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Immunometabolism in the Pathogenesis of Systemic Lupus Erythematosus: An Update

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Abstract

Purpose of review: To provide an update on state-of-the-art evidence on the role of immunometabolism reprogramming in the pathogenesis of systemic lupus erythematosus (SLE).

Recent findings: Mitochondrial dysfunction and enhanced oxidative stress, along with specific defects in other metabolic pathways, can promote dysregulation of innate and adaptive immune responses in SLE. These abnormalities appear to be driven by genetic and epigenetic factors, modulated by stochastic events. In addition to extensive descriptions of abnormalities in immunometabolism of lupus lymphocytes, recent studies support the critical role of dysregulation of metabolic pathways in innate immune cells including neutrophils, macrophages and dendritic cells, in SLE pathogenesis. Recent abnormalities described in lipid metabolism have been associated with SLE disease activity and related damage. Promising therapeutic strategies that target these metabolic abnormalities have recently been described in SLE.

Summary: Fundamental new insights regarding the role of mitochondrial dysfunction in innate immune dysregulation in SLE pathogenesis have recently emerged. Defects in specific molecular pathways pertinent to immunometabolism in SLE have been described. New insights in translational medicine and promising therapeutic targets have been proposed based on these recent findings.

Keywords

Systemic lupus erythematosus; immunometabolism; mitochondrial dysfunction; oxidative stress; glycolysis

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Introduction: Relevance of immunometabolism in the context of SLE.

Immunometabolism comprises the different metabolic pathways involved in immune cells' effector functions in response to energy-demanding environmental challenges.(1) In many immune cells, energetic demands of resting cells rely on fatty acid oxidation (FAO) and oxidative phosphorylation (OXPHOS). Upon activation, increasing energetic requirements promote a metabolic switch to promptly generate ATP from other metabolic pathways including basic nutrients such as glucose and glutamine, in order to fulfill rapid cell proliferation and differentiation rates.(2, 3) SLE is a highly heterogenous autoimmune syndrome characterized by immune dysregulation that promotes the generation of autoantibodies directed to nuclear antigens, as well as an enhanced activation, differentiation and effector function of immune cells, which culminates in tissue damage. Metabolic reprogramming of adaptive and innate immune elements might contribute to the disturbed immune homeostasis in SLE.(3) Accordingly, the aforementioned pathways have been described to be dysregulated in SLE. In addition, mitochondrial dysfunction, oxidative stress and enhanced activity of the mechanistic target of rapamycin (mTOR) pathway have been reported to play pathogenic roles in SLE.(4)(Figure 1) The translational implications for these findings are substantial and may lead to novel therapeutic targets.(5)

Text of review:

Mitochondrial dysfunction and oxidative stress

❖ **Mitochondrial DNA (mtDNA) oxidation and release and formation of anti-mtDNA autoantibodies.—**The role of mitochondrial dysfunction in the pathogenesis of SLE has been extensively studied recently. Among the several abnormalities described in immune cells are mitochondrial membrane hyperpolarization, enhanced reactive oxygen species (ROS) production and defective ATP generation and, particularly in T cells, decreased intracellular glutathione (GSH) levels, which promotes their inappropriate activation and aberrant immune responses along with enhanced apoptosis and defective clearance of apoptotic bodies.(6, 7) In neutrophils, enhanced synthesis of mitochondrial ROS (mROS), driven by immune complexes and observed in lupus low density granulocytes (LDGs), promotes mtDNA oxidation and neutrophil extracellular trap (NET) formation.(8) The externalization of oxidized mtDNA in NETs promotes interferogenic responses in target cells through the cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS)-Stimulator of Interferon Genes (STING) pathway and the development of lupus-like disease.(8) In a recent study, Kim *et al.* described that aberrant oligomerization of the voltage dependent anion channel (VDAC) in the mitochondrial outer membrane (MOM) during oxidative stress, results in its interaction with short mtDNA fragments and the release of this DNA into the cytoplasm.(9) There, mtDNA cytoplasmic release also activates the cGAS-STING pathway, promoting intracellular upregulation of type I interferon (IFN)-stimulated genes (ISGs).(8, 9) Increased levels of VDAC1 oligomers in lupus murine splenocytes and human SLE mononuclear cells have been documented. Furthermore, pharmacological inhibition of VDAC oligomerization using a small molecule promoted the attenuation of clinical and immunologic features of murine lupus, decreased levels of circulating mtDNA and NET formation.(9) These recent studies suggest that the generation

of oxidized genomic and mitochondrial DNA fragments can promote proinflammatory responses with deleterious effects on immune regulation.

Oxidized mtDNA has been reported to be retained within the mitochondria in SLE, due to a defective disassociation from transcription factor A mitochondria (TFAM), which in normal conditions is a necessary step prior to the lysosomal degradation of oxidized mtDNA.(10) In addition, Becker *et al.* recently reported increased levels of autoantibodies to MOM and mtDNA in both murine and human SLE, with anti-mtDNA antibodies being associated with lupus nephritis (LN) and elevated anti-dsDNA antibodies.(11) Pisetsky *et al.* found that anti-MOM antibodies were associated with lupus disease activity and specific clinical and laboratory features such as arthritis, renal disease, anti-dsDNA levels and complement consumption.(12) While these findings need to be confirmed in larger prospective cohorts, these studies support a putative pathogenic role for autoantibodies and other responses to mitochondrial components in SLE.

❖ **Oxidative stress in SLE.—**Supporting the role of mROS in promoting the type I IFN signature in SLE, Fortner *et al.* documented increased oxidative and glycolytic metabolism in $CD4^{-}CD8^{-}$ TCR-$\alpha\beta^{+}$ ($B220^{+}$) T cells from lupus-prone MRL-*lpr* mice, along with enlarged and rounded-shape mitochondria, which favored spontaneous oligomerization of the mitochondrial antiviral stimulator (MAVS) protein and in parallel with the upregulation of ISGs expression in that T cell subset.(13) In addition, enhanced type I IFN signature in SLE $CD4^{+}$ T cells has been recently described to depend on mitochondrial respiration, since *in vitro* treatment with metformin inhibited electron transport chain (ETC) complex I and thus reduced ISGs expression in healthy control and SLE $CD4^{+}$ T cells upon exposure to IFN-α.(14)

mTOR signaling pathway abnormalities

❖ **Aberrant activation of the mTOR pathway in SLE.—**Multifactorial enhancement of the phosphoinositide-3 kinase (PI3K)/AKT/mTOR pathway in SLE has been extensively studied in murine models and humans and described to play pathogenic roles in immune dysregulation in this disease. Katsuyama *et al.* recently studied the role of serine/arginine-rich splicing factor 1 (SRSF1), an RNA-binding protein, whose expression is decreased in lupus T cells and that in normal conditions suppresses mTOR complex 1 (mTORC1) activity by promoting the expression of its negative regulator phosphatase and tensin homolog (PTEN).(15) Low SRSF1 levels associated with disease activity in SLE subjects, and correlated with lymphopenia and levels of the anti-apoptotic protein Bcl-xL in their T cells.(16) Additionally, some genetic and epigenetic factors have been found to contribute to the increased mTORC1 activity in SLE.(17–20)

❖ **Functional consequences of enhanced mTOR pathway.—**Enhanced mTOR signaling pathway in SLE has been described to play pathogenic roles in SLE through various mechanisms including the promotion of B and T cell differentiation, the latter associated with shifts toward Th1, Th17 and Th22 differentiation, while hindering Treg differentiation and autophagy..(21, 22) Zheng *et al.* recently reported that mTOR pathway activation favors enhancer of zeste homolog 2 (EZH2) upregulation in lupus T cells,

which promotes proinflammatory epigenetic changes, by increasing glycolysis and then suppressing the microRNAs miR-26a and miR-101.(23) The role of the mTOR pathway in SLE pathogenesis goes beyond T cells, as recently reported by Murayama *et al.*, who found that the mTOR inhibitor rapamycin suppressed 2'3'-cGAMP-induced IFN-α production in lupus monocytes, conventional dendritic cells (cDCs) and plasmacytoid DCs (pDCs), by downregulating the cGAS-STING pathway.(24) Moreover, the mTOR pathway has been described to be important in promoting the expansion and function of myeloid cells induced by TLR7 agonists and type I IFNs in two murine lupus models.(25) However, the precise mechanisms involved in this induction remain to be elucidated.

Glucose metabolism abnormalities

Various glucose pathways defects have been implicated in SLE.(3) Aerobic glycolysis is characteristically increased in activated SLE B and T cells, including $CD4^{-}CD8^{-}$ TCR-$\alpha\beta^{+}$ T cells, which parallels rapid proliferation followed by enhancement of spontaneous cell death. In this regard, Secinaro *et al.* recently described the role of methylation-controlled J protein (MCJ), another negative regulator of ETC complex I, which favors caspase-3 activity in coordination with glycolysis and, therefore, prevents characteristic OXPHOS-driven T cell survival. MCJ expression was found to be enhanced in the highly proliferative and glycolytic $CD4^{-}CD8^{-}$ TCR-$\alpha\beta^{+}$ T cells *in vivo* from MRL-*lpr* mice, promoting upregulated caspase-3 activation and increased rates of cell death that might contribute to inflammatory responses.(26) Enhanced glycolysis seemed to be required for the ability of naive $CD4^{+}$ T cells to differentiate into Th17 cells in the same mouse model, and this was partially dependent of glutamine metabolism, as will be further discussed below.(27) Furthermore, a 10-fold increased surface expression of the glucose receptor GLUT1 and increased transcription of high glycolysis-related genes were documented in $CD4^{+}$ T cells from active SLE patients during Th17 polarizing conditions.(28) This phenomenon was facilitated by calcium/calmodulin-dependent protein kinase 4 (CaMK4), which binds to pyruvate kinase M2 that is the final rate-limiting enzyme in glycolysis, to promote its activity.(29, 30) Additionally, pyruvate dehydrogenase (PDH) enzymatic activity is inhibited in lupus Th17 cells to promote conversion of pyruvate to lactate rather than pyruvate to acetyl coenzyme A (acetyl-CoA) that enters the tricarboxylic acid (TCA) cycle. This was in turn modulated by overexpressed cAMP response element modulator/inducible cAMP early repressor (CREM/ICER) through the downregulation of PDH phosphatase expression.(31) Of note, CaMK4 expression in $CD4^{+}$ T cells was involved in mTOR pathway upregulation and correlated with SLE disease activity.(22, 30) A recent report on GLUT1-deficient macrophages supports the crucial role of this receptor in the metabolism of macrophages and in the development of proinflammatory subsets and oxidative stress.(32) Thus, GLUT1-mediated glycolysis may be an important player in the adaptive and innate immune abnormalities seen in the context of autoimmunity.

Abnormalities in the metabolism of amino acids

Amino acids provide another source of energy for immune cell effector function, and dysregulation of their metabolic pathways has been associated with T cell activation disturbances. Kono *et al.* recently highlighted the critical role of glutaminolysis, a stepwise process in which the most abundant amino acid in circulation, glutamine, is converted

to α-ketoglutarate, in modulation of Th17 differentiation in a lupus model. Specifically, pharmacologic and genetic silencing of glutaminolysis first enzyme glutaminase 1 (Gls1), which converts glutamine to glutamate, in naive MRL-*lpr* CD4+ T cells cultured under Th17-polarization conditions, showed decreased Th17 differentiation rates and glycolysis. This effect was mediated, at least in part, by reducing Hypoxia-inducible factor 1α (HIF-1α) protein levels.(27)

Lipids metabolism abnormalities

While abnormalities in lipid metabolism have been less explored in the pathogenesis of SLE, some recent findings suggest a relevant role due to their high association with oxidative stress, given that they are main components of cellular membranes. An increased generation of oxidized lipids and their products in SLE patients has been well described and suggested as putative metabolic biomarkers in this disease and its associated vascular damage.(33) The proatherogenic “lupus lipid profile” is present in many SLE subjects and consists of increased low-density-lipoproteins (LDL), very-LDL (VLDL) and triglycerides, along with reduced levels of high-density-lipoproteins (HDL).(34, 35) Furthermore, lipidomic analyses have unveiled increased serum levels of oxidized LDL (ox-LDL) in SLE along with higher levels of autoantibodies and immune complexes to ox-LDL in those active subjects. (36) Additionally, several proteomic and lipidomic changes in SLE HDL promotes the loss of their cholesterol efflux capacity and anti-inflammatory and anti-oxidative properties. (34) Abnormalities in lipid metabolism could also contribute to T cell dysfunction in SLE, including abnormal glycosphingolipid metabolism that can promote T cell signaling defects and has been suggested as a potential therapeutic target in a lupus prone model. (33, 37) Current evidence suggests that intake of fiber-derived short-chain and omega-3 polyunsaturated fatty acids (FA) could attenuate lupus disease activity by dampening B cell differentiation and class-switched autoantibodies, ISGs and chemokine-related gene expression.(38, 39)

Immunometabolism: From the bench to the bedside.

There have been several recent reports that translate the metabolic abnormalities observed in preclinical models. For instance, Carlucci *et al.* reported that increased levels of lupus LDGs are associated with impaired HDL cholesterol efflux.(40, 41) This is considered to be driven, at least in part, by the ability of LDGs to synthesize higher amounts of NETs which in turn oxidize HDL through myeloperoxidase and other enzymes contained in these lattices.(42) Purmalek *et al.* recently reported that non-calcified coronary plaque burden (NCB) in SLE subjects was negatively associated with HDL and positively associated with VLDL, as measured by nuclear MR (NMR) spectroscopy. Circulating glycoprotein acetylation (GlycA), a novel inflammatory marker that has been related with cardiovascular events in several conditions, was indeed positively associated with NCB and insulin resistance. Moreover, dysregulation of lipoprotein fractions in these patients was significantly associated with SLE disease activity and specific autoantibody profiles.(35) These findings reinforce that pro-inflammatory and proatherogenic HDL particles in SLE promote vascular damage, at least in part, by dampening cholesterol efflux capacity.

Novel therapeutic strategies regarding immunometabolism in SLE

Since mROS and oxidative stress are determinant in the formation of oxidized mtDNA-enriched NETs and in the enhanced type I IFN signature in SLE patients, some therapeutic strategies targeting their pathogenic role have been recently emerged.(Table 1) For instance, Blanco *et al.* demonstrated that idebenone, a synthetic coenzyme Q10 analog with potent antioxidant effects and previously reported to be effective in other conditions associated with mitochondrial dysfunction, ameliorated lupus disease activity, organ damage and immune dysregulation in two mouse models of lupus. This included significant improvements in overall survival, kidney function, vasculopathy and inflammatory gene expression, at least in part, due to the modulation of mitochondrial metabolism and mROS-driven NET formation.(43) Similarly, administration of MitoQ, another mitochondria-targeted antioxidant containing ubiquinol attached to a lipophilic cation that facilitates membrane permeabilization and mitochondrial matrix access, led to improvements in renal disease, neutrophil mitochondrial metabolism and NET formation in MRL-*lpr* mice. Moreover, $CD4^{-}CD8^{-}$ TCR-$\alpha\beta^{+}$ T cells from MitoQ-treated mice revealed decreased levels of MAVS oligomerization, along with reduced serum IFN-α.(13) In contrast with the model that used idebenone, the role of MitoQ in other organ manifestations and modulation of immune cell subsets is less clear and requires further study.(13, 43) The therapeutic potential of metformin should be further studied but data reported so far supports that targeting mitochondrial respiration could be beneficial in SLE as another add-on therapy, along with its known positive effects on lipid and glucose metabolism, oxidative stress and immune regulation.(14, 44, 45) Cornaby et al. recently reported the therapeutic efficacy of the combination of metformin with Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4)-Ig (abatacept) on preventing the development of lupus nephritis in a murine model.(46) Promising treatments targeting mitochondrial dysfunction in SLE, such as the above mentioned VDAC oligomerization small molecule inhibitor, have recently emerged.(9, 47)

Novel therapeutic strategies for SLE targeting mTOR and glycolysis pathways have been proposed.(30, 48, 49) For instance, recent reports have reinforced beneficial effects of rapamycin or sirolimus for renal and non-renal manifestations of SLE.(50–53) Similarly, the beneficial effect of the GSH precursor N-acetylcysteine (NAC) on lupus disease activity by inhibiting mTOR in T cells was demonstrated in a clinical trial.(54) Additionally, the mTOR inhibitor INK128 has reported promising effects on lupus development by targeting inflammation-induced myeloid cells and by impairing their differentiation into macrophages in glomerulonephritis, even more effectively than rapamycin.(30) CaMK4 inhibition favored decreased expression of glycolysis-related proteins during T cell activation as well as Th17 differentiation in MRL-*lpr* mice and active SLE subjects.(30, 55) In the same way and similar to other autoimmune conditions(28), direct inhibition of glucose transporters has also demonstrated to attenuate lupus features in two murine models by reducing glycolysis in activated T cells, which is compensated by an increased FAO and pentose phosphate pathway (PPP). Furthermore, *in vitro* experiments have revealed decreases in T cell expansion and Th1Th17 polarization and enhanced Treg differentiation.(56) Nevertheless, the precise molecular mechanisms involved in this phenomenon and the putative clinical impact of this T cell modulation remains to be determined, as there are some discrepancies between the *in vivo* and *in vitro* findings. As previously mentioned, glutaminolysis is

another potential therapeutic target in SLE, given that Gls1 inhibition showed beneficial effects *in vitro* and *in vivo*.(27) Finally, along with their favorable impact on primary and secondary prevention of cardiovascular events, the lipid-lowering drugs statins can attenuate SLE disease activity through different immunomodulatory effects, such as downregulation of proinflammatory cytokines, TLR2 signaling and major histocompatibility complex class-II (MHC-II) expression.(57, 58) Taking this together, targeting metabolic reprogramming in SLE might complement immunosuppressive standard therapies in the future, although more evidence is needed to clarify the efficacy and safety of these new therapeutic strategies in the context of an extraordinarily complex syndrome such as SLE.

Conclusions

Increasing evidence supports an important role for disturbances in immunometabolic pathways in the pathogenesis of SLE. These disturbances involve numerous immune cell subsets of the innate and adaptive arms. As more is learned about how various molecular metabolic pathways impact immune function, more promising therapeutic targeting strategies may emerge that could positively impact SLE by complementing current therapies and limiting the adverse effects of immunosuppressive drugs.

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Key points

- Immunometabolism reprogramming is critical in the pathogenesis of SLE through a complex crosstalk between innate and adaptive immune responses.
- Mitochondrial dysfunction and oxidative stress contribute to the distinctive increased type I IFN signature in SLE.
- Abnormalities in various immunometabolism pathways such as mTOR, glycolysis and glutaminolysis favor the differentiation and skewing towards proinflammatory immune cell subsets in SLE.
- Abnormalities in lipid metabolism may contribute to drive to immune dysregulation and premature cardiovascular disease in SLE.
- Targeting immunometabolism defects in SLE might complement immunosuppressive standard therapies.

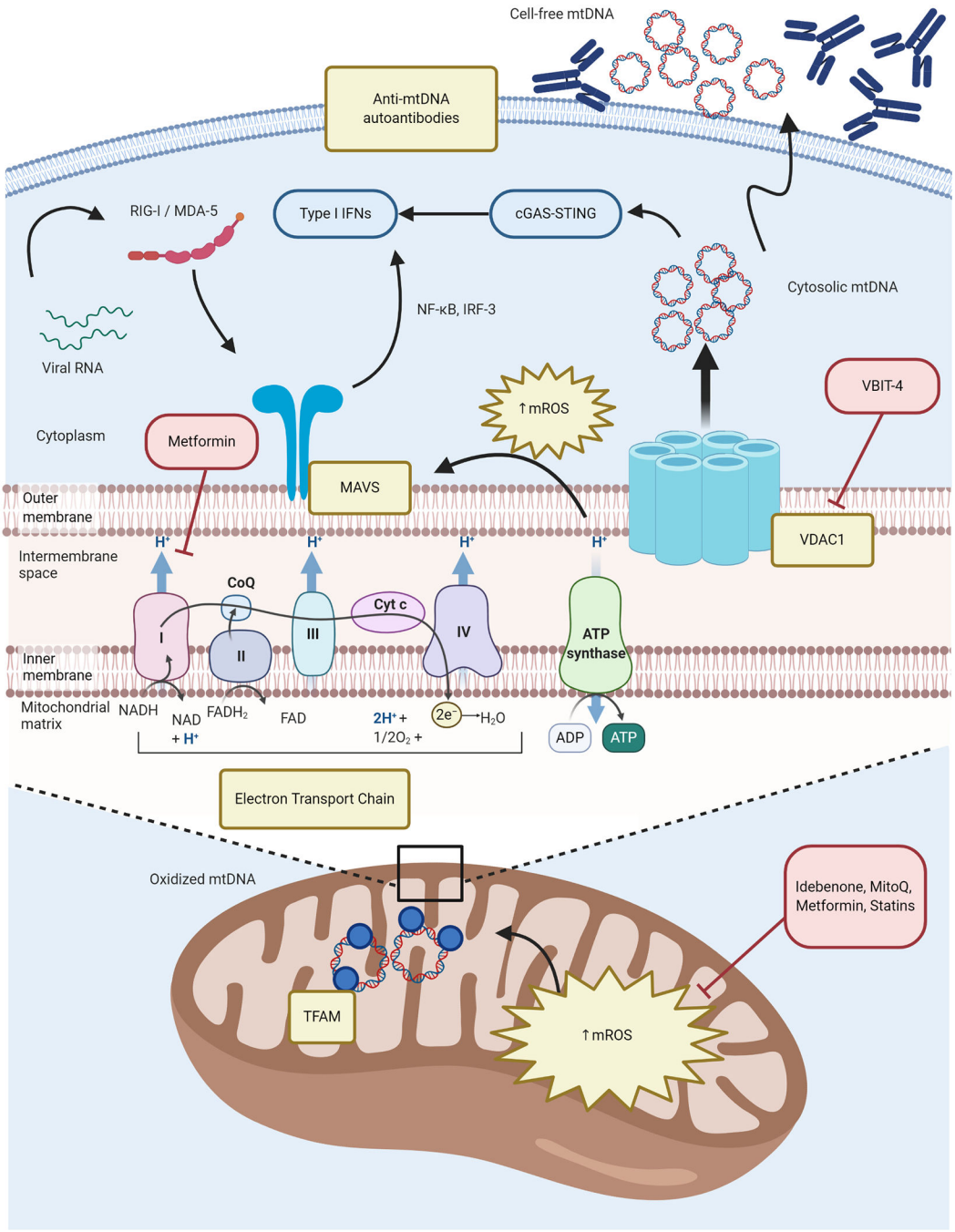

Figure 1. Mitochondrial dysfunction and oxidative stress in SLE.

Chronically increased OXPHOS in immune cells promotes enhanced generation of mROS and enhanced type I IFN responses. Excessive mROS synthesis promotes MAVS oligomerization in the MOM that is essential for antiviral immune responses but dysregulated in SLE. Enhanced oxidative stress along with a putative defective disassociation of mtDNA from TFAM in the mitochondrial matrix, facilitates the oxidation of mtDNA. Increased VDAC oligomers in the MOM interact with oxidized mtDNA fragments and facilitating their release into the cytoplasm, where they activate

the cGAS-STING pathway and upregulate ISG expression. Additionally, autoantibodies to free-cell mtDNA may contribute to lupus immune dysregulation. Perturbations in immunometabolism pathways described in SLE are depicted in yellow boxes; novel therapeutic strategies targeting some of these specific defects are depicted in red boxes. cGAS-STING = cyclic guanosine monophosphate-–adenosine monophosphate synthase (cGAS)-Stimulator of Interferon Genes (STING); CoQ = coenzyme Q10; Cyt c = cytochrome c; IFNs = interferons; IRF-3 = Interferon regulatory factor 3; MAVS = mitochondrial antiviral stimulator; MDA-5 = melanoma differentiation-associated protein 5; mROS = mitochondrial reactive oxygen species (ROS); mtDNA = mitochondrial DNA; NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells; OXPHOS = oxidative phosphorylation; RIG-I = retinoic acid-inducible gene I; SLE = systemic lupus erythematosus; VDAC1 = voltage-dependent anion channel 1.

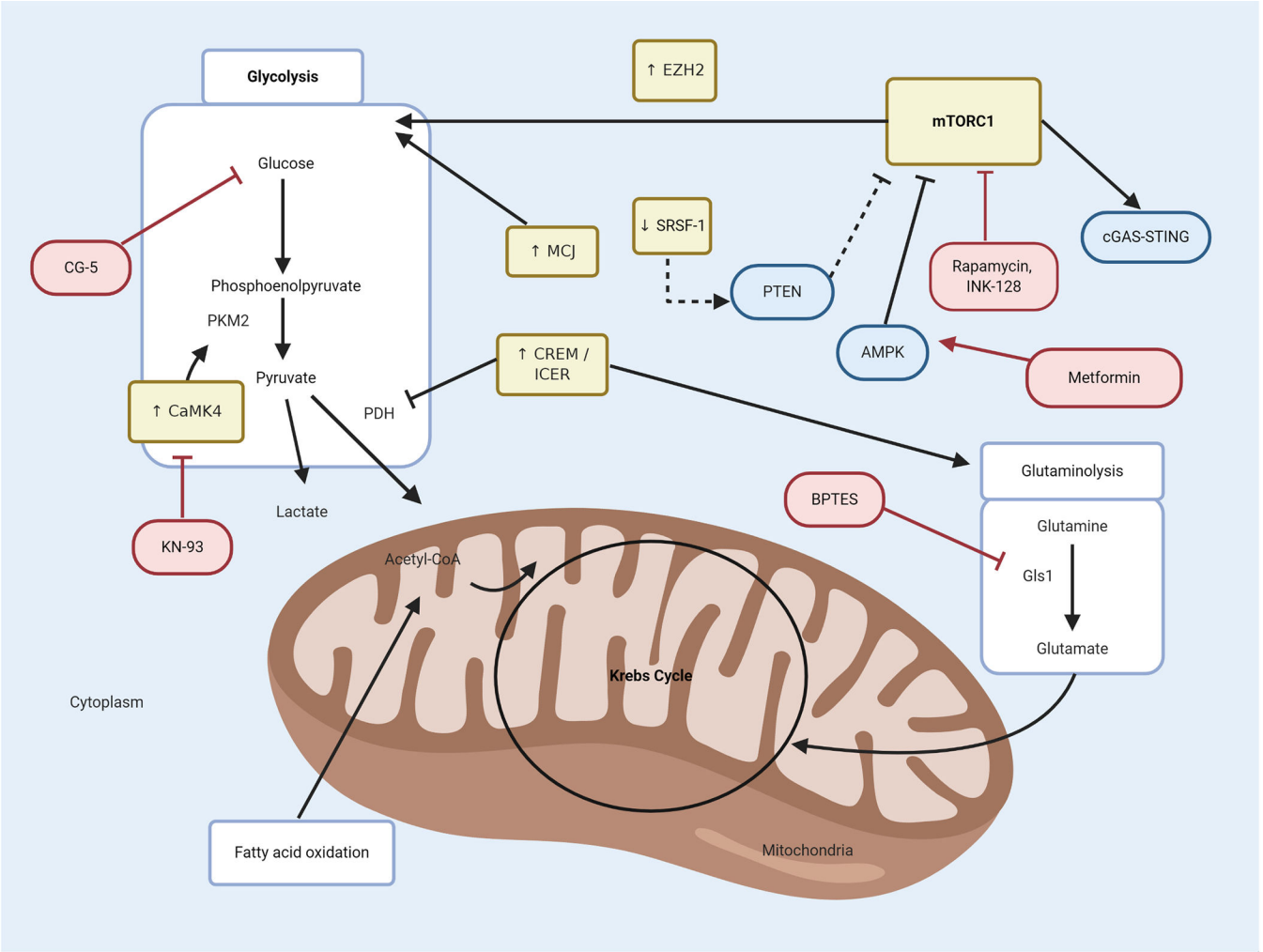

Figure 2. Glycolysis, glutaminolysis and mTOR pathway defects in SLE.

Specific defects in immunometabolism pathways in SLE, such as mTOR, glycolysis and glutaminolysis, interact in an orchestrated manner to promote dysregulation of immune cells. GLUT1 and high glycolysis-related genes are enhanced in lupus. In addition, upregulation of mTOR pathway, increased levels of MCJ protein and enhanced CaMK4 (which binds to PKM2) perpetuate a highly glycolytic state in lymphocytes. The mTOR pathway is triggered by low levels of SRSF-1 protein which, in normal conditions promotes the expression of the negative regulator of mTORC1, PTEN. Treatment with metformin inhibits mTOR pathway and attenuates lupus-like disease by enhancing AMPK. In lupus Th17 cells, overexpressed CREM/ICER inhibits PDH enzymatic activity, which favors the shift from pyruvate to lactate instead of pyruvate to acetyl-CoA. Furthermore, CREM/ICER activates the glutaminolysis pathway, with a putative role in SLE, as the inhibition of the Gs1 enzyme attenuates lupus-like disease. Perturbations in immunometabolism pathways described in SLE are depicted in yellow boxes; novel therapeutic strategies targeting some of these specific defects are depicted in red boxes. Acetyl-CoA = acetyl coenzyme A; AMPK = AMP-activated protein kinase; CaMK4 = calcium/calmodulin-dependent protein kinase 4; cGAS-STING = cyclic guanosine monophosphate-–adenosine monophosphate synthase

(cGAS)-Stimulator of Interferon Genes (STING); CREM/ICER = cAMP response element modulator/inducible cAMP early repressor; EZH2 = enhancer of zeste homolog 2; Gls1 = glutaminase 1; MCJ = methylation-controlled J protein; mTORC1 = mammalian target of rapamycin complex 1; PDH = pyruvate dehydrogenase; PKM2 = pyruvate kinase M2; PTEN = phosphatase and tensin homolog; SRSF1 = serine/arginine-rich splicing factor 1.

Table 1.

Novel therapeutic strategies that target immunometabolism in SLE.

Biological process targeted	Targeted molecule	Drug	Model	Proposed mechanism in SLE	Reference
Mitochondrial dysfunction and oxidative stress	mROS	Idebenone	MRL-*lpr*, NZM2328	• Mitochondrial metabolism and mROS-NETosis modulation.	Blanco et al.(43)
		MitoQ	MRL-*lpr*	• Mitochondrial metabolism and mROS-NETosis modulation. • Reduced MAVS oligomerization and IFN-α.	Fortner et al.(13)
	HRES-1/Rab4 and Rab5	3-PEHPC	MRL-*lpr*	• Downregulation of IL-10. • Reversal of Drp1 protein depletion; reduction of mitochondrial mass in T and B cells and macrophages.	Caza et al.(47)
	VDAC1	VBIT-4	MpJ-Fas^{lpr}	• Decreased cell-free mtDNA and ISG expression. • mROS-NETosis modulation.	Kim et al.(34)
mTOR pathway	mTORC1	Rapamycin (sirolimus)	MRL-*lpr*, NZB/W F1, *Srsf1*-cKO mice, human SLE	• Downregulation of proinflammatory cytokines. • Decreased Tfh cell infiltration. • Restoring Th17/Treg balance and increasing $CD8^+$ memory T cells. • Targeting cGAS-STING pathway and ISG expression in myeloid cells.	Katsuyama et al.(15) Zhang et al.(51) Eriksson et al.(50) Zhao et al.(52) Yap et al.(53) Murayama et al.(24)
	GSH	NAC	NZB × NZW F1, human SLE	• Increased GSH levels in PBLs and reversed mTOR activity. • Enhanced mitochondrial mass and hyperpolarization, and apoptosis of $CD4^-CD8^-TCR\text{-}\alpha\beta^+$ T cells. • Increased Treg cells count.	Lai et al.(54)
	mTORC1/2	INK-128	MRL/*lpr*, Pristane-induced lupus mice	• Impairing $CD11b^+Gr1^+$ cell differentiation.	Shi et al.(25)
	AMPK, ETC	Metformin	B6.*Sle1.Sle2.Sle3*, NZB/W mice, Roquin$^{san/san}$ mice, human SLE	• Synergistic effect with 2-DG to reduce glycolysis and OXPHOS, and IFN-γ production. • Restored IL-2 production and decreased ISGs expression in $CD4^+$ T cells. • Reduced GC B cells and autoantibodies production. • Restoring Th17/Treg cells balance.	Yin et al.(44) Titov et al. (14) Lee et al.(45)
Glycolysis	CAMK4	KN-93	MRL-*lpr*, human SLE	• Restoring Th17/Treg cells balance. • Decreased glycolysis-related proteins expression in T cells under Th17-polarizing conditions. • mTOR pathway downregulation.	Koga et al.(30, 55)
	Glucose transporters	CG-5	B6.NZM2410.*Sle1.Sle2.Sle3*, human SLE	• Decreased glycolysis-related proteins expression and increased FAO and PPP in activated $CD4^+$ T cells. • Restoring Th17/Treg cells balance. • Reduced GC B cells and autoantibodies production.	Li et al.(56)
Glutaminolysis	Gs1	BPTES	MRL-*lpr*, human SLE	• Decreased $CD4^-CD8^-TCR\text{-}\alpha\beta^+$ T cells counts and Th17 differentiation. • Decreased glycolysis favored by reduced HIF-α levels.	Kono et al.(27)
Lipids metabolism	HMG-CoA reductase	Statins	gld.apoE$^{-/-}$ mice, NZB/W F1, human SLE	• Downregulation of proinflammatory cytokines, TLR2 and MHC-II expression.	Tan et al.(57) Ruiz-Limón et al.(58)

Curr Opin Rheumatol. Author manuscript; available in PMC 2023 August 29.

Biological process targeted	Targeted molecule	Drug	Model	Proposed mechanism in SLE	Reference
				• Cholesterol and lipid metabolism, oxidative stress and mitochondrial activity modulation in monocytes.	
	GlcCer synthase	Genz-667161	MRL-*lpr*	• Reduction of GSL hexosylceramide and ganglioside GM3 levels.	Nowling et al.(37)

2-DG = 2-deoxyglucose; AMPK = AMP-activated protein kinase; CaMK4 = calcium/calmodulin-dependent protein kinase 4; cGAS-STING = cyclic guanosine monophosphate-–adenosine monophosphate synthase (cGAS)-Stimulator of Interferon Genes (STING); Drp1 = dynamin-related protein 1; ETC = electron transport chain; FAO = fatty acid oxidation; GC = germinal center; GlcCer synthase = UDP-glucose:ceramide glucosyltransferase; Gls1 = glutaminase 1; GSH = glutathione; GSL = glycosphingolipids; HIF-1α = hypoxia-inducible factor 1α; HMG-CoA = 3-hydroxy-3-methyl-glutaryl-coenzyme A; ISGs = type I interferon (IFN)-stimulated genes; MAVS = mitochondrial antiviral stimulator; MHC-II = major histocompatibility complex class-II; mROS = mitochondrial reactive oxygen species (ROS); mtDNA = mitochondrial DNA; mTOR = mammalian target of rapamycin; mTORC1 = mTOR complex 1; mTORC1/2 = mTOR complex 1 and 2; NAC = N-acetylcysteine; OXPHOS = oxidative phosphorylation; PBLs = peripheral blood lymphocytes; PPP = pentose phosphate pathway; SLE = systemic lupus erythematosus; SRSF1 = serine/arginine-rich splicing factor 1; VDAC1 = voltage-dependent anion channel 1.