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Fine tuning of immunometabolism for the treatment of rheumatic diseases

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Abstract

All immune cells depend on specific and efficient metabolic pathways to mount an appropriate response. Over the past decade, the field of immunometabolism has expanded our understanding of the various means by which cells modulate metabolism to achieve the effector functions necessary to fight infection or maintain homeostasis. Harnessing these metabolic pathways to manipulate inappropriate immune responses as a therapeutic strategy in cancer and autoimmunity has received increasing scrutiny by the scientific community. Fine tuning immunometabolism to provide the desired response, or prevent a deleterious response, is an attractive alternative to chemotherapy or overt immunosuppression. The various metabolic pathways used by immune cells in rheumatoid arthritis, systemic lupus erythematosus and osteoarthritis offer numerous opportunities for selective targeting of specific immune cell subsets to manipulate cellular metabolism for therapeutic benefit in these rheumatologic diseases.

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Inflammatory and autoimmune diseases are driven by the activation and effector functions of both innate and adaptive immune cells. In addition to neutrophils and other cells involved in acute inflammation, macrophages and dendritic cells are activated to promote T and B lymphocyte responses in rheumatologic diseases such as systemic lupus erythematosus (SLE)[1] and rheumatoid arthritis (RA)[2]. Osteoarthritis (OA), although generally considered non-inflammatory, can present with an inflammatory phenotype and the inflammatory processes involved in this disease are increasingly recognized[3]. In each of these diseases, inflammatory cytokines stimulate immune cells[4] or monocyte-to-osteoclast differentiation to promote autoimmunity or bone resorption and degradation[5,6]. Although these rheumatologic diseases have unique characteristics, in each setting haematopoietic cells must be stimulated to gain effector functions and differentiate. The signalling and gene expression changes that accompany these cellular activation and differentiation events have been well studied, but it is now apparent that the metabolism of disease-effector cells is also tightly regulated[6–9]. Each inflammatory cell, and even anti-inflammatory cell, undergoes metabolic reprogramming upon activation and these changes are essential for disease. Therefore, targeting the metabolic pathways involved offers a new avenue for potential treatment of rheumatologic diseases. Because immunological functions are associated with specific metabolic programmes, this approach affords the particularly attractive possibility that inhibiting the appropriate pathway could lead to selective, cell-specific blockade. In this Perspectives article, we discuss the various metabolic pathways used by immune cells to attain optimal responses and explore the possibility and key principles of manipulating these pathways for therapeutic benefit in rheumatologic diseases, with a focus on RA, SLE and OA.

Cellular metabolic reprogramming

Activation of immune cells leads to changes in metabolic pathways

Resting lymphocytes, macrophages and dendritic cells all use catabolic metabolic pathways that switch to anabolic programmes after activation by antigens, cytokines or stimulation of innate pattern-recognition receptors by pathogen-associated or damage-associated molecular patterns (PAMPs and DAMPs, respectively)[7]. This switch supports resting cell survival and immune surveillance as well as growth and effector function of stimulated cells. Resting T cells take up glucose, amino acids and lipids at a low rate and flux these fuels through glycolysis, glutaminolysis and fatty acid oxidation to maximize mitochondrial oxidative metabolism[7]. This mode of metabolism generates maximal ATP and is associated with a long T cell lifespan[10–13]. Given the need to maintain osmolarity through the sodium–potassium ATPase and the energy demands of rapid chemotaxis and cytoskeletal remodelling during this surveillance mode of resting lymphocytes[14], it is not surprising that metabolism in resting immune cells is programmed to actively support the most efficient ATP-generating processes.

Lymphocyte stimulation leads to abrupt changes in metabolic pathways in these cells. Stimulation of T cells through the T cell receptor in conjunction with co-stimulation leads to a sharp increase in glycolysis and glutaminolysis[15–17] (FIG. 1). Simultaneously, activated T cells decrease mitochondrial fatty acid oxidation in order to conserve lipids for new

membrane synthesis[18,19]. Co-stimulatory signals have key roles in this transition; CD28 augments glucose uptake and glycolysis in activated T cells[16], whereas inhibitory receptors, such as cytotoxic T-lymphocyte protein 4 (CTLA4) and programmed cell death protein 1 (PD-1), can decrease glycolysis and instead promote mitochondrial fatty acid oxidation[15,20–22]. In part, these regulators act through control of signalling via phosphatidyl-inositol 3-kinase (PI3K), AKT and mechanistic target of rapamycin (mTOR)[23]. Resting B cells undergo a similar metabolic shift upon activation. Stimulation of B cells through antigen receptors or Toll-like receptors (TLRs) leads to upregulation of the glucose transporter GLUT1 and glycolysis[24,25]. As in T cells, this metabolic reprogramming is dependent on mTOR signalling, as deficiency of regulatory-associated protein of mTOR (RAPTOR) and mTOR complex I (mTORC1) or alteration of the PI3K pathway disrupts B cell development and activation, and can impair class-switching in germinal centres[26–28]. Ultimately, as an immune response ceases, memory lymphocytes revert to oxidative pathways that are essential to enabling persistence of memory and robust secondary responses[10,12]. Memory lymphocytes can, however, retain enhanced metabolic features that facilitate rapid and strong secondary responses[29,30].

Dendritic cells and macrophages differ from lymphocytes in that proliferation is not as important a cellular goal following activation. The ability to mature and gain effector function (including the differentiation of monocytes into osteoclasts) is, however, essential for these cells. Macrophages and dendritic cells are activated in response to PAMPs and DAMPs, including TLRs, and this activation increases glycolysis to promote inflammatory function and maturation[31–35]. TLR signalling through serine/threonine-protein kinase TBK1 leads to AKT activation and mTORC1 signalling to promote this glycolytic switch[36–38]. Increased glycolysis both promotes inflammation and can enhance ‘trained immunity’, a process that, although not specific in the same way as adaptive immune responses, can lead to improved secondary innate responses[32,39]. In addition to enabling enhanced biosynthesis of effector molecules and cytokines, this metabolic reprogramming supports the growth of essential cell structures, such as the endoplasmic reticulum and Golgi[37], which have critical roles in the cell biology of effector function.

Metabolic programmes are specific for immune cell subsets and functions

A critical aspect of the metabolic reprogramming events described above is that they are not uniform in a given cell type, but instead utilize specific pathways that are essential for particular cell subsets and functions (FIG. 1). This specificity was first demonstrated in classical ‘M1’ macrophages and alternatively activated ‘M2’ macrophages, in which activation with IL-4 led to a peroxisome proliferator-activated receptor γ co-activator 1-β (PGC1β)-dependent increase in oxidative metabolism that contrasted with the more glycolytic metabolism of macrophages activated by IFNγ and the TLR4 ligand lipopolysaccharide[40]. Indeed, these metabolic pathways were linked to the functions of the cells, as promoting increased glucose uptake by GLUT1 expression enhanced proinflammatory macrophage activity[35], whereas promoting mitochondrial lipid oxidative pathways stimulated anti-inflammatory macrophage function[40,41].

Although OA is characterized by subchondral sclerosis[42], inflammation and innate immunity can contribute substantially to disease pathogenesis[3]. The differentiation of monocytes/macrophages into osteoclasts that contribute to inflammation in OA also depends on specific metabolic programmes. In particular, hypoxia and the hypoxia-inducible factors HIF-1α and HIF-2α promote osteoclast differentiation[43,44]. Increased lactic acid, which can suppress glycolysis, also promotes generation of osteoclasts[45]. Together, these findings support the model that different macrophage-derived subsets have distinct metabolic programmes that promote, and are intimately linked to, cell function and fate.

Subsequent to these early studies in macrophages, T cell subsets were also found to utilize distinct metabolic programmes[46], with particular differences noted between regulatory T (T_{reg}) cells and $CD4^+$ effector subsets, including type 1 T helper (T_H1), T_H2, and T_H17 cells[19,46,47]. Effector T cells are largely glycolytic downstream of mTOR signals[48] that differentially affect specific CD4 subsets through mTORC1 or mTORC2 (REF. 49), whereas T_{reg} cells preferentially utilize a mitochondrial oxidative metabolism consisting of lipid and pyruvate oxidation[19,46,47]. Indeed, whereas lipid synthesis is required for T_H17 cells, and overproduction of lipids can lead to T cell phenotypes associated with autoimmunity[50], lipid oxidation promotes T_{reg} cell differentiation[51]. This alternative metabolic programme is regulated by the T_{reg} cell transcription factor FOXP3 (REFS 52,53) as well as by PGC1α and hSIRT3 (also known as NAD-dependent protein deacetylase sirtuin-3, mitochondrial)[54]. *In vivo*, effector T cells depend on GLUT1 (REF. 55) as well as the amino acid transporters solute carrier family 1 member 5 (SLC1A5, also known as ASCT2 or neutral amino acid transporter B(0))[56] and solute carrier family 7 member 5 (SLC7A5, also known as large neutral amino acids transporter small subunit 1 or LAT1)[57], whereas T_{reg} cells can function independently of these transporters[55–57]. T_{reg} cells can, however, initiate glycolysis, in a manner dependent on mTORC1 activation for proliferation[58–60] following activating or inflammatory signals[52]. Increased glycolysis in T_{reg} cells augmented proliferation but also reduced the suppressive capacity of these cells[52]. This switch between maximal T_{reg} cell proliferation or suppressive capacity was controlled in part by the PI3K–AKT–mTORC1 pathway, and constitutive activation of AKT or mTORC1 led to accumulation of poorly suppressive T_{reg} with low phenotypic stability[52,61–63]. Tight regulation of mTOR activity is thus required for T_{reg} cell function. In other $CD4^+$ T cell subsets, such as T follicular helper cells, metabolism seems to be more balanced and relies on both glycolysis and oxidative phosphorylation[64,65]. Metabolism in macrophages and dendritic cells is also regulated by mTORC1 and mTORC2 signalling[66,67]. In particular, signalling through mTORC1 can promote glycolysis, which can enhance M1 macrophage activation[35,41,66], whereas M2 macrophages utilize oxidative metabolism that is regulated by signal transducer and activator of transcription 6 (STAT6) and PGC1β[40]. Inhibition of mTOR kinase can, therefore, alter macrophage metabolism and might affect macrophage subsets.

Immunometabolism in disease

Chronic encounters with autoantigens and inflammatory signals can sharply alter immunometabolism in ways that differ from the response to acute stimulation. Indeed, chronic viral infections diminished glucose metabolism in T cells[68]. Alterations in

immunometabolism in inflammatory diseases reveals insight into disease processes and potential therapeutic targets.

Systemic lupus erythematosus

Metabolomics analyses of sera from patients with SLE have revealed a variety of considerable alterations in metabolites and metabolic pathways that correlate with disease activity and manifestations[69–71]. Although serum metabolites can be affected by multiple cell types and tissues, several metabolic pathways have been shown to differ between T cells of healthy individuals and patients with SLE, and between healthy and lupus-prone animals. Mitochondrial glucose oxidation can be increased[72] and mitochondria have been shown to be hyperpolarized in chronically activated T cells in SLE[73,74]. Persistent mitochondrial hyperpolarization leads to production of reactive oxygen species (ROS), which can sensitize T cells to necrosis, leading to the release of self-antigens and perpetuation of the autoimmune response[75]. The *Sle1c* locus conferred chronic $CD4^+$ T cell activation in the NZB mouse model of lupus[76]. This locus can be further divided, and the *Sle1c2* susceptibility locus contains only two genes, one of which, *Esrrg*, encodes oestrogen-related receptor γ (ERRγ), a nuclear receptor that regulates oxidative phosphorylation and mitochondrial function. Studies by Perry *et al.* in $CD4^+$ T cells from mice expressing the *Sle1c2* locus showed decreased mitochondrial mass and chronic mitochondrial hyperpolarization compared with wild-type $CD4^+$ T cells[77]. Interestingly, B6.*Sle1c2* $CD4^+$ T cells produced more IFNγ than controls. Increased proliferation and activation of B6.*Sle1c2* $CD4^+$ T cells could be attributable to decreased expression of ERRγ — in breast cancer cells, a decrease in levels of ERRγ led the cells to undergo aerobic glycolysis and expend ATP[78]. Although Perry *et al.*[77] did not demonstrate that decreased *Essrg* expression in *Sle1c2* $CD4^+$ T cells, or the effects of this decrease on mitochondrial function, were directly responsible for increased T_H1 skewing, studies have shown that increased glycolysis due to overexpression of GLUT1 in $CD4^+$ T cells increases IFNγ production[16]. Most importantly, the studies in B6.*Sle1c2* mice further confirm a role for mitochondrial metabolism in rheumatologic diseases and suggest that altered T cell metabolism is, in part, genetically programmed.

In addition to changes in glucose metabolism, $CD4^+$ T cells from patients with SLE also display defects in lipid metabolism. T cells from these patients show increased levels of glycosphingolipids and cholesterol, as well as increased expression of the nuclear receptor oxysterols receptor LXRβ (also known as liver X receptor β), which has a role in cellular lipid metabolism and trafficking[79,80]. Treatment of $CD4^+$ T cells from patients with SLE with an LXR antagonist led to decreased glycosphingolipid production, and blockade of glycosphingolipid biosynthesis in these cells restored normal T cell function[50].

Whole-body metabolism can also be affected in SLE, which could influence autoimmunity. Although the underlying mechanisms are poorly understood, patients with SLE had significantly elevated fasting levels of insulin, indicating a predilection for insulin resistance and metabolic disease[81]. This phenomenon was recapitulated in a mouse model of lupus whereby B6.*Sle1.Sle2.Sle3* mice spontaneously developed glucose intolerance without being fed a high-fat diet[82]. Whereas immune dysfunction might contribute directly to the

sequelae of metabolic syndrome, such as atherosclerosis[83], altered metabolic hormones and lipids can also modulate immunity, promoting B cell dysfunction[82] and effector T cell differentiation and function[84–86].

Rheumatoid arthritis

Chronic stimulation and the synovial microenvironment alters T cell metabolism in RA. T cells of patients with RA have reduced expression of 6-phosphofructo 2-kinase/fructose-2, 6-bisphosphatase 3 (PFKFB3)[87]. This enzyme is a key regulator of fructose-2, 6-bisphospate, the allosteric activator of phospho fructokinase, and lower PFKFB3 will lower glycolysis while increasing flux to the pentose phosphate pathway and generation of NADPH[7,87]. Elevated NADPH can neutralize ROS, which, although damaging at high concentrations, are otherwise essential to promote T cell activation[88]. Indeed, restoration of T cell ROS could suppress synovial inflammation[89]. In addition to direct changes in T cells, the hypoxic environment in the RA synovium[90] creates a situation similar to the chronic mitochondrial hyper-polarization seen in SLE. The formation of the synovial pannus restricts the availability of oxygen to infiltrating immune cells, which might contribute to altered glucose and mitochondrial metabolism[90].

Osteoarthritis

Altered metabolism contributes to OA but the underlying mechanisms are less firmly established than in SLE or RA. Nevertheless, increased glucose uptake, as determined by ^{18}F-fluorodeoxyglucose PET imaging, correlated with OA progression[91]. The hypoxic environment of the OA synovium might promote osteoclast differentiation and function[9]. Furthermore, metabolic syndrome can exacerbate OA[92], and advanced glycation end products (AGEs) can activate the AGE-specific receptor (RAGE) to impair osteoblast growth and function and promote receptor activator of NF-κB ligand (RANKL, also known as TNF ligand superfamily member 11) and osteoclastogenesis[92,93]. Indeed, chondrocyte-synthesized RANKL might promote bone destruction in OA[94]. The role for mitochondria in osteoclast differentiation was established by genetic deletion of a component of electron transport complex I, Ndufs4, in mice. Deletion of Ndufs4 led to greater differentiation of precursor cells into macrophages rather than osteoclasts[95], supporting a model in which mitochondrial oxidative metabolism promotes osteoclastogenesis. This balance is complicated, with oxidative metabolism seemingly important for osteoclast differentiation and glycolysis seemingly important for bone resorption[96].

Targeting immunometabolism

Rationale for targeting immunometabo-lism in rheumatologic diseases

Given the metabolic changes associated with immune cell activation and function, as well as the altered metabolism of T cells, macrophages and dendritic cells in rheumatologic diseases, a key question is to what extent is it possible to target metabolism with new therapies? The observation of aerobic glycolysis (the Warburg effect) in cancer cells has led to cell metabolism being considered an attractive potential target for cancer treatment for a number of years[97]. However, the effects of strategies directly inhibiting metabolic pathways have been disappointing or generally modest[97]. One very important difference between

successful cancer therapies and successful therapies to control inflammatory diseases is that cancer cells must be fully eliminated, whereas simply halting effector function would be sufficient in immunologic diseases. When targeting immunometabolism in autoimmunity, therefore, blocking a metabolic pathway to the extent that apoptosis is induced is not necessary[98]. Rather, it is essential only to impair a pathway sufficiently so as to alter specific cell functions. A variety of pathways could, in principle, be targeted to modulate an immune response. Effector T cells, for example, require high rates of glycolysis and amino acid uptake, whereas T_{reg} cells are less dependent on or can even be independent of these pathways[55–57]. Therefore, it is reasonable to hypothesize that inhibition or modulation of glycolytic pathways could shift the balance of effector and regulatory T cell subsets to provide a favourable outcome in autoimmune disorders. Each of these pathways has multiple metabolic steps and specific enzymes or nutrient transporters amenable to pharmacologic intervention.

Principles of targeting immunometabolism in rheumatologic diseases

Several key principles will dictate approaches to pharmacologic modulation of immunometabolism in rheumatologic diseases (BOX 1). For example, unlike kinase signalling pathways, metabolic pathways are not generally amplificatory and weak inhibitors might be most useful. With kinases, the potential for exponential expansion of signalling cascades typically makes it essential to inhibit the vast majority of kinase activity to elicit a functional effect. Metabolic pathways, by contrast, are limited by the levels of metabolites and conservation of mass. Thus, modest inhibition of a kinase might achieve little, but modest inhibition of a metabolic pathway could have a strong effect. This paradigm is evident in the action of metformin, a weak inhibitor of mitochondrial electron transport complex I[99] that can nonetheless leads to multiple effects that modify cell function and survival, including reducing T_H17 cells and osteoclasts in a model of RA[100] and promoting T_{reg} cell differentiation[46,100]. It stands to reason that this treatment strategy would also be beneficial in other autoimmune disorders characterized by effector T cell dysregulation, such as SLE. Additionally, specificity of a therapeutic approach targeting metabolic pathways can arise not only from restricted expression of the target, but from the dependence of specific cell populations on specific metabolic pathways. Ideally, a pharmacologic target would be selectively expressed only in the target cell type. However, an equivalent outcome can be achieved if the drug target is only essential in a specific population of cells. This seems to be the case for many potential targets in immunometabolism. Such a strategy could be employed by inhibiting HIF-1α to block the development of T_H17 cells and promote T_{reg} cell differentiation in RA and OA. HIF-1α is specifically required for glycolysis in T_H17 cells, and does not play a part in other T cell subsets. Thus, although fundamental metabolic pathways might be shared, the selective reliance of immune cell subsets or populations on specific metabolic programmes renders those cell populations susceptible to inhibition.

Several strategies might be used to modulate immunometabolism in rheumatologic diseases. In addition to targeting key metabolic regulatory signalling pathways, such as the mTOR pathway[48,49], or direct inhibition of metabolic events, such as nutrient uptake or enzyme function, metabolic pathways could be modulated at bifurcation points in order to shift metabolic flux from one pathway to another. Pyruvate metabolism might provide such a

target. Two of the major fates of pyruvate are conversion to lactate by lactate dehydrogenase (LDH) or uptake into mitochondria to generate acetyl-CoA for oxidation by pyruvate dehydrogenase (PDH). Inflammatory effector T cells favour pyruvate conversion to lactate, whereas T_{reg} cells favour pyruvate oxidation[19]. The flux of pyruvate towards lactate or acetyl-CoA can be regulated by PDH kinase (PDHK) phosphorylation and the inhibition of PDH. Thus, effector T cells utilize PDHK to maintain LDH-mediated conversion of pyruvate to lactate. Inhibition of PDHK relieves PDH inhibition to promote pyruvate conversion to acetyl-CoA and impairs effector T cell function while promoting T_{reg} cell differentiation. This strategy has shown promise in relieving inflammation and promoting T_{reg} cells in models of disease including collagen-induced arthritis[101], asthma[102], alloreactivity[103] and experimental autoimmune encephalitis (EAE)[19].

Immunometabolic therapeutic targets

There are many potential targets from which to choose to modulate autoimmunity and improve rheumatologic disease outcomes. Some metabolic processes are already targeted by standard of care treatments for these diseases. Methotrexate, for instance, has many modes of action, including potential inhibition of Janus kinase (JAK)– STAT signalling[104]. Inhibition of one-carbon metabolism (a network of pathways involved in amino acid metabolism and nucleotide synthesis) by methotrexate might also have important inhibitory functions on cell growth, redox balance and epigenetics[105]. Other key areas could also provide focal points for new drug development (FIG. 2); indeed, several examples now exist in which pharmacologic targeting of metabolism has had protective effects against immune-mediated diseases. In an important proof-of-principle study, inhibition of T cell metabolic pathways protected lupus-prone mice from disease: Yin *et al*. showed that treatment with the non-metabolizable glucose analogue 2-deoxy-D-glucose (2-DG) plus metformin reversed cytokine and autoantibody production in an animal model of lupus[106]. Furthermore, *in vitro* production of IFNγ by T cells from patients with SLE was normalized by metformin treatment. The combination of 2-DG and metformin would suppress both glycolysis and mitochondrial metabolism. The extent to which such dual metabolic inhibition might be broadly necessary in the treatment of rheumatologic diseases is unclear, but the metabolic plasticity of T cells might require this approach.

Beyond combinations of 2-DG and metformin, targeting amino acid metabolism could prove a promising approach. One potential therapeutic strategy is inhibition of glutamine uptake and metabolism. Glutamine is a non-essential amino acid that is used at high rates to support anabolic metabolism and its uptake is rapidly increased during T cell activation via the transporter SLC1A5 (REFS 56,107). Importantly, SLC1A5 deficiency attenuates T_H1 and T_H17 responses and prevents the onset of EAE in experimental mouse models[56]. The amino acid transporter SLC7A5 is also essential for T cell activation[57] by supporting amino acid uptake essential for mTORC1 activity. Given the wide role of amino acids in anabolic metabolism and intracellular signalling, mechanisms that regulate these pathways are promising targets for modulation of immune cell function in inflammatory diseases. Strategies to suppress glycolysis, mitochondrial metabolism and amino acid metabolism could have far-reaching applications beyond autoimmunity. A 2015 study demonstrated that the combination of 2-DG and metformin, with the addition of an inhibitor of glutamine

metabolism, reduced rejection of skin allografts or heart transplants in mice whereas the individual treatments had minimal effects[108].

Regulation of ROS is also critical for immunological function[88], and mitochondrial ROS production could be a target. Indeed, the F_1F_0-ATPase inhibitor Bz-423 (REF. 109) does not block ATP production but rather leads to increased ROS and can protect against lupus and graft-versus-host disease in animal models, in part by inducing lymphocyte apoptosis[110,111]. PDHK1 can also regulate mitochondrial ROS via regulation of pyruvate flux into the TCA cycle. Indeed, inhibition of PDHK1 led to increased ROS that promoted T_{reg} cells and could protect from EAE[19]. In addition, the mitochondrial ROS scavenger MitoQ reduced mitochondrial anti-viral signalling (MAVS) activation and attenuated IFNγ production[32,112].

A number of other metabolic events have promise as targets in rheumatologic diseases. Given the role of hypoxia in RA and OA, targeting the stability of HIF-1α or HIF-2α and the hypoxic response might offer protection from multiple aspects of joint inflammation[113]. Similarly, modulators of glycolysis, such as PFKFB3 (REF. 114) or LDH[115], can suppress T cell activation or regulate IFNγ production. With these approaches, direct inhibition of a central carbon glucose metabolism pathway raises concerns of broad toxicity. However, in the studies discussed above the effects *in vivo* were surprisingly modest. This outcome is probably due to the partial inhibitory effect of each of these strategies and the selective dependence on those pathways of metabolically active inflammatory cells.

Challenges and future directions

Immunometabolism offers the opportunity to selectively target specific immune cell subsets by modifying the metabolic pathways essential for their function. This concept represents a paradigm shift away from targeting specific signalling pathways that might be active in a wide range of cells. However, a concern is that although only selected cells might require high fluxes through specific metabolic pathways, the extent to which other cell types might also activate and periodically rely on those same pathways remains unclear. Adverse effects of putative metabolic therapies are, therefore, critical challenges. This is particularly true for chronic diseases, which can require long-term treatment. Proliferative or metabolic tissues, such as the gut, liver, muscle and β cells, could be especially sensitive.

Despite these concerns, metabolic pathways are already being targeted, including by standard-of-care therapies, and some metabolic therapies are already standard of care. Other therapies certainly have metabolic implications that might contribute to their mechanisms of action. Methotrexate, for example, inhibits one-carbon metabolism yet is standard-of-care treatment for RA. Also, metabolic changes following inhibition of mTOR signalling certainly contribute to immune suppression[48]. A potential benefit of targeting immunometabolism to modulate immunity is that the selective use of pathways by effector or regulatory T cells or macrophages may enable short-term treatments to shift immune cell populations and provide durable protection from inflammation and disease. Thus, a short therapy period could provide benefit and reduce the potential for adverse effects. The immunometabolism field is rapidly evolving and our increasing knowledge of the metabolic pathways that promote effector and regulatory immune cell differentiation or the generation

of osteoclasts might now provide rational strategies to exploit the metabolic requirements of each subset.

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Box 1

Key principles in immunometabolism pharmacology

Specificity

A critical goal in targeting any pathway is specificity for a population of cells that drives the disease phenotype. Because metabolic pathways are, in principle, shared between all cells, target specificity is a concern when developing new therapies. However, despite potentially shared expression of enzymes, specificity arises from the requirements of immune cells to maintain high metabolic fluxes through specific pathways to elicit specific functions.

Redundancy

Typically, multiple isoforms of each enzyme or multiple transporters for each nutrient exist. Only specific cell populations rely on a given enzyme isoform or transporter, so inhibition of these proteins will affect only that particular population of cells.

Plasticity

Metabolic pathways can adapt to shifts in nutrient availability. Thus, blockade of a specific pathway can simply elicit plasticity and many cells can adjust to bypass the block or to utilize a different pathway. However, these changes in the cellular metabolic programme can modify the function of immune cells. A shift in pathways that might be insufficient to induce apoptosis or block proliferation might nevertheless shift the fate of a T cell or macrophage to reduce or modify inflammatory function.

Partial inhibition

Because metabolic pathways are limited by conservation of mass and, unlike kinase signalling cascades, do not generally amplify, a partial inhibition can lead to a large functional effect.

Durability of response

Concerns of adverse effects will be reduced if the fate of immune cells is shifted so as to elicit durable responses to time-limited or episodic treatment.

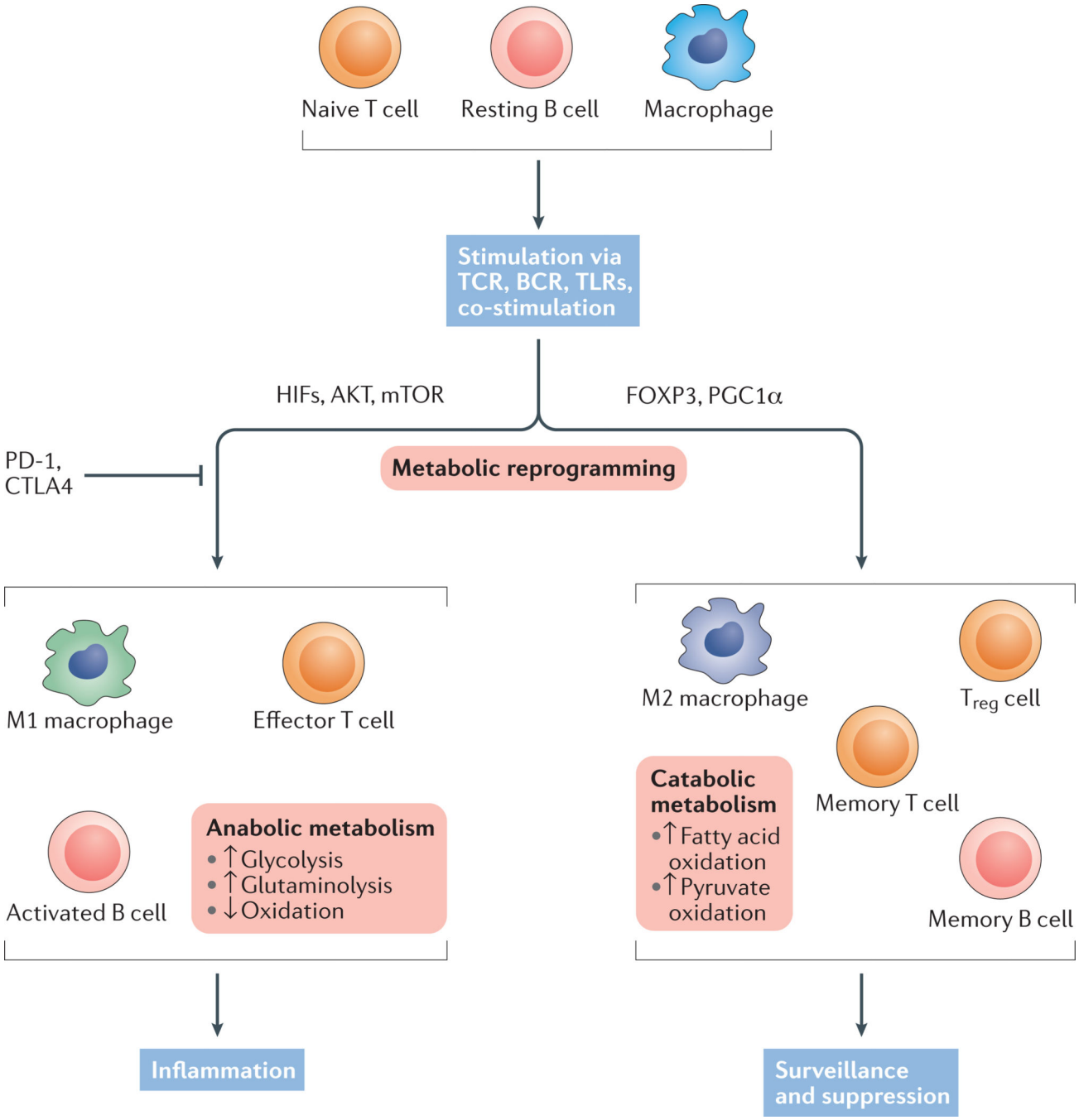

Figure 1. Metabolic reprogramming of immune cell populations matches immunological function

Naive T cells, resting B cells and macrophages utilize a catabolic and oxidative metabolic programme. After stimulation via antigen receptor with co-stimulation or through pattern-recognition receptors such as Toll-like receptors (TLRs), these immune cells undergo metabolic reprogramming. Effector lymphocytes or inflammatory macrophages induce an anabolic meta bolic programme with highly increased nutrient uptake for glycolysis and glutamine metabolism. Regulatory cells or alternatively activated macrophages, by contrast, primarily utilize a programme of lipid and pyruvate oxidation. These programmes are

important to the function of each subset; if the cellular metabolism does not match the cell fate, immune cells will fail to gain appropriate functional capacity. BCR, B cell receptor; CTLA-4, cytotoxic T lymphocyte protein 4; HIF, hypoxia-inducible factor; mTOR, mechanistic target of rapamycin; PD-1, programmed cell death protein 1; PGCla, peroxisome proliferator-activated receptor γ co-activator 1-α; TCR, T cell receptor; T_{reg} cell, regulatory T cell.

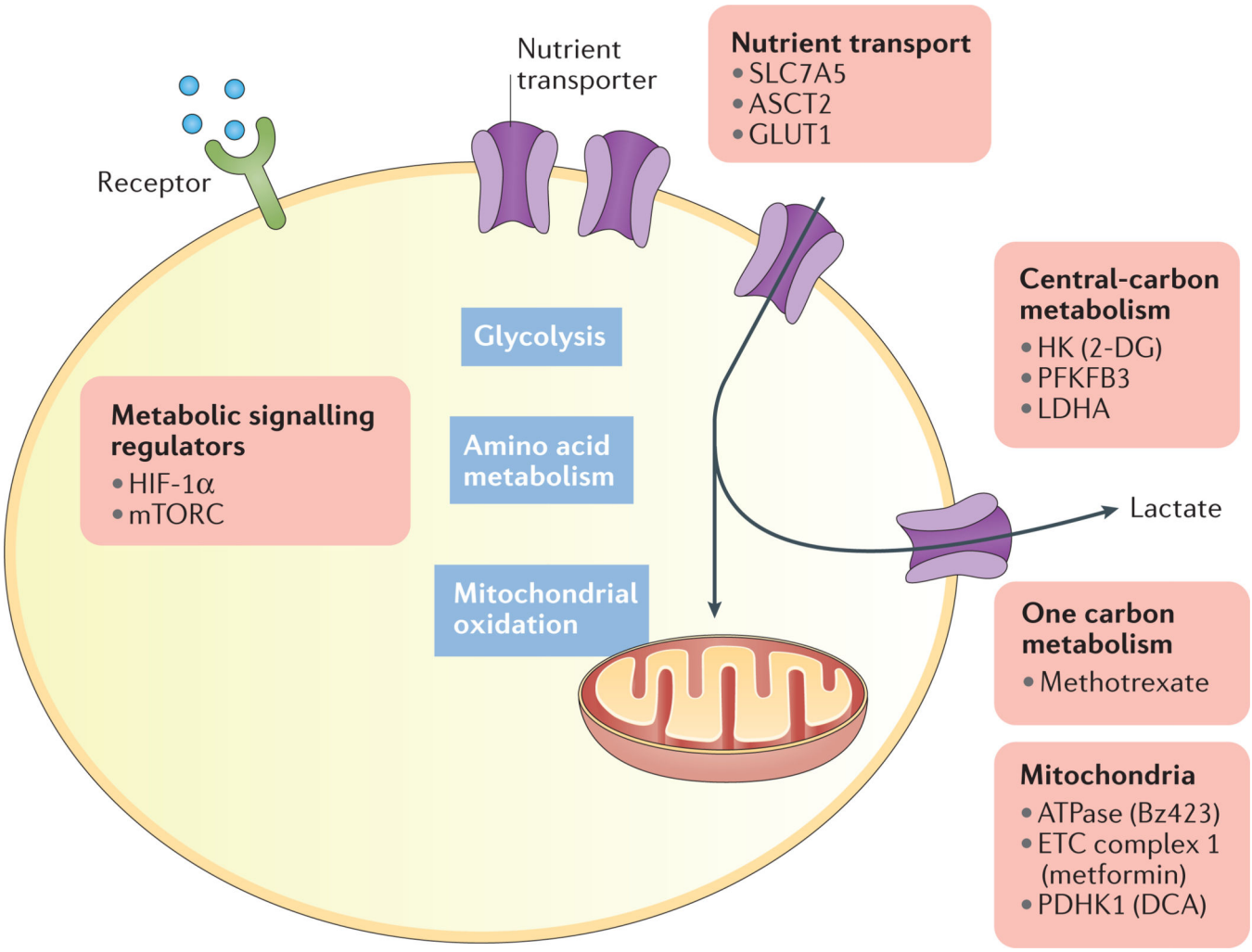

Figure 2. Metabolic processes to target in the treatment of rheumatologic diseases

Metabolic areas and key current or potential targets for drugs to modify immunometabolism and shift immune cell subsets and fate are indicated. 2-DG, 2-deoxy-d-glucose; ASCT2, solute carrier family 1 member 5; DCA, dichloroacetate; ETC, electron transport chain; GLUT1, glucose transporter 1; HIF-1α, hypoxia-inducible factor 1α; HK, hexokinase; LDHA, lactate dehydrogenase A; mTORC, mechanistic target of rapamycin complex; PDHK1, pyruvate dehydrogenase kinase 1; PFKFB3. 6-Phosphofructo 2-kinase/ fructose-2,6-bisphosphatase 3.