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Lactate modulation of immune responses in inflammatory versus tumour microenvironments

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Abstract | The microenvironment in cancerous tissues is immunosuppressive and pro-tumorigenic, whereas the microenvironment of tissues affected by chronic inflammatory disease is pro-inflammatory and anti-resolution. Despite these opposing immunological states, the metabolic states in the tissue microenvironments of cancer and inflammatory diseases are similar: both are hypoxic, show elevated levels of lactate and other metabolic by-products and have low levels of nutrients. In this Review, we describe how the bioavailability of lactate differs in the microenvironments of tumours and inflammatory diseases compared with normal tissues, thus contributing to the establishment of specific immunological states in disease. A clear understanding of the metabolic signature of tumours and inflammatory diseases will enable therapeutic intervention aimed at resetting the bioavailability of metabolites and correcting the dysregulated immunological state, triggering beneficial cytotoxic, inflammatory responses in tumours and immunosuppressive responses in chronic inflammation.

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Similar metabolic microenvironments lead to differing immunological states in cancer and immune-mediated inflammatory diseases (IMIDs), such as rheumatoid arthritis and multiple sclerosis. The tumour microenvironment (TME) creates a niche that favours tumour growth over antitumour immune surveillance, which in part is facilitated by the accelerated metabolism of tumour cells and cancer-associated fibroblasts. As a result, the tissue is depleted of local resources, forcing neighbouring immune cells to deal with high concentrations of metabolites, particularly lactate, in the absence of nutrients, which drives immunosuppression and favours tumour growth. In contrast to the TME, the inflammatory disease microenvironment, exemplified by the arthritic synovium, features high levels of inflammatory cell subsets such as T helper 1 (T_H1) cells, T helper 17 (T_H17) cells and inflammatory macrophages, and an impairment in the functionality of $CD4^+CD25^+$ regulatory T (T_{reg}) cells. Collectively, this perpetuates IMID pathology. Similar to the TME, lactate, which is produced by both stromal fibroblasts and infiltrating immune cells with an active metabolism, is a key driver of the inflamed tissue microenvironment. For a long time, lactate has been viewed as the end product of glycolysis and considered to be simply a waste product. Despite the first evidence of lactate accumulation in muscles reported in 1808, only in the past 30 years have we begun to understand new and unexpected biological functions of this molecule. Lactate is now recognized as an important carbon source for cellular metabolism and as a signalling molecule both in normal, chronically inflamed tissues and in cancerous tissues. However, the cellular response to lactate in the TME is quite different to that occurring in the context of chronic inflammation, and therefore new studies in this context hold potential for multiple clinical applications. Here, we assess the recent literature to formulate hypotheses — worth exploring experimentally in the near future — as to how such opposing responses are achieved.

Control of immune responses by lactate

Studies in the past few years have revealed several mechanistic details of how immune cells respond to the local build-up of lactate and other metabolites in diseased tissues. This reflects a notable change in our understanding of the modulation of local immune responses, whereby metabolites are now recognized as some of the most ancient signalling molecules on the evolutionary scale. Below we describe some of the metabolic pathways that are modulated by high lactate levels and are relevant to the establishment and progression of chronic inflammatory diseases and cancers.

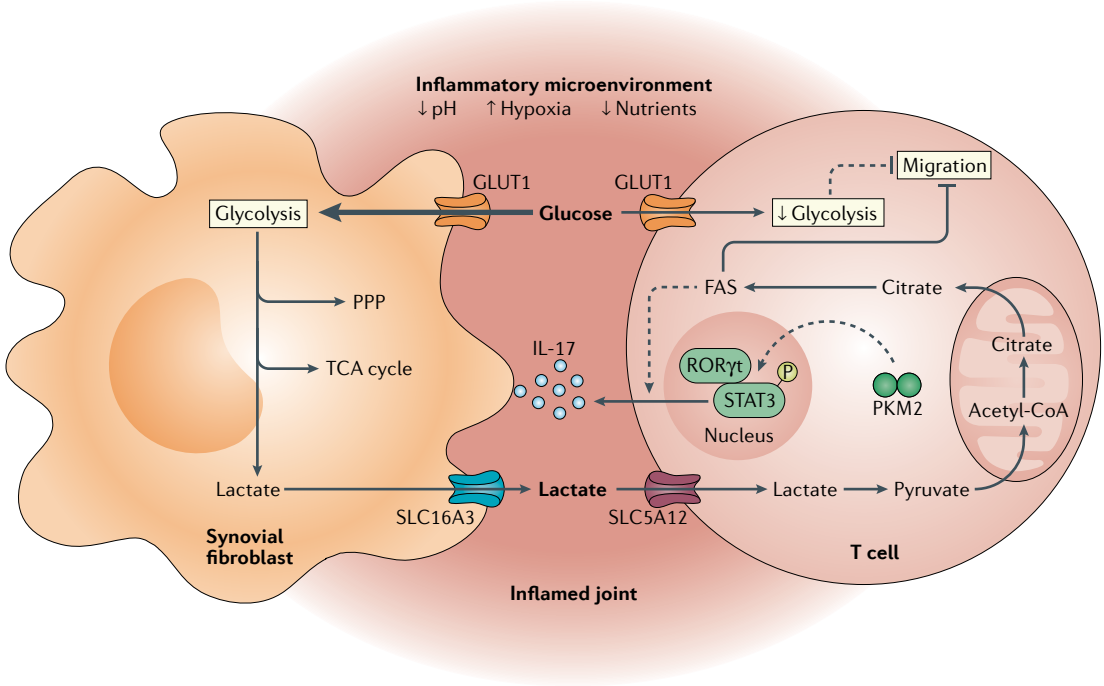

Fig. 1 | **Immunomodulatory effects of lactate in the inflammatory disease microenvironment — arthritic synovium as a paradigm.** Proliferation and rapid activation of synovial fibroblasts require a switch in cell metabolism characterized by increased glucose uptake and glycolysis. In addition, some metabolic intermediates diverge into the pentose phosphate pathway (PPP) to support cell proliferation and survival, and into the tricarboxylic acid (TCA) cycle to support fatty acid synthesis (FAS) and oxidation. As a consequence of increased glycolysis, lactate accumulates in the arthritic joint. Lactate is not simply a by-product of metabolism but exerts important immunomodulating effects. It is internalized by T cells through the enhanced expression of specific transporters. Once in the cytoplasm, lactate inhibits glycolysis while inducing IL-17 production via pyruvate kinase M2 isoform (PKM2)–signal transducer and activator of transcription 3 (STAT3) signalling and FAS. Thus, in inflamed sites, such as the inflamed synovium in rheumatoid arthritis, lactate acts as an amplifier of inflammation leading to the entrapment of T cells and production of pro-inflammatory cytokines. GLUT1, glucose transporter 1; P, phosphorylation; RORγt, retinoic acid receptor-related orphan receptor-γt; SLC16A3, solute carrier 16A3; SLC5A12, solute carrier 5A12.

Lactate dehydrogenase. Lactate dehydrogenase exists in two different isoforms, LDHA and LDHB, which can assemble in five different combinations to form homotetramers or heterotetramers, in a tissue-dependent manner. LDHA is responsible for the conversion of pyruvate into lactate and NAD^+, whereas LDHB converts lactate into pyruvate, fuelling oxidative metabolism.

LDHA can promote T cell effector functions by increasing acetylation and transcription of interferon-γ (*IFNG*), thus highlighting the crucial role of LDH in inflammation[1]. It is well established that cytotoxic T cells and other effector T cells are highly dependent on glycolysis for their proliferation and cytokine production, and therefore become inactive under conditions of low glucose levels and high lactate concentrations[2]. By contrast, T_{reg} cells are less dependent on glycolysis and, instead, rely on oxidative phosphorylation for their energy production[3]. Accordingly, lactate treatment reduces effector T cell function without affecting T_{reg} cell function. In addition, LDH inhibition with GSK2837808A can restore effector T cell functions even in the presence of lactate[4], which suggests that the effects of lactate on these immune cells are highly dependent on LDH. We recently showed that exposure to lactate causes a decrease in glucose uptake and a relative increase in intracellular NADH by activated $CD4^+$ T cells[5] (FIG. 1). Therefore, high concentrations of lactate lead to its conversion into pyruvate by LDH, resulting in the production of NADH and consequent inhibitory feedback on glycolysis.

Suppression of LDHA activity in macrophages with the inhibitor FX11 has anti-inflammatory effects due to the downregulation of pro-inflammatory cytokines, inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX2) via inhibition of mitogen-activated protein (MAP) kinase phosphorylation[6]. The same LDH inhibitor reduces ATP levels and induces oxidative stress and cell death in cancer[7]. Several studies support the role of lactate and LDHA in tumour progression[8]. Indeed, C57BL/6 mice transplanted with short hairpin RNA-mediated LDHA knockdown Pan02 pancreatic cancer cells develop smaller tumours than mice receiving control Pan02 cells. In the same model, natural killer (NK) cells from LDHA-depleted tumours show higher cytolytic activity[9]. This finding is in line with other studies showing that increased LDH activity leads to tumour immune escape by inhibiting the function of immune cells[9,10]. For example, LDHA-associated lactate accumulation in melanomas was shown to inhibit tumour surveillance by T cells and NK cells[10]. The inhibitory effect was proposed to involve lactate-induced downregulation of nuclear factor of activated T cells (NFAT) in T cells

and NK cells, resulting in reduced IFNγ production. Hence, LDH activation can have both pro-inflammatory and anti-inflammatory effects in a context-dependent manner.

Although LDH is predominantly a cytoplasmic enzyme, it can also be found in the nucleus where it binds to mRNA, suggesting that LDH has a role in post-transcriptional modification of gene expression. For instance, LDH binds to the AU-rich element of RNA encoding granulocyte–macrophage colony-stimulating factor (GM–CSF)[11]. The enhanced expression of LDH in cancer may thus favour tumour growth, either through its enzymatic or its gene regulatory function. Aerobic glycolysis has been linked to the induction of immune cell responses including expression of *IFNG* via 3′ untranslated region-mediated mechanisms. For instance, GAPDH can bind to the 3′ untranslated region of *IFNG* mRNA, suppressing translation[11]. However, in another study, LDH was shown to promote *IFNG* expression independently of its 3′ untranslated region[1]. Further studies are needed to highlight additional non-enzymatic activities of LDH.

PKM2. Pyruvate kinase (PK) is a glycolytic enzyme that catalyses the irreversible dephosphorylation of phosphoenolpyruvate to pyruvate, with concomitant production of ATP. Among the various isoforms of PK, PKM2 is receiving particular attention for its multiple functions in immune cells and cancer cells, including functions beyond glucose metabolism[12]. The dimeric form of PKM2 can direct glucose metabolism towards biosynthetic pathways, including the pentose phosphate pathway[13], can enter the nucleus as a kinase to regulate transcription and can also maintain mitochondrial function by binding to the outer mitochondrial membrane[14].

PKM2 can regulate immune cell metabolism and functions via its role in the Warburg effect. Recent studies have also shown that PKM2 expression is increased in several inflammatory disorders, such as in patients with active Crohn's disease[15] and in intestinal tissue of mice subjected to sulfonic acid-induced colitis[16]. Indeed, the dimeric form of PKM2 is increased in lipopolysaccharide (LPS)-activated macrophages[17] and can regulate high mobility group box 1 (HMGB1), which in turn leads to the stimulation of pro-inflammatory cytokines[18]. Nuclear PKM2 can phosphorylate the transcription factor signal transducer and activator of transcription 3 (STAT3), promoting IL-6 and IL-1β production[19]. Accordingly, we recently showed that high levels of lactate, comparable to those present at inflammatory sites, induce PKM2 translocation to the nucleus of $CD4^+$ T cells, resulting in the phosphorylation of STAT3 and increased expression of IL-17 (FIG. 1). *N*,*N*′-diarylsulfonamide (DASA), which stabilizes the PKM2 tetramer and, thus, inhibits dimeric PKM2 translocation to the nucleus, reduces the expression of IL-17 (REF.[5]). Similarly, TEPP-46, another inhibitor of PKM2 nuclear translocation, reduces T_H17 cell polarization and the development of experimental autoimmune encephalomyelitis (EAE)[20]. Dimeric PKM2 was also shown to have a crucial role in macrophage activation during inflammation through stabilization of hypoxia-inducible factor 1α (HIF1α) and regulation of HIF1α-dependent genes[21].

In cancer cells, PKM2 dimers can translocate into the nucleus to stabilize HIF1α and induce the expression of glycolytic genes[21]. However, PKM2 has a wide range of binding partners; it interacts with the RNA binding protein HuR, regulating HuR subcellular localization, cell cycle progression and glioma cell growth[22], and with the AU-rich protein tristetraprolin (TTP). Interaction with PKM2 destabilizes TTP by proteasome degradation and regulates cell proliferation in breast cancer[23]. PKM2 can also promote the adaptation of cancer cells to oxidative stress, via the translocation of PKM2 into mitochondria, with subsequent phosphorylation and stabilization of BCL-2 (REF.[24]). The interaction of PKM2 with nuclear factor-κB (NF-κB) and HIF1α in the nucleus is responsible for the increased secretion of vascular endothelial growth factor A (VEGF-A) and blood vessel formation in growing tumours[25]. It was also reported that PKM2, via inducing the release of chemokines such as CC-chemokine ligand 8 (CCL8), CCL2 and CXCL1, promotes the recruitment of tumour-associated macrophages and myeloid-derived suppressor cells to the TME. These cells exert immunosuppressive functions by inducing T_{reg} cells and suppressing the function of NK cells[26]. Dimeric PKM2 can also regulate the expression of programmed cell death protein 1 ligand 1 (PDL1) in tumour-associated immune cells by binding to hypoxia-response elements in the PDL1 promoter, thus creating an immunoevasive tumour milieu[27].

MAVS. Mitochondrial antiviral signalling protein (MAVS) mediates activation of NF-κB and interferon regulatory factor 3 (IRF3) in response to viral infection, with subsequent expression of type I interferons such as IFNβ. The cascade that leads to the production of interferons starts with the activation of innate immune receptors, including retinoic acid-inducible gene I (RIG-I)-like receptors and Toll-like receptors[28]. Besides its role in innate immune receptor signalling, it was recently reported that MAVS can act as a lactate sensor. MAVS inactivation by direct binding to lactate inhibits RIG-I-like receptor signalling activation and type I interferon production[29]. MAVS associates with the mitochondria via hexokinase 2 (HK2). In this conformation, the glycolytic pathway is facilitated. Upon RIG-I-like receptor activation, MAVS binding to HK2 is reduced, whereas its binding to RIG-I increases, with consequent release of HK2 from the mitochondria and inactivation. Following interaction with lactate, MAVS is no longer able to bind to the mitochondria and therefore RIG-I–MAVS complex formation and interferon production are inhibited. Given that type I interferons play a crucial role in the regulation of immune cells, such as dendritic cells, T_{reg} cells and cytotoxic T cells, this could be a mechanism by which lactate promotes inhibition of immune surveillance in the TME.

However, in the context of chronic inflammation, we recently found increased mitochondrial localization of HK2 in $CD4^+$ T cells following lactate treatment[5]. As voltage-dependent anion channel-dependent binding of HK2 to the outer membrane of mitochondria promotes

Pentose phosphate pathway
A metabolic pathway that is parallel to glycolysis and that generates NADPH, a substrate used for lipogenesis and glutathione regeneration, and ribose 5-phosphate, a precursor for nucleotide synthesis in proliferating cells.

Warburg effect
A phenomenon observed in rapidly dividing cells or when robust transient responses are needed that is characterized by the conversion of glucose into lactate, even in the presence of normal levels of oxygen.

Experimental autoimmune encephalomyelitis
(EAE). A demyelinating disease of the central nervous system used as a common animal model for multiple sclerosis.

Tumour-associated macrophages
Immune cells that induce an immunosuppressive tumour microenvironment through the release of growth factors, proteolytic enzymes and inhibitory immune checkpoint proteins.

Myeloid-derived suppressor cells
A group of phenotypically heterogeneous myeloid cells that contribute to tumour expansion and chronic inflammation progression by inducing immunosuppressive mechanisms, angiogenesis and drug resistance.

Mitochondrial antiviral signalling protein
(MAVS). A mitochondrial adaptor protein activation of which induces the release of cytokines and triggers an immune response.

cell survival[30], our findings could explain the persistence and survival of T cells infiltrating chronically inflamed tissues, such as the rheumatoid synovium.

Fatty acid synthesis from lactate and other substrates. Fatty acid synthesis (FAS) plays a key role in modulating the activities of immune cells, in both physiological and pathological conditions. The increased energy requirement of activated immune cells is associated with increased glycolysis, with subsequent elevated levels of pyruvate. This metabolite is then converted into lactate and secreted. However, some pyruvate can be converted into acetyl-CoA and citrate inside the mitochondria. Citrate is then exported into the cytoplasm and used as the main metabolic fuel for FAS[31].

Lipid metabolism plays a crucial role in macrophage polarization towards an inflammatory phenotype. Whereas fatty acid oxidation or gluconeogenesis fuels the anti-inflammatory function of alternatively activated macrophages (referred to as M2 macrophages), increased glycolysis is crucial in classically activated macrophages (M1 macrophages) not only for faster ATP production but also to obtain citrate, via the tricarboxylic acid (TCA) cycle, to sustain de novo FAS[32]. Indeed, fatty acid synthase (*Fasn*) deletion was shown to reduce the recruitment of macrophages to adipose tissue in a model of diet-induced inflammation in mice[33].

During T cell activation, many genes controlling the biosynthesis of fatty acids are upregulated through the recruitment of sterol regulatory element binding proteins (SREBPs). Moreover, increased acetyl-CoA carboxylase 1 (ACC1) and FASN activity were correlated with the pathogenicity of T_H17 cells. Soraphen A, an inhibitor of ACC1, blocks the differentiation of $CD4^+$ T cells to T_H17 cells, and favours T cell differentiation to $FOXP3^+$ T_{reg} cells. This mechanism leads to reduced severity of EAE[34]. Consistently, we showed that in the presence of lactate, at concentrations similar to those identified at inflammatory sites, $CD4^+$ T cells upregulate the de novo synthesis of fatty acids, leading to enhanced production of IL-17 and reduced cell motility[5], although the detailed mechanisms of such control are still under investigation (FIG. 1).

Normal cells rely primarily on fatty acid uptake and oxidation. By contrast, even in the presence of lipids in the microenvironment, it has been shown that cancer cells reactivate de novo FAS, indicating that this pathway has a key role in their metabolism[35]. One of the most important implications of FAS activation is that cancer cells modify their membrane composition and fluidity, becoming more resistant to chemotherapy[36]. FAS activation in immune cells also contributes to altered functions of these cells within the TME, such as reduced immunostimulatory capacity of tumour-resident dendritic cells. Indeed, FAS inhibition with C75 or TOFA enhanced dendritic cell capacity for antigen capture, as well as their capacity to activate allogeneic and antigen-restricted $CD4^+$ and $CD8^+$ T cells[37]. As FAS regulates several cellular processes in both inflammatory diseases and cancer, the modulation of this metabolic pathway holds great promise for therapy.

Lactate shuttle functions

Lactate shuttles between producer and consumer cells in the body, playing a crucial role in physiology, including as an important energy source, gluconeogenic precursor and signalling molecule. For example, in skeletal muscle, fast-twitch fibres are glycolytic and produce lactate, which is then imported by slow-twitch fibres[38]. Similarly, in neuron–glia metabolic coupling in the brain, glycolytic astrocytes export lactate as an energy source for adjacent neurons[39]. The vectoral transport of lactate from glycolytic cells (fast-twitch fibres and astrocytes) to oxidative cells (slow-twitch fibres and neurons) is provided, in part, by the specialized transport of solute carriers, known as the lactate shuttle. Below we discuss the various, often opposing, functions of lactate in inflammatory disease microenvironments and TMEs.

Lactate in the inflammatory disease microenvironment. In the context of inflammatory disease, lactate triggers a series of intracellular signals that promotes a chronic inflammatory process[5,8,40,41]. Most inflammatory sites are hypoxic and HIF1α is a key regulator of the cellular response to hypoxia. The lactate-mediated response to prolonged hypoxia, however, appears to be functionally uncoupled from HIF1α, as it uses NDRG family member 3 (NDRG3)[42]. NDRG3 is degraded in a PHD2/VHL-dependent manner in normoxia, similar to HIF1α; however, in prolonged hypoxic conditions, it is protected from degradation by binding to lactate. The resulting increase in NDRG3 levels, irrespective of HIF1α, leads to activation of a RAF–ERK signalling pathway that controls hypoxia-related pathophysiological responses, including inflammation and angiogenesis. In addition, pharmacological or genetic inhibition of LDHA limits NDRG3 protein accumulation in a dose-dependent manner. These events are reversed by lactate without affecting HIF1α protein levels[42].

In the arthritic synovium, lactate modulates immune cell functions in various ways, namely migration and cytokine production (FIG. 1). In T cells, lactate induces a 'stop migration' signal, which contributes to their entrapment in the inflammatory site. These events are mediated by the lactate transporters SLC5A12 and SLC16A1 (the latter also known as MCT1), which are selectively expressed by $CD4^+$ and $CD8^+$ T cells, respectively[43]. Interestingly, lactate-mediated inhibition of T cell motility in the inflamed tissue is coupled with decreased glycolysis. $CD4^+$ T cells, in the presence of sodium lactate, show reduced expression of several glycolytic enzymes and glucose flux that makes them unable to egress from the inflamed tissue and causes their entrapment in it[5,43] (FIG. 1). These data align with reports showing that naive $CD4^+$ T cells in rheumatoid arthritis have low basal glycolysis due to downregulation of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFKFB3). The consequence of such downregulation is a shunt of glucose-6-phosphate (G6P) towards the pentose phosphate pathway with production of NADPH and altered activation of ataxia telangiectasia mutated (ATM), an important enzyme involved in regulation of the cell cycle. Overall, these changes result in a high proliferative capacity of $CD4^+$ T cells in rheumatoid

arthritis and a switch to pro-inflammatory subsets, such as T_H1 cells and T_H17 cells, leading to chronic inflammation[44,45].

$ATP^{low}pyruvate^{low}NADPH^{hi}$ $CD4^+$ T cells in rheumatoid arthritis also display enhanced FAS, leading to accumulation of cytoplasmic lipid droplets and upregulation of the podosome scaffolding protein TKS5. $TKS5^{hi}$ $CD4^+$ T cells from patients with rheumatoid arthritis form actin-rich, cortactin-rich membrane ruffles, which increase their ability to infiltrate the inflammatory tissue. All of these effects are reversed as a result of FAS inhibition[46]. Arguably, FAS is responsible not only for increased infiltration of $CD4^+$ T cells in the inflamed site but also for their retention at the site[5] (FIG. 1).

In inflamed tissues, activated $CD4^+$ T cells 'sense' high levels of lactate via SLC5A12 and preferentially differentiate into inflammatory subsets[5,43,47,48]. Indeed, the activation of specific lactate-induced or SLC5A12-induced metabolic pathways plays a crucial role in the pathogenesis of rheumatoid arthritis, contributing to $CD4^+$ T cell infiltration and differentiation into T_H17 cell and T follicular helper cell subsets in the arthritic synovium (FIG. 1), features that correlate with the presence of ectopic lymphoid structures in the same inflammatory milieu[5,40,49].

SLC5A12 inhibition, and hence reduced lactate uptake, restores T cell functions and dampens inflammation in a mouse model of arthritis[5], suggesting that it could represent a novel therapeutic target to resolve inflammation in IMIDs. The elevated metabolic requirement of synovial cells leads to the build-up of lactate in the synovial fluid of patients with rheumatoid arthritis[50]. Although there is no definite link between lactate concentration in synovial fluid and disease activity, synovial lactate levels have been found to be a reliable indicator to distinguish inflammatory arthritis from septic arthritis[51]. Similarly, it has been shown that LDH iso-enzymes are higher in serum and synovial fluid of patients with rheumatoid arthritis compared with patients with osteoarthritis[52], and LDH activity is augmented in rheumatoid arthritis synovial tissues compared with healthy controls[53]. Lactate can also function as a ligand for Gi-protein-coupled receptor 81 (GPR81). Activation of this receptor leads to the downregulation of cAMP and protein kinase A (PKA) signalling[54]. Another molecular mechanism induced by the activation of GPR81 involves the modulation of β-arrestin[55]. Via the activation of this mechanism in monocytes and macrophages, lactate reduces inflammation in models of pancreatitis and hepatitis[55].

Lactate in the TME. In 1923, Otto Warburg first observed the phenotypic characteristics of cancer cells, exhibiting high glucose uptake and excessive lactate formation even in the presence of sufficient oxygen, which subsequently was referred to as the Warburg effect, also termed aerobic glycolysis, and remains a hallmark of cancer[56,57]. Lactate produced by cancer cells is further secreted into the extracellular space and plays a critical role in promoting cancer progression by creating an active niche that shapes tumour pathogenesis and evolution. One of the main features of most tumours is hypoxia, signalling of which is mediated by HIF1α (REF.[58]). HIF1α can activate Snail and Twist, two transcription factors involved in E-cadherin modulation, promoting invasion and resistance to chemotherapy[59]. Furthermore, hypoxia leads to malfunctioning of blood vessels, as a consequence of modulation of VEGF, angiopoietin 2 and angiopoietin-like 4, and facilitates the migration of cancer cells through blood vessels[60]. Hypoxia is also responsible for increased production of reactive oxygen species, which can cause drug resistance via the activation of NF-κB, nuclear factor erythroid 2 (NRF2), JUN and HIF1α (REF.[61]). A growing body of studies indicates that proton-coupled lactate efflux from cancer cells or stromal cells plays a crucial role in preservation of the acidic phenotype and increases tumour progression by modulating the TME, including cell invasion, angiogenesis, survival signalling, metastasis development and escape from immune surveillance[62]. Extracellular acidosis suppresses T cell-mediated immunity, and numerous studies have revealed that neutralization of tumour acidity improves antitumour responses to immunotherapy. An extracellular pH of 6.0–6.5 can induce an anergic state in human and mouse tumour-specific $CD8^+$ T cells, with reduced cytolytic activity and cytokine production[63]. Treatment with proton pump inhibitors has proved effective in restoring T cell functions[63]. The mechanism underlying the effect of acidosis on T cell functions involves, at least in part, inhibition of mTORC1 (REF.[64]). Indeed, low pH reduces the expression of iNOS, CCL2 and IL-6 in M1 macrophages, but increases the expression of M2 macrophage markers in the context of the TME[65]. Extracellular acidification also suppresses the antitumoural activity of NK cells via mTOR inhibition[66].

Extracellular lactate levels can be sensed by several cell types, including cancer cells[67], T cells[4,43], NK cells[68], dendritic cells[69] and macrophages[70], triggering intracellular signalling that fine-tunes cell behaviour and strongly influences their functions in the TME (FIG. 2). Lactate-induced GPR81 activation participates in cancer growth, acting as a survival pathway and regulating the expression of genes involved in lactate uptake and metabolism[71]. Tumour-derived lactate was shown to induce an M2-like polarization of both THP1 human monocytic cells and LPS-activated human monocytes[72,73]. Although an ERK–STAT3 signalling pathway was proposed to contribute to lactate-induced M2 macrophage polarization[62], other studies suggest that HIF1α stabilization can also be involved[74]. In addition, lactate can activate G-protein-coupled receptor 132 (GPR132) in macrophages to promote the M2-like phenotype, and genetic ablation of *Gpr132* in macrophages leads to reduced M2-like features in tumour-associated macrophages and decreased lung metastasis in a mouse breast cancer model[70]. Moreover, a recent study showed that lactyl groups derived from lactate can be used for post-translational modifications of histone proteins with ensuing elevated expression of M2 marker genes, such as *IL6* and *ARG1* (REF.[75]). Intriguingly, lactate inhibits the differentiation of monocytes into dendritic cells[76,77], suggesting that high lactate levels in the TME might hamper dendritic cell formation and accumulation. High lactate

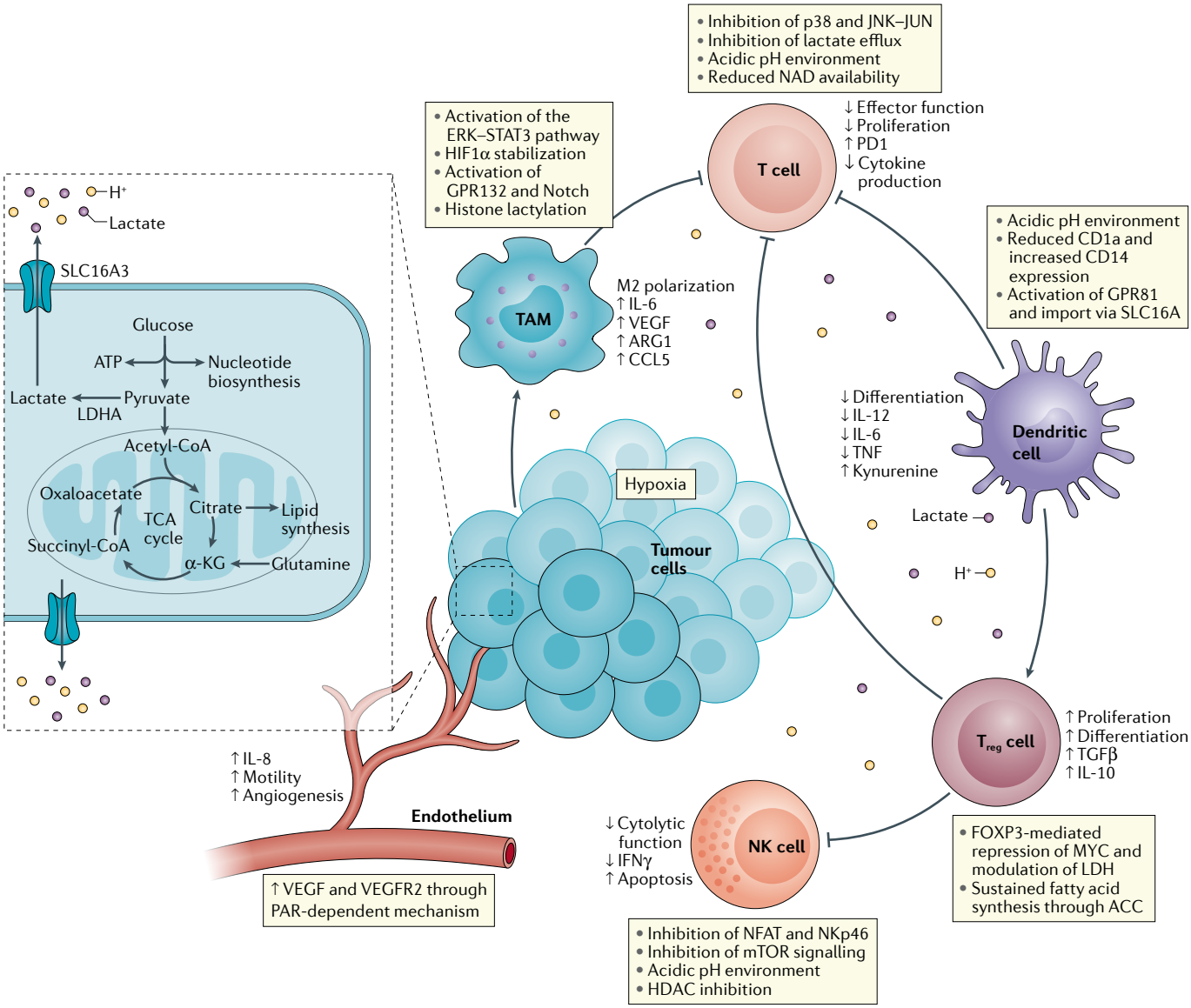

Fig. 2 | **Lactate in the tumour microenvironment.** The tumour microenvironment (TME) is characterized by the presence of various cell types, including tumour, stromal and immune cells, as well as blood vessels. In this metabolically hostile microenvironment, tumour cells use most of the nutrients, thus affecting functions of the infiltrating immune cells. Moreover, as a consequence of the Warburg effect, tumour cells secrete large amounts of lactate into the extracellular microenvironment, leading to acidosis, angiogenesis and immunosuppression. Indeed, lactate is reported to be one of the most prominent metabolites of the TME that modulates the metabolism of innate and adaptive immune cells, inhibiting the activation and proliferation of $CD8^+$ T cells, natural killer (NK) cells and dendritic cells. Lactate positively affects the $CD4^+CD25^+$ regulatory T (T_{reg}) cell metabolic profile, enabling their maintenance in the acidic TME and potentiating their immunosuppressive functions. Furthermore, lactate favours the polarization of alternatively activated macrophages, which have an anti-inflammatory (M2-like) phenotype, participate in angiogenesis and tissue remodelling, and promote tumour growth and invasion. Taken together, these observations show that lactate is a major permissive factor for tumour growth. ACC, acetyl-CoA carboxylase; ARG1, arginase 1; CCL5, C-C-chemokine ligand 5; FOXP3, forkhead box P3; GPR132, G-protein-coupled receptor 132; GPR81, Gi-protein-coupled receptor 81; HDAC, histone deacetylase; HIF1α, hypoxia-inducible factor 1α; IFNγ, interferon-γ; α-KG, α-ketoglutarate; LDHA, lactate dehydrogenase A; NFAT, nuclear factor of activated T cells; PAR, poly-ADP ribosylation; SLC16A3, solute carrier 16A3; STAT3, signal transducer and activator of transcription 3; TAM, tumour-associated macrophage; TCA, tricarboxylic acid; TGFβ, transforming growth factor-β; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2.

levels in the TME also oppose lactate efflux from T cells, leading to their decreased cytokine production and cytotoxic activity[78,79]. Moreover, lactate in the TME inhibits NK cell function by reducing their cytolytic function and increasing the number of myeloid-derived suppressor cells that inhibit natural killer cytotoxicity[68]. In addition, lactate can prevent the activation of NFAT in both T cells and NK cells, resulting in diminished IFNγ production[10], which is in contrast to the effects of lactate on IFNγ production in inflammatory settings[1]. Conversely, the expression of FOXP3 in T_{reg} cells was recently shown to support metabolic adaptations of T_{reg} cells to sustain their survival and suppressive functions in low-glucose and high-lactate environments[4].

The expression levels of LDHA can be regulated by HIF1α, MYC and p53, which are associated with malignancy and facilitate epithelial-to-mesenchymal transition, angiogenesis and increased invasion[80]. Downregulation or loss of LDHB expression represents a crucial and early event in cancer development, including prostate, breast and pancreatic cancers[81–83], and is correlated with high proliferation, increased tumour cell invasion and unfavourable patient survival outcomes[43,67]. In glucose-deprived conditions, LDHB-mediated lactate use supports autophagy to sustain metabolic fitness and growth of cancer cells[84]. A previous study showed that changes in LDHB expression are often associated with early metabolic adaptations[85], suggesting that lactate production and use may engage metabolic adaptations for cancer cells to support the development of metastasis. Accordingly, bone metastatic breast cancer cells release large amounts of lactate[86]. As lactate is a key fuel for osteoclasts, this finding suggests that osteotropic tumour cells may release lactate to promote the differentiation and metabolic reprogramming of osteoclasts, allowing tumour cells to invade the metastatic niche. In addition, lactate stimulates the release of VEGF by endothelial cells for wound healing[87–89] and tumour-associated angiogenesis[90,91]. Furthermore, in glioma cells, lactate induces the expression of transforming growth factor-β2 (REF.[92]), a key regulator of cancer cell migration, invasion, epithelial-to-mesenchymal transition and metastatic niche formation[93,94]. Taken together, these findings suggest that lactate and LDH expression can support metabolic adaptation in cancer cells and tumorigenesis.

Conclusions and perspectives

The mechanisms recently elucidated for the control of the immune response by metabolites, locally, in the diseased tissues of cancer and IMIDs have tremendous therapeutic implications. We discuss the most important therapeutic implications in the following sections (TABLE 1).

Opportunities and challenges for metabolic intervention in cancer. Targeting lactate transporters, such as with the small molecule AZ3965, which affects both SLC16A1 and SLC16A7, to reduce lactate levels in tumours, resulted in promising preclinical success[95]. AZ3965 has been reported to be successful in models of Burkitt lymphoma expressing SLC16A1, as well as breast cancer, gastric cancer and small cell lung cancer[95]. Another example is the small molecule α-cyano-4-hydroxycinnamate (CHC), which reduces glioblastoma cell proliferation, migration and survival[96]. However, SLC16A3 can compensate for SLC16A1 activity after inhibition of SLC16A1. This mechanism can offer additional metabolic vulnerabilities for therapeutic interventions[97,98]. An additional therapeutic approach is inhibition of the conversion of pyruvate into lactate through the inactivation of LDHA. In a mouse model of non-small cell lung cancer, inactivation of LDHA reduced cancer cell survival and proliferation[99], leading to decreased tumorigenesis

Table 1 | **Opportunities and challenges for metabolic intervention in cancer and immune-mediated inflammatory diseases**

Target	Drug	Mechanism of action
Metabolic intervention in cancer		
LDHA	*N*-hydroxyindoles[100]	Compete with pyruvate and NADH
	Galloflavin[101]	Binds the free enzyme
Lactate transporters	AZ3965 (REF.[95])	Inhibits SLC16A1 and SLC16A7
	α-Cyano-4-hydroxycinnamate[96]	Inhibits SLC16A1 and SLC16A7
	AR-C155858 (REF.[95])	Inhibits SLC16A1 and SLC16A7
CTLA4	Ipilimumab[3]	Binds to CTLA4, blocking the inhibitory signal, which enables CTLs to kill cancer cells
PD1	Nivolumab, pembrolizumab, pidilizumab[3]	Bind to PD1, blocking its interaction with PDL1 and PDL2
PDL1	BMS935559, MPDL3280A, MSB0010718C (REF.[3])	Bind to PDL1, blocking its interactions with both PD1 and B7.1 receptors
Metabolic intervention in immune-mediated inflammatory diseases		
Hexokinase	2-Deoxy-D-glucose[113,114]	Inhibits hexokinase
PKM2	TEPP-46 (REF.[20])	Activates and stabilizes PKM2 tetramers
GAPDH	4-Octylitaconate[130]	Inhibits enzymatic activity
PDK1	Dichloroacetate[3]	Inhibits PDK1
NRF2	Dimethyl-fumarate[115–119], 4-octylitaconate[130]	Activate NRF2
FAS	Soraphen A[34]	Inhibits acetyl-CoA carboxylases
Respiratory chain (complex I)	Metformin[112,120–122]	Inhibits complex I, impeding the generation of mitochondrial ATP and, thus, enhancing cytoplasmic ADP:ATP and AMP:ATP ratios
Lactate transporters	3C7 (REF.[5])	Inhibits SLC5A12
GLUT1	CG-5 (REF.[127]), WZB117 (REF.[128])	Inhibit glucose transport

CTL, cytotoxic T lymphocyte; CTLA4, cytotoxic T lymphocyte-associated antigen 4; FAS, fatty acid synthesis; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GLUT1, glucose transporter 1; LDHA, lactate dehydrogenase A; NRF2, nuclear factor erythroid 2; PD1, programmed cell death protein 1; PDL1, programmed cell death protein 1 ligand 1; PDK1, pyruvate dehydrogenase kinase 1; PKM2, pyruvate kinase M2 isoform; SLC16A1, solute carrier 16A1; SLC5A12, solute carrier 5A12.

and disease regression, which indicates that LDHA is essential for cancer cell survival and could be a viable target for the treatment of non-small cell lung cancer[99]. *N*-hydroxyindoles are a class of LDH inhibitors that compete with pyruvate and NADH. These molecules have been shown to be effective in reducing growth and invasiveness of pancreatic ductal adenocarcinoma and cervical cancer cells[100]. Galloflavin is a non-competitive LDHA inhibitor that reduces breast cancer and hepatocellular carcinoma cell growth and induces apoptosis[101]. Many of these LDH inhibitors have been tested in combination with other drugs, such as gemcitabine and EO9, showing increased therapeutic capacity[102,103]. Of note, targeting LDHA in tumour cells was shown to re-evoke T cell-mediated and NK cell-mediated immunosurveillance in mouse tumour models[10]. Despite these findings suggesting that targeting lactate production and accumulation in tumours is an attractive cancer treatment, how these treatments impact host antitumour immunity and synergize with current cancer immunotherapies, such as immune checkpoint blockade, is largely unexplored, particularly considering that they also work, at least in part, through modulation of metabolism in the TME. The identification of more potent and selective LDHA inhibitors and SLC16A3 inhibitors could open up new perspectives in anticancer therapies in the near future.

Given that extracellular acidosis has a key role in cancer progression, pH regulation in the TME can bring beneficial and adjuvant effects in cancer therapy. Both small molecules and antibodies targeting pH regulators, such as different isoforms of carbonic anhydrase and anion exchangers, monocarboxylate transporters, Na^+/HCO_3^- co-transporters and Na^+/H^+ exchangers, might prove effective. In addition, neutralization of tumour acidity improves antitumour responses to immunotherapy with checkpoint inhibitors, such as antibodies against cytotoxic T lymphocyte-associated antigen 4 (CTLA4) and programmed cell death protein 1 (PD1)[63].

These findings suggest that the metabolic crosstalk occurring in the TME may represent a unique opportunity for drugs that were originally developed for targeting cancer metabolism. Most importantly, we may further boost the therapeutic outcomes of cancer immunotherapy by restoring metabolic fitness of host antitumour immunity. On the other side of the coin, a further challenge will be that by boosting T cell responses via immune checkpoint blockade and modulating their metabolism, we may induce inflammatory conditions in patients with cancer, such as the reported inflammatory arthritis[104], a clinical observation that may explain the contrasting immune effects of certain metabolites in the TME versus the inflammatory disease microenvironment.

Opportunities and challenges for metabolic intervention in IMIDs. In recent years, the use of new technologies, including metabolomics and lipidomics, has provided insights into the pathogenesis of IMIDs. Alterations in metabolic profiles, combined with the hyperactivation of metabolic pathways, are hallmarks of IMIDs and can be potential therapeutic targets. Indeed, the distinctive metabolic requirements of immune cells provide a unique opportunity to differentiate effector from regulatory functions. Similarly, immune cells can be metabolically reprogrammed to modulate their effector functions and memory capability.

Several drugs currently in use for the treatment of IMIDs affect metabolic signalling pathways, such as nucleotide metabolism (that is, methotrexate) or glycolysis (that is, glucocorticoids)[105,106]. Similarly, disease-modifying anti-rheumatic drugs modulate metabolic pathways[107,108]. Targeting metabolic pathways showed promising results for reducing inflammation in both in vitro and in vivo models of arthritis and systemic lupus erythematosus[107,109–112]. T cells in patients with rheumatoid arthritis represent an excellent example of how modifications of certain metabolic pathways are necessary to reprogramme cellular functions, and how targeting these modifications is a useful and promising therapeutic strategy. It has been shown that T cell motility and invasiveness into inflamed joints is regulated by increased FAS and lipid droplet formation, and that the inhibition of these pathways can reduce the pro-arthritogenic behaviour of these cells[71].

Glycolytic enzymes, such as hexokinase, PFKFB3, PKM2 and enolase, are identified as possible therapeutic targets to reduce inflammation in several IMIDs, such as rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis[19,44,110]. Inhibition of hexokinase with 2-deoxy-D-glucose (2DG) in a mouse model of arthritis reduces joint inflammation and the number of T_H17 cells[113]. 2-DG can also reduce antibody production and proliferation of B cells, as well as the migration of dendritic cells[114]. In mouse models of systemic lupus erythematosus, disease severity was reduced after treatment with metformin and 2-DG (REF.[112]). Cytosolic PKM2 activation with TEPP-46 also inhibits the proliferation of T_H1 cells and T_H17 cells, and reduces the severity of EAE[20]. This is due to the inhibition of PKM2 nuclear translocation and, accordingly, we have recently shown that the inhibition of this translocation reverts the lactate-induced production of IL-17 in $CD4^+$ T cells[5]. Inflammatory and autoimmune diseases with a strong T_H17 cell component could be effectively treated with drugs that can abolish or reduce the response of these cells. For instance, it has been reported that targeting pyruvate dehydrogenase kinase 1 (PDK1) with dichloroacetate reduces the proliferation and function of T_H17 cells, ameliorating disease in models of colitis and EAE[3]. Similarly, inhibition of FAS with Soraphen A reduces T_H17 cell differentiation, while promoting T_{reg} cell expansion[34]. In the same vein, targeting the TCA cycle (that is, via *PDHK1* knockdown)[3] or treatment with the TCA cycle substrate dimethyl-fumarate (DMF) reduced the clinical score of disease in EAE[115]. Although the molecular mechanisms are not fully known, DMF has been shown to exert numerous beneficial effects under various conditions of chronic inflammation. The main immunomodulating effects of DMF therapy in multiple sclerosis are represented by a reduced amount of B cells and cytokine production[116], increased cytotoxicity of NK cells[117] and induction of anti-inflammatory T_{reg} cells[118]. Many of these effects could be due to the ability of DMF to stabilize the transcription factor NRF2 (REF.[119]). Metformin is an inhibitor of the mitochondrial

electron transport chain at complex I and, as a consequence of the reduced ATP production, leads to AMPK activation and increased fatty acid oxidation[120]. It has been reported that through this mechanism, metformin inhibits the production of effector T cells, while promoting the production of memory T cells, and its anti-inflammatory actions have proved effective in suppressing the development of autoimmune diseases in mice[121]. However, some of the effects of metformin are AMPK-independent, such as the inhibition of MYC and HIF1α (REF.[122]).

Targeting metabolic intermediates such as lactate[5,123], succinate[124], acetate[125] or lipid mediators[126] is also becoming an attractive avenue, and lactate transporters are gaining attention as novel therapeutic targets in IMIDs. Indeed, SLC16A3 and SLC5A12 are upregulated, respectively, by synovial fibroblasts and $CD4^+$ T cells in rheumatoid arthritis[5,120]. Pharmacological or genetic inhibition of these transporters modulates rheumatoid arthritis synovial fibroblasts and $CD4^+$ T cell effector functions in vitro and reduces the severity of disease in mouse models of arthritis[5,43,123]. Inhibition of the glucose transporter GLUT1 with CG-5 leads to T_{reg} cell polarization and reduced T_H1 and T_H17 cell differentiation in a mouse model of lupus[127]. Another inhibitor, WZB117, has been shown to be effective in reducing inflammatory gene expression in patients with psoriasis[128]. An important role for itaconate in regulating macrophage inflammation, via inhibiting succinate dehydrogenase, was also demonstrated[129]. The itaconate analogue 4-octylitaconate has anti-inflammatory effects with reduced expression of pro-inflammatory cytokines in a mouse model of septicaemia[130].

Overall, targeting specific metabolic pathways is becoming a useful and promising therapeutic strategy in IMIDs and future research in immunometabolism is expected to provide new drugs that can modulate the activity of immune cells more selectively and with fewer side effects.

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