

REVIEW

Metabolic Control of Immune System Activation in Rheumatic Diseases

Andras Perl

Metabolic pathways mediate lineage specification within the immune system through the regulation of glucose utilization, a process that generates energy in the form of ATP and synthesis of amino acids, nucleotides, and lipids to enable cell growth, proliferation, and survival. CD4+ T cells, a proinflammatory cell subset, preferentially produce ATP through glycolysis, whereas cells with an anti-inflammatory lineage, such as memory and regulatory T cells, favor mitochondrial ATP generation. In conditions of metabolic stress or a shortage of nutrients, cells rely on autophagy to secure amino acids and other substrates, while survival depends on the sparing of mitochondria and maintenance of a reducing environment. The pentose phosphate pathway acts as a key gatekeeper of inflammation by supplying ribose-5-phosphate for cell proliferation and NADPH for antioxidant defenses. Increased lysosomal catabolism, accumulation of branched amino acids, glutamine, kynurenine, and histidine, and depletion of glutathione and cysteine activate the mechanistic target of rapamycin (mTOR), an arbiter of lineage development within the innate and adaptive immune systems. Mapping the impact of susceptibility genes to metabolic pathways allows for better understanding and therapeutic targeting of disease-specific expansion of proinflammatory cells. Therapeutic approaches aimed at glutathione depletion and mTOR pathway activation appear to be safe and effective for treating lupus, while an opposing intervention may be of benefit in rheumatoid arthritis. Environmental sources of origin for metabolites within immune cells may include microbiota

and plants. Thus, a better understanding of the pathways of immunometabolism could provide new insights into the pathogenesis and treatment of the rheumatic diseases.

Introduction

Metabolic pathways exert profound influence over the development of unicellular and multicellular organisms. Engagement of antigen receptors and costimulatory molecules, growth factors, hormones, cytokines, environmental factors, and other regulatory cues shape the development of the immune system by mechanisms of action that lead to reprogramming of metabolic gene expression in a cell type-specific manner. In fact, the heterogeneity of cells within both the innate and the adaptive immune systems depends on the supply of metabolites that allow for lineage-specific differentiation. This review integrates recent discoveries in metabolomics and genetics with immunologic pathways of pathogenesis to delineate checkpoints for the diagnosis of autoimmune rheumatic diseases and elucidate additional targets for the treatment of these diseases.

Role of metabolic pathways as regulators of the immune response and inflammation

Cells face a tantalizing choice between speed and efficiency when selecting metabolic pathways to meet their needs for proliferation, differentiation, and survival. Lineage specification within the immune system depends on metabolic pathways that regulate glucose utilization for generation of energy in the form of ATP and for synthesis of amino acids, nucleotides, and lipids to enable cell growth, proliferation, and survival. While rapidly proliferating proinflammatory CD4+ T cells preferentially produce ATP through glycolysis, cells with an anti-inflammatory lineage, such as memory and regulatory T cells, favor the generation of mitochondrial ATP (1). During conditions of metabolic stress and a shortage of nutrients, cells rely on autophagy of proteins and organelles to secure amino acids

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and other substrates, while survival of the cells depends on the sparing of mitochondria and maintenance of a reducing environment. The pentose phosphate pathway (PPP) is a key gatekeeper of inflammation, acting via the supply of ribose-5-phosphate (R5P) for cell proliferation and NADPH for antioxidant defenses (2).

The PPP enzyme transaldolase (TAL) exerts control over the production of NADPH, which maintains glutathione (GSH) in a reduced state in human T cells (3,4). As originally documented, TAL regulates the elevation of mitochondrial transmembrane potential ($\Delta\Psi_m$), a process that has also been termed mitochondrial hyperpolarization (MHP) and identified as a checkpoint of T

cell activation and apoptosis (5). Although MHP occurs transiently during T cell activation, it persists in patients with systemic lupus erythematosus (SLE), causes the depletion of GSH and ATP, and leads to a predisposition to proinflammatory cell death via necrosis (6).

During periods of metabolic stress and nutrient deprivation, increased catabolism in lysosomes, accumulation of branched amino acids, glutamine, kynurenine, and histidine, and depletion of GSH and cysteine activate the mechanistic target of rapamycin (mTOR), a kinase that has recently been recognized as an arbiter of lineage development within both the innate and the adaptive immune systems (Figure 1). Targeting

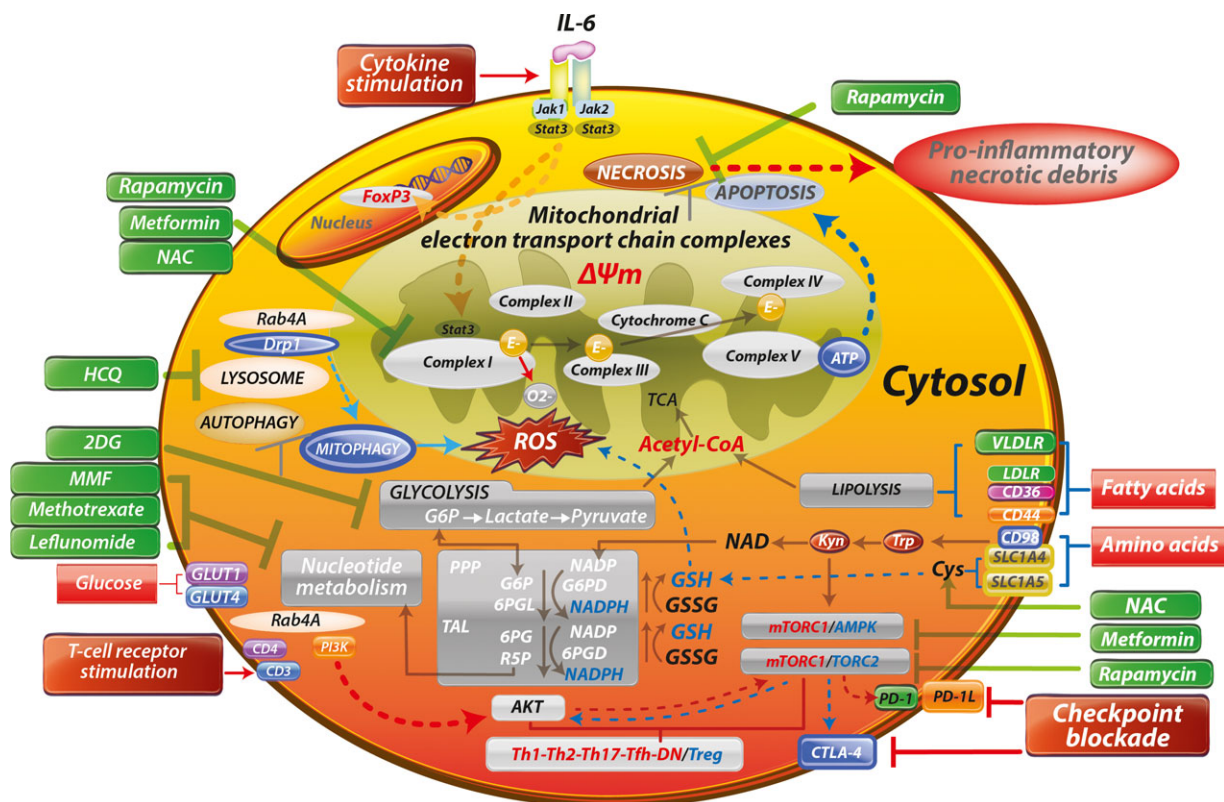


Figure 1. Schematic diagram of metabolic pathways controlling activation and lineage specification in the immune system. Depicted surface receptors and intracellular transducers exemplify those that operate in T cells, regulate or are regulated by metabolic pathways, and exhibit genetic linkage with systemic lupus erythematosus (SLE) and other autoimmune diseases. Characteristics of mitochondrial dysfunction include blocked electron transport chain (ETC) activity, elevated mitochondrial transmembrane potential ($\Delta\Psi_m$) or mitochondrial hyperpolarization, and diminished mitophagy, which contribute to accumulation of oxidative stress-generating mitochondria and depletion of ATP and glutathione (GSH). Reactive oxygen species (ROS) are generated by electron (E) transfer to O_2 at complex I. These metabolic changes underlie the activation of mechanistic target of rapamycin complex 1 (mTORC1), which promotes glycolysis in CD4⁺ T cells, further enhancing the accumulation of mitochondria in necrosis-prone, proinflammatory double-negative (DN) T cells and depleting Treg cells. Thus, key metabolic features of T cell dysfunction in SLE are balancing of energy production between the mitochondrial ETC and glycolysis, and securing of amino acids during starvation through autophagy of proteins and organelles while mitochondria are selectively retained. The direction of signaling is indicated by arrows (red = increase, blue = decrease). Drugs that affect metabolism are shown in green. IL-6 = interleukin-6; NAC = *N*-acetyl-cysteine; Drp1 = dynamin-related protein 1; HCO = hydroxychloroquine; TCA = tricarboxylic acid; 2DG = 2-deoxyglucose; Acetyl-CoA = acetyl-coenzyme A; VLDLR = very low-density lipoprotein receptor; MMF = mycophenolate mofetil; LDLR = low-density lipoprotein receptor; G6P = glucose-6-phosphate; PPP = pentose phosphate pathway; G6PD = glucose-6-phosphate dehydrogenase; 6PGL = 6-phosphogluconolactonase; GSSG = oxidized glutathione; TAL = transaldolase; 6PG = 6-phosphogluconate; 6PGD = 6-phosphogluconate dehydrogenase; AMPK = AMP-dependent protein kinase; PI3K = phosphatidylinositol 3-kinase; R5P = ribose-5-phosphate; PD-1 = programmed death 1; Tfh = follicular helper T cells.

Table 1. Metabolic pathways affected by systemic lupus erythematosus susceptibility genes*

Metabolic pathway, gene	Primary function	Metabolic pathway, gene	Primary function
Glucose metabolism			
TCF7	Transcription	Adipogenesis	
TLR7	RNA binding	ARID5B†	Transcription
SOCS1	Signal transduction	CXorf21	Unknown
IRF5†	Transcription	STAT4†	Transcription
IRF7	Transcription	IL12A	Cytokine
IRF8†	Transcription	CD80	Signal transduction
LYN	Tyrosine kinase	Apoptosis	
SLC15A4	Histidine transporter	TNFSF4	Signal transduction
PRKCB	Protein kinase	ELF1	Transcription
BLK†	Tyrosine kinase	Autophagy/mTOR	
ITGAM	Cell adhesion	TNIP1‡	Signal transduction
IFIH1	RNA helicase	IRAK1†	Signal transduction
TYK2†	Tyrosine kinase	miR146a	RNA processing
IL10	Cytokine	ATG5†	E3 ubiquitin ligase
IKZF2	Transcription	UHRF1BP1	DNA methylation
PRPS2	PRPP synthesis	WDFY4†	E3 ubiquitin ligase
Lipid metabolism		ATG16L2	Unknown
BANK1	Scaffold protein	PLD2	Phospholipid hydrolysis
AFF1	Transcription	PRDM1	Transcription
RASGRP3	GTPase signaling	PTPN22†	Tyrosine phosphatase
JAZF1†	Transcription	RAD51B†	DNA repair
XKR6	Unknown	TET3	DNA methylation
DHCR7	Cholesterol reductase	DRAM1	Lysosomal function
SH2B3†	Signal transduction	TNFAIP3†‡	Ubiquitin ligase
Mitochondrial metabolism		PPP2CA	Protein phosphatase
TREX1	DNA exonuclease	UBE2L3	Ubiquitin conjugation
NMNAT2	NAD(P) biosynthesis	SLC15A4	Histidine transport
CSK	Tyrosine kinase	Clearance of cell death debris	
PDHX	Pyruvate dehydrogenase	C1Q	Ig binding
Oxidative stress		FCGR2B†	Ig binding
MSH5	DNA repair	FCGR2A†	Ig binding
IKZF1	Transcription	CR2	EBV receptor
IKZF3	Transcription	C1R	Ig binding
ETS1†	Transcription	C4B	Ig binding
NCF2	NADPH oxidase	C4A	Ig binding
mTOR		DNASE1	DNA degradation
SLC15A4	Histidine transport		

* Literature references are listed in Supplementary Table 1 (available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40223/abstract>). PRPP = phosphoribosylpyrophosphate; mTOR = mechanistic target of rapamycin; EBV = Epstein-Barr virus.

† Gene also associated with rheumatoid arthritis.

‡ Gene also associated with psoriatic arthritis.

the immunometabolism for therapeutic interventions requires a detailed map of the interconnected pathways supporting disease-specific expansion of proinflammatory cells (Figure 1). Recent approaches targeting the depletion of GSH and activation of mTOR appear to be safe and effective in the treatment of lupus (7), while an opposing intervention may benefit patients with rheumatoid arthritis (RA) (8). Importantly, metabolites within immune cells ultimately derive from the environment; thus, comprehensive profiling may pinpoint microbiota and plants as sources of origin. Therefore, cultivating a better understanding of the pathways of immunometabolism could provide new insights into the pathogenesis and treatment of autoimmune rheumatic diseases.

Integration of genetic and environmental factors with immunometabolic pathways in analyses of autoimmune disease pathogenesis

Both genetic and environmental factors contribute to the pathogenesis of autoimmune diseases (9). However, with the exception of complement gene deletions, most of the lupus susceptibility loci identified in genome-wide association studies (GWAS) confer only minor changes in disease risk (10). Integrated analyses in which genetic factors are included point to the relevance of a limited number of metabolic pathways in autoimmune rheumatic diseases (Table 1; specific source citations listed in Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art>).

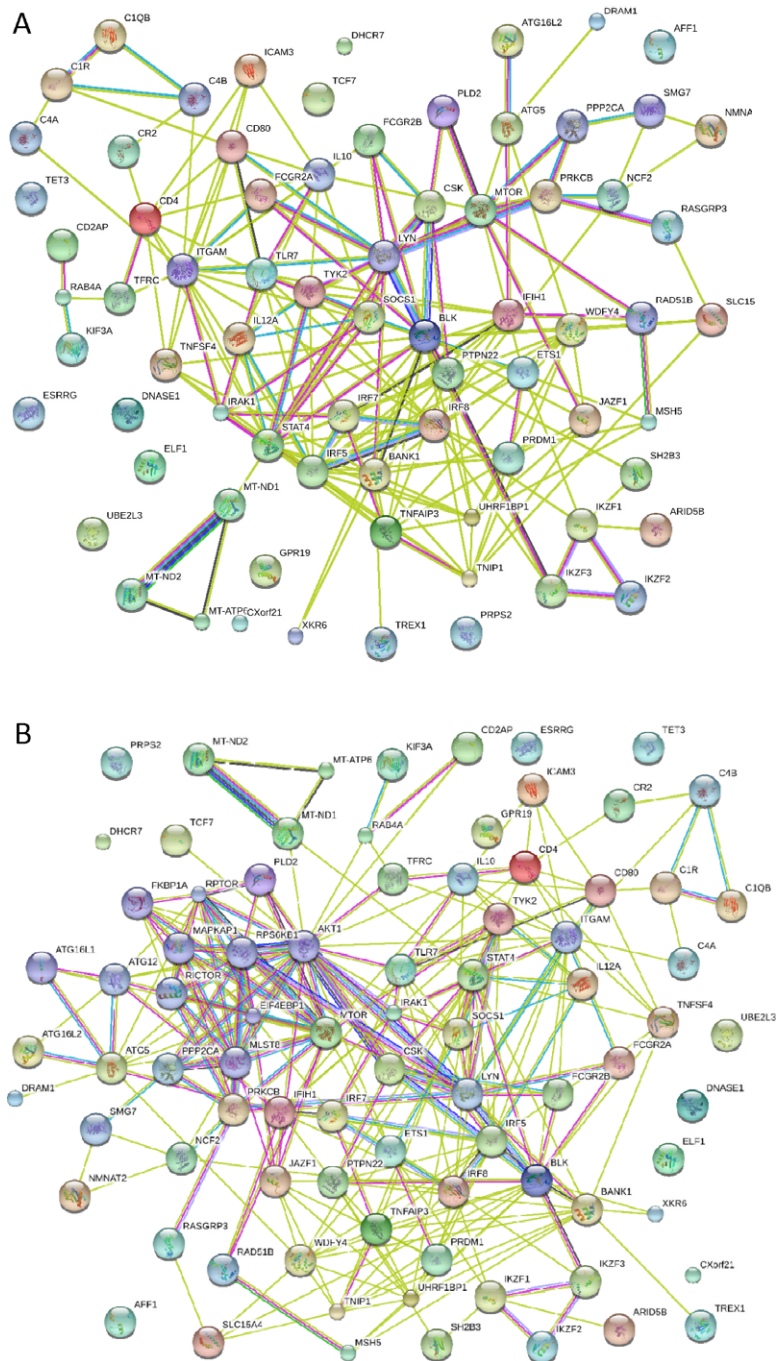


Figure 2. Interactome of lupus susceptibility genes, constructed using Strings software (version 9.0; <http://string-db.org>) via evidence-based protein–protein interactions. **A**, Panel of imputed genes linked to the pathogenesis of systemic lupus erythematosus via polymorphic genetic markers or functionally relevant mutations. **B**, Panel of imputed genes (expanded from the panel in **A**) based on evidence allowing for inclusion of 10 additional interactors, appearing to center around the mechanistic target of rapamycin–autophagy pathway.

40223/abstract). These pathways include the following: 1) glycolysis; 2) the mitochondrial tricarboxylic acid (TCA) cycle, electron transport chain (ETC), and oxidative phosphorylation, which provide energy in the form of ATP; 3)

the pentose phosphate pathway (PPP), which is an essential source of R5P for the production of nucleic acids in support of cell proliferation, and NADPH for lipid biosynthesis and maintenance of a reducing environment and

protection against oxidative stress (2); 4) lipid metabolism and adipogenesis; 5) uptake and biosynthesis of amino acids; and 6) selection of cell death pathways between the physiologic process of apoptosis and pathologic process of proinflammatory cell necrosis and clearance of cell death debris (Figure 1).

As shown in Figure 2A, the evidence-based interactome of lupus susceptibility genes reveals a network of relationships that are connected through kinases and phosphatases. The serine/threonine kinase mTOR has been imputed to play a role in this network on the basis of observations of lupus development in patients harboring activating gene mutations (11). Allowing for the inclusion of 10 more interactors in this network leads to recentering of the network around the mTOR-autophagy pathway (Figure 2B). Notably, several lupus susceptibility genes have also been associated with RA and with psoriatic arthritis (PsA) (Table 1 and Supplementary Table 1). Construction of a map of these integrated metabolic and genetic pathways, as shown in Figure 1, could provide further insights into the pathogenesis of autoimmunity. Of note, the influence of metabolic genes on rheumatic diseases is not solely exerted through the immune system. In fact, the susceptibility genes often indirectly regulate the immune system by influencing the metabolism of adipocytes (12), hepatocytes (13), or endothelial cells (14). It is intriguing to consider that individual single-nucleotide polymorphisms that, by themselves, confer a relatively minor genetic risk can coalesce to bring about major changes in metabolite fluxes, such as shifting glucose utilization from glycolysis to the PPP, TCA cycle, or biosynthesis of amino acids or lipids (Figure 1). As noted in Table 1 (see also Supplementary Table 1), most autoimmune disease susceptibility genes transduce metabolic signals.

Influence of the environment on the host immunometabolome

Disease concordance rates in identical twins are only 15% for RA (15) and 25% for SLE (16), which suggests that environmental factors have an important role in the pathogenesis of these autoimmune diseases (9). These environmental factors include microbiota, such as viruses and bacteria, and also nutrients, drugs, and toxins, such as ultraviolet (UV) light, smoke, and other pollutants. Clearly, each of these ecologic factors affect the metabolism, as substrates, inducers, or suppressors of metabolic genes both inside and outside of the immune system. With respect to microbiota, both exogenous and endogenous viral RNA and DNA activate intracellular nucleic acid sensors (17). Viral RNA stimulates Toll-like receptor 7

(TLR-7)/TLR-8 as well as retinoic acid gene I (RIG-I)-like helicases. RIG-I associates with the mitochondrial antiviral signaling (MAVS) protein, which is then activated by oxidative stress in patients with SLE (18).

In a study that performed metabolome fingerprinting of fresh stool samples, SLE patients were effectively distinguished from matched healthy subjects (19). Colonization with segmented filamentous bacteria has previously been found to enhance interleukin-17 (IL-17) receptor signaling (20). A survey of 16S ribosomal RNA genes showed that body mass index (BMI) has an effect on SLE at the level of the metabolite landscape, but not at the level of microbial composition. Moreover, the depletion of *N*-acetyl-muramic acid and *N*-acetyl-glucosamine, which are peptidoglycans of the bacterial cell wall, is a distinguishing feature in patients with SLE. Of note, *N*-acetyl-muramic acid is an inducer of inflammatory arthritis (21). Accumulation of plant-derived shikimate-3-phosphate and its responsiveness to *N*-acetyl-cysteine (NAC) may be attributed to distortions in the activity of the PPP in SLE (22).

Disease-specific changes to the immunometabolism

Genetic and environmental factors influence the immunometabolism in a disease-specific manner. Differences among autoimmune syndromes are reflected by preferential involvement of cell types that mediate organ-specific proinflammatory changes, such as fibroblasts in scleroderma skin and fibroblast-like synoviocytes (FLS) in RA joints. Conspicuously, T cells in SLE patients and T cells in RA patients show opposite changes in redox signaling, as discussed in detail below and depicted in Figure 3.

SLE. *Role of oxidative stress as a central pathway of lupus pathogenesis.* Compartmentalized oxidative stress is a prominent feature of metabolic changes in SLE (23). As recently unveiled, oxidative stress underlies the interferon (IFN) signature via the stimulation of MAVS protein

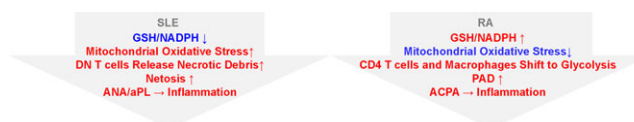


Figure 3. Contrasting influence of oxidative stress between systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) in terms of pentose phosphate pathway activity, depletion of glutathione (GSH) and NADPH, and generation of pathogenic antinuclear antibodies (ANAs) and antiphospholipid autoantibodies (aPL). Peptidylarginine deiminase (PAD) converts arginine to citrulline and triggers immunogenicity of self antigens and production of anti-citrullinated peptide antibodies (ACPAs) in patients with RA. DN = double-negative.

oligomerization in SLE (18). Mitochondrial reactive oxygen species are generated by electron transfer to molecular oxygen at complex I of the ETC (Figure 1). Oxidative stress may also be triggered by environmental factors, e.g., UV light, drugs, viruses, and bacteria. Oxidized mitochondrial DNA initiates the IFN signature via netosis (24). Paradoxically, NADPH production by the PPP is required for NADPH oxidase activity in neutrophils (25), indicating that glucose metabolism contributes to netosis. Expansion of necrosis-prone double-negative (DN) T cells promotes inflammation, a process that has been attributed to the release of the proinflammatory cytokines IL-4 (26) and IL-17 (27) and oxidized DNA and proteins (28). Alternatively, an inability to generate oxidative stress in phagocytic cells due to mutations of NADPH oxidase contributes to the development of discoid lupus (29). Presumably, the persistence of bacterial DNA and their CpG motifs triggers inflammation in these patients (30).

Balance of oxidative stress maintained by PPP and GSH metabolism. A key feature of oxidative stress is the depletion of GSH and cysteine, which is detectable in the lymphocytes of SLE patients (6). Comprehensive metabolome studies all point to the depletion of cysteine (22), which is a molecular target and rationale for the use of NAC for the treatment of SLE (31). Although the loss of GSH suggests that it has a causative role in oxidative stress, the underlying metabolic pathways remain incompletely characterized. GSH depletion occurs subsequent to a loss of NADPH and the accumulation of 3-carbon to 7-carbon sugars in SLE (22), indicating that glucose utilization in the PPP is diminished or inefficient. In CD4+ T cells, increased glycolysis may siphon glucose-6-phosphate (G6P) away from the PPP and limit the production of NADPH (32) (Figure 1). G6P is metabolized by G6P dehydrogenase (G6PD) to generate NADPH in the oxidative branch of the PPP. In a subsequent enzymatic reaction, 6-phosphogluconate dehydrogenase also generates NADPH as well as R5P, an essential substrate for nucleotide biosynthesis and cell proliferation (Figure 1). Increased metabolic flux through the nonoxidative branch of the PPP is supported by enhanced expression and enzymatic activity of TAL (2,33). The accumulation of sedoheptulose-7-phosphate, a unique substrate of TAL (2,34), is also consistent with involvement of this PPP enzyme.

Kynurenine was found to be a top metabolic indicator of SLE, when assessed relative to that in matched healthy donors (22,35). Importantly, the accumulation of kynurenine may stem from the depletion of NADPH, which is a cofactor of kynurenine hydroxylase (36). This mechanism is compatible with previous observations of the concurrent reversal of NADPH depletion and kynurenine accumulation in patients treated with NAC (22). Similar

to branched amino acids (valine, leucine, and isoleucine) (37), kynurenine also stimulates mTOR complex 1 (mTORC1) (22). Thus, the NAC-responsive accumulation of kynurenine is a biomarker of oxidative stress and a metabolic trigger of mTORC1 activation in SLE (22).

Activation of the mTOR pathway elicited by oxidative stress. Oxidative stress has been implicated in abnormal sphingolipid production, a biomarker of lupus nephritis (38). The sphingosine-1-phosphate (S1P) receptor (S1PR) pathway involves mTORC1, acting to promote the development of Th1 cells over Treg cells (39) (Figure 1). Accordingly, sphingosine kinase and S1PR-mediated signaling have been targeted for the treatment of autoimmunity in patients with multiple sclerosis, those with lupus, those with RA, and those with inflammatory bowel disease (Table 2; specific source citations are listed in Supplementary Table 2, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40223/abstract>).

Contribution of oxidative stress to the immunogenicity of autoantigens. Oxidative stress triggers the immunogenicity of phospholipid antigens (40). As a model of oxidative stress-induced production of antiphospholipid antibodies (aPL), mice deficient in the PPP enzyme TAL display oxidative stress in the liver, which is attributed to mTORC1-dependent expression of NADH:ubiquinone oxidoreductase core subunit S3 (NDUFS3), a pro-oxidant subunit of ETC complex I. Notably, rapamycin selectively blocks NDUFS3 expression and aPL production in both TAL-deficient and lupus-prone mice. The PON1 gene is secreted by the liver into the bloodstream, where it degrades oxidized phospholipids. PON1 is depleted in the serum of TAL-deficient mice, as well as in the serum of patients with the antiphospholipid syndrome (APS) (41) and patients with SLE (42). Therefore, PON1 may be a transmitter of metabolic liver disease that instigates APS (43).

Dysregulated autophagy underlying oxidative stress. During increased demand for or short supply of nutrients, cells turn to alternative resources, such as degradation of dispensable organelles via autophagy. Given that enhanced autophagy involves an increase in endosome traffic and elevated expression of Rab4A, the resulting depletion of dynamin-related protein 1 facilitates cell survival by retention of oxidative stress-generating mitochondria (44,45). In addition to oxidative stress, cell traffic to the lysosomal membrane and sensing of amino acid sufficiency account for the activation of mTORC1 (7). Whereas mTORC1 is activated (31,33), mTORC2 is reduced in patients with SLE (46) (Figure 1).

The involvement of mTOR in lupus pathogenesis is further supported by the therapeutic blockade of

Table 2. Pharmacologic targeting of metabolic pathways in the rheumatic diseases*

Drug	Mechanism of action	Molecular target	Disease
Methotrexate	Purine metabolism	DHFR	RA, PsA
Azathioprine	Guanine metabolism	TPMT/PRT	RA
Mycophenolate	Guanine synthesis	IMPDH	SLE
Leflunomide	Pyrimidine metabolism	DHODH	RA
Apremilast	PKA	PDE4	PsA
Hydroxychloroquine	Autophagy	Lysosomal ATPase	RA, SLE, PsA
Corticosteroid	Glycolysis, autophagy	GCR	SLE, RA, PsA
Rapamycin	Autophagy	mTORC1	SLE, lupus nephritis, SSc, RA/JRA, SS
Everolimus	Autophagy	mTORC1	PH
OSI-027	ATP-competitive	mTORC1/mTORC2	SSc, RA
NAC	Antioxidant	GSH	SLE, RA/CIA, SS, ILD
Metformin	Antioxidant	ETC complex I	SLE, CIA
Fingolimod	Receptor modulator	S1P receptor	SLE, RA, MS, IBD
DHS1P	S1P antagonist	PTEN	SSc
PAT-048	Autotaxin inhibitor	LPA synthesis	SSc

* Literature references are listed in Supplementary Table 1 (available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40223/abstract>). DHFR = dihydrofolate reductase; RA = rheumatoid arthritis; PsA = psoriatic arthritis; TPMT/PRT = thiopurine methyltransferase/phosphoribosyltransferase; IMPDH = inosine monophosphate dehydrogenase; SLE = systemic lupus erythematosus; DHODH = dihydroorotate dehydrogenase; PKA = protein kinase A; PDE4 = phosphodiesterase 4; GCR = glucocorticoid receptor; mTORC1 = mechanistic target of rapamycin complex 1; SSc = systemic sclerosis; JRA = juvenile RA; SS = Sjögren's syndrome; PH = pulmonary hypertension; GSH = glutathione; ILD = interstitial lung disease; ETC = electron transport chain; CIA = type II collagen-induced arthritis; S1P = sphingosine-1-phosphate; MS = multiple sclerosis; IBD = inflammatory bowel disease; LPA = lysophosphatidic acid.

T cell hyperactivity and nephritis by rapamycin both in mice and in patients with lupus (Table 2 and Supplementary Table 2). The contraction of proinflammatory, necrosis-prone DN T cells and expansion of Treg cells have each been proposed as mechanisms of action for rapamycin (26). Oxidative stress apparently lies upstream of mTORC1 activation in T cells, since NAC has similar immunologic effects (31). Activation of AMP-dependent protein kinase (AMPK), which inhibits mTORC1, has been shown to have clinical benefit in mouse models of lupus (32). Moreover, mTORC1 is activated in B cells (47) and promotes plasma cell development in lupus-prone mice (48). Thus, similar to that observed in T cells (33,44), mTORC1 activity and autophagy are also enhanced in lupus B cells (48,49).

RA. Unlike in SLE (32), CD4⁺ T cells in RA exhibit diminished glycolytic activity (50), thus rendering them more inclined to utilize the PPP for production of NADPH (8). CD4⁺ T cells in patients with RA also show diminished autophagy without changes in mTOR activity (50). In contrast to the above-mentioned elevations in NADPH levels, GSH is diminished in the peripheral blood (51) as well as synovial T cells (52) of patients with RA. Whereas cysteine production is reduced, cystine and homocysteine levels are elevated in the sera of RA patients (53), reflective of the effects of oxidative stress in RA. These findings suggest that oxidative stress is compartmentalized and there is a discordance between the NADPH and GSH pools in RA T cells (Figure 3). In

contrast to the findings in SLE, peripheral blood RA T cells do not exhibit MHP (6) and do not have increased mitochondrial ETC activity (54).

The concept of increased glycolysis occurring in RA is supported by observations of the accumulation of lactate in RA joints (55). Combined studies of metabolic flux and genetic factors in RA FLS unveiled evidence of synovial hypoxia with mitochondrial dysfunction and a switch to glycolysis. These findings apparently support the typical RA characteristics of abnormal angiogenesis, cellular invasion, and pannus formation. Importantly, such metabolic changes were found to be correlated with the extent of inflammation, as detected by hybrid positron emission tomography/magnetic resonance imaging (56). Although T cells do not show mTOR activation, monocytes and FLS do, and therefore these cells have served as targets for therapeutic intervention with rapamycin in animal models and in patients with RA and those with juvenile RA (Table 2 and Supplementary Table 2). In particular, rapamycin blocks the invasiveness of FLS in RA patients (57). Deficiency of indoleamine 2,3-dioxygenase, which catabolizes tryptophan into kynurenine, has been implicated in the pathogenesis of RA and its animal model, type II collagen-induced arthritis (CIA) (Table 3; specific source citations are listed in Supplementary Table 3, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40223/abstract>). Changes in the levels of tryptophan and kynurenine have also been shown in

Table 3. Nutraceutical targeting of metabolic pathways in the rheumatic diseases*

Nutrient	Mechanism of action	Disease or model	Outcome
Extra-virgin olive oil	Antioxidant	Pristane nephritis	Protection
Acidic drinking water	Microbiome shift	SNF1 lupus	Protection
Polyunsaturated fatty acid	CD4+ T cells	(NZB × NZW)F1 lupus	Protection
Fish oil	IL-1, IL-6, TNF	(NZB × NZW)F1 lupus	Protection
Apo A-I mimetic L-4F	aPL	ApoE ⁻ /CD95 ⁻ lupus	Protection
Taurine	Antioxidant	(NZB × NZW)F1 hepatitis	Protection
Indole-3-carbinol	Antioxidant	(NZB × NZW)F1 lupus	Protection
Triterpenoid	Antioxidant/mTOR	MRL/lpr nephritis	Protection
Omega-3 fatty acid	TNF blockade	CIA	Protection
Curcumin	BAFF	CIA	Protection
Fructo-oligosaccharides	Microbiota	Colitis/HLA-B27	Protection
Weight gain	Oxidative stress	MRL/lpr nephritis	Exacerbation
High-fat diet	Apo E	Lupus-like nephritis	Exacerbation
High-fat diet	LDL receptor	Lupus-like nephritis	Exacerbation
High-fat diet	TLR-4	CIA	Exacerbation

* Literature references are listed in Supplementary Table 2 (available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.40223/abstract>). IL-1 = interleukin-1; TNF = tumor necrosis factor; Apo A-I = apolipoprotein A-I; aPL = antiphospholipid antibodies; mTOR = mechanistic target of rapamycin; CIA = type II collagen-induced arthritis; LDL = low-density lipoprotein; TLR-4 = Toll-like receptor 4.

the sera and synovial fluid of patients with RA and patients with ankylosing spondylitis (AS) (Table 3 and Supplementary Table 3).

Other rheumatic diseases. In patients with AS, in addition to the role of HLA-B27, GWAS studies have implicated endoplasmic reticulum aminopeptidases (ERAPs) in disease pathogenesis. ERAPs process peptides for presentation by major histocompatibility complex class I (58). Protective variants confer reduced enzymatic activity. Interactions between ERAP-1 and HLA-B27 affect peptide handling during antigen presentation (59). Activation of the insulin-like growth factor 1 receptor in T cells from patients with AS has been shown to stimulate the phosphatidylinositol 3-kinase (PI3K)–Akt–mTOR axis (60). Thus, mTOR activation and enhanced autophagy may interact to shape the development of proinflammatory T cells in patients with AS (Figure 1).

Activation of mTORC1 drives the expansion of Th17 cells, which orchestrates the emergence of inflammation in the skin and joints of patients with PsA (61). GWAS studies have linked Raptor, a component of mTORC1, to psoriasis (62). Moreover, the activation of mTORC1 is supported by evidence of increased phosphorylation of mTOR and S6 kinase in psoriatic skin lesions (63). The activation of mTORC1 may result from increased expression of programmed death 1 (PD-1) in T cells of patients with PsA (64). Up to 40% of PD-1 antibody-treated patients with cancer developed a skin disease resembling psoriasis (65). Such an impact of PD-1 blockade involves mitochondrial oxidative stress-dependent mTORC1 activation (66), indicating that the outcome of PD-1 signaling in terms of its effects on the mTOR

pathway may be specific to cell type. Therefore, a combination treatment regimen involving anti-PD-1 in conjunction with NAC or rapamycin may offer clinical benefit.

Genetic factors and metabolic pathways that regulate oxidative stress have been linked to scleroderma and progressive systemic sclerosis (67,68). Oxidative stress is a trigger of transforming growth factor β (TGF β) (69), which plays a central role in the activation and production of collagen by fibroblasts in the skin and parenchymal organs (70). In response to TGF β , mTORC1 activity appears essential to sustain the proliferation of fibroblasts (71). Expectedly, rapamycin blocks the TGF β -induced proliferation of fibroblasts (72) and production of type I collagen (73). In accordance with the concept of a pathogenic role of oxidative stress, intravenous NAC may have clinical efficacy in scleroderma patients with Raynaud's phenomenon (74) and those with interstitial lung disease (75).

Metabolic targets of treatment in rheumatic diseases

Glucocorticoids have revolutionized the treatment of patients with arthritis and other inflammatory diseases since the mid-20th century (76). They bind to the glucocorticoid receptor and regulate transcription of genes involved in metabolism (77). The efficacy of glucocorticoids has been linked to inhibition of glycolysis (78), while the stimulation of autophagy (79) and mTOR activity (80) are mechanisms that have been identified as underlying the resistance to glucocorticoids.

Most conventional disease-modifying antirheumatic drugs (DMARDs), including methotrexate, mycophenolate mofetil, and leflunomide, target purine or

pyrimidine nucleotide metabolism (Table 2 and Supplementary Table 2). The newly introduced DMARD Apremilast also targets purine metabolism, since it increases cAMP levels and cAMP-dependent protein kinase A activity (Table 2 and Supplementary Table 2). Although hydroxychloroquine has long been used as a DMARD, its mechanism of action is newly attributed to blockade of autophagy through the inhibition of lysosomal acidification (81) (Figure 1). Surprisingly, the autophagy inducer rapamycin and other rapalogues are also beneficial in autoimmune diseases (7). Inhibitors of PI3K or AKT and activators of AMPK, which act upstream of mTORC1, are also being tested for efficacy in autoimmunity (Table 2 and Supplementary Table 2). However, unlike rapamycin, the AMPK activator metformin has not reduced the severity of nephritis in lupus-prone mice, except when this treatment was combined with 2-deoxyglucose (2DG), which blocks glycolysis (32).

The therapeutic use of NAC in SLE has been supported by its effects on oxidative stress and the depletion of GSH in T cells (6) as well as by the depletion of cysteine in both the lymphocytes and plasma of patients with SLE (22,35). DHS1P and fingolimod block S1P signaling and the downstream activation of mTORC1 (Table 2 and Supplementary Table 2). Based on their synergistic mechanism of action, rapamycin, NAC, fingolimod, and metformin may be combined for the blockade of mTORC1 activity at multiple levels (Figure 1). Future clinical trials should be directed at rigorously testing such combination treatments in order to maximize the therapeutic benefit, rather than relying on the clinical efficacy of single medications that target distinct metabolic pathways either sensed or impacted by mTOR.

Effect of nutrients on autoimmune rheumatic diseases

In addition to conventional drugs, diet and nutraceuticals may influence autoimmunity. Studies both in humans and in animals have shown that a high-calorie and high-fat diet predispose individuals to the development of RA and lupus and its serious comorbidities, glomerulonephritis and atherosclerosis (Table 3 and Supplementary Table 3). However, subsets of lipids, e.g., fish oil, extra-virgin olive oil, and terpenoids, have antioxidant properties and reduce the severity of nephritis in patients with SLE (Table 3 and Supplementary Table 3). Along these lines, calorie intake and the composition of dietary lipids can affect the levels of adipokines, oxidative stress, and disease activity in patients with RA (Table 3 and Supplementary Table 3). A predisposition to multiple autoimmune diseases in patients with celiac disease, which is

characterized by sensitivity to the wheat protein gluten, is attributed to multiple genetic factors, although secondary deficiency of nutrients may also be a contributing factor (82). The lysosomal receptor SLC15A4, which transports histidine, has been genetically linked to lupus via the mTOR pathway-mediated activation of B cells and dendritic cells (Table 1 and Supplementary Table 1). Among the amino acids, kynurenine is a natural ligand of the aryl hydrocarbon receptor (AhR) (83). Activation of mTORC1 by kynurenine (22) is consistent with the concept of a regulatory cross-talk occurring between the AhR and mTOR pathways (84). Whereas the levels of kynurenine and its precursor, tryptophan, are increased, the levels of cysteine, histidine, glutamine, and glutamate are depleted in patients with SLE (22,35). Thus, designer diets with a predetermined composition and concentration of amino acids may represent a new avenue in patients with SLE and other rheumatic diseases.

Unmet needs and future directions

For the future, the large number of unidentified metabolites and mapping of their origin from nutrients, host cell metabolism, or microbiota represent significant instrumental, data-handling, and theoretical challenges. While rheumatic disease susceptibility genes regulate metabolic pathways in a cell type-specific manner (Table 1 and Supplementary Table 1), metabolites themselves also exert control over gene expression through epigenetic mechanisms (85). Moreover, commonly used and clinically effective DMARDs, such as methotrexate, and medications that target metabolic diseases, such as metformin (Table 2 and Supplementary Table 2), affect the immune system in intricate ways, dictated by various genetic, nutrient, and environmental factors (Figure 1). Taking into account such levels of complexity represents a significant unmet need of clinical trial design, since the chosen end points should inform about efficacy and predict responders and nonresponders. Focused efforts should further delineate the metabolites that control the skewing toward a proinflammatory lineage, as these metabolites represent biomarkers of pathogenesis and targets for treatment. Given that checkpoint blockade with anti-PD-1 involves mitochondrial oxidative stress-dependent mTORC1 activation (66), a combination treatment regimen with NAC or rapamycin may offer clinical benefit by averting iatrogenic autoimmunity in patients with cancer. Importantly, the use of nutraceuticals in combination with biologic agents that target pathways of pathogenesis could also eliminate or reduce the unwanted side effects of traditional immunosuppressants.

Conclusions

Metabolic pathways regulate the development of the immune system, including lineage specification and cell proliferation and survival, which occurs in a cell type-specific manner in response to cues from growth factors, hormones, cytokines, deprivation or overload of nutrients, and microbiota. This review has mechanistically connected the specific metabolites and their receptors that have been genetically linked to disease susceptibility with nutrient-dependent immune system activation. The metabolites identified include those that regulate lineage specification within the adaptive and innate immune systems during the pathogenesis of common and potentially fatal autoimmune rheumatic diseases.

Rapidly proliferating proinflammatory T cells and B cells and macrophages generally favor glycolysis over fatty acid oxidation for ATP generation. Mitochondrial ATP production is reduced in patients with SLE (6), a process that has been attributed to blocked ETC activity, GSH depletion, and oxidative stress (54). There is a clear contrast in glucose utilization and redox signaling in T cells between patients with SLE and patients with RA. Whereas patients with SLE exhibit increased metabolism of glucose through glycolysis and the PPP, glucose is preferentially metabolized by the PPP in RA T cells, which exhibit greater NADPH production due to the activation of G6PD (7). Based on the efficacy of blockade of glycolysis by 2DG in mice (1) and the enhancement of NADPH by NAC (8), an approach that has shown remarkable clinical efficacy in patients with SLE (9,10), an increased flux of glucose through the PPP appears to be a desirable outcome in lupus (Figures 1 and 3). Thus, SLE patients (9) and mice with lupus benefit from treatment with antioxidants (1), whereas RA patients and mice with CIA apparently do not experience such a clinical benefit (7). Unlike in RA (11), oxidative stress-induced mTOR activation contributes to autoimmunity in lupus, psoriasis, PsA, AS, and rheumatic diseases in cancer patients treated with checkpoint inhibitors (12). Importantly, mTOR activation also underlies glucocorticoid resistance (6). Therefore, these considerations warrant an integrated genetics- and metabolome-based systems biology approach toward understanding the pathogenesis and development of personalized treatments in the autoimmune rheumatic diseases.

AUTHOR CONTRIBUTIONS

Dr. Perl drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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