‘B cells, where do they get their energy from!?’ – New insights into immunometabolism in the pathogenesis of systemic lupus erythematosus

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The role of B lymphocytes in the pathogenesis of systemic lupus erythematosus (SLE) has been extensively investigated over recent years with autoantibodies directed against nuclear components one of the hallmarks of the disease. Indeed, a positive anti-nuclear antibody (ANA) is now deemed an essential component for diagnosis according to ACR/EULAR classification criteria (1). However, there is still much to learn about the role of the humble B cell in the pathogenesis of the disease, as has been demonstrated by Sumikawa *et al* in their paper entitled 'An enhanced mitochondrial function through glutamine metabolism in plasmablast differentiation in systemic lupus erythematosus' (2).

The field of immunometabolism (the study of immune cell bioenergetics), has grown significantly over the past two decades with over 12,000 articles published on the mitochondrion alone last year (compared with 3,500 publications in 2000). Immunological activation in response to either invading pathogen or self-antigen results in a rapid reaction being propagated involving cells of both the innate and adaptive response, which immediately proliferate and initiate their effector functions. This sudden increase in cell number and activity requires a significant supply of energy in the form of adenosine triphosphate (ATP), which can be produced via mitochondrial respiration (oxidative phosphorylation) or the breakdown of glucose (glycolysis). In health, circulating naïve B lymphocytes rely predominantly on low level glycolysis that allows them to conserve energy and ultimately improves viability over time (3, 4). During activation, an upregulation in this glycolytic dependent metabolism is the predominant source of ATP production (5).

The rapid expansion in the field of immunometabolism has in part been driven by novel technology that allows for my precise measurements of cellular metabolism and the application

of this technology to the study of immune bioenergetics in SLE is not new, however the primary focus has not been the B cell until more recently.

There is already an abundance of literature describing the changes in T lymphocyte metabolism in the immune response to cancer, infections, and in a variety of autoimmune conditions (including SLE). Previous studies in mouse models of the lupus have described markedly higher levels of both oxidative phosphorylation and glycolysis in $CD4^+$ T cells when compared with healthy mice, thus suggesting that enhanced metabolism plays a role in the chronic immune activation observed in the disease (6). Furthermore, $CD4^+$ T cells have not only shown amplified energy metabolism but also increased mitochondrial transmembrane potential, suggesting that even at a resting state they are already primed for a rapid upregulation in effector function (7). In addition, there is now a growing appreciation of the metabolic changes that result in abnormal antigen presenting cell behaviour in SLE with mitochondrial dysfunction in both macrophages and dendritic cells previously observed (5).

Until recently the role of abnormal bioenergetics in B cell biology has often gone understudied and underappreciated. Of the paucity of studies that have been undertaken, many have focused on understanding how changes in metabolic processes controls the Germinal Centre reaction in murine lymphoid tissues. This means that many unexplored opportunities remain for understanding B cell immunometabolism using cells derived from human tissues and blood during health and disease. Researchers taking advantage of this field, that is ripe for exploration, have shown that B cell immunometabolism is potentially altered in SLE and links closely with autophagy (8).

In the study, Sumikawa *et al* focus on immunometabolism in B cells and specifically plasmablasts, a subtype of B lymphocytes that has been previously shown to be prevalent in higher numbers in SLE and correlate with disease activity (9). The authors sought to identify evidence of abnormal B cell metabolism in 41 patients with SLE and 29 healthy controls. The patient population varied in terms of treatment and disease activity (with a high predominance of mucocutaneous, musculoskeletal and haematological manifestations included). Several techniques including Seahorse respirometry (a real-time measure of cellular oxidative phosphorylation and glycolysis), flow cytometry, mass spectrometry and electron microscopy were employed to evaluate energy metabolism. A key finding of the study is that B cells isolated from SLE patients show enhanced mitochondrial membrane hyperpolarisation, which as mentioned above has been similarly observed in SLE derived T cells. The degree of B cell hyperpolarisation correlated with disease activity (as measured by SLEDAI-2K). Through a variety of cell culture assays, the authors also demonstrated that glutaminolysis, the process by which glutamine is transformed into TCA cycle metabolites, played a vital role in the differentiation into plasmablasts and antibody production *in vitro*.

This study provides further evidence that targeting immunometabolism may be a novel and effective therapeutic option in the management of SLE in future. The authors propose that through inhibiting glutamine pathways it may be possible to influence B cell immunometabolism and ultimately ameliorate the autoimmune response. Metformin was shown to inhibit glutamine metabolism, suppress hyperactive B cell mitochondrial function and in turn reduce plasmablast differentiation. This supports previous studies that have demonstrated that Metformin also can metabolically reprogramme T cells and suppress lupus-like disease in animal models (6). Interestingly, previous studies in experimental mouse models of lupus have found that through specific inhibition of Glutaminase 1 (the first enzyme required

for glutaminolysis), it is possible to downregulate glycolytic energy metabolism and reduced differentiation of Th17 cells (a T cell subpopulation that have been implicated in the pathogenesis of SLE) (10).

To conclude, previously T cells have been shown to have an almost inexhaustible ability to upregulate energy metabolism for activation and maintenance of the autoimmune response characteristic of SLE. Sumikawa *et al* now provide new evidence to support that a similar phenomenon is also observed in B cells in the disease. However, the metabolic changes that provide cells with sufficient stamina to maintain this constant state of activation is only beginning to be understood. Finally, this study proposes that immunological metabolic reprogramming may represent a novel approach to treatment of SLE by suppressing this overactive immune response. It remains to be seen whether this therapeutic potential can be fully realised and translated into the clinical trial arena in future.

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