Editorial

Immunometabolism in Autoimmune Diseases Special Issue

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The activation of immune cells and their differentiation in specialized effector subsets rely on specific cellular metabolic programs. It is therefore not surprising that a number of immunometabolic alterations have been reported in patients with autoimmune diseases, as well as in mouse models of these diseases. The metabolic programs that sustain the activation of healthy lymphocytes are reviewed by Bystrom et al. [1], which are contrasted with the metabolic programs that have been found in $CD4^+$ T cells and B cells in autoimmune diseases, with a focus on rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). These two rheumatic diseases share $CD4^+$ T cells that are fueled by an over-activated mTOR signaling, but that differ by many other metabolic pathways, even when considering the same type of cells, such as Th17 cells. The specific metabolic phenotypes of $CD4^+$ T cells were reviewed in detail comparatively between RA and in SLE by Wu et al. [2]. RA T cells shunt glucose away from glycolysis and energy building toward the pentose phosphate pathway (PPP) and cell-building biosynthesis, which leads to a hyper-reduced state. This defect, rooted in the miss-location of AM PK that limits is activation, increases T cell mobility and their ability to invade the inflamed joints. On the opposite, SLE T cells present an increased glycolysis and mitochondrial metabolism leading to oxidative stress. The molecular pathways that support metabolic defects in SLE T cells is further reviewed by Vukelic et al. [3]. In addition to increased glycolysis and mitochondrial oxidation, there is also evidence from mouse models that SLE T cells present an enhanced glutamine metabolism involved in the expansion of Th17 cells as well as follicular helper T (Tfh) cells, both of which being pathogenic in SLE. Finally, altered lipid metabolism related to lipid rafts and plasma membrane sphingolipids has been linked to the activation of SLE T cells. Mangal et al. provide an extensive review of the metabolic programs that support a broad array of immune cells, some of them with known alterations in RA, and others with potential defects that have not been investigated and may contribute to RA [4].

Building a detailed understanding of metabolic defects in autoimmune diseases, more specifically in RA and SLE T cells has leveraged the therapeutic potentials of metabolic targeting in these diseases. These translational potentials are reviewed by Piranavan et al. [5]. A number of experimental drugs targeting key metabolic enzymes or processes have shown efficacy in mouse models. The inhibition of mTOR with rapamycin

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and complex I of the mitochondrial electron transport chain have in addition shown efficacy in small clinical trials in SLE patients. Interestingly, several drugs that are used to treat patients with autoimmune rheumatic diseases target directly or indirectly metabolic pathways, a topic that is reviewed by Mangal et al. with a focus on RA [4]. For example, methotrexate, a standard treatment for RA, inhibits folate metabolism, and may have therapeutic benefits through multiple metabolic pathways. Finally, promising advances have been made with bioengineering approaches to manipulate the immune system. Mangal et al. discuss how these approaches could be applied to immunometabolism to develop cell-specific highly effective therapies for autoimmune diseases [4].

Less is known about the contribution of specific immunometabolic alterations in other autoimmune diseases. Building on the advances that have been made in RA and SLE, Martins and Pignatelli discuss how a better understanding of the metabolic programs that drive pathogenic $CD4^+$ and $CD8^+$ T cells in type 1 diabetes (T1D) would lead to a better understanding of disease pathogenesis, which in turn could be integrated into effective immunotherapies [6]. They also discuss how the hyperglycemic microenvironment that characterize diabetes may skew T cell effector functions toward inflammatory phenotypes, a very promising area of investigation that is largely unexplored. Wilson and Moore review the metabolic programs that are known to support B cell activation and differentiation from their emergence in the bone marrow to antibody-secreting plasma cells [7]. They then review what is known about alterations in some of these programs in the B cells of T1D patients and mouse models. This includes an abnormal expression of genes regulating glucose metabolism in T1D B cells. This knowledge may lead to novel therapeutic targets for this immune subset that has so far been resistant to therapeutic targeting in T1D.

Hayes et al. [8] review metabolic defects in multiple sclerosis (MS). They propose that vitamin D deficiency contributes to demyelination, a key feature of the disease, by decreasing the expression of stearoyl-coA synthase in oligodendrocytes, which is required for nervonic acid synthesis and myelin stability. They also report that vitamin D deficiency may contribute to the pathogenic imbalance between regulatory T (Treg) and Th17 cells in MS, and how obesity may contribute to vitamin D deficiency, and therefore to the exacerbation pf MS severity in susceptible individuals.

Treg cell differentiation and function plays a crucial role in preventing autoimmunity. The immunometabolism of Treg cells in autoimmune diseases remains largely unexplored, as addressed in several papers in this issue. The major energy source in Treg cells comes from fatty acid oxidation (FAO), which is the mitochondrial aerobic process responsible for producing acetyl CoA from fatty acids to fuel the TCA cycle [3,6]. There are conflicting results regarding the number of Treg cells and their suppressive function in RA patients [4], but the assessments of their

metabolic status is currently lacking [1]. In SLE; inflammasome-related IL-18/IL-1β signaling has been associated with abnormal T cell responses, especially the Th17/Treg balance [2], and mTOR inhibition in SLE patients, inhibits Th17 cell proliferation and increases Treg numbers [1,5,6]. However, mTOR inhibition did not expand Treg cells in T1D patients [6]. A vital question in MS research is why the Treg cells from MS patients are functionally defective and unstable. However, beside the potential contribution to vitamin D deficiency [8], their metabolic status is unknown.

The field of immunometabolism in autoimmune diseases is growing rapidly in two main directions, one translational and the other mechanistic. Novel approaches to therapeutically target the metabolism of immune cells are being explored in preclinical models as well as in patients with autoimmune diseases, as discussed in some of the reviews in this special issue. The molecular circuits linking specific metabolic processes to immune cell functions are also actively investigated. In one of such studies, Zheng et al. showed that high glycolysis and mTORC1 activation found in the $CD4^+$ T cells of SLE patients increase the expression of EZH2, a regulator of histone tri-methylation at lysine 27 (H3K27me3) [9]. EZH2 expression is increased in SLE T cells, which contributes to their epigenetic shift toward inflammatory phenotypes. This result suggests the existence of an amplification loop between activated inflammatory T cells and glycolysis/mTORc1 activation though chromatin modification. EZH2 is also critical in maintaining a Foxp3-dependent gene program in Treg cells, and glycolysis-driven EZH2 expression in T cells is required for cytokine production in the context of anti-tumor responses [10].

Overall, these papers show that the study of immunometabolism is a fast-growing field that promises to bring a better understanding of disease pathogenesis by uncovering novel pathways, some of which may be targetable to improve therapeutic outcomes.

CONFLICTS OF INTERESTS

The authors do not have conflicts of interest to disclose.

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