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Metabolic Factors that Contribute to Lupus Pathogenesis

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Abstract

Systemic lupus erythematosus (SLE) is an autoimmune disease in which organ damage is mediated by pathogenic autoantibodies directed against nucleic acids and protein complexes. Studies in SLE patients and in mouse models of lupus have implicated virtually every cell type in the immune system in the induction or amplification of the autoimmune response as well as the promotion of an inflammatory environment that aggravates tissue injury. Here, we review the contribution of CD4⁺ T cells, B cells, and myeloid cells to lupus pathogenesis and then discuss alterations in the metabolism of these cells that may contribute to disease, given the recent advances in the field of immunometabolism.

Keywords

lupus; autoimmunity; T cells; B cells; myeloid cells; immunometabolism

I. INTRODUCTION

Excellent reviews have been written in the past 5 y on systemic lupus erythematosus (SLE),^{1, 2} including the contribution of genetic factors,^{3, 4} the role of T cells,^{5, 6} follicular helper T (T_{fh}) cells,^{7, 8} dendritic cells (DCs),^{9, 10} B cells,^{11, 12} endosomal Toll-like receptor (TLR) signaling,¹³ and anti-double-stranded DNA (dsDNA) antibodies¹⁴ as well as the current status of therapeutic targets.^{15–21} The purpose of this article is to summarize the involvement of CD4⁺ T cells, B cells, and myeloid cells in SLE and focus on how alterations in the metabolism of these cells may contribute to SLE pathogenesis.

Immunometabolism is a relatively new field, and its principal focus is on the type of metabolic substrate, essentially glucose, fatty acids (FAs), and glutamine, that is used and how is it essential for the energy status and anabolic capacity of a cell. Insufficient energy or metabolite levels, as well as reduction/oxidation imbalance, can trigger cell death. This can lead not only to cellular imbalance, such as lymphopenia in lupus,²² but also to a rich source

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of autoantigens in the form of cellular debris.²³ In addition to substrate use for energy generation and production of biosynthetic intermediates, mitochondrial metabolism provides substrates for epigenetic modifications of DNA and histones. Proper balance of epigenetic substrates provides a well-documented but poorly understood layer of regulation of the immune system.²⁴ Finally, some of the metabolite intermediates produced in the mitochondria also serve as inflammatory signals, such as succinate in myeloid cells.²⁵ Following the landmark study in which Frauwirth and colleagues showed that CD28 activation triggered glycolysis in T cells,²⁶ a growing number of studies have revealed that immune cells, and T cells in particular, are functionally regulated by their metabolic substrate use.^{27–30} A general theme is that resting T cells rely on mitochondrial oxidative respiration (OXPHOS), favoring FA oxidation. Antigen-mediated stimulation and acquisition of effector functions trigger a drastic metabolic reprogramming, with up-regulation of glucose use and activation of mitochondria-independent glycolysis as the major source of building blocks necessary to cope with massive proliferation as well as synthesis of effector molecules. On the other hand, regulatory Foxp3⁺ T (Treg) cells and memory T cells, which share an anergic/quiescent phenotype with resting T cells, mostly depend on FA oxidation as a source of energy. On the basis of these drastic differences in metabolic requirements and the critical role of effector T cells in autoimmune diseases and cancer, T-cell metabolism has been proposed as a target for immunotherapy.²⁸

Far less is known about the metabolic requirements of other immune cells that have a critical role in SLE. B cells rely on glucose once activated through their receptor, by interleukin-4 (IL-4)³¹ or lipopolysaccharides (LPSs),³² but their substrate use is more balanced than that of activated T cells.³³ Plasma cells (PCs) as terminally differentiated effector B cells are likely to have specific metabolic requirements.³⁴ Given the indispensable role of PCs in SLE, and the potential different contribution of short- and long-lived PCs to the disease,³⁵ their specific metabolic requirements may identify therapeutic targets. DCs and macrophages also undergo substantial metabolic reprogramming in response to stimulation in the form of “danger signals” from pathogens or self, cytokines, or environmental cues. It has been suggested that metabolic checkpoints also control tolerance induction versus immunogenicity.^{36, 37} Little is known about the metabolic requirements of neutrophils, but a recent study has shown that asymmetrical adenosine triphosphate (ATP) production and mechanistic target of rapamycin (mTOR) signaling are required for neutrophil chemotaxis.³⁸ Finally, activated natural killer cells up-regulate both glycolysis and respiration³⁹ as well as their cytokine production, especially interferon- γ (IFN γ), which is glucose dependent.⁴⁰

Only a few studies, mostly with T cells, have addressed whether alterations in cellular metabolism are found in SLE patients or in mouse models of lupus. In addition to reviewing these studies, we consider how alterations in the metabolism of other cell types, B cells, DCs, macrophages, and neutrophils might contribute to lupus pathogenesis, given the current knowledge of the respective involvement of each of these cell types in SLE and regulation of their effector functions by metabolic programming.

II. CD4⁺ T CELLS IN SLE

A. Pathogenic Effector CD4⁺ T-Cell Subsets in SLE

1. Th17 cells—The discovery of Th17 cells has been one of the most important advances in T-cell immunology since the discovery of Th1 and Th2 cells. Th17 cells preferentially produce IL-17A, -17F, -21, and -22 and have important roles in the development of allergic and autoimmune diseases as well as in protective mechanisms against bacterial and fungal infections.⁴¹ Th17-cell differentiation from naive CD4⁺ T cells is regulated by several cytokines including transforming growth factor- β (TGF- β), IL-6, and IL-21, which activate signal transducer and activator of transcription 3 (STAT3)- and interferon regulatory factor 4 (IRF4)-dependent expression of retinoic acid receptor-related orphan receptor- γ t (ROR γ t), the master regulator of Th17 differentiation.⁴² Other transcription factors, such as ROR α , basic leucine zipper transcription factor ATF-like (Batf), runt related transcription factor 1 (Runx1), and I κ B ζ , encoded by the gene nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor, zeta (Nfkbiz), also regulate Th17-cell differentiation in cooperation with ROR γ t. In addition to CD4⁺ Th17 cells, CD4⁻ CD8⁻ CD3⁺ double negative (DN) T cells produce large amounts of IL-17.

Reports generally agree on the increased circulating Th17 cells^{43–47} and increased IL-17A⁴⁸ in the peripheral blood of SLE patients. Furthermore, IL-17⁺ DN T cells are expanded in SLE patients, and these cells were found in nephritic kidneys.⁴⁹ However, the specific involvement of Th17 cells or their prototypical IL-17A in SLE remains controversial in mouse models of SLE. It has been reported that the Th17/IL-17A axis has no major role in lupus pathogenesis, because neither knocking out IL-17A in MRL/MpJ-Faslpr/J (MRL/lpr) mice nor treatment with anti-IL-17A blocking antibodies in NZBWF1/J (BWF₁) mice reduced kidney pathology.⁵⁰ However, several studies showed direct evidence for a role of IL-17 in the pathogenesis of SLE. Among these studies, IL-17-deficient mice were protected from autoantibody production and glomerulonephritis in the pristane-induced model of lupus.⁵¹ DN IL-17- producing T cells are expanded in MRL/lpr mice, specifically in their inflamed kidneys.⁵² IL-23R deficiency was protective of autoimmune pathogenesis in B6.lpr mice,⁵³ and B6.lpr:IL-17RA^{-/-} mice displayed a reduction in crescentic glomerulonephritis induced by type I IFN.⁵⁴ Similarly, deficiency in IRF4, which decreased the number of Th17 cells, was protective in B6.lpr mice.⁵⁵ Moreover, IL-17 is produced in large amounts by CD4⁺ T cells in the BXD₂ model of lupus,⁵⁶ and IL-17⁺ T cells play a critical part in expanding autoreactive germinal centers (GCs) in these mice.⁵⁷ Transcription of IL-17A is increased in T cells from SLE patients as the result of increased cAMP-responsive element alpha (CREM α) *trans*-activation of the *IL17A* gene through direct binding to a cyclic adenosine monophosphate (cAMP)-responsive element site in the proximal promoter.⁵⁸ The increased production of IL-17 in lupus has also been linked to calcium/calmodulin-dependent protein kinase IV (CAMK4), a multifunctional serine/threonine kinase found at high levels in T cells in SLE patients⁵⁹ and MRL/lpr mice.⁶⁰ Finally, increased Th17 differentiation was reported in naïve T cells cocultured with stool microbiota from SLE patients as opposed to healthy controls.⁶¹

Several approaches have been tried to inhibit or normalize Th17 differentiation in mouse models of lupus. Treatment with an IL-23 blocking antibody had beneficial effects in MRL/lpr mice.⁶² Targeting the IL-17/-23 axis with biologics has demonstrated efficacy in psoriasis and psoriatic arthritis.⁶³ It remains to be determined whether these treatments would be beneficial in SLE. One promising therapy is based on the fact that IL-17A⁺ CD4⁺ T cells are enriched for specificity against a peptide (amino acids 131–150) from the U1–70 spliceosomal protein in MRL/lpr mice as well as SLE patients.⁶⁴ This tolerogenic peptide called lupuzor has been tested in clinical trials with response rates of ~25% or 40% based on two different treatments.⁶⁵ CAMK4 inhibition is another promising venue because its pharmacologic inhibition increased the survival of MRL/lpr mice and decreased IL-17 production by T cells from SLE patients.⁶⁶ Several treatment protocols have resulted indirectly in a reduction of the Th17-cell compartment. Blockade of leptin signaling was beneficial in MRL/lpr mice, at least in part through targeting Th17 cells.⁶⁷ Targeting CD22 decreased Th17 and Th1 differentiation and showed beneficial effects in MRL/lpr mice.⁶⁸ Finally, piperlongumine, a natural product with anti-inflammatory properties, has recently been shown to decrease Th17-cell numbers as well as levels of various cytokines including IL-17, conferring beneficial effects in MRL/lpr mice.⁶⁹

2. Th1 and Th2 cells—As with Th17 cells, the involvement of Th1 cells and their hallmark cytokine IFN γ remains controversial in SLE. Lower levels of IFN γ but high levels of IL-12, which drives Th1-cell differentiation, have been found in the serum of SLE patients.⁴⁸ Reports also exist of reduced circulating Th1 cells in SLE patients.^{45, 47} Other studies, including ours,⁷⁰ have found the opposite, with a positive correlation between the frequency of circulation Th1 cells and disease activity.⁷¹ Furthermore, a recent retrospective study showed that elevation of circulating IFN γ precedes the production of autoantibodies as well as type I IFN activity in SLE patients.⁷² Studies in mice are in general agreement that Th1 cells are important in lupus pathogenesis.^{71, 73} Deletion of the IFN γ gene in MRL/lpr mice⁷⁴ or the IFN γ receptor gene in BWF₁ mice⁷⁵ significantly reduced autoimmune pathology. However, results from a recent clinical trial with AMG-811, an antibody against IFN γ developed by AMGEM, have not been published but appear to be lackluster.

Far less is known about the role of Th2 cells or IL-4 in SLE. IL-4 deficiency is protective in the MRL/lpr mouse.⁷⁴ In the Fc γ RIIB^{-/-} Yaa mouse model of lupus, immunoglobulin 3 (IgE) amplifies autoimmune inflammation through the activation of basophils.⁷⁶ A recent study has shown that elevated IgE correlated with disease activity in SLE patients and that IgE triggered type I IFN responses in plasmacytoid DCs (pDCs).⁷⁷ However, the relationship between elevated IgE levels and Th2 cells has not been explored, and normal levels of circulating IL-4 have been reported in SLE patients.⁴⁸

3. Tfh cells—Tfh cells are CD4⁺ helper T cells specialized for provision of help to B cells, which has an essential role in GC formation, affinity maturation, and the development of most high-affinity antibodies and memory B cells.⁷⁸ Tfh cells are found within and in proximity to GCs in secondary lymphoid organs, and their memory compartment also circulates in the blood.⁷⁹ The *sanroque* mutation in the “really interesting new gene”

(RING)-type ubiquitin ligase *Roquin* gene has shown that Tfh-cell expansion is intimately linked to excessive GC formation, overproductive pathogenic autoantibodies such as anti-dsDNA IgG, and end-organ damage.^{80, 81} The percentage of IL-21–producing circulating Tfh (cTfh) cells is increased in SLE patients^{82–86} and correlates with disease activity.⁸³ In addition, Tfh-like cells are found in SLE kidneys,⁸⁷ suggesting that they are pathogenic. Subsets of human cTfh cells have been defined based on their chemokine (C-X-C motif) receptor 3 (CXCR3) and chemokine (C-C motif) receptor 6 (CCR6) expression and shared properties with effector T cells: CXCR3⁺CCR6[−] cTfh1, CXCR3[−]CCR6[−] cTfh2, and CXCR3[−]CCR6⁺ cTfh17.⁷⁹ An expansion of the cTfh2 and cTfh17 relative to cTfh1 subsets has been reported in SLE patients, with a positive correlation between the frequency of cTfh2 cells and disease activity.^{83, 88, 89} Whether these cTfh2s have a Th2 origin is not clear. In SLE patients, OX40L expressed by myeloid antigen presenting cells (APCs) promotes aberrant Tfh response via TLR7 activation. The frequency of circulating OX40L-expressing myeloid APCs is also positively correlated with disease activity as well as frequency of inducible T-cell costimulator⁺ (ICOS⁺) blood Tfh. This provides a rationale to target OX40L as a therapeutic modality for SLE.⁹⁰ In addition, the level of PD-1, encoded by the gene *Pdcd1*, programmed cell death 1, which is expressed on the surface of Tfh cells, is positively correlated with disease activity⁸³ and both IFN γ and IL-17 production⁹¹ in SLE patients. Furthermore, the frequency of PD-L1–expressing neutrophils is elevated in patients with SLE and correlates with disease activity and severity of SLE.⁹² An expansion of Tfh cells has also been reported in lupus-prone mice,⁹³ including in B6.NZM2410.Sle1.Sle2.Sle3 triple congenic (TC) mice.⁷⁰ This expansion occurs early before disease manifestation, with 2-mo-old TC mice showing a frequency of Tfh cells at a number twice that of B6 mice, supporting a causative role.

Given the overwhelming evidence for a pathogenic role of Tfh cells in SLE, therapeutic targeting of Tfh cells has been proposed for SLE patients through a number of approaches,⁷ and clinical trials (AMG-557, MEDI-570) targeting the ICOS/ICOS ligand (ICOSL) pathway are underway. A reduction in the number of Tfh cells by blocking the IL-21 pathway has beneficial effects in BXSB/MpJ (BXSB. Yaa)⁹⁴ and BWF₁ lupus mice.⁹⁵ In BWF₁ mice, the levels of Tfh cells and GC B cells are dependent on maintenance of the ICOS/B7RP-1 pathway, whereas treatment with an anti-B7RP-1 antibody (Ab) ameliorates disease manifestations and leads to a decrease in Tfh cells and GC B cells.⁹⁶ Nonspecific targeting has also produced beneficial effects associated with a reduction in the number of Tfh cells. Methylprednisone and dexamethasone, two standard-of-care immunosuppressive drugs, decrease the levels of cTfh cells in SLE patients.⁹⁷ In addition, disease reversal observed in lupus-prone mice treated with the metabolic inhibitors 2-deoxy-d-glucose (2DG) and metformin was associated with a dramatic reduction in the number of Tfh cells to B6 levels.^{70, 98}

4. Treg Cells—Treg cells are crucial mediators of self-tolerance in the periphery. They differentiate in the thymus, where interactions with thymus-resident APCs, an instructive cytokine milieu, and stimulation of the T-cell receptor (TCR) lead to the selection into the Treg lineage and induction of Foxp3 gene expression. Scurfy mice that are deficient in Foxp3 expression develop skin symptoms with lymphohistiocytic infiltrate,

glomerulonephritis, and anti-dsDNA antibodies, which supports the hypothesis of Treg involvement in lupus. Treatment of BWF₁ mice with Treg cells delayed disease induction.⁹⁹ We have shown that *Pbx1-d*, the dominant negative allele of the *Pbx1* gene that is associated with lupus in the NZM2410/J mouse model, results in defective maintenance and induction of Treg cells in murine and human T cells^{100, 101} and increased resistance of effector T cells to Treg-mediated suppression.¹⁰² The involvement of Treg cells in human SLE has been the subject of many studies that have yielded disparate results. Some of this disparity is likely due to the different markers that have been used to identify these cells.^{44–46, 103–105} In addition to its role in Th17 cell induction mentioned earlier,⁶⁶ CAMK4 overactivity in lupus contributes to impaired IL-2 production and decreased Treg-cell numbers or function.¹⁰⁶ Impaired IL-2 production in SLE has led to recent trials of a low dose of hrIL-2 to expand the Treg compartment.¹⁰⁷ Ex vivo treatment of SLE cells with IL-2 increased CD25 expression on Treg cells but not in T effectors. A 5-d treatment cycle in patients increased the frequency of FOXP3⁺ CD127^{lo} Treg cells, with variable increases in T effector populations.¹⁰⁷

B. Metabolic Characteristics of CD4⁺ T Cells in SLE

1. mTOR Complex Involvement in SLE—The mTOR complex (mTORC) integrates environmental cues, energy, and nutrient levels and orchestrates in response metabolic transcriptional and translational programs to maintain homeostasis. The distribution and activation of mTORC1 and mTORC2 varies among T-cell types.¹⁰⁸ Th1 and Th17 cells require mTORC1 activation, whereas mTORC2 activation favors Th2 differentiation. It is well documented that mTOR inhibition with rapamycin promotes Treg expansion, although mTORC1 signaling is required for Treg suppressive function, possibly by inhibiting the mTORC2 pathway.¹⁰⁹ Tfh cells have been recently reported to be relatively independent of mTORC1 activation.¹¹⁰ However, *Roquin*, which controls the expression of a number of genes involved in Tfh differentiation,¹¹¹ blocks AMP-activated protein kinase (AMPK) activation, leading to mTORC1 activation, which is required for Tfh development.¹¹² In addition, mTORC2 activation has been indirectly shown to be linked to Tfh differentiation.¹¹³ Recent studies have found that retention of activated mTORC1 during asymmetric cell division in CD8⁺ T cells bestow the daughter cell with effector functions, whereas the mTORC1^{low} daughter cell acquires memory properties.^{114, 115} It is likely that a similar asymmetric distribution of mTORC1 exists between effector and memory CD4⁺ T cells.

mTORC1 activation has been demonstrated in CD4⁺ T cells of SLE patients¹¹⁶ and has been proposed to serve as a biomarker of autoimmune inflammation.¹⁰⁸ Treatment of SLE patients with rapamycin is effective in SLE patients^{117, 118} and in BWF₁ mice.¹¹⁹ mTORC1 activation was also observed in CD4⁺ T cells from several strains of lupus-prone mice.^{70, 98} Interestingly, treatment of these mice with 2-DG and metformin normalized mTORC1 activation concomitant with disease reversal.⁷⁰

2. Glucose Metabolism—After activation, T cells dramatically up-regulate glucose metabolism to create increased energy and building block materials to meet the large demand created by cell proliferation on synthesis of effector molecules. In addition to

oxidation in mitochondria, activated T cells use glucose through reduction of pyruvate into lactate (aerobic glycolysis), which occurs in the presence of sufficient oxygen.³⁰ Specific genes in the glycolytic pathway are involved in T-cell activation leading to autoimmune phenotypes. After activation, CD4⁺ T cells dramatically up-regulate the expression of the Glut1 glucose transporter.¹²⁰ *Glut1* transgenic mice accumulate activated CD4⁺ T cells and produce autoantibodies late in life,¹²¹ directly linking glucose metabolism to autoimmunity. Moreover, overexpression of *Glut1* in CD4⁺ T cells leads to an expansion of effector T cells, whereas AMPK activation decreases *Glut1* expression and expands the amount of Treg cells,¹²² demonstrating a differential requirement of glucose metabolism in effector and regulatory T cells. Conversely, *Glut1*-deficient CD4⁺ T cells produce less severe inflammatory diseases such as graft-versus-host disease (GVHD) and irritable bowel syndrome.¹²⁰ *Glut1* expression is similar in CD4⁺ T cells of lupus-prone and healthy mice, but other genes such as *Hif1a* involved in the glycolytic pathway are differentially expressed.^{70, 98} *Hif1a* is a transcription factor that controls the cellular response to hypoxia that has recently received considerable attention in the context of T-cell differentiation and effector functions.¹²³ *Hif1a* activates the expression of a large number of key glycolytic genes such as *Glut1* and, accordingly, is required for Th17 differentiation.¹²⁴ The role of *Hif1a* in Treg differentiation and function is more complex, and both positive and negative regulations have been reported.¹²³ A hypoxic signature and high levels of *Hif1a* expression have also been reported in nephritic kidneys,²⁰ but the role of hypoxia and *Hif1a* in SLE T cells has not yet been specifically addressed.

We have shown that CD4⁺ T cells of both SLE patients and lupus-prone mice present elevated glycolysis and OXPHOS, and accordingly, the activation and function of these T cells were normalized by inhibiting glucose metabolism with 2DG and mitochondrial respiration with metformin.^{70, 98} A recent study showed that effector memory (EM) CD4⁺ T cells from healthy donors require high levels of glucose metabolism and mitochondrial respiration for survival, proliferation, and IFN γ production.¹²⁵ Using a combination of metabolic inhibitors and the addition of metabolic intermediates has shown that the glucose requirement of EM CD4⁺ T cells is to supply pyruvate for oxidation, leading to increased mitochondrial membrane potential and reactive oxygen species (ROS) production. These results are very similar to what we and other investigators have observed with SLE CD4⁺ T cells. Glucose is largely used to fuel OXPHOS in CD4⁺ T cells from BWF₁¹²⁶ and TC mice⁹⁸, and high IFN γ production by these T cells depends on both glucose and mitochondrial metabolism.⁷⁰ Furthermore, elevated ψ m and ROS production are characteristics of SLE CD4⁺ T cells.¹²⁷ An expansion of EM CD4⁺ T cells is found in SLE patients¹⁰¹ and lupus mice, including the TC model,¹²⁸ which could explain the striking similarities in the metabolism of healthy EM CD4⁺ T cells and SLE CD4⁺ T cells. We have shown, however, that naïve CD4⁺ T cells from lupus mice also presented a dual elevation of glycolysis and OXPHOS.⁷⁰ This suggests that SLE T cells present EM metabolic characteristics before overt signs of activation, which may contribute to enhanced survival of low-affinity autoreactive T cells and/or enhanced effector functions of these T cells. The mechanism leading to this hyper-metabolism in lupus T cells is unknown, but the fact that it is found in young predisease mice suggests that it may have a genetic origin. None of the many lupus susceptibility genes that have been identified through genome-wide association

studies has an obvious link to metabolism. However, we have identified in the NZM2410 lupus-prone mouse a hypomorphic allele of the estrogen receptor-related γ gene (*Esrrg*) that is associated with increased CD4⁺ T-cell activation, IFN γ production, and defective Treg maintenance.¹²⁹ In metabolically active tissues, estrogen-related receptor γ (ERR γ) transactivates genes that control mitochondrial biogenesis and FA oxidation.^{130–133} *Esrrg*-deficient mice die soon after birth, due to the critical need for their myocardium to switch from glycolysis to FA oxidation.¹³⁴ More recent studies have shown that ERR γ orchestrates the transcriptional program that activates glucose OXPHOS and ATP production essential for the function of pancreatic β cells¹³⁵ and neurons.¹³⁶ These results strongly suggest that ERR γ also has a role in regulating T-cell function by controlling mitochondrial metabolism, a hypothesis that we are in the process of testing.

3. Glutamine and Amino Acid Metabolism—Effector T-cell differentiation and function requires the expression of amino acid transporters such as *Asct* for glutamine and CD98 for branched amino acids.¹³⁷ In addition, sensing of amino acid levels has a direct role in mTORC1 activation.²⁹ Glutaminolysis is essential to sustain T-cell activation and proliferation.^{138, 139} Blocking use of glutamine with the drug 6-diazo-5-oxo-L-norleucine (DON) inhibits activation-induced proliferation in vitro as well as in response to immunization with a nominal antigen.¹³⁸ In addition, DON treatment in combination with glucose inhibition was very effective in preventing allograft rejection through the inhibition of inflammatory T cells.¹⁴⁰ Furthermore, glutamine oxidation is the major energy source for alloreactive T cells in a GVHD setting.¹⁴¹ Enzymes involved in glutaminolysis are expressed at higher levels in CD4⁺ T cells from lupus-prone TC mice,⁷⁰ suggesting that it contributes to the high level of OXPHOS observed in these cells and that DON treatment may also be beneficial for SLE T Cells.

4. Lipid Metabolism—Several aspects of lipid metabolism are involved in T-cell function. Cholesterol and glycosphingolipids are major constituents of lipid rafts, which are aggregated in lupus T cells.¹⁴² Normalization of lipid raft synthesis restored normal signaling in human lupus T cells^{143, 144} and decreased lupus pathology in MRL/lpr mice.¹⁴⁵ On the other end, sterol efflux is controlled by ATP-binding cassette transporter subfamily A member 1 and G member 1 (ABCA1 and ABCG1) transporters that are regulated by oxysterol nuclear liver X receptor (LXR). LXR and ABCG1 activation decreased T-cell proliferation¹⁴⁶ and an LXR agonist down-regulated Th17 polarization.¹⁴⁷ Moreover, in vitro polarized mouse Th17 cells are characterized by an increased cholesterol uptake and biosynthesis coupled with decreased metabolism and efflux, leading to the production of specific sterol-sulfate conjugates that activate ROR γ .¹⁴⁸ Finally, cholesterol/ lipid biosynthetic metabolism is necessary for the proliferation and suppressive function of Treg cells in an mTORC1-dependent manner.¹⁰⁹ FA synthesis is also a critical checkpoint in the differentiation of inflammatory T cells in the mouse.¹⁴⁹ This process is controlled by acetyl-CoA carboxylase (ACC), and ACC1-deficient mice are resistant to induction of experimental autoimmune encephalitis, a model of multiple sclerosis that depends on the expansion of Th17 over that of Treg cells. Given the evidence implicating Th17 cells in SLE, it would be of great interest to explore the role of FA synthesis in SLE T cells. Finally, FA oxidation is a major source of energy for Treg cells¹²² as well as memory T cells that

perform de novo synthesis of FAs for lipolysis in a “futile cycle.”¹⁵⁰ We have found increased FA intake and mitochondrial transport in CD4⁺ T cells from TC lupus-prone mice,⁷⁰ suggesting, as for glutamine, that FA oxidation contributes to the increased OXPHOS observed in SLE T cells.

III. B CELLS

B-cell tolerance is essential for preventing SLE pathogenesis, primarily by reducing the secretion of autoantibodies with potential pathogenic specificities.¹⁵¹ These autoantibodies are produced by PCs, and most of them are generated post-GC reactions. Differentiation of effector B cells and antibody production are metabolically demanding activities. Several studies have shown that B cells increase their rate of glycolysis and OXPHOS after activation by a range of stimuli.^{31, 33, 152} A recent study of B-cell metabolism indicated that c-Myc, but not HIF1 α , is important for the glycolytic response.³³ Both HIF1 α and c-Myc directly bind the promoters of genes encoding for glycolytic enzymes and glucose transporters. Interestingly, B-cell receptor (BCR) stimulation increased both glycolysis and oxidative phosphorylation, whereas a pronounced increased glycolysis was observed in TCR-stimulated T cells,³³ which indicates that B and T cells have a different metabolic demand after antigen stimulation. Indeed, protein kinase C β (PKC β) is required for BCR-induced glycolysis, but PKC δ , which controls self-antigen-induced B-cell tolerance,¹⁵³ has no effect.¹⁵⁴ In addition, contrary to T cells, mTORC1 is not involved in the regulation of glycolysis in BCR-stimulated B cells.¹⁵²

In SLE pathogenesis, autoantibodies are confined to nucleoprotein complexes that are released from dying cells and activate TLRs.¹⁵¹ Unlike BCR stimulation, TLR stimulation with LPSs increases glycolysis, which points to different metabolic pathways being mobilized by different stimuli. Recently, it was shown that PC differentiation under TLR stimulation leads to increased ATP-citrate lyase (ACLY) expression, which produces cytosolic acetyl-CoA from mitochondria-derived citrate for glucose-dependent de novo lipogenesis.³² This study indicates that ACLY represents a critical metabolic checkpoint for PC differentiation. Chronic exposure of B cells to self-antigens resulted in a failure to up-regulate glycolysis and OXPHOS by BCR and TLR stimulation,³³ which is the first experimental result, to the best of our knowledge, that links B-cell metabolism to autoimmunity. However, all data generated from B-cell metabolic analysis have been from experiments using in vitro stimulated splenic B cells, and the metabolic profile of distinct B-cell subsets is currently unknown. Therefore, a better understanding of B-cell metabolism, including a potentially different metabolism in autoreactive B cells, could contribute to the therapeutic targeting of autoreactive B cells.

Autophagy is a process by which cells respond to metabolic stress, and autophagy is inhibited by mTORC1 activation. Autophagy is required for PC differentiation and function, as shown in mice with a B-cell-specific deletion of *Atg5* that have normal GC B cells but defective long-lived PCs.¹⁵⁵ It is not known whether PCs undergo autophagy to cope with the high metabolic demand placed by immunoglobulin synthesis, but it has been proposed that autophagy regulates ER expansion, which is a key feature of PC biology.³⁴ Interestingly, increased levels of autophagy have been found in the B cells of lupus-prone BWF₁ mice and

SLE patients.¹⁵⁶ Accordingly, eliminating autophagy from mature B cells in B6.*lpr* mice significantly reduced the production of IgG autoantibodies and autoimmune pathology.¹⁵⁷ Remarkably, total IgM and IgM autoantibodies were less affected in these mice, suggesting that class-switched pathogenic PCs may have a higher requirement for autophagy. This requirement may have translational applications: Spliceosomal peptide (P140) ameliorates clinical symptoms in SLE patients and lupus-prone MRL/*lpr* mice, and P140 attenuates autophagy in B cells.¹⁵⁸ Because protein synthesis is the major cellular function of PCs, it is not surprising that mTORC1 constitutive activation promotes PC differentiation.¹⁵⁹ As previously noted, mTORC1 is activated in SLE T cells,¹¹⁶ but it is unknown whether this is also the case for SLE PCs and whether rapamycin not only normalizes SLE T cells¹¹⁷ but also PCs.

IV. MYELOID CELLS

There has been renewed interest in exploring the contribution of different subsets of myeloid cells to lupus.^{160–162} Below we summarize what is known about the contribution of three main types of myeloid cells (DCs, macrophages and polymorphonuclear neutrophils) to initiation and promotion of lupus.

A. DCs

DCs are game changers of the immune response because they have the potential to induce both activation and tolerance.¹⁶³ DCs are considered to be essential for breaking peripheral tolerance in lupus, although the exact mechanism by which that is achieved is not completely understood. Three different DC subsets referred as myeloid DCs (mDCs), pDCs, and monocyte-derived DCs (moDCs) have been found to contribute to progression of lupus in distinct manners.^{160, 162, 164}

The type I IFN signature, a hallmark feature in the majority of lupus patients, has been associated with the aberrant activation of both mDCs and pDCs.^{165, 166} Immune complexes formed by nucleic acids or proteins, primarily derived from uncleared apoptotic debris and autoantibodies, activate pDCs through TLR7 and TLR9. After activation, pDCs secrete vast amounts of type I IFNs that have multiple roles in lupus: autocrine activation of DCs, promotion of B-cell activation and antibody production, and survival and expansion of activated T cells.¹⁶⁷ Type I IFNs convert DCs into efficient APCs by up-regulating the expression of costimulatory markers such as CD80, CD86, and major histocompatibility complex class II.^{165, 168, 169} Direct evidence for the involvement of type I IFN and pDCs in lupus comes from several types of mouse studies. Administration of IFN α using an adenovirus vector accelerated disease onset and raised serum levels of inflammatory cytokines such as BAFF, IL-6, TNF- α as well as anti-dsDNA auto-antibodies.^{170, 171} Depletion experiments suggested a salient role of pDCs during the early stages of the disease.^{172, 173} Furthermore, genetic deletions of pDCs greatly ameliorated disease in several spontaneous models of lupus.^{174, 175} Finally, a detailed phenotypic characterization of pDCs in seven lupus-prone mouse strains has shown an expanded number and functional impairments of pDCs in each, but the nature of the impairment varied among strains.¹⁷⁶ The serum of lupus patients is rich with immune complexes and proinflammatory cytokines,

such as IFN- α , IL-6, and IL-10, which induce the differentiation of DCs from monocytes. Murine moDCs induced by lupus serum overexpress CD40, 80, and 86; present antigens from dying cells; and activate CD4⁺ T cells. In addition, these moDCs exhibit low levels of inhibitory receptors on their surface and secrete large quantities of IL-6, IL-8, and BAFF.^{177–179} These studies suggest a feed-forward mechanism by which immune complexes and inflammatory cytokines, including type I IFNs, accelerate the differentiation of monocytes into proinflammatory DCs that amplify inflammation in lupus.

We have shown that BMDCs from lupus-prone TC mice are more efficient in inducing B-cell proliferation, antibody production, and chemokine secretion than B6 BMDCs in vitro in an IL-6- and IFN- γ -dependent manner.^{180, 181} Furthermore, IL-6 from TC DCs also impaired the regulatory T-cell compartment,¹⁸² thus exhibiting a multilayered role in disease progression. Constitutive depletion of all CD11c⁺ cells showed a complex role for DCs in the autoimmune pathology of MRL/lpr mice.¹⁸³ cDCs were required for the expansion and differentiation of T cells but not for their initial activation; however, cDCs were required for the development of kidney interstitial infiltrates, which are an essential component of lupus nephritis. A significant role of cDCs in end-organ tissue damage in lupus was further supported by the protective role of ICOSL deletion in DCs on kidney pathology but not on autoimmune responses in MRL/lpr mice.¹⁸⁴ Another level of complexity was revealed when, unexpectedly, MYD88 deletion in MRL/lpr DCs has no effect on nephritis but ameliorated dermatitis, whereas MYD88 depletion in B cells ameliorated both autoimmunity and renal pathology.¹⁸⁵

Despite discrepancies, the unique positioning of DCs as a bridge between innate and adaptive immunity bolsters the argument in favor of a pathogenic role for DCs in lupus and has resulted in the emergence of DC-targeted therapeutic strategies. Tolerogenic moDCs are being generated and pulsed with specific antigens for use in clinical studies.¹⁶⁴ So far, to the best of our knowledge, no tolerogenic studies have been performed in lupus. A better understanding of DC biology is still required to bring DCs into therapeutic approaches for lupus, including a better understanding of their metabolism, which has recently been shown, as it is for T cells, to be a critical regulator of activation and effector functions.¹⁸⁶ The metabolic requirements of quiescent DCs differ from their activated counterparts. Resting granulocyte-macrophage colony-stimulating factor (GM-CSF) induced BMDCs to use FAs to fuel OXPHOS. The metabolic requirements of resting cDCs and pDCs remain unexplored. TLR-stimulated murine BMDCs switch from initial dependence on OXPHOS to aerobic glycolysis. This switch depends on the production of TLR-induced inducible nitric oxide synthase (iNOS) that inhibits the electron transport chain (ETC) and diverts metabolic demands toward glycolysis.¹⁸⁷ Ex vivo TLR-activated cDCs use an iNOS-independent pathway directed by TLR-induced autocrine type I IFN signaling to switch to glycolysis. Inhibiting glycolysis with 2DG significantly hampered DC activation and T-cell priming. Glycolysis also supports FA synthesis, which is essential for DC function. Glycolysis is therefore a prime requisite for activation of DCs.^{36, 188} DC differentiation from monocytes in the presence of GM-CSF and IL-4 turns on mitochondrial biogenesis by up-regulating peroxisome proliferator-activated receptor γ coactivator-1 α expression. Blocking the ETC abolished DC differentiation, showing the complete dependence on mitochondria for initiating DC differentiation. Citrate accrual during this process serves as an intermediate for

FA synthesis, thus showing parallels for the requirement of FA synthesis in both differentiated and activated DCs.^{36, 188}

The phosphatidylinositol 3-kinase (PI3K)/AKT pathway is the central regulator of anabolic and glycolytic pathways. The importance of the mTOR complex downstream from PI3K/AKT in initiating glycolysis has been determined using its negative regulator rapamycin. Rapamycin blocked in vitro differentiation and survival of DCs and reduced the number of DCs in vivo. Likewise, deletion of phosphatase and tensin homolog, a negative regulator of PI3K, expanded the numbers of both CD8a⁺ and CD103⁺ DCs, but did not alter pDCs and CD8a⁻ DCs,³⁶ suggesting that the various DC subsets have specific metabolic requirements. Similar to T cells, AMPK activation suppressed TLR-induced glycolysis and consequent activation of DCs. The reverse effect was observed when AMPK was knocked out, thus showing that AMPK was an important regulator of DC activation. The promising benefits of AMPK targeting have been explored using its activator, 5-aminoimidazole-4-carboxamide (AICAR), in a murine asthma model, in which airway inflammation was attenuated by reducing DC infiltration.¹⁸⁹

It is likely that the aberrant activation of monocyte-derived inflammatory DCs in lupus relies on glycolysis, and we can expect to find decreased expression of OXPHOS genes such as succinate dehydrogenase (SDHA; complex 2 of ETC) and enhanced expression of glycolysis genes such as HIF-1 α in DCs derived from lupus-prone mice and patients. However, this has yet to be verified. If lupus DCs rely solely on aerobic glycolysis, the therapeutic treatment of lupus mice with metformin and 2DG, which is very effective on CD4⁺ T cells,^{70, 98} may have little effect on DCs, because 2DG inhibition of activation is cancelled out by metformin, promoting glycolysis. This also is yet to be determined.

B. Monocytes and Macrophages

Monocytes and macrophages are implicated at multiple levels in the etiology of lupus.^{190, 191} These cells have been separated into classically and alternatively activated subsets in humans and into inflammatory and noninflammatory subsets in mice, as described in detail in other reviews.^{192, 193} There is no association between frequency or number of circulating monocytes and SLE manifestations. However, increasing evidence has emerged showing that activated monocytes accumulate in inflamed sites (especially in kidneys) of SLE patients, and these monocytes have been directly correlated with impaired renal function and anti-dsDNA autoantibody levels.¹⁹⁰ Several studies have reported that monocyte function or activation contributes to SLE pathogenesis. Fc γ R expression and function in these cells are dysregulated in lupus. Fc γ R single-nucleotide polymorphisms have emerged as risk alleles for the disease through several functions, including transcription factor binding and expression and ligand interaction.¹⁹⁴ The activating receptor CD64 (Fc γ R1) is highly expressed in monocytes, and there is a positive correlation between CD64 expression and renal dysfunction markers in SLE patients. Likewise, higher levels of ICAM-1, a protein involved in transmigration and inflammatory cytokine production, and CD40, a protein that activates T cells through CD40L, were found in lupus monocytes.¹⁹⁰ Finally, the aberrant behavior of monocytes in SLE, including their increased expression of CD64 and the CD169 (sialoadhesin); their accumulation in inflamed sites; and increased

expression of IL-6, IL-10, and BAFF, has been credited as contributing to type I IFN activity.^{165, 190}

Both macrophages and monocytes have an impaired phagocytic ability in SLE.^{190, 191, 195} This stems from intrinsic defects, including a decreased expression of CD44¹⁹⁰ and an enhanced response to CSF-1, which leads to defective renal repair; unresolved inflammation; and early onset nephritis in MRL/lpr mice.¹⁹⁶ A feed-forward loop has also been implicated to exist between neutrophil extracellular traps (NETs) and macrophages through activation of inflammasomes. NETs and LL-37, an antimicrobial peptide that NETs contain, activate the inflammasome, which is enhanced in macrophages in SLE patients. The resulting release of IL-18 and $\text{IL-1}\beta$ can stimulate neutrophils to undergo NETosis, thus amplifying the loop and production of proinflammatory cytokines.¹⁹⁷

Metabolic studies in macrophages began more than 40 years ago when it was determined that activated human and murine macrophages exhibited decreased oxygen consumption and increased rates of glycolysis in comparison with resting cells.¹⁹⁸ Most of the subsequent metabolic discoveries have been generated from mouse studies. As for other immune cells, there is a tight link between metabolic state and macrophage phenotype. M1 macrophages or the classically activated subset use glycolysis as their core metabolic source.^{186, 198} The Krebs cycle intermediate succinate favors the production of $\text{IL-1}\beta$ by regulating HIF-1 α .¹⁹⁹ LPS activation completely converts the energy needs of macrophages from OXPHOS to glycolysis through succinate and HIF-1 α , and this process is highly dependent on the availability of glucose.²⁰⁰ The Krebs cycle is considered to be broken at two places in M1 macrophages: after citrate and succinate synthesis, and both of these intermediates are essential for promoting the inflammatory phenotype of M1 macrophages.²⁰¹ Citrate accumulation leads to the production of inflammatory mediators such as nitric oxide (NO), ROS, and prostaglandins. NO is essential for bactericidal and phagocytic functions of macrophages. Apart from glycolysis, the pentose phosphate pathway (PPP) is also activated in M1 macrophages to generate nicotinamide adenine dinucleotide phosphate (NADPH) for the production of ROS, NO, and biosynthetic intermediates. The metabolic events starting from glycolysis to reduction through the PPP until the production of inflammatory mediators through the broken Krebs cycle provide M1 macrophages with enough energy and biosynthetic materials to meet their rapid functional demands.^{186, 198} M2 macrophages or the alternatively activated subset use oxidative metabolism to meet a long and sustained response against parasites. Unlike M1 macrophages, their Krebs cycle is functional, and PPP activity is highly limited.^{186, 202} Macrophage polarization seems to follow distinct metabolic pathways, so the translation of metabolic shifts to disease has gained significance because some disorders clearly lean toward either phenotype.^{203, 204} The manipulation of macrophage polarization has also met with relative success, clinically in regard to ovarian carcinoma,^{205, 206} showing that therapeutically targeting macrophage metabolism might be a viable option in the future, even for SLE.

C. Neutrophils

The presence of a granulopoiesis signature in the blood of SLE patients²⁰⁷ and neutrophil proteins in their urine^{208, 209} suggest a role for neutrophils in the pathogenesis of the

disease. In addition, the abundance of apoptotic neutrophils in the blood,²¹⁰ their defective clearance,²¹¹ the common occurrence of neutropenia²¹² and the enhanced ability of lupus neutrophils to form aggregates^{213, 214} display the multifaceted ways in which these granulocytes could be involved in lupus. A more direct mechanism was proposed when a link between NETosis and pDC activation was identified.^{215, 216}

Neutrophils die and release their intracellular contents in the form of long fibrils that entrap pathogens and mediate their killing through the release of antimicrobial peptides stuck within these fibrils; they have been referred to as extracellular traps, and the mechanism is named NETosis.²¹⁷ Lupus patients have inherent deficiencies in the clearance of cellular debris including these NETs,^{218–220} so antimicrobial peptides that they contain combine with free DNA and activate pDCs through TLR9.²¹⁶ Activated pDCs in turn secrete IFN α and amplify the inflammatory loop in lupus by acting as a positive feedback involving mDCs, neutrophils, and pDCs themselves.^{221, 222} In addition, autoantibodies against the antimicrobial peptides that have been found in the serum of lupus patients activate neutrophils. Antiribonucleoprotein autoantibodies that are commonly found in SLE patients also induce NETs and further enhance the secretion of IFN α from pDCs. These mechanisms show an alternate route by which pDCs perpetuate disease progression in lupus and introduce a new player—neutrophils—into the milieu.

Apart from conventional neutrophils, a distinct subset of neutrophils called low-density granulocytes (LDGs) have been identified in SLE patients.²²³ The phenotypically immature LDGs display an activated phenotype and secrete large amounts of proinflammatory cytokines such as type I IFN, TNF α , and IFN γ . LDGs are also cytotoxic to endothelial cells and are likely involved in vasculitis and end-organ damage in SLE.²²³ Neutrophils have mainly been associated with end-organ damage in lupus, and NET-inducing neutrophils have been detected in skin and kidney of patients, showing the relevance of NETosis in disease pathogenesis.²²⁴ The depletion of neutrophils decreased serum levels of autoantibodies BAFF and IFN γ and lowered the frequencies of IFN γ -producing T cells and GC B cells in a murine model.²²⁵ Similarly, depletion of LDGs restored the functional capacity of endothelial progenitor cells.²²³ However, the deletion of NADPH oxidase, an essential enzyme for production of ROS (which is required for NETosis) in MRL/lpr mice, increased the severity of disease, thus displaying the complex interplay between ROS and lupus.²²⁶

Neutrophils are primarily glycolytic.²²⁷ They possess few mitochondria,²²⁸ which favors aerobic glycolysis rather than OXPHOS.²²⁹ Accordingly, HIF1 α plays a critical part in neutrophil function.^{230–232} Phagocytosis primarily occurs under hypoxic conditions, and the bactericidal activities of phagocytes are regulated through HIF1 α , which directs the expression of the leukocyte β 2 integrin CD18,^{233, 234} the production of antimicrobial peptides and granule proteases, and controls the apoptosis of functional neutrophils through the NF- κ B pathway.²³¹ Mitochondria participate in neutrophil apoptosis through the release of proapoptotic proteins to the cytosol.²³⁵ SLE neutrophils display defective processing of oxidized mitochondrial DNA following inactivation of mitochondrial transcription factor A (TFAM) by autoantibodies. This results in the extrusion of oxidized mitochondrial DNA in NETs, which has a high capacity for inducing type I IFN production.²³⁶ These results suggest that preventing TFAM activation represents a novel therapeutic target in SLE.

The direct influence of metabolic changes in controlling the functions of neutrophils has been studied in diabetes, where the amount of insulin dictates the levels of enzymes involved in glycolysis and glutamine metabolism. The persistent defects observed in neutrophil activities in diabetes patients have been attributed to these metabolic changes and are corrected by insulin treatment.^{237, 238} Although a similar study has not been done in lupus, the consistent reports of increased apoptosis, inflammatory phenotypes, and mitochondrial defects in lupus neutrophils suggest that their cellular metabolism might be highly skewed. Furthermore, a complex interplay among mitochondrial, purinergic, and mTOR signaling pathways has been recently described to control the chemotaxis of neutrophils,²³⁹ also suggesting metabolic options to intervene in normalizing neutrophil functions in SLE.

V. CONCLUSIONS

SLE is a complex disease involving a large number of immune cell types and functional pathways. The emerging field of immunometabolism is unraveling an intricate multilayered system of regulation that has common threads but also cell- and stimulus-specific characteristics. The ability to use metabolic targets as tools to modify immune responses is already being widely explored in the field of cancer. The field is still nascent in inflammatory and autoimmune diseases but holds promise as shown not only by studies in SLE⁷⁰ but also in rheumatoid arthritis (RA),²⁴⁰ GVHD,^{141, 241} coronary artery disease,²⁴² and transplantation.¹⁴⁰ One must be cautious, however, in hoping to find a universal approach to dampen immune inflammation through metabolic targeting. Indeed, two rheumatic autoimmune diseases, SLE and RA, share a dysregulation of CD4⁺ T-cell metabolism, but in opposite directions—with hyperoxidation in SLE and hyperreduction in RA.²⁴³

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ABBREVIATIONS

2DG	2-deoxy-d-glucose
cTfh	circulating Tfh
DCs	dendritic cells
DN	double negative
DON	6-di-azo-5-oxo-L-norleucine
EM	effector memory
FAs	fatty acids
GCs	germinal centers
IFN	interferon

LDGs	low-density granulocytes
mTOR	mammalian (or mechanistic) target of rapamycin
NETS	neutrophil extracellular traps
OXPHOS	mitochondrial oxidative respiration
PCs	plasma cells
pDCs	plasmacytoid DCs
PPP	pentose phosphate pathway
SLE	systemic lupus erythematosus
TC	B6.NZM2410.Sle1.Sle2.Sle3 triple congenic
Tfh	follicular helper (CD4 ⁺ T cells)
Treg	regulatory Foxp3 ⁺ T cells

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