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Metabolic Abnormalities and Oxidative Stress in Lupus

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Abstract

Purpose of review—Upon antigen exposure, immune cells rely on cell-specific metabolic pathways to mount an efficient immune response. In autoimmunity, failure in critical metabolic checkpoints may lead to immune cell hyper-activation and tissue damage. Oxidative stress in autoimmune patients can also contribute to immune dysregulation and injury to the host. Recent insights into the immune cell metabolism signatures specifically associated with systemic lupus erythematosus (SLE) and the consequences of heightened oxidative stress in patients are discussed herein.

Recent findings—Glucose metabolism inhibitors, mTOR pathway modulators, and PPAR- γ -activating compounds demonstrate therapeutic benefit in experimental models of lupus. Mitochondrial-derived reactive oxygen species (ROS) and molecular modifications induced by oxidative stress appear to be detrimental in lupus. Effective therapies tailored towards the reconfiguration of metabolic imbalances in lupus immune cells and the reduction of mitochondrial ROS production/availability are currently being tested.

Summary—A paucity of knowledge exists regarding the metabolic needs of a number of immune cells involved in the pathogenesis of SLE, including myeloid cells and B cells. Nonetheless, SLE-specific metabolic signatures have been identified and their specific targeting, along with mitochondrial ROS inhibitors/scavengers, could show therapeutic advantage in lupus patients.

Keywords

immunometabolism; immune cell activation; reactive oxygen species; oxidative stress; systemic autoimmunity; systemic lupus erythematosus (SLE)

Introduction

The emerging field of immunometabolism has provided critical insights into the metabolic changes that immune cells undergo upon activation [1,2]. Reprogramming of immune cell metabolism is required to sustain the energy demands of effector functions such as differentiation, clonal expansion, secretion of proinflammatory mediators, phagocytosis, and

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tissue migration. Importantly, defects in key metabolic pathways/checkpoints have been identified in autoimmunity [3,4].

Systemic lupus erythematosus (SLE) is an autoimmune syndrome characterized by dysregulated innate and adaptive immune responses and enhanced risk for multi-organ damage and cardiovascular disease [5]. Because dysfunctional metabolic reprogramming can directly influence and exacerbate defective immune responses, interrogation of the metabolic status of immune cells in SLE has become a topic of interest [3]. While recent studies have aimed to characterize the bioenergetics of differentiated/activated CD4⁺ T cells in SLE, less is known regarding the metabolic configuration of other immune cells implicated in the pathogenesis of lupus. Moreover, SLE is associated with enhanced oxidative stress, as well as an increased prevalence of metabolic syndrome, features that also contribute to accelerated atherosclerosis and cardiovascular events in this disease. Nutrients, besides providing sources of energy, can also promote the activation of immune cells depending on their quality (i.e., oxidation) and availability (i.e., over-nutrition). Consequently, a better understanding of the breakdown in host metabolic control, aberrant immune cell metabolism, oxidative stress, and the crosstalk between these phenomena, will be a worthwhile effort towards the development of improved treatment options for SLE patients.

In this Review, we consider the most recent investigations related to immunometabolism and redox status in SLE, as well as discuss potential metabolic targets that may lead to the resolution of inflammation and the attainment of energy homeostasis in lupus patients. Where information is lacking, we explore immunometabolism-related advances in the oncology field, which may inform future areas of study in autoimmunity.

Metabolism and its Regulation in Lymphocytes

Glucose catabolism is the primary source of adenosine triphosphate (ATP) generation in the immune system. While resting lymphocytes rely on oxidative phosphorylation (OXPHOS) to produce ATP, activated T and B cells shift their metabolic configuration toward aerobic glycolysis, whereby pyruvate is reduced to lactate even in the presence of oxygen. Intermediates of glycolysis can then enter the pentose phosphate pathway (PPP), where anabolic building blocks and reducing equivalents are generated. This metabolic switch is known as the Warburg effect [6].

The transcription factor c-Myc is critical in driving the activation-induced reprogramming of T cells by targeting a range of glycolytic genes [7]. The transcription factors estrogen-related receptor α (ERR α) and hypoxia inducible factor-1 α (HIF-1 α), which responds to oxygen levels, also promote the expression of genes involved in metabolic reconfiguration [8–10]. Among these genes, the expression of *GLUT1*, the major glucose transporter found on T cells, is highly upregulated following T cell receptor (TCR) engagement and under hypoxic conditions [11,12]. Indeed, T cell-specific overexpression of Glut1 did not alter T cell development but augmented effector functions upon activation, and ultimately resulted in signs of autoimmunity in older mice [11]. Recently, the differential expression of GLUT1 on healthy donor-derived T cells was shown to modulate their effector function, with a direct

correlation noted between GLUT1 levels and TCR-induced proliferative ability, as well as with IFN γ -secretion capacity [12].

Similar to the positive transcriptional control of glycolytic genes by the aforementioned factors, negative regulators of glucose metabolism exist. Recent work by Chan and colleagues demonstrates that the transcription factors PAX5 and IKZF1, which are important for B cell development, are charged with restricting ATP levels in B cells, and thus preventing leukemic transformation [13]. Another recently reported regulator of B cell metabolism is the metabolic sensor Gsk3 [14], which was shown to limit glucose consumption and maintain quiescence. Along the same lines, B cell-specific deletion of the adaptor protein Traf3 results in enhanced B cell survival, which depends on elevated glucose metabolism, and is achieved through the upregulation of Glut1 and hexokinase 2 (Hk2), an enzyme that catalyzes the first step in glycolysis [15]. It will be of interest to determine whether the expression of these regulatory factors is negatively affected in animal models of lupus and in patients with SLE. Indeed, B cells chronically stimulated with B-cell activating factor (BAFF), a cytokine associated with SLE [16], have been shown to undergo metabolic reprogramming (i.e. enhanced glycolysis), and subsequently synthesize more antibodies [17], indicating that defects in the control of B cell metabolism reconfiguration might influence the pathogenesis of SLE.

In addition to glucose, amino acids are important substrates for lymphocytes as they provide a source of energy as well as precursors required for *de novo* synthesis of nucleic acid and proteins [18–20]. Lipids and fatty acids are also critical nutrients for lymphocytes; not only are they integral components of cell membranes, but they are also a high energy source [21,22]. To date, the overarching theme in lymphocyte metabolism is that, as opposed to the glycolytic phenotype of activated effector T cells, memory and regulatory T cells can also metabolize amino acids and fatty acids, and generate ATP through OXPHOS. In contrast, activated B cells increase glycolysis and OXPHOS equally. The details of these pathways are beyond the scope of this review and have been extensively described elsewhere [23–29].

Targeting Metabolic Pathways in SLE Lymphocytes

In contrast to the glycolytic switch of activated healthy lymphocytes, repetitive TCR-engagement in lupus was previously suggested to result in the preferential use of OXPHOS through enhanced mitochondrial metabolism [30]. However, more recent work showed that SLE CD4⁺ T cells exhibit, not only higher basal and activated mitochondrial oxidative metabolism, but also higher glycolytic activity [31]. Accordingly, combination therapy with metformin, which transiently inhibits mitochondrial respiratory-chain complex 1 resulting in down-modulation of mitochondrial respiration, and 2-Deoxy-D-glucose (2-DG), a glycolytic inhibitor, ameliorated disease pathology in an experimental model of SLE [31].

Interestingly, when the reduction of pyruvate to lactate was blocked in the same mice with dichloroacetate (DCA), a drug that enhances the import of pyruvate into the mitochondria for oxidation, no improvements were noted [31]. Additionally, the survival of long-lived plasma cells, which are associated with pathogenicity in SLE, was recently found to be dependent on pyruvate flux into the mitochondria [32]. These studies imply that targeting glucose oxidation [i.e., through the inhibition of the mitochondrial pyruvate complex

(MCP)], rather than the reversal of the Warburg effect, could be a putative effective target in SLE patients. Whether other immune cells in SLE patients metabolize glucose with the same predisposition towards oxidation remains to be tested.

In addition to dampening mitochondrial respiration, metformin also alters immunometabolism and inflammation through the activation of 5' adenosine monophosphate-activated protein kinase (AMPK), a nutrient-sensor that modulates glucose and lipid metabolism, and brings about the negative regulation of the mechanistic target of rapamycin (mTOR). mTOR is a serine/threonine protein kinase that makes up the catalytic subunit of two protein complexes, mTOR Complex 1 (mTORC1) and 2 (mTORC2) [33]. In patients with SLE, mTORC1 activity is enhanced, and therapeutic intervention with rapamycin or *N*-acetylcysteine (NAC) prevents the proinflammatory cell death of CD4⁺CD8⁻ (double-negative, DN) T cells and the depletion of regulatory T cells (Tregs), two reported characteristics of SLE (reviewed in [34]). Recently, metformin was also tested in *sanroque* mice (*Roquin*^{san/san}), which develop lupus-like autoimmunity due to a mutation in the ubiquitin ligase member, Roquin, a negative regulator of follicular helper T (Tfh) cells and autoantibody responses [35]. Oral administration of metformin in *Roquin*^{san/san} mice, not only normalized T cell responses [i.e. reduced the frequencies of Tfh and T helper 17 (Th17) cells, while enhancing Treg numbers], but also suppressed the development of autoantibody-producing plasma cells and germinal center formation via the AMPK-mTOR signaling pathway [36]. These studies indicate that elucidating key metabolic programs involved in the pathogenesis of SLE may facilitate the modulation of multiple immune cell subsets with a single target and/or therapy.

Another factor linking metabolism and autoimmunity is the peroxisome proliferator-activated receptor gamma (PPAR γ). PPAR γ is a transcription factor involved in fatty acid and glucose metabolism. Previously, pioglitazone, a PPAR γ agonist and drug used to treat type 2 diabetes mellitus, was shown to be protective against vascular and renal disease in murine SLE, while also improving the function of CD4⁺ T cells derived from SLE patients, suggesting a protective role of PPAR γ in autoimmunity [37,38]. In a recent study, Liu *et al.* investigated the dose effect of PPAR γ expression in the immune response through genetic manipulation [39]. Aged PPAR γ hypomorphic mice developed SLE-like autoimmunity, which was T cell-dependent, but showed a Th17 bias, as opposed to the IFN γ -association noted in human SLE T cells [38,39]. The therapeutic potential of pioglitazone is currently being tested in patients with SLE (NIH Clinical Research Study # 15-AR-0060). Of note, pioglitazone is a member of a class of compounds, which have been shown to specifically inhibit pyruvate flux into the mitochondria [40]. Therefore, the protective mechanism of action of pioglitazone, in addition to PPAR γ -activation, might include normalization of the aforementioned defects in pyruvate oxidation in SLE T cells.

Metabolism of Other SLE-Associated Immune Cells

Given the range of autoantibodies produced in SLE, it is not surprising that significant research in the field has historically focused on the characterization of B cell responses and B-T cell interactions. However, an increasing body of work has led to the evolution of this B cell-dominant view to include other leukocytes, such as natural killer (NK) cells, dendritic

cells, macrophages, and neutrophils [41]. SLE-specific metabolic signatures have not been systematically explored in these cells; nonetheless, their activation also results in metabolic reconfiguration. For instance, human NK cells are classified by the expression of CD56, with CD56^{dim} cells being the more mature and predominant circulating NK subset. It was recently reported that CD56^{bright} NK cells, despite displaying lower cytotoxic capacity, are more metabolically active upon stimulation, and this allows them to produce higher levels of IFN γ [42]. Similarly, the metabolism of mast cells is reprogrammed once activation occurs. In response to antigen-IgE immune complexes, mast cells enhance their glycolytic capacity, and, while mitochondrial respiration is not enhanced, it is still required for effective degranulation of the cells [43].

The activation-induced outcomes of macrophage and dendritic cell (DC) function are also dependent on the type of metabolism adopted [44–46]. Briefly, classically activated M1 macrophages derive their energy through glycolysis, while alternatively activated macrophages (M2) utilize OXPHOS, particularly fatty acid oxidation (FAO). Like M1 macrophages, activated DCs upregulate their glucose uptake and lactate production; however, glycolysis provides metabolic intermediates required to fuel fatty acid synthesis, whereas ATP is generated by OXPHOS [47]. In contrast, tolerogenic DCs, like M2 macrophages, rely on FAO as their energy source [45]. Of interest, recently published data indicate that FAO is not needed for M2 polarization [48]. Indeed, disruption of FAO in myeloid cells did not change the degree of M2 polarization in response to IL-4 [48]. Because the requirement of FAO in M2 macrophage polarization was originally demonstrated through chemical inhibition of FAO (i.e. with etoxomir), this study emphasizes the need for careful interpretation of experiments involving chemical inhibitors, as these might have off-target effects. Recent studies also suggest that inhibition of succinate dehydrogenase switches proinflammatory macrophage phenotype into an anti-inflammatory phenotype in which oxidative metabolism and IL-10 production are enhanced, while glycolysis, mitochondrial membrane potential, succinate oxidation, and mitochondrial ROS production are reduced [49]. Furthermore, the metabolism of plasmacytoid DCs (pDCs) can be drastically altered by type I interferons (type I-IFNs; cytokines crucial in SLE pathogenesis [50–52]). Indeed, exposure to type I-IFNs induces an autocrine pathway of increased OXPHOS and type I-IFN production in pDCs, which is fueled by enhanced FAO and dependent on type I-IFN receptor and PPAR α signaling [53]. This amplification pathway may be of particular relevance in SLE.

The metabolic requirements of neutrophils have been relatively overlooked. This is likely due to the fact that neutrophils have few, albeit functional, mitochondria and have been shown to be primarily glycolytic [54]. However, the energy fluxes that neutrophils undergo to fulfill the energy requirements of chemotaxis, phagocytosis, and the release of neutrophil extracellular traps (NETs), remain to be fully elucidated [55–57]. The pathogen-killing ability of neutrophils is dependent on the activity of NADPH oxidase (NOX), which is comprised by Nox2, p22-phox, p47-phox, and p67-phox. Recently, an intriguing NADPH oxidase-glycolysis activation loop was identified in stimulated neutrophils [58], as Nox2 activity was required for the stimulation-induced increase in glycolysis. The latter was also dependent on the phosphorylation of 6-phosphofructo-2-kinase (PFK-2) [58]. PFK-2 catalyzes the production of fructose-2,6-biphosphate, which activates phosphofructo-1-

kinase (PFK-1), the rate-limiting enzyme of glycolysis. Additionally, asymmetric mTOR signaling and OXPHOS were recently implicated in the chemotaxis of neutrophils [59]. In regards to NET release, metformin was previously found to inhibit NET formation, or NETosis, *in vitro* [60]. Still, whether this effect was in fact due to a direct contribution of OXPHOS to NETosis, or due to a reduction in mitochondrial reactive oxygen species (ROS) production and, therefore, lower generation of immunogenic oxidized mitochondrial DNA (mtDNA) [51], remains to be determined.

Role of ROS in Tissue Damage and Immune Cell Activation in Lupus

ROS have been associated with a variety of disorders due to their capacity to modify cellular components and metabolites. In lupus patients, heightened oxidative stress results in increased levels of oxidized lipoproteins, which are pathogenic *in vivo* and induce further oxidative damage [61]. In fact, lupus high-density lipoprotein (HDL), which tends to be oxidized in patients, lacks vasculoprotective properties and instead promotes proinflammatory responses [62]. Moreover, increased cell membrane lipid peroxidation in lupus can lead to the formation of lipid-derived reactive aldehydes (LDRA), including malondialdehyde (MDA), phosphorylcholine (PC), and 4-hydroxynonenal (4-HNE), which can then bind to and alter proteins, rendering these immunogenic [63,64]. Counterintuitively, 4-HNE has been recently shown to inhibit neutrophil function, including glycolysis, phagocytosis, and oxidative burst [65]; however, NET-formation capacity and mitochondrial ROS production were not explored. A recent study reported that the presence of LDRA-specific immune complexes correlates with disease activity in lupus patients [66], supporting a proinflammatory role of these lipid modifications. In another study, IgM antibodies against MDA and PC were found to negatively correlate with markers for atherosclerosis risk, in association with enhanced apoptotic cell death clearance and reduced LDRA-induced oxidative stress upon IgM binding [67]. Cell damage associated with excessive exposure to oxidative stress and other environmental factors can be assessed by quantification of histone H2AX phosphorylation, which is indicative of DNA double-strand breaks. In accordance with enhanced oxidative stress in lupus, H2AX phosphorylation was found to be elevated in peripheral blood cell subsets and correlated with disease activity [68]. These data implicate lipoprotein-mediated pathways and oxidative stress in particular in the increased tissue damage and propensity of cardiovascular events in lupus patients.

Conversely, a deficiency in NOX2 activity due to a missense mutation in the p47phox (NCF1) subunit of NOX is associated with enhanced risk to develop lupus and other autoimmune diseases [69]. Further, when greater copy numbers of *NCF1* are present, corresponding with enhanced NOX2-derived ROS, protection against lupus was reported [69]. This is akin to individuals with chronic granulomatous disease (CGD), which lack NOX activity and have an increased risk for autoimmune disease development and exhibit type I-IFN signatures [70]. Thus, the source and location of ROS production appears to be important for disease pathogenesis. Indeed, in a recent study, stimulation of neutrophils with ribonucleoprotein (RNP)-immune complexes, led to increased levels of mitochondrial ROS, which resulted in mitochondria hypopolarization and the release of NETs enriched in oxidized mtDNA [51]. Low density granulocytes (LDGs), a distinct subset of proinflammatory, NETosis-prone neutrophils present in the peripheral blood of SLE patients

[71], also display enhanced mitochondrial ROS synthesis [51]. NETosis in LDGs is at least in part dependent on mitochondrial ROS production, as treatment with the mitochondrial ROS scavenger MitoTempo significantly abrogates the extrusion of NET structures in these cells [51]. Neutrophils exposed to extracellular superoxide also display enhanced NET formation and this is associated with concomitant liver injury [72]. Of consequence, the study by Lood *et al.*, demonstrated that oxidized mtDNA has interferogenic potential through a STING-dependent pathway [51]. Various cell subsets and pathways have been shown to be drivers of type I-IFN production in lupus [50–52,73]. Despite the pathogenic role of type I-IFNs in SLE, these cytokines are crucial in the protection against viruses. During a viral infection, mitochondrial antiviral signaling (MAVS) protein forms a complex with retinoic acid gene I (RIG-I)-like helicases to promote the expression of type I-IFN genes. Buskiewicz *et al.* recently showed that in lupus patients, enhanced mitochondrial ROS synthesis led to RIG-I-independent MAVS oligomerization and subsequent type I-IFN production independent of infection [74]. Taken together, these results suggest that mitochondrial dysfunction and ROS production contribute to the pathogenesis of lupus. However, the mechanisms leading to enhanced mitochondrial ROS production in SLE remain to be fully elucidated. In line with studies mentioned above, multiple mitochondria-related parameters, including ROS production, mitochondria swelling, polarization status, enzymatic activity of mitochondrial complexes, and levels of mediators of the intrinsic pathway of apoptosis, were recently demonstrated to be altered in lupus patients compared to healthy volunteers [75]. In lupus-prone mice, liver mitochondrial dysfunction has been shown to be controlled by mTORC1, and is therefore responsive to rapamycin treatment [76]. Given the reduced expression of the mitophagy facilitator dynamin-related protein 1 (Drp1) preceding lupus onset [76], accumulation of damaged mitochondria is a likely culprit in disease progression. Furthermore, mitochondrial Complex I dysfunction and subsequent mitochondrial ROS production induced by imiquimod (a TLR7 agonist and mediator of lupus-like disease [77]), led to NLRP3 inflammasome activation in a recent study [78]. As NLRP3 inflammasome activation has been associated with SLE pathogenesis [79], the aforementioned study provides additional evidence potentially linking mitochondrial defects in lupus with downstream proinflammatory cascades that promote disease progression.

Immunometabolism therapeutic targets and SLE

Signatures corresponding with metabolic imbalances and elevated oxidative stress have been identified in the sera of lupus patients [80]. Accordingly, targeting metabolic defects in animal models of SLE with the combination of metformin and 2-DG ameliorates disease pathology [31]. Similarly, mitochondrial ROS inhibition with MitoTempo reduces disease severity in a mouse model of lupus [51]. In models of skin damage due to oxidative stress, a topical mitochondria-targeted redox-cycling nitroxide mitigated the impairment [81]. Whether these therapies can improve human disease, and whether their combination have synergistic effects, remain to be determined. In a recent trial of NAC in SLE, the drug was well-tolerated and reduced disease activity via the mTOR pathway [82]. Indeed, mTOR pathway modulators appear to be viable therapies, and the use of rapamycin as a therapeutic option has also been tested animal models of lupus and in humans ([34,76,83,84]; Trial ID: NCT00779194). The role of the PPAR γ -agonist pioglitazone is currently being investigated

in proof-of-concept trials. Information gleaned from the aforementioned studies and from ongoing investigations could identify further pathway- and immune cell-specific targets towards the development of personalized therapies in SLE.

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Key Points

- Disease-specific immunometabolic imbalances and excess oxidative stress are characteristics of SLE
- Reconfiguration of metabolic defects in lupus immune cell subsets has therapeutic potential in experimental models and in isolated human cells
- A better understanding of immune cell-specific metabolic dysfunction in lupus is needed for improved treatment options
- Excessive mitochondrial reactive oxygen species (ROS) production in lupus is associated with multiple pathogenic pathways in disease progression
- Combination therapies targeting immunometabolic and mitochondrial ROS could have synergistic effects in SLE

Figure 1. Immune cell metabolism in lupus

Depicted in this diagram is a simplified overview of the metabolic pathways and factors discussed, as well as therapeutics that have been tested to reconfigure imbalances in lupus immune cell metabolism. Lupus immune cells are characterized by enhanced glucose internalization and subsequent glycolysis, as well as heightened glucose oxidation by the mitochondria. Increased glucose uptake can also feed the pentose phosphate pathway for the generation of reducing equivalents and nucleotide biosynthesis. Known positive regulators of this reprogramming are ERR- α , HIF-1 α and c-Myc. B cell-specific negative regulators include PAX5, IKZF1, Gsk3, Traf3. Glycolysis can be chemically inhibited by 2-deoxy-D-glucose (2-DG). Dysfunctional mitochondria in SLE leads to enhanced reactive oxygen species (ROS) production. Metformin reduces ROS production and inhibits AMPK, which in turn inhibits mTOR, a pathway implicated in lupus pathogenesis. Pioglitazone activates the PPAR- γ signaling pathway, thereby dampening inflammation, and also prevents the transport of pyruvate into the mitochondria, which is aberrantly increased in lupus immune cells. Amino acids and fatty acids are critical fuel sources and are required for immune cell activation and function.