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Metabolic determinants of lupus pathogenesis

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Summary

The metabolism of healthy murine and more recently human immune cells has been investigated with an increasing amount of details. These studies have revealed that the challenges presented by immune cells to respond rapidly to a wide variety of triggers by adjusting the amount, type and utilization of the nutrients they import. A concept has emerged that cellular metabolic programs regulate the size of the immune response and the plasticity of its effector functions. This has generated a lot of enthusiasm with the prediction that cellular metabolism could be manipulated to either enhance or limit an immune response. In support of this hypothesis, studies in animal models as well as human subjects have shown that the dysregulation of the immune system in autoimmune diseases is associated with a skewing of the immunometabolic programs. These studies have been mostly conducted on autoimmune $CD4^+$ T cells, with the metabolism of other immune cells in autoimmune settings still being understudied. Here we discuss systemic metabolism as well as cellular immunometabolism as novel tools to decipher fundamental mechanisms of autoimmunity. We review the contribution of each major metabolic pathway to autoimmune diseases, with a focus on systemic lupus erythematosus (SLE), with the relevant translational opportunities, existing or predicted from results obtained with healthy immune cells. Finally, we review how targeting metabolic programs may present novel therapeutic venues.

Keywords

Lupus; metabolism; glucose; glutamine; metabolic inhibitors

1. Introduction

The immune system has evolved to respond to challenges from pathogens with rapidly proliferating immune cells equipped with highly specialized effector functions that are performed changes in cellular programs that produce new effector molecules, such as antibodies and cytokines. The energetic requirements to meet these challenges have only been investigated recently, although immune cells, were routinely cultured in laboratories with large amounts of nutrients, especially glucose and glutamine. It was first shown in 2002 that the ligation of the co-stimulatory receptor CD28 upregulated glucose uptake by $CD4^+$ T cells by activating the PI3K pathway[1]. This simple *in vitro* experiment was the first to

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establish a mechanism connecting cellular metabolism and immune activation. A requirement for glycolysis was established for B cell activation and differentiation a few years later, when it was shown that B cell receptor signaling also activated glucose uptake through the PI3K pathway[2]. These two seminal studies have launched the field of immunometabolism with an ever growing number of studies to characterize the energy needs of the immune system and to define the specific metabolic programs used by immune cells to achieve rapid growth and polarization into highly specialized effector functions[3]. Initially focused on the metabolism of immune cells, studies performed in mouse models or with patients with autoimmune diseases have later associated their impaired immune system with metabolic abnormalities, which were predicted to present novel therapeutic targets[4,5]. Early on, parallels have been established between rapidly proliferating activated lymphocytes and tumor cells both relying on glycolysis in the so-called Warburg effect[6]. Cellular metabolism research in oncology is still largely leading the field, with the goal of dissecting intricately dysregulated metabolic networks in both tumors and infiltrating immune cells[7,8]. Recent publications have reviewed how immunometabolism controls rheumatic diseases[9], including systemic lupus erythematosus (SLE)[10], which is, with rheumatoid arthritis, the autoimmune disease with the most advanced understanding of cellular metabolism.. This includes small clinical trials in which lupus patients have seen a reduction in disease activity following treatment with metabolic inhibitors[11,12]. Here, we review how the major metabolic pathways control the activation and differentiation of the immune cell types that are involved in lupus, as well as the studies that have been directly conducted in lupus pre-clinical models or in lupus patients. These studies are summarized in Table 1 along with the treatments with metabolic inhibitors that have been successful in pre-clinical models of the disease. Table 1 also includes metabolic inhibitors that should be evaluated in these pre-clinical models based on their efficacy on specific immune cell types that have a major impact on lupus development.

2. Lupus and systemic metabolism

Immunometabolism commonly refers to the metabolic processes that regulate immune cell responses at the cellular level. Systemic nutrient availability and utilization by the whole organism, and how it may impact the metabolism of immune cells has not been considered to the same extent. It is however well established that obesity induces inflammation, and a recently published study showed that high dietary glucose promotes the differentiation of Th17 cells in mouse models of colitis and experimental autoimmune encephalomyelitis (EAE)[13], a model of multiple sclerosis, an autoimmune disease with pathogenic T cells as SLE. Surprisingly, high dietary glucose did not increased circulating blood sugar nor enhanced glycolysis in T cells, a process necessary for Th17 polarization[14]. Instead, high dietary glucose accelerated TGFβ processing by increasing ROS production. Th17 cells have been implicated in lupus pathogenesis[15]. It is therefore tantalizing to predict that high glucose consumption may aggravate disease in lupus patients, a hypothesis that should be tested in mouse models. It should be noted it is not known whether a reduction in glucose consumption has a protective effect in autoimmunity.

Metabolic syndrome (MetS) corresponds to a cluster of metabolic abnormalities including hypertension, abdominal obesity, dyslipidemia, hyperglycemia and insulin resistance, in

which chronic inflammation and oxidative stress have been proposed as potential mechanisms. SLE patients present a higher risk for developing MetS than healthy controls (HCs)[16,17]. A multivariate analysis has associated MetS with disease activity and steroid exposure in a cohort of SLE patients[18]. Since MetS increases the risk of cardiovascular events in the general population[19], it is also likely that SLE patients with MetS are also at higher risk for cardiovascular disease. Indeed, MetS has been associated with organ damage and vascular events[20], as well as increased subclinical atherosclerosis in SLE patients[21]. Obese women followed over a period of 20 years as part of the Nurses Health Studies (NHSII) had an increased risk of developing SLE compared to lean controls[22], and obesity during teenage years increased this risk further[23]. As another part of manifestations commonly associated with MetS, SLE patients have an increased frequency of dyslipidemia[24]. Interestingly, dyslipidemia expands the number of autoimmune follicular helper T (Tfh) cells and germinal centers (GC)[25]. It is therefore possible that dyslipidemia contributes to the expansion of the number of Tfh cells in SLE patients, a phenotype that correlates with disease activity[26]. Therefore, these results obtained in a mouse model suggested that dyslipidemia enhances autoimmune pathology. Collectively, these findings suggest that MetS could contribute to the development of cardiovascular complications in SLE patients. The validation of a mutual enhancement between MetS and SLE will requires detailed epidemiologic studies in large cohorts of patients as well as mechanistic studies in mouse models combining features of both diseases.

One of such mechanistic studies was conducted in ApoE or Ldlr-deficient chimeric mice carrying the bone marrow of lupus-prone mice and fed with an atherogenic Western diet. In these mice, dyslipidemia increased the production of autoantibodies and the severity of autoimmune pathology[27]. The mechanism responsible for these findings was identified as an expansion of the number of Tfh cells by IL-27 produced by DCs in response to lipids in a TLR4-dependent manner[27]. The importance of this pathway was validated by blocking IL-27, which reduced autoantibody levels and the number of Tfh cells in the chimeric atherogenic mice. Furthermore, higher IL-27 concentrations were found in patients with hypercholesterolemia. An independent study has reported elevated levels of IL-27 produced by DCs in lupus-prone mice, as well as in SLE patients, which were directly dependent on type I IFN signaling[28]. These results suggest a link between IL-27, type I IFN, autoimmunity and dyslipidemia, with a mutual enhancement of the two types of pathogenesis. *ApoA1*-deficiency greatly reduces HDL levels in mice, which present cholesterol-engorged enlarged lymph nodes and also develop an autoimmune syndrome with anti-dsDNA autoantibodies and a spontaneous activation of $CD4^+$ T cells[29]. These reverse genetic experiments suggested that the dyslipidemia induced by an impaired cholesterol import or efflux promotes systemic autoimmunity.

On the opposite spectrum from MetS, calorie restriction (CR) has been shown to modulate immune cells toward less inflammatory phenotypes, some of which may be directly involved in lupus pathogenesis. T cell phenotypes associated with aging, including memory cell accumulation and reduced naive cell frequencies, were both attenuated by CR[30]. Another study has found however that memory T cells accumulated in the bone marrow during CR where they were protected and displayed enhanced functionality[31]. Additionally, fasting reduced the number of gut-associated B cells in Peyer's patches, directly by apoptosis for

GC B cells and indirectly by migration to the bone marrow for naïve B cells[32]. Upon re-introduction of calories, naïve B cells migrated back to Peyer's patches[32]. Therefore, it is possible that CR may modulate B cell populations and autoantibody levels in lupus. Within the innate immune system, circulating monocyte frequency and functionality were reduced in response to fasting in both humans and mice, which improved clinical parameters in EAE[33]. Similarly, intermittent fasting was protective in EAE[34,35], and protection was mediated at least in part by microbiota changes[35]. Protective microbiota changes have also been observed in response to CR in a model of induced colitis and in human inflammatory bowel disease[36], suggesting that it may be a major mechanism for the immunomodulatory effect of CR.

Evidence suggests that CR is protective in murine models of SLE[37] (Table 1). CR in NZB/W lupus-prone mice prolonged lifespan[38], prevented renal immune complex deposition[39], and modulated renal aquaporin expression[40], the latter of which is associated with renal disease[41]. CR also suppressed lupus nephritis in NZB/W mice in parallel with a reduced presence of platelet-derived growth factor (PDGF) and thrombin receptor in renal tissue, which are known to be involved in glomerular inflammation[42]. These studies suggest that CR attenuates parameters associated with kidney pathology in murine models of lupus. Remarkably, CR delays and attenuates disease in NZB/W mice to a similar extent as cyclophosphamide, a cytotoxic drug that is used in the clinic to treat severe lupus, by reducing autoantibody levels, B cell activation, and IL-10 production in addition to increasing IL-2 levels[37]. Additionally, CR decreased pro-inflammatory cytokine production in NZB/W mice[43]. Overall, studies suggest that CR has a protective effect in lupus by modulating autoimmune phenotypes in murine models. However, these promising results have not been validated in SLE patients, in which CR did not change disease activity[44]. This study was however limited by very short (6-weeks) duration and a small cohort size, and did not account for the use of immunomodulatory drugs. Therefore, the potential benefits of CR in SLE should be still considered as an open question. Moreover, the specific mechanisms of the potential beneficial effects of CR in lupus have not been elucidated. On the opposite side of systemic metabolism, it would be of great interest to investigate whether the increased frequency of Th17 cells observed in mice with a high glucose intake[13] could also accelerates lupus pathology.

It is also possible that the effects of CR are indirect and mediated by adipokine alterations. Adipokines are a group of peptides including leptin and adiponectin synthesized by white adipose tissue (WAT) that regulate energy homeostasis, but are also involved in inflammation[30]. Altered levels of adipokines have been reported in patients with MetS[45] and with SLE, as detailed below. Leptin regulates energy homeostasis in the neuroendocrine system by increasing satiety to simultaneously limit food intake and promote energy utilization. Leptin contributes to inflammation through both innate and adaptive mechanisms, which may be due to its structural similarity to several pro-inflammatory cytokines, including IL-6[46]. High levels of circulating leptin correlate with disease activity in SLE patients[21,47–51]. Fasting decreases the production of leptin and expands the frequency of $FOXP3^+$ regulatory (Treg) cells in SLE patients leading to a reduced disease activity[52]. However, SLE patients with reduced serum leptin have also been reported in some studies[53,54], while others show no difference between SLE patients and HCs[55].

Genetic variations in the leptin and leptin receptor genes are associated with some clinical parameters of SLE such as photosensitivity and pericarditis, in spite of a lack of association with genetic susceptibility to SLE[56]. High leptin levels in SLE patients correlate with vascular stiffness parameters, increased risk for atherosclerosis, and with increased inflammatory atherosclerotic biomarkers[57,58]. Furthermore, high levels of circulating leptin correlate with subclinical atherosclerosis in SLE patients with MetS[21]. Additionally SLE patients with plaque present higher leptin levels than SLE patients without plaque[58]. Therefore, high leptin levels may link some of the manifestations of MetS and SLE.

Leptin levels also influence immune cell functions. Leptin signaling is necessary for murine Th17 effector functions[59], and it skews human and mouse T cells toward a Th1 phenotype *in vitro*[60,61], which is relevant to SLE patients who present an increased frequency of Th1 cells and IFNγ production. Transgenic expression of leptin in pigs results in a lupus-like disease characterized by increased anti-dsDNA antibodies, renal immune complex deposition, nephritis, and decreased frequency of Treg cells[62]. Leptin levels inversely correlate with the frequency of Treg cells in SLE patients[48]. Leptin deficiency in MRL/lpr lupus-prone mice was protective for disease development and it increased the frequency of Treg cells[63]. Likewise, leptin inhibited Treg cell polarization *in vitro* and its neutralization resulted in Treg cell expansion in NZB/W mice[64]. In this same study, leptin administration accelerated disease, whereas blocking leptin delayed disease progression[64]. Leptin deficiency in MRL/lpr mice also lowered serum IL-17 levels[63]. Similarly, leptin enhanced Th17 responses in NZB/W mice by inducing RORγt expression[63,65] and increasing Th17 polarization *in vitro*[63]. Leptin has also been shown to increase glycolysis in murine T cells and consequently enhance effector function[66]. Therefore, there is a consistent association between high leptin levels and enhanced pro-inflammatory effector T cell populations. In addition to its effects on T cells, leptin activates B cells and augments the production of pro-inflammatory cytokines as well as that of IL-10[67,68]. Interestingly, these T cell phenotypes may be induced indirectly by leptin promoting the clearance of apoptotic cells by macrophages, which increases the availability of phagocytized self-antigens to stimulate autoreactive T cells in NZB/W mice[69,70]. In summary, leptin activates B cells, increases the frequency of Th17 and Th1 cells while decreasing the frequency of Treg cells, and it may due at least in part to increased self-antigen availability, all of which are lupus-relevant phenotypes.

Adiponectin is another adipokine synthesized by WAT and it is generally considered to be an anti-inflammatory cytokine. Adiponectin gene polymorphisms are not associated with SLE risk[71], but high levels of adiponectin have been reported in SLE patients with and without lupus nephritis. Correlations with disease activity are however contradictory[50,55,72–74]. PBMCs of SLE patients present higher amounts of adiponectin transcript and protein as compared to HCs, but there is no correlation between adiponectin expression levels and clinical parameters or disease activity indexes[75]. Moreover, increased adiponectin levels in MRL/lpr mice do not promote disease progression[76]. Thus, both adiponectin and leptin levels are increased in lupus, but only leptin appears to contribute to disease phenotypes by modulating immune cell functions.

3. Cholesterol homeostasis in lupus

The function of immune cells is regulated by cholesterol through multiple mechanisms. First, cholesterol is an integral part of all cell plasma membranes, and a limiting factor for membrane synthesis, and hence, for cellular proliferation. A second function of cholesterol that is more specific to immune cells is its regulation of lipid raft assembly, thus regulating signaling in major pathways such as TCR, BCR TLRs and MHC, which are all lipid-raft dependent[77–79]. A direct demonstration of the immune regulatory role of cholesterol through this pathway was provided by the analysis of mice with ApoE-deficient dendritic cells (DCs), in which the impaired removal of cholesterol from the membrane led to an accumulation of lipid rafts. This promoted MHC-II clustering and increased antigen presentation, which, in turn, expanded pro-inflammatory $CD4^+$ T cells that supported skin allograft rejection, independently of dyslipidemia[80]

Cholesterol homeostasis balances synthesis, import into the cells, and efflux outside the cell. Cholesterol is synthesized by the HMG-CoA reductase, the therapeutic target of statins, and whose expression is regulated by the transcription factor SREBP[81]. Cellular import of cholesterol is performed by apolipoprotein E (ApoE) and the low density lipoprotein receptor (LDLR). The opposite efflux of cholesterol from immune cells is performed by apolipoprotein A1 (ApoA1) and the high density lipoprotein receptor (HDLR) mediate through the expression of liver X receptor (LXR)-regulated genes, such as the ATP-binding cassette transporters ABCA1 and ABCG1.

Cholesterol synthesis is low in immune cells relative to other cell types such as hepatocytes. Directly relevant to SLE, type I IFN promotes cholesterol import over synthesis[82]. This observation predicts that lupus-immune cells that are exposed to high levels of type I IFN would depend on a high cholesterol uptake for their proliferation and activation. Therefore, LXR agonists that promote cholesterol efflux should have a beneficial effect on lupus pathology. This hypothesis was verified in a pristane-induced model of diffuse alveolar hemorrhage, in which the protective effect of an LXR agonist reprogrammed IFN-induced M1 macrophages to an M2-macrophage like phenotype[83]. Similarly, LXR-deficiency resulted in the development of systemic autoimmunity in mice with a defect in apoptotic cell clearance, while a LXR-agonist reduced autoimmune manifestations in the B6.lpr model of lupus[84]. The contribution of LXR-regulated cholesterol homeostasis was also demonstrated by the analysis of *Abca1/g1* deficient mice, which presented lymphadenopathy and glomerulonephritis[85,86]. Interestingly, DCs were the functional cell type in these mice in which alterations in cholesterol efflux was responsible for immune activation. *Abca1/g1* deficiency activated the inflammasome in DCs, which proliferated and secreted cytokines that ultimately expanded lupus-associated effector lymphocyte populations, namely Th1, Th17 and Tfh cells, GC B cells, and plasma cells[86]. As expected, *Abca1/g1* deficiency enhanced lipid-raft associated signaling, such as inflammatory responses to TLR4 activation in macrophages[87], and TCR signaling and proliferation in T cells[88]. It is not clear, however, why, contrary to DCs, these phenotypes did not lead to autoimmunity, and further studies are necessary to better understand cell-specific and intrinsic mechanisms of immune cell activation by cholesterol efflux. Given the association of MetS and lupus, it would also be of

great interest to link circulating cholesterol levels with cellular immune metabolism and activation.

4. Metabolite profiles in lupus

Metabolite profiling of SLE patients has revealed differences with HCs[89–92]. Serum metabolite profiles also differ between patients separated by disease activity scores[89], and between SLE patients with and without lupus nephritis[92]. Additionally, the metabolome of SLE patients is different from that of patients with other autoimmune diseases such as primary Sjogren's syndrome and systemic sclerosis[89], suggesting that these metabolic signatures are not a global result of autoimmunity, but rather are specific to SLE. Compared to HCs, SLE patients have increased metabolites related to oxidative stress[89–91], and decreased amino acids[89–92]. Some decreases of amino acids such as arginine[89] could increase the levels of nitric oxide metabolites related to oxidative stress, which play a role in the pathology of SLE[93]. One of the amino acids with the most altered level in SLE patients is tryptophan[89,94–96]. SLE patients have depleted levels of tryptophan, and opposite alterations in the levels of its proximal metabolites, decreased serotonin and increased kynurenine levels[94–99]. It is possible that these metabolite alterations are a reflection of upregulated indolamine 2,3-dioxygenase (IDO1) expression[94,95]. In fact, it has been hypothesized that an increased IDO1 expression in lupus is due to the type I IFN signature observed in patients[95], as IFNα is known to upregulate IDO1. IDO1 protein levels were increased upon *in vitro* stimulation of a cell line with serum from SLE patients[95]. Regardless of the mechanisms responsible for the altered tryptophan metabolism, it is correlated with disease activity in SLE patients. Depleted serotonin in SLE patients inversely correlated with nephritis and anti-dsDNA autoantibodies[95] and the kynurenine/tryptophan ratio correlated with severe fatigue[94]. Kynurenine was also one of the most increased metabolites in SLE peripheral blood leukocytes (PBLs) and it allowed for discrimination between responder and non-responder SLE patients to a treatment with N-acetylcysteine (NAC)[100]. Furthermore, kynurenine activated mTOR in healthy PBLs[100], suggesting that this metabolite may directly influence cellular metabolism. Along with altered amino acids, dyslipidemia and hypercholesterolemia were also found in SLE patient metabolite profiles[89–92,101–103]. 25-hydroxyvitamin D3 is significantly depleted in SLE serum[104–106], suggesting that the loss of immunomodulatory vitamin D metabolites may play a role in pathogenesis. Indeed, vitamin D deficiency inversely correlates with SLE disease activity in addition to other clinical parameters[105,107].

A recent analysis found significant differences in fecal metabolite profiles between SLE patients and HCs[108], which ultimately could allow for a non-invasive screening for SLE-associated biomarkers. Similar to serum profiles, the most altered fecal metabolites were related to amino acid, lipid, and vitamin metabolism, as well as an enriched nitrogen and tRNA biosynthesis in SLE patient fecal contents[108]. Fecal metabolomics may be important considering increasing reports of altered SLE fecal microbiomes both in patients and murine models of lupus[109–115]. Pathway analyses of serum metabolite profiles also suggested an altered gut microbial metabolism in SLE patients compared to HCs[101,116], including an increase in total free fatty acids (FFAs) and short chain fatty acids (SCFAs) synthesized by bacteria[112]. Additionally, disrupted metabolic pathways were found in the urine of SLE

patients compared to HCs including amino acid, TCA cycle, and purine/pyrimidine metabolism[116].

A major challenge in metabolomic studies in SLE is the use of cytotoxic and immunosuppressive drugs, such as steroids, which could themselves shift metabolite profiles. In addition, the links between systemic and cellular metabolic alterations are largely unknown, and it is not clear if alterations in systemic levels of specific nutrients impact availability at the cellular level. Nonetheless, studies have highlighted energy homeostasis, oxidative stress, and amino acid metabolism as major global metabolic pathways that are disrupted in SLE patients.

5. MTOR activation in lupus

Mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK) are major sensors of the cellular energy status, which represents a major regulation of the activation and differentiation of immune cells[117]. High levels of AMP, in response to either poor nutrient availability and reduced ATP production, or high ATP consumption activate AMPK. Activated AMPK restores intracellular ATP levels by reducing its consumption, mostly by inhibiting protein synthesis, while promoting ATP synthesis through metabolic processes such as fatty acid oxidation (FAO) and glucose uptake, as well as cellular processes such as autophagy[118]. Activated AMPK also inhibits the activation of mTOR, a kinase complex that promotes energy consuming processes. The catalytic subunit of mTOR signals through two multimeric complexes, mTORC1 and mTORC2, which only differ by their scaffold proteins RAPTOR and RICTOR, respectively. Activation of both complexes promotes glucose metabolism, linking mTORC and glycolysis.

Metformin is a drug with multiple targets, one of which is the activation of AMPK[119]. SLE patients that received metformin as an add-on treatment to their standard of care showed disease improvement[120]. Metformin also showed some efficacy in mouse models of lupus[121–123]. mTOR activation has been to be directly implicated in the $CD4^+$ T cell phenotypes of lupus-prone mice[121] and lupus patients[124]. It has been recognized early that treatment with rapamycin, an mTOR inhibitor, reduced the severity of disease in nephritic NZB/W mice[125]. More importantly, the therapeutic efficacy of inhibition mTOR has been demonstrated in patients with refractory SLE, in which treatment with sirolimus improved disease activity and reduced prednisone exposure[126], two major end-points in lupus clinical trials. Sirolimus may also have therapeutic potentials for patients with refractory lupus nephritis[127]. The encouraging results obtained by these two independent one-arm, open-label, retrospective studies indicate a need for follow-up double-blind larger clinical trials in ethnically diverse patient populations to identify the lupus patients that may benefit from mTOR blockade. Further, the identity of the effective cellular targets of AMPK activation by metformin or mTOR inhibition in lupus patients is unclear. Surprisingly, a reduced number of effector memory $CD8^+$ T cells was the best predictor of the therapeutic response to sirolimus in SLE patients[126], although the role of this T cell subset is yet undefined in lupus. These findings urge caution in the extrapolation of studies with *in vitro* treatment of purified immune cell populations or cell-specific genetic targeting, which may lead to significant results, but with little relevance to the action of the drug when administered to patients.

Studies in mice have shown that mTOR activation promotes the differentiation of Th1, Th17[128], as well as Tfh T cells[129], which are T cell subsets associated with lupus[130,131]. On the other hand, AMPK activation promotes the expansion of the Treg cell subset. Treg cells in which AMPK activation is impaired by the deletion of *Lkb1*, its upstream kinase, presented an impaired function that promoted a Th2-dominant severe autoimmune phenotype[132,133]. A complex role of mTOR in Treg cells has emerged from genetic targeting experiments. MTOR limits the maintenance of long-lived central Treg cells, but promotes the differentiation of effector Treg cells[134]. *Mtor* deficiency reduced the frequency of Treg cells, resulting in the expected corresponding spontaneous effector T-cell activation that has been reported for other Treg altering mutations[135]. PP2A is a serine-threonine phosphatase that prevents the development SLE by limiting the production of IL-2 and IL-17 by $CD4^+$ T cells[136]. *Pp2a*-deficient Treg cells were impaired as a result of an increased mTORC1 activation, resulting in a severe systemic autoimmune phenotype[137]. Overall, these results showed that Treg cells require an intermediate level of mTOR activation, and that dephosphorylation by PP2A is one of the mechanisms by which this balanced activation is maintained. Follicular regulatory T (Tfr) cells are GC-specific Treg cells, and the number or function of Tfr cells may be defective in lupus patients[138]. As for their Treg cell precursors, the function and differentiation of Tfr cells also requires mTORC1-activation[139]. Overall, these results suggest a profound mTOR-dependence of the T cell subsets that have been associated with lupus and that limiting mTOR activation in $CD4^+$ T cells is required to prevent the development of systemic autoimmunity.

In addition to $CD4^+$ T cells, mTOR is over-activated in the B cells of SLE patients, and it correlates with plasmablast numbers and disease activity[140]. In the $Roquin^{san/san}$ lupus-prone mouse, treatment with either metformin or rapamycin inhibited B cell differentiation into GC B and plasma cells, and reduced disease activity, which implicated the AMPK/mTOR pathway in the activation of autoreactive B cells[123]. These results also suggest that a high basal level of mTOR activation may set a lower threshold for B cell activation and differentiation, although neither study in SLE patients or in the $Roquin^{san/san}$ mice could distinguish B-cell intrinsic mTOR activation. In fact, the role of mTOR in B cells is not well understood, with evidence for contributions to B cell development, differentiation, survival and function that may differ between specific differentiation stages[141]. Genetic ablation showed that a more preeminent role of mTORC1 activation in the early pro-B to small pre-B cell stages in the bone marrow as compared to the peripheral resting immature and recirculating mature B cells[142]. Negative selection of self-reactivity is a critical checkpoint for transitional B cells, which then mature into resting follicular B cells that achieve metabolic quiescence by simultaneously dimming mTORC1 and activating AMPK in both humans and mice[143]. In peripheral B cells, deletion or inhibition of the mTORC1 pathway reduced GC development, the production of high-affinity antibody, and class-switch recombination in mice after immunization[144,145]. Neither inducible deletion of *Raptor* nor acute treatment with rapamycin had measurable effects on either naive or antigen-specific memory B cells after immunization[146], suggesting that mTORC1 activation is not required for these B cell subsets. However, both rapamycin and *Raptor* deletion in B cells eliminated newly formed plasma cells and pre-existing GCs[146]. Interestingly, antibody production was decreased in a reversible manner by these two approaches, but the frequency of long-lived

bone marrow plasma cells or their survival were unaffected[146]. Opposite results were obtained in plasma cells in which *Tsc1*, a negative regulator of mTORC1, was deleted. *Tsc1*$^{-/-}$ plasma cells showed an enhanced antibody production and its associated endoplasmic reticulum stress response, but displayed shorter lifespans[147]. The same phenotypes were displayed by plasma cells deficient in *Atg5*[148], a master regulator of autophagy, a process that is inhibited by mTORC1. These results suggest that long-lived plasma cells may require mTOR activation to maintain longevity, but that the production of autoantibodies by short-lived plasma cells may be enhanced by mTOR inhibition. Lupus autoantibodies are produced by both types of plasma cells[149], which illustrates the potential complexities of metabolic regulation of immune cell function in the setting of complex autoimmune diseases such as SLE. The effect of mTOR inhibition by sirolimus in SLE patients was not determined in B cells, and only a modest reduction of some autoantibodies was observed[126], although the study was underpowered for the analysis of treatment outcomes on autoantibody production. It is therefore still unclear whether lupus B cells or plasma cells have a functionally over active mTOR. Treatment of mice with Torin1, which inhibits both mTORC1 and mTORC2 signaling[150], reduced modestly the numbers of immature, marginal zone and transitional B cells[146]. These results compared to the effect of rapamycin[144–146], which targets primarily mTORC1, may suggest a role for mTORC2 signaling in naive B cell development and homeostasis, while mTORC1 affects the later stages in development[151]. Overall, more studies are needed on the consequences of either mTOR deletion or over-activation in the B cell subsets that are directly relevant to lupus, such as transitional B cells, GC B cells, short- and long-lived plasma cells. It would be also of great interest to determine whether that a high basal level of mTOR activation may set a different tolerance threshold allowing the escape of autoreactive B cells.

The role of mTOR in DCs is largely unknown, but it has been proposed that it integrates pattern recognition signals with energy status for optimal DC activation and effector functions[152]. DCs, including plasmacytoid dendritic cells (pDCs), are active participants in lupus pathogenesis, but it is unknown whether it involves mTOR activation. Overall, multiple studies with human cells and in mouse models have converged to demonstrate a central role for mTOR in lupus by potentially affecting multiple cell types. The therapeutic efficacy of the modulation of the mTOR – APMK axis with sirolimus and metformin, respectively, provides an incentive for detailed mechanistic studies in mouse models as well as in lupus patients.

6. The HIF pathway in lupus

Hypoxia-induced transcription factor *HIF1α*, the master regulator of the cellular response to hypoxia, exerts potent effects on the immune system that are not directly related to oxygen levels, such as the activation of glycolysis with the associated pro-inflammatory consequences described in the next section[153]. Th17 polarization is HIF1α-dependent[154], which suggested that targeting HIF1α could be beneficial in lupus. Th1 and Th17 differentiation was reduced by inhibiting HIF1α with echinomycin, and treatment with this drug reduced the manifestations of acute graft-versus-host disease (aGHVD) in a mouse model[155]. Furthermore, inhibition of *Hif1α* with RNAi ameliorated disease in MRL/lpr lupus-prone mice, which presented a strong reduction of IL-17 production[134]. Interestingly,

HIF1α protein expression in Th17 cells is regulated by glutaminase GLS1, through which glutaminolysis indirectly controls glycolysis in this T cell subset[15]. Accordingly, MRL/lpr mice treated with the GLS1 inhibitor BPTES showed attenuated lupus outcomes in a Th17-dependent manner, and BPTES decreased the polarization of Th17 cells in SLE patients[15].

Specific tissue microenvironments such as tumors or the inflamed kidneys in lupus nephritis[156] are hypoxic. Directly relevant to humoral autoimmunity and lupus, it has been recently recognized that cells in the GC microenvironment have to cope with low amounts of oxygen. A dynamic balance between metabolic activation and inhibition occurs in GC B cells in response to oxygen sensing[157,158]. Expression of HIF1α is higher in GC B cells than in other splenic B cells. In the GC light zone (LZ), hypoxia promotes a higher glycolytic rate, which increases B cell apoptosis, diminishes proliferation and impairs immunoglobulin class switching by limiting AID expression[157]. These features are required for the antigen-driven selection process in the GC LZ. Sustained hypoxia or HIF stabilization inhibits mTORC1 activity in B lymphoblasts in the DZ, which impairs their proliferation and class-switching[157]. These findings demonstrate that oxygen sensing and rapid switch to the corresponding metabolic program is an essential requirement of GC B cells. Cell-specific deletions as well as *in vitro* activation in hypoxic conditions have also shown that Hif1a expression is necessary for optimal $CD4^+$ T cell effector functions, including cytokine secretion and co-stimulation of B cells in humoral responses[159]. The production of high affinity autoantibodies by GC B cells that receive T cell help is highly relevant to lupus, and whether lupus GCs are regulated by the HIF pathway in the same manner as what has been described for non-autoimmune GCs is a question that remains to be answered.

7. Glycolysis and Lupus

Glycolysis refers to the conversion of glucose to pyruvate through eight metabolic intermediates in a process that generates two molecules of ATP. It also produced NADH, which donates an electron to complex I of the electron transport chain (ETC) to initiate oxidative phosphorylation (OXPHOS). Pyruvate has the one of two fates: oxidation in the Krebs cycle to produce of up to 38 molecules of ATP per molecule, or reduction into lactate when rapid cellular proliferation boosts the demand for metabolite intermediates, such as NAD. Glycolysis commonly refers to the lactate reduction of pyruvate, as opposed to glucose oxidative or mitochondrial (mt) metabolism.

Lupus $CD4^+$ T cells in either SLE patients or spontaneous mouse models are characterized by a high level of glucose metabolism[121], which is largely oxidation in the mt[122]. The high level of oxygen consumption and oxidation that have been reported in murine and human lupus $CD4^+$ T cells[121,160] is most likely largely used for this process. Glucose uptake through glucose transporters represents the first rate-limiting step of glycolysis. Glucose transporters are members of the large family of solute transporters (*Slc*) that serve as gate keepers of nutrient uptake and trafficking between cellular compartments. Only a fraction of Slc members have well characterized substrates and functions. Besides Glut1, the role of the other glucose transporters in immunometabolism is unknown, even when a differential expression has been validated, such as for *Glut6*, which is overexpressed in the spontaneous Tfh cells of lupus mice[161]. Glut1 is the glucose transporters that is expressed at the highest

level by T cells upon TCR and CD28 signaling[162]. Mice transgenic for *Glut1* accumulate activated CD4$^+$ T cells, produce autoantibodies and present an immune complex deposition in the glomeruli akin to an early stage lupus nephritis[163]. Furthermore, *Glut1* overexpression increased the numbers of Tfh and GC B cells, leading to elevated IL-21 and IgA production[129]. Although overexpression of *Glut1* in mice was not sufficient to induce lupus, SLE patients with active disease present a higher GLUT1 on effector memory CD4$^+$ T cells as compared to either HCs or patients with inactive disease, and this elevated GLUT1 level was associated with an elevated expression of calcium/calmodulin-dependent protein kinase 4 (CaMK4)[164]. CaMK4 is a major regulator of pathogenic T cells in lupus through its regulation of IL-2 and IL-17 expression[165]. Accordingly, the polarization of human Th17 cells, an effector subset that is highly dependent of glycolysis[154], was reduced by CaMK4 inhibition, which reduced GLUT1 expression. Moreover, CaMK4 inhibition decreased the production of glycolytic intermediates by activated CD4$^+$ T cells from MRL/lpr lupus prone mice[164]. These results showed a functional link between CaMK4 and glycolysis in T cells and suggests that the beneficial effect of CaMK4 inhibition in lupus[166] may be due at least in part through the mitigation of immunometabolism.

Importantly, these studies have translational implications by predicting that the inhibition of glycolysis would have beneficial effects in lupus. Treatment of lupus-prone mice with 2-Deoxy-D-glucose (2DG), a glucose analog that inhibits the first reaction of glycolysis, prevented disease, but had only partial therapeutic effects[121,122]. 2DG was sufficient to eliminate the production of autoantibodies, but had little effect on the IFNγ-producing effector memory CD4$^+$ T cells[161]. The combination of 2DG with metformin, which inhibits complex I of the mt electron transport chain (ETC)[167], reduced the number of these pathogenic T cells and reversed lupus pathogenesis in mice[121]. These results indicate that targeting glycolysis, either alone or in combination with other drugs such as metformin, presents a therapeutic potential for lupus[12]. 2DG has been used in clinical trials in oncology without successful outcomes and with some safety concerns[168]. Other glycolytic enzymes have been targeted in mouse models in which inflammatory and/or autoreactive T cells play a role. Inhibiting 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) was very effective in controlling alloantigen activation of CD4$^+$ T cells in a GVHD model[169]. Pyruvate kinase M2 is a glycolytic enzyme that also activates STAT3-mediated transcription when it translocates as a dimer to the nucleus. Blocking this process by enforcing the tetramer configuration reduced glycolysis and the production of inflammatory cytokines in macrophages obtained from patients with atherosclerosis[170]. Perhaps more relevant to lupus, PKM2 is required for Th1 and Th17 polarization[171]. Accordingly, preventing PKM2 dimerization also reduced glycolysis in CD4$^+$ T cells and was protective in EAE[171,172]. Inhibition of either PFKFB3 or PKM2 has not been tested yet in lupus models. Pyruvate dehydrogenase (PDH) represents an essential node in glucose utilization by directing pyruvate to OXPHOS rather than glycolysis. PDH is converted from an inactive to an active form by pyruvate dehydrogenase phosphatase catalytic subunit 2 (PDP2), which is directly involved in Th17 polarization in lupus. Indeed, memory Th17 cells from SLE patients present a reduced PDP2 expression and over-expression of PDP2 in CD4$^+$ T cells from either MRL/lpr mice or SLE patients suppressed Th17 differentiation. This PDH checkpoint of energy production may be ultimately regulated by the transcription factor ICER/CREM in

Th17 cells[173], in a model consistent with the glycolytic requirements of Th17 cells[154] and the expansion of Th17 cells in SLE patients[130]. Finally, dimethyl fumarate, a derivative of the Krebs cycle intermediate fumarate, inactivates GAPDH, which is upstream of pyruvate, therefore inhibiting both branches of glycolysis. Dimethyl fumarate decreasing the differentiation and function of Th1 and Th17 cells, and ameliorates disease in EAE[174]. Dimethyl fumarate is effective in treating multiple sclerosis[175], and discoid lupus in small open-label clinical trials[176,177], in which the cellular and molecular targets of the drug have not been investigated.

As an alternative to inhibit glycolytic enzymes, the pharmacological targeting of GLUT1 has been considered to dampen the pathology induced by autoreactive T cells[178]. A proof-of-principle of the efficacy of this approach was obtained with a compound called CG-5, which blocked glucose uptake and glycolysis in murine and human $CD4^+$ T cells[179]. CG5 ameliorated autoimmune phenotypes and reduced the production of autoantibodies in a spontaneous and an induced model of lupus. In these lupus models, CG-5 reduced the numbers of activated $CD4^+$ T cells and GC B cells, inhibited Th1 and Th17 differentiation and also promoted Treg cell induction.

Multiple studies have shown that effector T cells have a higher requirement for glycolysis than naïve resting T cells, but this requirement varies among effector subsets, with Th17 and Th1 cells being highly glycolytic[180]. These studies have been however largely performed with *in vitro* polarization conditions, and a sophisticated isotope tracing analysis has challenged the high glycolysis requirement of activated T cells in physiological conditions in live mice[181]. Tfh cells in lupus mice present a high level of mTORC1 activation, and they are the most glycolytic $CD4^+$ T cells in these mice. Accordingly, the frequency of Tfh cells, as well as that of GC B cells and the resulting production of autoantibodies, were reduced to non-autoimmune levels by a treatment with 2DG in several mouse models of lupus[161]. Tfh cells from lupus mice express high levels of the lactate transporter Mct4 and produce high amounts of lactate, measured as extracellular acidification rate[161]. This suggests that autoreactive Tfh cells require glucose for anaerobic glycolysis. It has not been excluded, however, that mt metabolism of glucose is also required for the function of autoreactive Tfh cells.

The inhibition of glycolysis also limited the expansion of Tfh cells in the K/BxN mouse model of rheumatoid arthritis (RA). K/BxN mice treated with 2DG showed a reduced joint inflammation, which correlated with a decreased $CD4^+$ T and B cell metabolism and a reduced activation of both adaptive and innate immune cells[182]. Therefore these results showed that autoreactive Tfh cells are highly dependent on glucose in multiple genetic backgrounds and with diverse autoantigens, effectively linking glycolysis, mTORC1 activation and Tfh expansion in autoantibody-mediated diseases. The requirement for mTORC1 activation to expand the number of autoreactive Tfh cells has been established in the $Def6^{tr/tr}Swap70^{-/-}$ DKO mice, in which a dysregulated T cell signaling leads to a lupus-like phenotype[183]. Interesting, at least in this model, the critical role of mTORC1 in Tfh cells is to promote the translation of Bcl6, the master regulator of Tfh cell gene expression[184]. This finding was unexpected since it has been shown that Bcl6 inhibits cellular metabolism including glycolysis, at least *in vitro*[185]. The same result was obtained

in this study for the inhibitory receptor PD-1, which is highly expressed by Tfh cells[185]. Consistent with these findings, inhibiting glycolysis did not impair the induction of Tfh cells in response to protein immunization or to viral infection[161]. This suggests that autoreactive Tfh cells have a uniquely requirement for glucose, which may represent an Achilles' heel for their selective elimination.

Treg cells do not require glucose for either their differentiation or suppressive function[186]. However, the migration of Treg cells to the site of inflammation, a process often overlooked but essential to Treg function in vivo, depends on glycolysis[187]. This process is mediated through a secondary role of the glycolytic enzyme glucokinase, whose expression is induced by PI3K-mTORC2 activation in Treg cells. Glucokinase binds actin and remodels the cytoskeleton allowing for cell migration. This result illustrates that specific metabolic pathways, such as here the PI3K/mTORC2 pathway, may sustain different functions of specific immune cells. In a systemic disease such as lupus in which multiple organs may be affected and which Treg cells are defective in both mouse models and patients[188], treatment with glycolysis inhibitor may therefore have indirect detrimental consequences by increasing tissue inflammation.

Glucose is the main energy source during B cell activation and recent studies have uncovered context and stage specific glucose utilization during of B cell activation and differentiation[189]. B cells show increased glycolysis after activation by a range of stimuli, which result in HIF1α and c-Myc directly binding the promoter of genes encoding for glycolytic enzymes and glucose transporters in B cells[190–192]. Directly relevant to lupus, high levels of BAFF, an essential B cell growth factor that is overexpressed in lupus patients, increased glycolysis in B cells[190]. B cell differentiation after antigen stimulation is energetically demanding and GC B cells increase their glucose consumption and mitochondria mass in comparison to naïve B cells[158,193,194]. The β isoform of protein kinase C (PKCβ), which is highly abundant in B cells and mediates proliferative signaling downstream of the B-cell receptor (BCR), is required for BCR-induced glycolysis[195]. Loss of PKCβ in B cells reduced the activation of the energy-regulating kinase complex mTORC1, resulting in a defective metabolism and mt remodeling, which impaired GC formation and the generation of plasma cells[196]. Plasma cells continuously utilize glucose once they are fully mature[197]. However, plasma cell survival and antibody production are maintained in the absence of *Glut1*, suggesting that other transporters are involved in glucose uptake[190]. Interestingly, glycolysis enhanced by hexokinase-2 overexpression increases plasma cell differentiation over self-renewal and long-term survival, while the inhibition of glycolysis impaired both plasma cell differentiation and survival[198]. Long-lived plasma cells (LLPCs) consume high amounts glucose, which is predominantly for antibody glycosylation. However, LLPCs divert some of this glucose towards pyruvate generation and respiration, a process that is required for their survival[199]. These results show that glucose is required for both lifespan and antibody secretion, although through different metabolic pathways. Surprisingly, glucose metabolism in B cells has not been directly examined in the context of lupus. Although a normalization of GC B cell phenotypes has been reported in lupus mice treated with 2DG[161], it is unclear how much of this effect is B-cell intrinsic, or secondary to the effect of 2DG on Tfh cells.

Overall, a number of studies converge in identifying glycolysis as a pathway that may offer direct or indirect targets to limit the expansion of effector immune cells in autoimmune diseases leading to effective and maybe selective disease reduction. These promising results should however be validated in detailed disease-specific analyses of pre-clinical models to identify the specific pathways in the glucose flux and their cellular targets, as well as to what extent they are specific to autoreactive cells.

8. Oxidative phosphorylation and Kreb's cycle in lupus

The ETC is a series of four multimeric protein complexes in the mt inner membrane in which electrons are transferred from donor to acceptors to ultimately produce ATP and reactive oxygen species (ROS) in a process known OXPHOS[200]. The electron donors NADH and FADH2 are produced by the Kreb's cycle, which represents a chain of enzymatic reactions that oxidize fatty acids (FA), glutamine and acetyl-CoA derived from pyruvate. The Kreb's cycle is also a source of metabolite intermediates for the synthesis of amino acids and FA. Truncated or "broken" Kreb's cycles have been described in inflammatory conditions, leading to the accumulation of some of its metabolite intermediates, including ROS, instead of their recycling.

Type 1 IFN promotes OXPHOS and FA oxidation (FAO) in pDCs, which is critical for their activation and amplification of IFN production[201]. Since type 1 IFN production by pDCs is central to lupus pathogenesis, it is possible that OXPHOS inhibition specifically in pDCs would have beneficial effects. Although protocols to achieve cell-specific metabolic inhibition have not yet been identified, it is possible that the overactivation of a metabolic pathway in a specific cell type makes it a preferential target for inhibition, a hypothesis that needs to be formally tested. It is unknown whether other myeloid cells and B cells have altered OXPHOS or FAO metabolism in autoimmune diseases[202]. However, secondary signals delivered either by TLRs or T cell help are necessary to rescue BCR-activated B cells from mt dysfunction[189]. In addition, LLPCs, as stated above, require mt import of pyruvate[199]. Whether these metabolic determinants are altered in activated B cells and LLPCs in the context of lupus remains to be determined.

Multiple parameters of mt dysfunction has been reported in the $CD4^+$ T cells from SLE patients and lupus-prone mice, including increased mt mass, membrane hyperpolarization, production of ROS intermediates and ATP depletion[121]. The ultimate cause of mt dysfunction resulting in a hyperoxidative state of $CD4^+$ T cells in lupus is unknown, but may have a genetic basis. This is a largely unexplored hypothesis. However, in its support, the murine lupus gene corresponding to *Sle1c2* is *Esrrg*, which encodes for the nuclear receptor ERRγ that transactivates the expression of many genes involved in mt metabolism, including OXPHOS, in many cell types[203]. The NZM2410 lupus-prone mice carry a hypomorph allele of *Esrrg*, which is associated with $CD4^+$ T cells hyperactivation and defective Treg cells[203].

Oxidative stress characterizes the lupus immune system and promotes its activation at multiple levels[204]. Oxidized mtDNA, which is released by necrotic cells as well as by the extracellular traps (NETs) produced by activated neutrophils, has emerged as a major

stimulant of the production of type I IFN, and its circulating levels correlate with disease activity in SLE patients[205,206]. Moreover, $CD4^+$ T cells of SLE patients are depleted in glutathione, a major natural antioxidant. Accordingly, the by-products of oxidative stress have been tested as therapeutic targets in lupus. A treatment with N-acetyl-cysteine (NAC) that replenishes glutathione levels normalized the elevated oxygen consumption by lupus $CD4^+$ T cells *in vitro*[207]. Treatment of SLE patients with NAC decreased disease activity indexes in a double-blind placebo-controlled pilot study, with a reduction of mTOR activity in T cells[208]. Treatments with MitoTempo, another inhibitor of mt ROS production, delayed disease progression in MRL/lpr mice[206], and it should be further explored in other preclinical models of lupus. Additional pre-clinical studies and clinical trials with anti-oxidants will be necessary to identify cellular targets and define biomarkers that may predict clinical responsiveness[209].

A recent study revealed that kidney infiltrating T cells (KITs) in several models of lupus nephritis present a metabolically exhausted phenotype reminiscent to the exhaustion of tumor infiltrating lymphocytes[210]. OXPHOS and well as the spare respiratory capacity, which is defined as an energy reserve to be used upon challenge, were lost in both $CD4^+$ and $CD8^+$ KITs. It is unclear how metabolically exhausted T cells can participate to the disease process in lupus nephritis in mouse models[211,212] and patients[213,214]. Another unexpected finding related to OXPHOS in lupus was that C1q, a member of the complement pathway that initiates efferocytosis, modulates the mt metabolism of $CD8^+$ T cells in cGVHD, an induced model of SLE[215]. Mice deficient in C1q suffered a reduced cGVHD induction because C1q-deficient effector memory $CD8^+$ T cells presented diminished mt functions. This novel role of C1q in the regulation of mt metabolism in $CD8^+$ T cells needs to be further explored in the context of systemic autoimmunity in which little is known.

Although the mechanisms of mt dysfunction in lupus remain globally unexplored, its therapeutic potentials have been considered through the targeting of OXPHOS, glutaminolysis, FAO, and the Kreb's cycle. Succinate, which classically bridges the Krebs cycle and OXPHOS, is also a mediator of inflammation[216]. Succinate builds up in Treg cells in which mt complex III has been deleted and contributes to their dysfunction[217]. In addition, a novel $CXCR5^-CXCR3^+PD1^{hi}CD4^+$ T cell population provides help to B cells in the blood and the tubular interstitium of SLE patients in the form of succinate, along with IL-10, rather than IL-21[218]. Succinate accumulates in these helper T cells as a result of stimulation by oxidized mtDNA, high levels of ROS production and reverse electron transport, and it stabilizes HIF1α and increases glycolysis. Excess succinate secretion requires PD1 signaling in the CXCR5-negative helper T cells and binds the SUCNR1 succinate receptor cell expressed on B cells. SUCNR1 signaling was already known to induce pro-inflammatory phenotypes in innate immune cells, including RA[219] and MetS[220]. This novel study[218] now suggests that succinate sensing plays an essential role in the activation of autoreactive B cells in lupus. Itaconate is another metabolite that presents non-metabolic signaling functions. In addition to enhancing the oxidation of succinate to fumarate, and therefore reducing intracellular succinate accumulation, itaconate triggers multiple pathways to alleviate IL-17-driven inflammation[221]. Permeable itaconate, 4-octyl itaconate (OI) restricted the type 1 IFN response and the production of inflammatory cytokines by macrophages[222,223]. OI was tested in PBMCs from lupus patients in which it

decreased the production of pro-inflammatory cytokines, such as TNFα and IL-6, through the activation of NRF2 signaling[224]. These important recent developments in immunometabolism research should lead the implementation of studies to test whether Kreb's cycle metabolite intermediates that have secondary immune signaling functions could be targeted in lupus.

Metformin is a drug wide used to treat type 2 diabetes by preventing neoglucogenesis. Metformin transiently inhibits mt ETC complex I, decreasing OXPHOS and ATP production which indirectly leads to AMPK activation, with therefore the potential to interfere with key immunological processes. Metformin is anti-inflammatory by promoting the induction of Treg cell differentiation and blocking STAT3 activation, which has been attributed to either AMPK activation and mTORC1 inhibition, or increased FAO[225]. *In vitro*, metformin inhibits IFNγ production and promoted IL-2 production by $CD4^+$ T cells from SLE patients and lupus-prone mice[121]. A treatment combining metformin and 2DG reversed disease biomarkers in several lupus mouse models, which correlated with a decreased respiration in $CD4^+$ T cells[121]. Finally, metformin or other ETC inhibitors reduced the response of $CD4^+$ T cells from both HCs and SLE patients to type 1 IFN by inhibiting pSTAT1 Y701 phosphorylation[226]. This result suggests that metformin treatment may benefit SLE patients with a high type 1 IFN activity. As mentioned above, metformin added to standard-of-care treatment reduced the risk of disease flares and corticosteroid exposure in SLE patients with mild/moderate disease activity[120]. The mechanisms of action of metformin were not investigated in this study. Nonetheless, these promising results have led to a prospective, multicenter, double blinded, placebo controlled, clinical trial (NCT02741960) of metformin as an add-on therapy in SLE patients with mild disease activity.

Finally, ATP, the final product of ETC activity, has an immunoregulatory role beyond its primary metabolic function. Dying cells release ATP, which is transported back into cells by the P2X7 ATP receptor[227]. Deletion of P2X7 exacerbated autoimmune pathology in the pristane-induced model of lupus[228]. This phenotype was associated with an expanded number of Tfh cells and GC B cells. Conversely, treatment with a P2X7 pharmacological agonist (BzATP) reversed this process. Interestingly, the generation on foreign-antigen specific Tfh cells was not impaired by P2X7 deficiency. In accordance with these findings in mice, P2X7 expression and function are reduced in the PBMCs of lupus patients as compared to HCs[229]. These results suggest that P2X7 may provide another metabolic therapeutic target to reduce the number of pathogenic cell types or redirect their function in lupus. These results also support the hypothesis that autoreactive Tfh cells have unique metabolic requirements, which are fueled by glucose (see above), and dampened by extra-cellular ATP.

9. Fatty acid oxidation and lupus

Long chain free FAs are imported into immune cells by members of the SLC27 family and CD36, to be then incorporated into FA acetyl-CoA by long-chain FA-CoA ligase. FA acetyl-CoA are carried into mt by the carnitine shuttle, which is the rate-limiting step in FA catabolism. The two-carbon (acetate) units are then removed through β oxidation and combined with co-enzyme A (co-A) to form acetyl-coA, which enters the Kreb's cycle.

Etomoxir, an inhibitor of CPT1α, the enzyme that controls the carnitine shuttle, has been used to investigate FAO in immune cells. The role of FAO in any immune cells type has not yet been characterized in the context of autoimmune diseases. A number of findings potentially relevant to autoimmunity and lupus have however been obtained with non-autoimmune cells. Since Treg and memory T cells use FAO as their main energy source, etomoxir treatment of non-autoimmune mice impaired Treg cell differentiation and function while activated inflammatory T cell subsets remained untouched[186]. In inflammatory conditions represented by the GVHD model, different results were obtained with the most striking effect of etomoxir occurred in effector T cells, by suppressed alloreactive T cells while other T cell populations remained unperturbed[230]. Although the relative role of FAO relative to glycolysis or oxidation of glucose or glutamine has not been defined in these alloreactive T cells, these results suggest that inhibiting FAO could limit the activation of $CD4^+$ T cells in the context of autoimmune pathogenesis, including lupus. Caution should be used however in the interpretation of the results obtained from mice or cells commonly treated with supra-physiological doses of etomoxir, which deplete the pool of free coA, a central metabolite for the Kreb's cycle, FA synthesis, and histone acetylation[231,232]. Ideally, results obtained with etomoxir should be validated by a genetic approach directly targeting CPT1α.

Indirectly linked to FAO, the metabolism of the sugar D-mannose modulates immune responses by inducing Treg cell differentiation and decreasing the production of inflammatory cytokines[233]. Glycolysis is inhibited by D-mannose, forcing immune cells to switch to FAO, which generates mtROS, which, in turn, promotes TGF-β production with its well documented immunoregulatory effects[233]. These results illustrates how metabolic interventions should be interpreted carefully with a full assessment of complex interconnected metabolic networks, which may have unexpected consequences on immune activation. This study also suggests that D-mannose may be considered in pre-clinical models of autoimmunity in which Treg cell expansion may have a therapeutic benefit.

While the role of FAO has been mostly characterized in T cells, at least *in vitro*, FAO inhibition also prevented TLR9-induced activation of both conventional DCs and pDCs[234]. Although the production of type I IFN was not directly measured, the expression of IFN-induced CXCL10 was decreased by FAO inhibition in these cells. This study also found that pDCs were more sensitive than cDCs to FAO inhibition, which is consistent with pDCs heavily relying on OXPHOS and FAO for activation[201]. These results suggest that FAO could be a promising therapeutic target in lupus by reducing the pathogenicity of T cells and pDCs. However, its involvement in Treg cell maintenance and function would probably raise concerns. Another limitation to targeting FAO is the lack of small molecule inhibitors that can be used in pre-clinical models.

10. Branch chain amino acid and glutamine metabolism

In addition to being protein building blocks, specific amino acids are at the basis of many anabolic pathways, including the synthesis of lipids, nucleotides, glutathione, glucosamine, and polyamines. Furthermore, glutamine (Gln) is directly used to produce energy through the anaplerosis of the Kreb's cycle[235]. Amino acid synthesis also plays a major part in

immune activation, as simply illustrated by the dramatic increase in amino acid levels, including Gln in $CD4^+$ T cells activated *in vitro* through their receptor and CD28[236]. Moreover, branched chain amino acids (BCAA) such as leucine and Gln function as metabolic sensors of a cell energy status by directly activating mTORC1[237]. Tfh cells in lupus-prone mice display a specific solute carrier expression signature[161], which includes several amino acid transporters such as Slc7a5, Slc7a10, ASCT2 and LAT1/CD98. While the functional significance of this differential expression is currently unknown, it is increasingly recognized that a better understanding of the functional link between solute transporters in general, these amino acid transporters in particular, and the metabolic programing of immune cells, will unlock novel regulatory circuits of immune activation[238]. The lack of reagents, such as antibodies, inhibitors, and cell-specific deletions for many Slc members are still a major hurdle toward this goal.

Leucine metabolism contributes to autoimmune pathology as a checkpoint of mTORC1 signaling, which then controls glycolysis with the consequences described above on effector T cells and myeloid cells[239–241]. Leucine is transported into cells by SLC7A5, and subjected to a series of enzymatic reactions to produce to acetyl-CoA, which will enter the Kreb's cycle. The first rate-limiting reaction is a reversible transamination of leucine to α-ketoisocaproate, mediated by branched-chain aminotransferase (BCAT). There are two isoforms of BCAT based on their cellular location, mt BCAT2 and cytosolic BCAT1. BCAT1 is the most abundantly expressed BCAT isoform in human macrophages[242]. The inhibition of BCAT1 presented beneficial effects in pre-clinical models of RA and crescentic glomerulonephritis by reducing the producing of inflammatory cytokines by macrophages and reducing their infiltration in target organs[242]. This suggests that the consumption of leucine by the TCA cycle is pro-inflammatory in macrophages in inflammatory conditions.

Gln imported by ASCT2 / SLC1A5 is converted first to glutamate by glutaminase (GLS), then to α-ketoglutaric acid (αKG) by transaminases or GLUD1. αKG enters the Kreb's cycle or is converted by isocitrate dehydrogenases (IDH1 and IDH2) into (D)-2-hydroxyglutarate (2HG), which inhibits DNA and histone demethylases. This latter pathway places Gln metabolism as an essential gate to epigenetic regulation[243]. Glutaminolysis is a major determinant of the balance between Th17 and Treg cell differentiation, which may define its major role in autoimmune diseases. Gln is a major energy source for the Th17 cells[7]. Gln deprivation in the culture media promoted Treg differentiation from either naïve $CD4^+$ T cells[7] or Th1-polarized cells[244]. Another study reported that Gln depletion achieved either by transporter deficiency or deprivation in the culture media inhibited both Th1 and Th17 differentiation[245]. GLS inhibition however preferentially inhibited Th17 polarization[7,246]. *Gls* deficiency in T cells increased T-bet expression as well as the differentiation and effector functions of Th1 and $CD8^+$ cytotoxic cells, but these phenotypes were unstable, indicating that glutaminolysis was required for their optimal functions. Th17 cell differentiation was severely impaired in *Gls* deficient T cells[247]. The inhibition of 2HG production through glutamate oxaloacetate transaminase 1 (GOT1) also blocked Th17 polarization in favor of Treg cells but did not affect Th1 cells[248]. Thus, there is mounting evidence that glutaminolysis is essential for Th17 cells. The inconsistent findings between studies regarding the Gln requirements of Th1 cells may be due to differences in experimental conditions or indicate that glutaminolysis in Th1 may be compensated by

cytokines such as IL-2 or by yet undefined anaplerotic sources in certain conditions. In the context of lupus, Gls1 inhibition with BPTES ameliorated lupus manifestations in MRL/lpr mice in a Th17-dependent manner[15]. It is unknown whether this treatment would be as effective in other models in which Th17 cells play a lesser role. The requirements for glutaminolysis have been recently examined for the GC reaction in a mouse model of lupus. Contrary to glycolysis, glutaminolysis inhibition with the Gls1 inhibitor 6-diazo-5-oxo-l-norleucine (DON) greatly reduced immunization-induced as well as autoimmune GC responses in both lupus-prone and non-autoimmune mice[161]. GC B cells were nearly eliminated and Tfh cells presented a reduced expression of a number of genes associated with their function, including Bcl6. These results indicate that glutaminolysis is an absolute metabolic checkpoint for the development of all GCs. Lower levels of Gln were found in PBMCs from lupus patients than HCs, with an inverse correlation between Gln levels and disease activity[249]. This study concluded that Gln deficiency may contribute to mt dysfunction in SLE patients. This result may also be interpreted as SLE patients having a higher consumption of Gln, and it would be of great interest to determine whether it correlates with the frequency of specific T cell subsets in these patients.

Finally, as mentioned above, glutaminolysis regulates DNA demethylation. This epigenetic regulation of gene expression is produced through the conversion of 5-methylcytosine to 5-hydroxymethylcytosine by enzymes belonging to the TET family. This oxidation reaction occurs through the engagement of glutaminolysis metabolites, such as α-KG and 2-HG. High Gln utilization in differentiating Th17 cells results in an accumulation of 2-HG, which inhibits DNA demethylases, maintaining the *Foxp3* locus hypermethylated and silenced[248]. This process explains the bi-directional effect of glutaminolysis on Th17 and Treg cells. Despite an increased interest to understand the complex epigenetic regulation of autoimmune activation, including in lupus[250], Gln-driven epigenetic modifications have not been directly examined in this context. These studies should be a part of mechanistic investigations following up the promising results showing a protective effect of Gln inhibition.

Multiple studies have targeted Gln metabolism in an attempt to starve off tumors. Successful strategies include the inhibition of Gln transporters SLC1A5/ASCT2 and SLC7A11/LAT1 with V-9302 or GPNA, and with BCH or xCT system inhibitors respectively; blocking the first reaction of glutaminolysis with GLS1 inhibitors DON, CB-839, 968, or BPTES; or blocking glutamate dehydrogenase (GDH) with EGCG, and aminotransferase with AOA[251]. These drugs represent a promising tool box to use in pre-clinical models of autoimmunity, including in lupus. Glutaminolysis is a complex pathway that affects multiple cellular processes with far-reaching consequences that are still largely unexplored in autoimmunity. As illustrated by studies reviewed above, many steps from the Gln transporters to the many enzymatic reactions represent potential targets to treat lupus. Pre-clinical and mechanistic studies need to be carefully conducted to identify targets as well as long-term consequences on the entire immune system to avoid immunosuppression. A recent study has however generated a lot of enthusiasm by showing that tumor infiltrating T cells and the tumor cells have opposite Gln requirements allowing for a treatment with DON to simultaneously activate cytotoxic T cells and starve the tumor[252].

11. Lipid synthesis

FA synthesis is initiated by the conversion of acetyl-CoA into malonyl-CoA by the rate-limiting enzyme ACC1[253]. Subsequent steps are performed by fatty acid synthase (FASN), stearoyl-CoA desaturase (SCD), and the FA-coenzyme A ligase family to generate diacetyl- and triacetyl-glycerols and long-chained FA[254]. The majority of *de novo* synthesized FA are then directed to the plasma membrane incorporated into phospholipids or form lipid rafts to regulate the clustering of membrane-anchored receptors that is trigger signaling in immune cells[255].

Triglycerides, phosphoglycerides, or sphingolipids are forms for FA that directly regulate T cell responses not only as key components of cell membranes, but also as signaling molecules, and energy sources. The inhibition of FA synthesis in T cells by ACC1 deletion resulted in defective blasting and massive activation-induced cell death that prevented the induction of an antigen-specific $CD8^+$ T cell response. Interestingly, this defect was rescued by exogenous FA, indicating that it was the abundance, but not the source of FAs that controls the survival of antigen-activated $CD8^+$ T cells[256]. These results suggest that ACC1 may be a therapeutic target to modulate $CD8^+$ T cell activity. As mentioned above, the role of $CD8^+$ T cells in lupus is not well understood, but they may contribute to organ damage by direct cell killing, and therefore ACC1 inhibition may be beneficial. *Acc1* expression and the levels of activated phosphorylated ACC1 increased during Th17 cell differentiation. The functional consequence of this observation was demonstrated by the pharmacological inhibition or T cell-specific deletion of ACC1, which inhibited the polarization of human and murine Th17 cells in favor of Treg cell induction not only in vitro, but also in an EAE mouse model[257]. Similar to ACC1, FASN inhibition also reduced Th17 cell polarization, but it also uniquely boosted IFN-γ production by Th1 and Th1-like Th17 cells[258]. Again, it is not clear whether these differences are due to experimental differences or if they reflects the different roles of the metabolites produced by the two enzymatic reactions. Furthermore, it is still unknown how FA synthesis regulates $CD8^+$ T cell survival or inflammatory $CD4^+$ T cell polarization. Its profound effect on the Th17 / Treg balance is however reminiscent of Gln metabolism, and, as such, it is predicted to regulate lupus pathogenesis. However, the paucity of FA synthesis inhibitors suitable for *in vivo* treatments makes it a difficult hypothesis to test.

Glycosphingolipids (GSLs) are a major component of lipid rafts. A combination of increased synthesis and reduced recycling results in high levels of GSL in the $CD4^+$ T cells from SLE patients, which were directed by an increased LXRβ expression[259]. Pharmacological inhibition of GSL synthesis with N-butyldeoxynojirimycin (Miglustat), a clinically approved drug used to treat Gaucher disease, normalized the function in the lupus T cells, including their ability to induce anti-DNA antibody production by syngeneic B cells. An independent study confirmed the critical role of GSL in lupus T cells. The capacity of BTLA, an inhibitory receptor similar in function to CTLA-4 and PD-1, to restrain T cell activation is defective in SLE patients[260]. This is at least in part due to a poor BTLA recruitment to the immunological synapse, as shown by a treatment with a glucosylceramide synthase inhibitor, which normalized lipid metabolism as well as BTLA inhibitory function. Mechanistically, decreased glucosylceramide availability dissociated lipid rafts clustered

around TCR molecules, allowing BTLA recruitment and inhibition of TCR signaling[260]. These two studies convincingly linked GSL homeostasis to the strength of T cell activation in lupus, and warrant follow studies in animal models to assess *in vivo* therapeutic effects.

Finally, FA also form cytoplasmic lipid droplets[261], which have been found necessary for T cells to invade the joints of RA patients, in which the inhibition of FA synthesis prevented this process[262]. It has not been examined whether T cells that invade the inflamed organs of lupus patients, including the joints and the kidneys, are also dependent on *de novo* FA synthesis.

12. Conclusions and perspectives

Research in immunometabolism is a growing field that started with *in vitro* studies that proposed simple models in which effector immune cells switched upon activation from mt metabolism to aerobic glycolysis that was supported by a large increase in glucose uptake[263]. It has now been established that Gln and FA utilization also represent critical checkpoints of metabolic reprogramming regulating immune cell functions. Metabolic inhibitors and gene targeting of metabolic enzymes have been widely used to extend the reach of these findings mostly in mouse models, but also with some human cells. The vast majority of results were obtained with healthy mice and cells from healthy subjects. As reported in this review, a number of immunophenotypes directly relevant to autoimmunity can be manipulated through their metabolism, which should be directly tested in animal models, as well as in cells from patients with autoimmune diseases. As to be expected, multiple levels of complexity have been added to the initial models of metabolic reprograming controlling immune functions, which should be considered if immunometabolism is to be targeted for therapeutic purposes.

Many aspects of metabolic reprogramming may be specific to an immune cell type, with the most striking example being pDC activation by type I IFN relying on FAO[201], a unique process not found in other types of immune cells switching to glycolysis upon activation. A corollary of the cell specificity of metabolic pathways is that targeting one pathway to eliminate or expand the number of a specific cell type could be detrimental to another cell type also involved in disease. This is an issue technically difficult to address since beneficial effects of successful interventions with metabolic inhibitors have been correlated with changes in given cell populations, such as Th17 or Treg cells, but the direct cellular targets are unknown. Metabolic alterations may also be disease-specific, with stark differences even between two rheumatic diseases such as RA and SLE that present significant etiological overlaps. Indeed, antioxidants are beneficial for $CD4^+$ T cells in SLE while oxidative agents eliminate the pathogenicity of $CD4^+$ T cells in RA[160,264]. Therefore, it is unfortunate but critically important to not assume that the findings obtained for one autoimmune disease can be automatically translated to another autoimmune disease.

Metabolism is known for its intricate complexity at the biochemical level. Recent studies have added levels of complexity showing “moonlighting” functions of some metabolic enzymes, such as GAPDDH regulating IFNγ production[265], and metabolites, such as succinate or itaconate with previously unsuspected immune signaling functions[266]. Finally,

mitochondria have been solidly emerged as the command center of immune functions through an increasing number of mechanisms, not only as the major source of ATP production, but only through the generation of these metabolite intermediates including ROS production, and by providing a platform for RIG-I and NRLP-3 inflammasome signaling. The highly immunogenic mtDNA leading to type I IFN production[267].suggests that mt hyperoxidation is a key pathogenic feature of lupus. Therefore, the restoration of mt health is predicted to have a major therapeutic effect in lupus patients, but an effective treatment to achieve this goal has not yet been found.

Recent developments suggest that research in immunometabolism will lead to long-lasting impactful discoveries in the field of autoimmunity, including lupus. First, lupus is the first autoimmune disease in which metabolic inhibitors, mTOR inhibitors, NAC and metformin, have shown therapeutic benefits in patients and as well as others in several pre-clinical models (Table 1). Additional pathways and inhibitors should be tested based on their efficacy on inflammatory immune cells elicited in healthy mice. Second, a disease-specific cell-specific understanding of the metabolic alterations at the molecular level may provide novel mechanistic insights on autoimmune activation, which may in turn provide much needed novel therapeutic targets. Third, immunometabolism studies should explore whether metabolic inhibitors have therapeutic value added to standard-of-care treatments and to biologics that have not met endpoints in lupus clinical trials. Immunometabolism is already the target of methotrexate, a drug widely used in rheumatology that inhibits 1-Carbon metabolism[268]. The pre-clinical studies proposed this review conceived and interpreted in the framework of results obtained in normal mice, coupled with a deep characterization of the metabolic signatures of effector cells in mice and patients with autoimmune diseases should be prioritized to reap the therapeutic promises of metabolic targeting.

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Table 1.

Metabolic drugs or treatment with reported efficacy in lupus patients or in mouse models of lupus, or in other immune cells with relevance to lupus

Drug / Treatment[1]	Metabolic target	Immune target(s)[2]	SLE patients	Lupus models
CR	?	?	No effect (40)	NZB/W (36, 37–39,41)
LXR agonist T0901317	Cholesterol efflux	macrophages		Pristane-induced diffuse alveolar hemorrhage (81)
metformin	ETC complex 1, AMPK	pDCs (120) B cells (139) $CD4^+$ T cells (226)	Reduced flares, prednisone-sparing (120)	B6.Sle1.Sle2.Sle3 (121, 122) $Roquin^{san/san}$ (123)
Rapamycin, sirolimus	mTORC1	$CD4^+$ T cells, effector memory $CD8^+$ T cells (126) B cells (140)	Reduced disease activity, prednisone-sparing (124, 125)	$Roquin^{san/san}$ (123) NZB/W (125)
Echinomycin, RNAi	HIP1α	Th1 and Th17(154, 155)		GVHD (155) MRL/lpr (134)
CaMK4 inhibitor	Glycolysis	Th17 (165)	Reduced Th17 in vitro (163)	MRL/lpr (164, 166)
2DG	Glycolysis	$CD4^+$ T cells (121, 122), Tfh cells		B6.Sle1.Sle2.Sle3, NZB/W, B6.lpr, BXSB.Yaa, cGVHD (121, 122, 161)
PFKFB3 inhibitor	glycolysis	$CD4^+$ T cells (169)		
PKM2 stabilizer	Glycolysis, STAT3-target genes	Th1 and Th17 (171, 172)		
Dimethyl fumarate	glycolysis	Th1 and Th17 (174)	Discoid lupus (176, 177)	
CG5, WZB117	Glut1-mediated glucose uptake	$CD4^+$ T cells (179)		B6.Sle1.Sle2.Sle3, cGVHD (179)
NAC	oxidation	$CD4^+$ T cells (208)	Reduced disease activity and mTOR activation in $CD4^+$ T cells (208)	
MitoTempo	mtROS	Neutrophils, NETs (209)		MRL/lpr (209)
4-octyl itaconate	TCA cycle, Nrf2,	Macrophages, Th17 (222, 223)	Decreases inflammation in SLE PBMCs (223)	
P2×7 agonist, BzATP	Extracellular ATP	Tfh and GC B cells (228)		Pristane-induced lupus (228)
D-Mannose	Decreases glycolysis, increases FAO	Treg (233)		
BCAT1 inhibitor	Leucine transamination, TCA cycle	macrophages	Decreased inflammation in macrophages in vitro (241)	Crescentic glomerulonephritis (242)
BPTES, DON	glutaminolysis	Th17, Tfh, GC B cells		MRL/lpr (14) B6.Sle1.Sle2.Sle3, (161)
Soraphen A	FA synthesis	Th17 (259)		
glucosylceramide synthase inhibitor	glucosylceramide synthase	$CD4^+$ T cells (262)	restores BTLA functionality in lupus $CD4^+$ T cells (262)	

1. Drugs/ Treatments are listed in the order they appear in the text.

[2]Reported immune cells in which the drug has shown an effect. The list does not preclude other cell types that may also be targeted directly