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Metabolic regulation of pathogenic autoimmunity: therapeutic targeting

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Metabolism has recently emerged as an essential mechanism that regulates the immune system. Studies in healthy mice and, to a lesser extent, humans, have defined the metabolism of immune cells in response to various challenges. It is increasingly recognized that the overactive immune system that drives autoimmune diseases presents metabolic abnormalities that offer therapeutic opportunities. These novel therapeutic venues are supported by a few studies using metabolic inhibitors in mouse models and in small clinical trials. Reaching the full potential of targeting immuno-metabolism in autoimmune diseases requires a systemic cell-specific characterization of metabolic pathways in mouse models and cells from patients. Here, we review recent reports of immuno-metabolic alterations in autoimmune diseases, as well as alterations in immune effector pathways that have been implicated in autoimmunity, with a focus on systemic lupus erythematosus.

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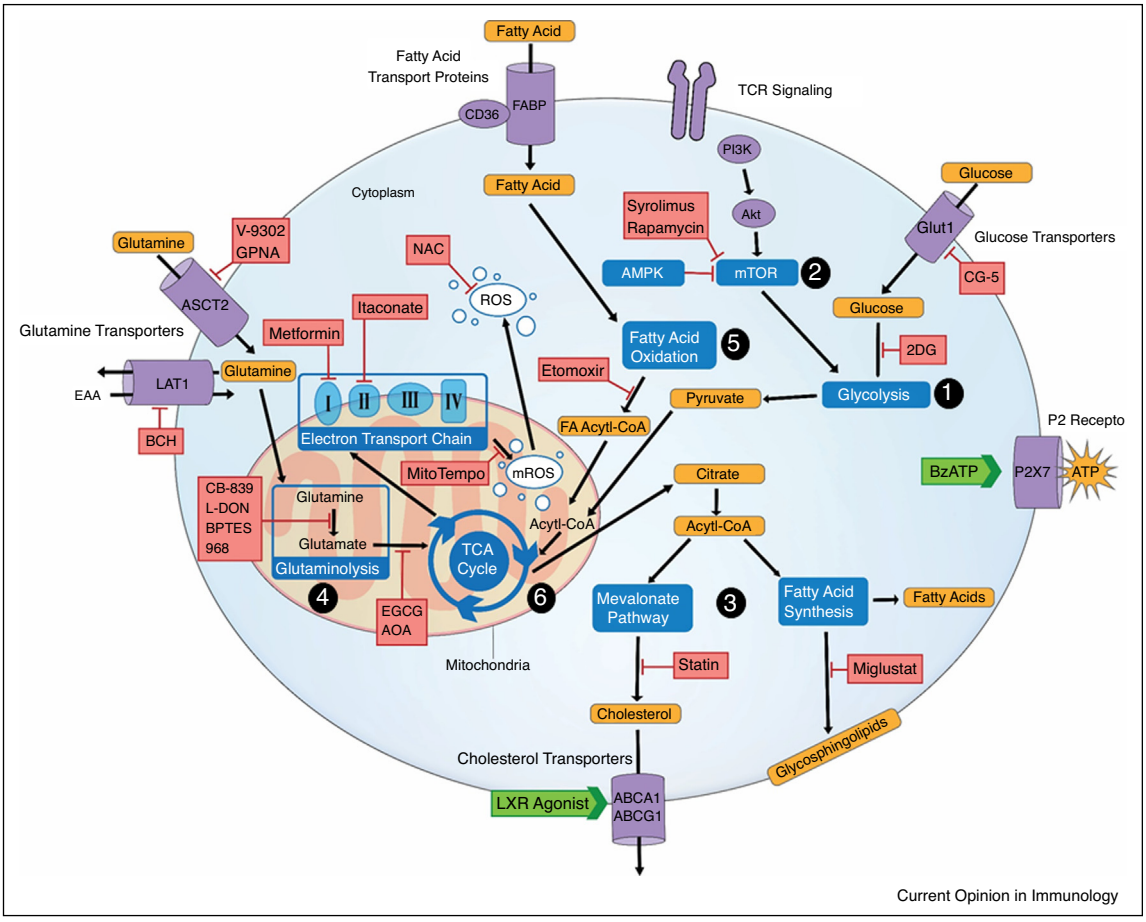
Introduction

Immune cells are inherently plastic, rapidly proliferating and moving from quiescence to an array of effector functions specific for the stimuli they encounter. These cellular processes require-specific metabolic substrates as well as specific utilizations of these substrates, which has been coined metabolic reprogramming. Evidence has accumulated that interfering with this metabolic reprogramming could prevent or redirect immune activation, largely using normal murine immune cells. In addition, several metabolites, such as tricarboxylic acid (TCA) cycle products succinate and itaconate, have been identified as signaling molecules with profound immunoregulatory properties [1,2,3••], while some glycolytic enzymes, such as Gapdh [4] or Pkm2 [5], moonlight as immunoregulators independently from their metabolic function. These findings have logically led to the concept that metabolic reprogramming could be targeted to either enhance or dampen immune response [6]. This hypothesis was supported by the findings that autoimmune activation in rheumatoid arthritis as well as in systemic lupus erythematosus (SLE) [7] was associated with metabolic defects. Furthermore, treatments with specific metabolic inhibitors showed therapeutic effects in mouse models of these diseases, as well as in SLE patients [8]. In this review, we summarize recent reports in which targeting-specific metabolic pathways has shown beneficial outcomes in autoimmune diseases, with a focus on SLE. Due the relatively limited number of these studies, we have also included metabolic targeting of pathways that are relevant to SLE pathogenesis, even when their direct testing in immune cells from SLE patients or mouse models has not yet been performed. These findings are summarized in Figure 1.

Glycolysis

Glycolysis is the pathway by which glucose is converted to pyruvate through eight metabolic intermediates including fructose-1,6-bisphosphate (Figure 1 pathway 1). It generates two molecules of ATP per glucose, as well as NADH, which initiates oxidative phosphorylation by donating an electron to the complex I of the electron transport chain (ETC). Pyruvate fuels the TCA cycle for oxidative degradation, leading to the production of an additional 25 molecules of ATP through the generation of electron donors for the ETC. Pyruvate can also be reduced to lactate in an anaerobic glycolysis, which regenerates NAD as well as many metabolite intermediates requires for cellular proliferation. $CD4^+$ T cells from lupus-prone mice or SLE patients show enhanced levels of glycolysis and mitochondrial (mt) respiration compared to healthy controls [8,9]. The inhibition of glycolysis with 2-deoxy glucose (2DG) is not sufficient to revert disease in lupus prone mice [9]. However, 2DG limits the expansion of highly glycolytic follicular helper T (Tfh) cells and germinal center (GC) B cells, as well as the production of anti-dsDNA antibodies [10••]. Tfh cells are required for both SLE pathogenesis and the protective humoral immune responses to pathogens. 2DG treatment of lupus-prone mice restricted the glycolytic demands of autoreactive Tfh cells, but did not impair antigen-specific Tfh cells induced by influenza virus or immunization [10••]. These results suggest that inhibiting glycolysis can

Figure 1



Metabolic pathways with potential therapeutic relevance in lupus.
Proteins are presented in purple, metabolic processes in blue and metabolites in orange boxes. Inhibitors are shown in red, while agonists are shown in green. Five major pathways referred to in the text are indicated by numbers in black labels: **1**: glycolysis; **2**: mTOR; **3**: lipid synthesis; **4**: glutaminolysis; **5**: FA oxidation; **6**: TCA cycle. Details and references are provided in the text.

uniquely target autoreactive Tfh cells while preserving protective immunity. This opens a new window of opportunity of selectively targeting cellular metabolism for the treatment of lupus or other autoimmune diseases. CG-5, a novel inhibitor of glucose transporters, blocked glycolysis in both mouse and human $CD4^+$ T cells and decreased $CD4^+$ T cell activation, GC responses and auto-antibody production in spontaneous and induced models of lupus [11]. These results suggest that targeting glucose metabolism by blocking either glucose import or utilization, has promising therapeutic potential in lupus.

mTOR

The mechanistic target of rapamycin (mTOR) is a kinase whose specificity is regulated by its co-factor: raptor for mTOR complex 1 (mTORC1) and rictor for mTOR complex 2 (mTORC2). mTOR has emerged as a key sensor of cellular metabolic state in response to activation and hormonal signals, and it is inhibited by AMPK, which is itself activated in response to low nutrient signals (Figure 1 pathway 2). In the immune system, mTOR is an important mediator of pro-inflammatory lineage specification in association with glycolysis. Activation of mTORC1 precedes the onset of SLE and associated co-morbidities and may act as an early marker of disease pathogenesis [12]. Inhibiting mTOR signaling with rapamycin promotes regulatory $CD4^+$ T cells (Treg) induction [13]. As first validated in mouse models, rapamycin treatment improved numerous disease biomarkers In SLE patients [12]. A single-arm, open-label, prospective trial of sirolimus (another mTOR inhibitor) in patients with refractory SLE disease showed a progressive improvement in disease activity and a reduced daily dose of prednisone [14••]. Interestingly, responsiveness to the treatment was associated with correction of pro-inflammatory T-cell lineage specification, including memory $CD8^+$ T cells, a subset that has not been characterized previously in SLE patients. Follow-up placebo-controlled

clinical trials in diverse patient populations are necessary to further define the role of mTOR blockade in the treatment of SLE. Another retrospectively study also suggested that sirolimus may serve as an alternative treatment for patients with lupus nephritis who do not tolerate standard treatment [15]. These results strongly suggest that targeting mTORC1 overactivation provides an opportunity to limit the severe side effects of conventional therapies.

Lipid synthesis

Lipid biosynthesis, which includes fatty acid (FA) biosynthesis and cholesterol biosynthesis, is a cytosolic process that initiates from acetyl-CoA (Figure 1 pathway 3). Fatty acids are catabolized to fuel cellular energy needs and provides building blocks for many structural and hormonal compounds. $CD4^+$ T cells from SLE patients display an accumulation and altered traffic of lipid raft-associated glycosphingolipids (GSLs). *N*-butyldeoxynojirimycin, a clinically approved inhibitor of GSL biosynthesis (Miglustat), corrected SLE $CD4^+$ T cell signaling and decreased anti-dsDNA antibody production in co-cultures with autologous B cells [16], suggesting that targeting GSL biosynthesis in $CD4^+$ T cells could be beneficial in SLE. Type I interferon (IFN) is a key mediator of SLE pathogenesis. Type 1 IFN signaling affects cellular lipid homeostasis by decreasing synthesis and increasing import of cholesterol and long chain FA in macrophages. Conversely, limiting cholesterol biosynthesis with statins activates the type 1 IFN pathway in a STING-dependent manner [17]. Therefore, interactions between type I IFN and cholesterol synthesis are specifically relevant for SLE pathogenesis, which is associated with high risk for atherosclerosis, cardiovascular disease and reduced plasma high-density lipoprotein (HDL) levels. HDL mediates cholesterol efflux through ATP binding cassette transporters A1 and G1 (ABCA1/G1), which are the key transcriptional targets of the liver X receptor (LXR). Mice with *Abca1/g1* deficiency in dendritic cells (DCs), but not in T cells or macrophages, presented an SLE-like phenotype with cholesterol accumulation and inflammasome activation [18]. These findings suggest that targeting cholesterol efflux in DCs with an LXR agonist may promote immune tolerance. Finally, reconstitution of atherosclerosis-prone mice with bone marrow from lupus-prone BXD2 mice resulted in increased autoantibody production and glomerulonephritis as compared to non-atherosclerotic conditions. This enhancement of autoimmune pathogenesis by dyslipidemia was linked to IL-27 production in DCs that expanded the number of Tfh cells [19•]. These studies indicate that targeting cholesterol metabolism could have the dual benefit of lowering cardiovascular co-morbidities and decreasing the primary manifestations of SLE.

Mitochondrial dysfunction

Mt dysfunction has been reported in the $CD4^+$ T cells from SLE patients and lupus-prone mice, with an increased mt mass, membrane hyperpolarization, production of reactive oxygen species intermediates (ROS) and ATP depletion [9]. The contribution of mt metabolism in $CD8^+$ T cells to lupus pathogenesis and a novel protective role of C1q in this process have been recently demonstrated in murine models [20•]. Also unexpectedly, highly dysfunctional $CD4^+$ and $CD8^+$ infiltrating T cells have been found in the kidneys of lupus-prone mice, with the characteristics of metabolic exhaustion, including a loss of oxidative phosphorylation (OXPHOS) [21•]. Although the determinants of mt dysfunction remain unclear in lupus, targeting its main metabolic processes, namely glutaminolysis, fatty-acid oxidation (FAO), the TCA cycle and OXPHOS has received increasing attention, as detailed below.

Glutaminolysis

Glutaminolysis includes glutamine (Gln) uptake, which is mediated by alanine-serine-cysteine transporter 2 (ASCT2/SLC1A5), and catabolism, which is initiated by the conversion of glutamine to glutamate by glutaminase (GLS), followed by the interconversion of α-amino (glutamate) and α-keto acids(α-ketoglutaric acid) by transaminases, and finally α-ketoglutaric acid enters the TCA cycle (Figure 1 pathway 4). The opposite contribution of glutaminolysis to the differentiation of Th17 and Treg cells has been thoroughly investigated in several models of autoimmune diseases [22]. Gln transporter deficiency or Gln depletion inhibited both Th1 and Th17 cell differentiation and enhanced the generation of Treg cells [23]. However, blocking the conversion of Gln to glutamate preferentially suppressed Th17 cells [24,25]. A recent study showed that the loss of glutamine synthase (*Gls*) increased T-bet expression to promote the differentiation and effector functions of $CD4^+$ Th1 and $CD8^+$ cytotoxic cells, although these cells became exhausted over time. *Gls* deficiency also impaired Th17 cell differentiation [25]. This inconsistency in different T cell subsets highlighted that Gln metabolism is context-dependent in T cells, with cytokines such as IL-2, and alternate anaplerotic sources may be involved. Glutaminolysis also regulates Tfh cells. Glutaminolysis inhibition with the Gln analogue 6-diazo-5-oxo-l-norleucine (DON) greatly reduced both immunization-induced as well as autoimmune humoral responses in a lupus-prone model [10••]. Although further studies are needed with pathogen-induced Tfh cells, these results suggest that glutaminolysis is required for the development of both autoreactive and induced germinal centers. These novel results collectively suggest a critical role of Gln in T cell activation and specificity, which is finely tuned in a context–specific manner, depending on the nature of the inducing signal, effector subset, cytokine milieu, and metabolic environment. This context-specificity

represents both a great opportunity and a challenge for therapeutic targeting.

Interventions targeting Gln metabolism have been extensively studied in oncology. These include the inhibition of Gln transporters SLC1A5/ASCT2 with V-9302 or GPNA, and SLC7A11/LAT1 with BCH or xCT system inhibitors, blocking Gln catabolism by inhibiting GLS1 with CB-839, 968, or BPTES, glutamate dehydrogenase (GDH) with EGCG, and aminotransferase with AOA, as well as treatments with the Gln analogue DON [26]. These modulators may also provide a promising strategy that should be explored in autoimmunity, including in lupus. The transporters and the enzymes at each step of Gln catabolism, as well the alternate anaplerotic sources that may compensate for Gln metabolites inducing changes of epigenetic marks and chromatin accessibility, are all the potential targets for metabolic regulations for future lupus therapy. It is possible, however, that the requirements of T cells for Gln are too broad and complex for targeting without unsafe profound immunosuppression.

Fatty acid oxidation

Long chain free FA enter the cells through specific transporters, such as the members of the SLC27 family and CD36, and are then incorporated into FA acetyl-CoA catalyzed by long-chain FA-CoA ligase. The carnitine shuttle is used for FA acetyl-CoA to enter the mitochondrion, which is the key limiting step in FA catabolism. A series of two-carbon (acetate) units is then removed through β oxidation to form acetyl-CoA after combined with co-enzyme A (co-A). Etomoxir inhibits CPT1α, a key enzyme in the carnitine shuttle (Figure 1 pathway 5). Etomoxir treatment of non-autoimmune mice restricts Treg cell differentiation and function without disturbing inflammatory T cell subsets, and the reliance of Treg cells on FAO has been confirmed *in vitro* [27]. In inflammatory conditions, however, etomoxir has the most striking effects on effector T cells, as shown in a model of graft versus host disease (GVHD) in which it repressed alloreactive T cells while other T cell populations remained unperturbed [28]. This result suggests that inhibiting FAO could be beneficial in some instances of autoimmune pathogenesis. The results from these treatments with etomoxir should be however interpreted with caution, since it was recently shown that the supra-physiological doses that have been used deplete the pool of free coA, and therefore inhibit the TCA cycle, fatty acid synthesis, and histone acetylation, instead of blocking carnitate mt export [29,30].

TCA cycle and the electron transport chain

The TCA cycle is a series of chemical reactions that oxidize acetyl-CoA derived from pyruvate, FA, and glutamine, to produce ATP, precursors of certain amino acids, as well as the reducing agent NADH (Figure 1 pathway 6). Although it is branded as a 'cycle', truncated or 'broken' TCA cycles as well as the accumulation of some of its metabolite intermediates or derivatives have been recognized. Succinate, a metabolite of both TCA and OXPHOS, has been identified as a mediator of immune pathology [1]. Its accumulation in Tregs in which mt complex III has been deleted contributes to their dysfunction [31]. Specifically relevant to autoimmunity, succinate, along with IL-10, expands a novel $CXCR5^{-}CXCR3^{+}PD1^{hi}CD4^{+}$ T cell population that provides IL-21-independent help to B cells in the blood and the tubular interstitium of SLE patients [32••]. Moreover, itaconate enhances the oxidation of succinate to fumarate, and induces a cascade of anti-inflammatory pathways that mitigate IL-17-driven inflammation [3••]. Permeable itaconate derivatives also restrict the type 1 IFN response and the production of inflammatory cytokines by macrophages [2,33]. These important new developments discovered in mouse models provide new venues to target TCA metabolite intermediates that play critical signaling role in immune cells.

Metformin, the first line therapy in treatment of patients with type 2 diabetes, interferes with key immuno-pathological mechanisms through the transient inhibition of mt ETC complex I, which indirectly leads to AMPK activation. Metformin promoted Treg cell induction and blocked STAT3 activation, which could be the result of AMPK activation and mTORC1 inhibition, or increased FAO [34]. Metformin also reduced excessive IFNγ production by $CD4^{+}$ T cells from SLE patients *in vitro* [9]. A treatment combining metformin and 2DG normalized T cell metabolism and reversed disease biomarkers in several lupus models [9]. In a proof-of-concept trial, metformin added to standard-of-care treatment reduced the risk of disease flares and the amount of corticosteroid exposure in SLE patients with mild/moderate disease activity [35]. These promising results are being followed up in a prospective, multicenter, double blinded, placebo controlled, clinical trial (NCT02741960). Finally, ETC inhibition by metformin or other inhibitors targeting downstream complexes reduces the expression of IFNα-stimulated genes in $CD4^{+}$ T cells by reducing pSTAT1 Y701 phosphorylation [36]. This suggests that metformin treatment could be beneficial in SLE patients with a high type 1 IFN activity.

Oxidative stress

Oxidative stress greatly contributes to the pathogenesis of SLE [7]. Neutrophilic extracellular traps (NETs) extrude oxidized mtDNA that stimulates the production of type I IFN and correlates with disease activity in SLE patients [37,38]. These results have globally identified ROS, including oxidized mtDNA, as promising targets for therapeutic intervention in lupus. Glutathione, a major antioxidant, is depleted in lupus immune cells. Increasing glutathione levels with *N*-acetyl-cysteine (NAC) normalized their elevated O_2 consumption *in vitro* [39]. In a double-blind placebo-controlled pilot study, NAC safely improved disease outcomes in SLE patients by reducing

mTOR activity in T lymphocytes [40]. Follow-up clinical trials with NAC or other anti-oxidants may refine cellular targets and identify biomarkers that predict clinical responsiveness [41]. MitoTempo, another inhibitor of mt ROS production, alleviated disease progression in MRL/lpr lupus mice [38], and may have further therapeutic applications.

ATP as an immune regulator

Extracellular ATP is released by dying cells to the cytosol and transported into cells by the P2X7 ATP receptor [42]. Pathogenic Tfh cells in murine models of lupus were expanded by the loss of P2X7, while a P2X7 pharmacological agonist (BzATP) reversed the process [43•]. This study provides another target and potential treatment that could be useful in reducing the function of pathogenic cell types in lupus by modulating metabolic pathways.

Conclusions

The concept of metabolic regulation of immune activation has started from a simple model in which activated effector immune cells switch from mitochondrial respiration to aerobic glycolysis to more complex processes involving glutamine and fatty acid utilization. Additional layers of complexity have been uncovered, such as cell-specific metabolic reprogramming, immune function of some metabolic enzymes and metabolites [44]. The majority of these ground-breaking studies have been conducted in normal mice, with a few in models of autoimmune diseases, and even fewer in patients with autoimmune diseases as reported in this review. Based on the existing collection of metabolic targets and their corresponding small molecule inhibitors, cellular metabolism offers a largely untapped of novel therapeutic targets, with potentially few side effects and the specific elimination of pathogenic immune cells without broad immunosuppression. Moving in that direction will require robust basic and translational research efforts outlined in Box 1 for SLE. In particular, it will be of particular interest to identify which patients are the most likely to benefit from treatments with specific metabolic inhibitors, and whether some of these inhibitors should be considered as add-on therapy. It should be considered that conventional treatments lower by themselves the metabolic activation of immune cells, as suggested by *in vitro* studies [9]. In addition, methotrexate, a drug commonly prescribed by rheumatologists, interferes with 1-Carbon metabolism [45]. Finally, efforts to target immunometabolism in autoimmune diseases should be conducted with the active knowledge of the numerous investigations ongoing in oncology to both target tumor cells and potentiate anti-tumor immune responses with metabolic inhibitors [46].

Box 1 Knowledge gaps and future directions to advance metabolic therapeutic targeting in SLE

1 Identify metabolic biomarkers in specific circulating immune cell types ($CD4^+$ T cells, B cells, monocytes) that are:

- Associated with disease activity or disease presentation.
- Predictive of lupus initiation or flares.
- Responsive to treatment with metabolic inhibitors and/or conventional therapy.

2 Identify metabolic targets to control disease activity through therapeutic intervention:

- Develop specific metabolic pathway interventions according to metabolic dysfunctions in the pathogenesis of SLE.
- Define metabolic markers that identify subsets of SLE patients that are responsive to specific metabolic interventions
- Determine whether targeting multiple pathways, such as glycolysis and ETC complex I, has a synergetic effect.
- To combine metabolic interventions with standard-of-care treatments, after determining whether they have intrinsic metabolic effects.

3 Prevent lupus complications through metabolic intervention:

- Preserve protective immunity against pathogens while controlling autoimmune disease activity.
- Disrupt the closed-loop amplification between dyslipidemia and autoimmunity, and prevent cardiovascular disease from lupus-aggravated dyslipidemia.
- To identify the metabolic reprogramming in the kidney that supports the progression of lupus nephritis, since the majority of kidney-infiltrating T cells are exhausted cells with low metabolic activity.

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Conflict of interest

The four authors of this study declare that they do not have any conflict of interest

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- •• of outstanding interest

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