytokine gene expression in T cells. *Immunity* **42**, 613–626 (2015).
125. Yue, X. *et al.* Control of Foxp3 stability through modulation of TET activity. *J. Exp. Med.* **213**, 377–397 (2016).
126. Li, Q. *et al.* Critical role of histone demethylase Jmjd3 in the regulation of CD4⁺ T-cell differentiation. *Nat. Commun.* **5**, 5780 (2014).
127. De Santa, F. *et al.* Jmjd3 contributes to the control of gene expression in LPS-activated macrophages. *EMBO J.* **28**, 3341–3352 (2009).
128. Peng, M. *et al.* Aerobic glycolysis promotes T helper 1 cell differentiation through an epigenetic mechanism. *Science* **354**, 481–484 (2016).
129. Cheng, S.-C. *et al.* mTOR- and HIF-1 α -mediated aerobic glycolysis as metabolic basis for trained immunity. *Science* **345**, 1250684 (2014).
130. van Loosdregt, J. *et al.* Regulation of T_{reg} functionality by acetylation-mediated Foxp3 protein stabilization. *Blood* **115**, 965–974 (2010).
131. Beier, U. H. *et al.* Sirtuin-1 targeting promotes Foxp3⁺ Tregulatory cell function and prolongs allograft survival. *Mol. Cell. Biol.* **31**, 1022–1029 (2011).
132. Lim, H. W. *et al.* SIRT1 deacetylates ROR γ t and enhances Th17 cell generation. *J. Exp. Med.* **212**, 607–617 (2015).
133. Zhang, J. *et al.* The type III histone deacetylase Sirt1 is essential for maintenance of T cell tolerance in mice. *J. Clin. Invest.* **119**, 3048–3058 (2009).
134. Canto, C., Menzies, K. J. & Auwerx, J. NAD⁺ metabolism and the control of energy homeostasis: a balancing act between mitochondria and the nucleus. *Cell Metab.* **22**, 31–53 (2015).
135. Buttgeriet, F., Smolen, J. S., Coogan, A. N. & Cajochoen, C. Clocking in: chronobiology in rheumatoid arthritis. *Nat. Rev. Rheumatol.* **11**, 349–356 (2015).
136. Netea, M. G. *et al.* Trained immunity: a program of innate immune memory in health and disease. *Science* **352**, aaf1098 (2016).
137. Weichhart, T., Hengstschlager, M. & Linke, M. Regulation of innate immune cell function by mTOR. *Nat. Rev. Immunol.* **15**, 599–614 (2015).
138. Delgoffe, G. M. *et al.* The mTOR kinase differentially regulates effector and regulatory T cell lineage commitment. *Immunity* **30**, 832–844 (2009).
139. Rolf, J. *et al.* AMPK α 1: a glucose sensor that controls CD8 T-cell memory. *Eur. J. Immunol.* **43**, 889–896 (2013).
140. Adamson, S. E. *et al.* Disabled homolog 2 controls macrophage phenotypic polarization and adipose tissue inflammation. *J. Clin. Invest.* **126**, 1311–1322 (2016).
141. Chou, C. *et al.* c-Myc-induced transcription factor AP4 is required for host protection mediated by CD8⁺ T cells. *Nat. Immunol.* **15**, 884–893 (2014).
142. Man, K. *et al.* The transcription factor IRF4 is essential for TCR affinity-mediated metabolic programming and clonal expansion of T cells. *Nat. Immunol.* **14**, 1155–1165 (2013).
143. Yang, Z. *et al.* Restoring oxidant signaling suppresses proarthritogenic T cell effector functions in rheumatoid arthritis. *Sci. Transl. Med.* **8**, 331ra38 (2016).
144. Chang, H. H. *et al.* A molecular signature of preclinical rheumatoid arthritis triggered by dysregulated PTPN22. *JCI Insight* **1**, e90045 (2016).
145. Maradit-Kremers, H., Nicola, P. J., Crowson, C. S., Ballman, K. V. & Gabriel, S. E. Cardiovascular death in rheumatoid arthritis: a population-based study. *Arthritis Rheum.* **52**, 722–732 (2005).
146. Bessant, R. *et al.* Risk of coronary heart disease and stroke in a large British cohort of patients with systemic lupus erythematosus. *Rheumatology (Oxford)* **43**, 924–929 (2004).
147. Ungprasert, P., Srivali, N. & Kittanamongkolchai, W. Risk of coronary artery disease in patients with ankylosing spondylitis: a systematic review and meta-analysis. *Ann. Transl. Med.* **3**, 51 (2015).
148. Ali, H., Ng, K. R. & Low, A. H. A qualitative systematic review of the prevalence of coronary artery disease in systemic sclerosis. *Int. J. Rheum. Dis.* **18**, 276–286 (2015).
149. Ungprasert, P. *et al.* Risk of coronary artery disease in patients with systemic sclerosis: a systematic review and meta-analysis. *Clin. Rheumatol.* **33**, 1099–1104 (2014).
150. Ungprasert, P., Suksaranjit, P., Spanuchart, I., Leeaphorn, N. & Permpalung, N. Risk of coronary artery disease in patients with idiopathic inflammatory myopathies: a systematic review and meta-analysis of observational studies. *Semin. Arthritis Rheum.* **44**, 63–67 (2014).

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All authors researched the data for the article, provided substantial contributions to discussions of its content, wrote the article and undertook review and/or editing of the manuscript before submission.

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