**Table 1. Examples of Autoimmune Diseases Affecting Different Organs**

| Primary Target Organ(s) | Disease | Prevalence[a] | Typical First Symptoms | Mechanism |
|---|---|---|---|---|
| Skin and Hair | | | | |
| Skin | psoriasis | ~2%–3% | skin redness, thickening, and scales | abnormal keratinocyte proliferation in the dermis and epidermis |
| Skin and oral mucosa | pemphigus vulgaris | ~0.01% | blisters and erosions | loss of cell adhesion in stratified squamous epithelia |
| Skin | vitiligo | ~0.5%–1% | milky white skin patches | destruction of melanocytes |
| Hair follicles | alopecia areata | ~0.1% | patchy hair loss on the scalp | weakness in the hair shaft leading to hair shaft breaking |
| CNS | | | | |
| Optic nerve, brain, spinal cord | multiple sclerosis | ~0.1% | visual loss, numbness, tingling, paresis, and spasticity | destruction of myelin |
| Hypothalamus | narcolepsy | ~0.03% | excessive daytime sleepiness, sleep attacks, sudden loss of muscular control | destruction of orexin-producing neurons |
| Optic nerve, spinal cord | neuromyelitis optica | ~0.004% | resembles MS, but attacks are more severe | destruction of myelin, autoantibodies against aquaporin-4 |
| Endocrine and Exocrine Glands | | | | |
| Pancreas | type 1 diabetes | ~0.4% | increased thirst, frequent urination, weight loss, | destruction of insulin- producing β cells |
| Thyroid gland | Graves disease (hyperthyroidism) | ~0.5% | anxiety, irritability, hand tremors, weight loss, enlarged thyroid gland, bulging eyes, palpitations | autoantibodies against the thyrotropin receptor on thyroid follicular cells leading to increased synthesis of thyroid hormone |
| Thyroid gland | Hashimoto's disease (hypothyroidism) | ~0.1% | many, changeable and unspecific, including fatigue, sensitivity to cold, puffy face, constipation, pale and dry skin | fibrosis and atrophy of thyrocytes leading to decreased synthesis of thyroid hormone |
| Tear and salivary glands | Sjögren's syndrome | ~0.2%–1% | dry eyes and mouth | loss of function of exocrine glands |
| Gastrointestinal System | | | | |
| Entire gastrointestinal tract, but especially the ileum, patchy lesions | Crohn's disease | ~0.2%–0.3% | diarrhea, abdominal pain, bloody stool, fever, fatigue | transmural inflammation |
| Rectum and sometimes also the colon, uninterrupted lesions | ulcerative colitis | ~0.2%–0.4% | abdominal pain, rectal pain and bleeding, urgency but inability to defecate, fever, fatigue | mucosal inflammation |
| Small intestine | celiac disease | ~0.7% | loose stools, abdominal discomfort | flattening of villi and elongation of crypts |
| Stomach | autoimmune gastritis | uncertain | anemia, gastritis, vitamin B12 deficiency, and impaired food protein degradation | destruction of acid-producing parietal cells |
| Liver | primary biliary cholangitis | ~0.03% | tiredness, itching | destruction of small bile ducts |
| Liver | autoimmune hepatitis | ~0.02% | nonspecific, mild fatigue, often no symptoms of liver disease but elevation of liver enzymes in peripheral blood | destruction of hepatocytes |

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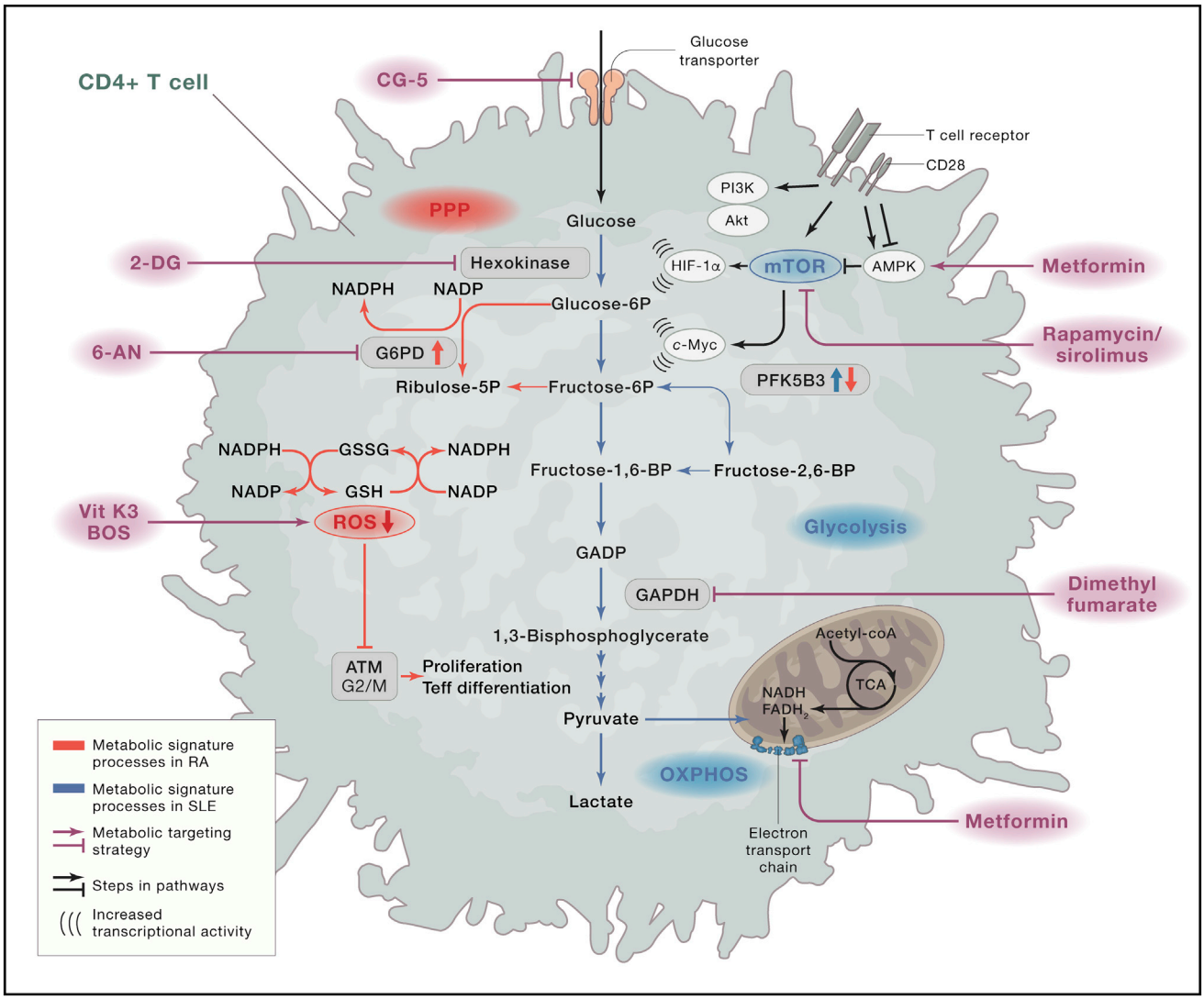


**Figure 1. Examples of Abnormal Metabolic Pathways and Potential Targeting Strategies**

The metabolic signature of CD4+ T cells in systemic lupus erythematosus (SLE) is elevated glycolysis, oxidative phosphorylation (OXPHOS), and enhanced mTOR activity (blue). Dual inhibition of OXPHOS by metformin and hexokinase/glycolysis by 2-deoxyglucose (2-DG) or inhibiting the glucose transporter by CG-5 inhibitor reverses SLE markers *in vitro* and *in vivo* (Yin et al., 2015). Metformin is also suggested to reduce mTOR overactivity through activation of 5' adenosine monophosphate-activated protein kinase (AMPK). Sirolimus, targeting mTOR, has shown clinical effects in SLE patients (Lai et al., 2018), and dimethyl fumarate, used to treat multiple sclerosis and psoriasis, has been shown recently to exert its effect through suppression of GADPH, leading to downregulation of aerobic glycolysis (Kornberg et al., 2018). In rheumatoid arthritis, CD4+ T cells show decreased 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFK5B3) but enhanced glucose-6-phosphate dehydrogenase (G6PD) enzyme activity in addition to increased NADPH and glutathione (GSG), reflecting that glucose is diverted from glycolysis into the pentose phosphate pathway (PPP; red). Increased NADPH and GSG levels cause ROS depletion, which is linked to cell cycle regulation via the enzyme ataxia telangiectasia mutated (ATM) protein kinase, responsible for cell cycle arrest at the G2/M checkpoint. Thus, lack of ATM activity, as observed in rheumatoid arthritis T cells, can lead to hyperproliferation and maldifferentiation (Yang et al., 2016). Inhibition of G6PD with 6-aminonicotinamide (6-AN) rebalances glucose utilization, normalizes ROS levels, and reduces cell proliferation. Furthermore, replenishing ROS levels with oxidative agents such as vitamin K3 or buthionine sulfoximine (BOS) restores ATM activity and suppresses synovial inflammation in a mouse model. Notably, the rheumatoid arthritis and SLE CD4+ T cells in these examples were characterized at early disease stages, suggesting strategies for early disease intervention.

individual taxa of commensal gut bacteria, such as *Enterococcus gallinarum* (Manfredo Vieira et al., 2018) and *Lactobacillus reuteri* (Zegarra-Ruiz et al., 2019), from the gut to secondary lymphoid organs has been linked to systemic lupus erythematosus-like disease in mice. This disease could be prevented by vaccination against *E. gallinarum* or by feeding *L. reuteri* with dietary resistant starch that induced expansion of *Clostriales*, which is known for its capacity to produce short-chain fatty acids (SCFAs) by fermentation of dietary fiber. SCFAs are increasingly being recognized as important metabolites in intestinal immune homeostasis, and numerous studies have established divergent host effects, such as reducing intestinal permeability, inducing Tregs (Arpaia et al., 2013; Atarashi et al., 2013; Smith et al., 2013), and promoting long-term survival of