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In Context

IN CONTEXT

Something old, something new: Na^+/K^+/ATPase as a mechanism of intrarenal B cells viability in lupus nephritis

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Lupus nephritis (LN) remains one of the most severe manifestations of systemic lupus erythematosus (SLE) [1]. Available treatments have demonstrated a limited response rate [2]. Importantly, irreversible kidney damage can be seen in biopsies from patients with LN despite receiving standard immunosuppressive treatment [3].

B cells are a cornerstone in the pathogenesis of LN. Their role does not end with autoantibodies production—B cells also act as antigen-presenting cells, promote differentiation and activation of T cells, and secrete cytokines that promote the maturation of naïve B cells into memory or plasma cells, among others [2]. In 2011, Chang *et al.* showed clonal expansion of B cells in LN kidney biopsies and T cell:B cell aggregates that correlate with immune complexes deposition [4]. Despite the important role of B cells in LN, the LUNAR (Lupus Nephritis Assessment with Rituximab) and BELONG (A Study to Evaluate Ocrelizumab in Patients With Nephritis Due to Systemic Lupus Erythematosus) clinical trials for B cell depletion failed to achieve their primary end-points [2].

The mechanisms of intrarenal B cell viability and activity regulation are not fully understood. In a set of sophisticated experiments, Chernova *et al.* analyzed mechanisms of intrarenal B cells' adaptation to high sodium environment in the kidney [5]. The concept of the study was based on findings presented by Carranza-León *et al.*, who found in an analysis of 23 patients with SLE a correlation between higher muscle sodium content and greater severity of the disease [6].

First, Chernova *et al.* showed in lupus-prone mice that intrarenal B cells are mainly found in the hypernatremic inner medulla. To explain how different degrees of hypertonicity influence B-cell viability, two experiments were conducted to increase interstitial sodium content in the kidney. In animals on a high sodium diet and in water deprivation experiments, B-cells death was demonstrated, confirming that hypertonic microenvironment resulted in B-cell depletion.

Although high sodium environment in the kidney was shown to decrease B-cell survival, the exact process responsible for this phenomenon remained incompletely characterized. The authors questioned whether one of the main mechanisms to handle hyperosmolar stress in the kidney, such as the upregulation of Na^+/K^+/ATPase in tubular epithelial cells, was responsible for facilitating this survival also in B cells. They found that the expression of Na^+/K^+/ATPase was upregulated on intrarenal B cells and mediated *in vitro* survival of B cells from lupus-prone mice in high [Na^+]. Subsequently, the authors observed that Na^+/K^+/ATPase inhibition by ouabain given for 16 days to lupus-prone mice decreased intrarenal B-cells number and lowered proteinuria, although without changing the degree of interstitial inflammation.

As well as the expression of γ-Na^+/K^+/ATPase subunit being shown to be upregulated in response to a high sodium environment in the kidney, authors also showed its significantly higher expression on intrarenal B cells compared with non-renal

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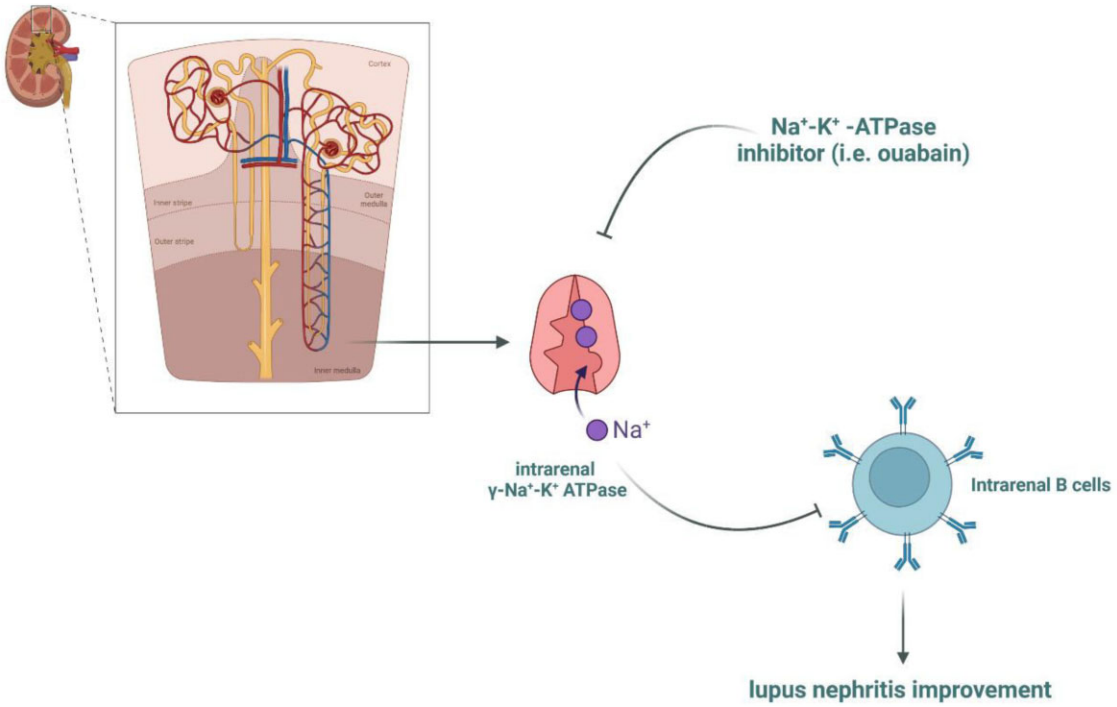

Figure 1: Increased expression of Na^+/K^+/ATPase promotes B-cell survival in the high sodium concentration environment of the inner medulla in the kidney. In LN, a high number of intrarenal B cells in lupus-prone mice and human samples was found, and γ-Na^+/K^+/ATPase subunit is mainly expressed on B cells. Inhibition of intrarenal B cells' Na^+/K^+/ATPase by ouabain or lowered γ-Na^+/K^+/ATPase expression reduce proteinuria in LN. Created with BioRender®.

B cells populations. On the other hand, in mice lacking γ-Na^+/K^+/ATPase, a decrease in B-cells survival and proteinuria was observed, as in previous experiments (Fig. 1). Finally, a high expression of α-Na^+/K^+/ATPase and γ-Na^+/K^+/ATPase was found on B cells in kidney biopsy specimens of patients with class IV and V LN, with the γ subunit being the most specific for B cells.

In summary, the authors showed that Na^+/K^+/ATPase may be involved in the survival of intrarenal B cells in LN. By blocking this exchanger B-cell depletion was demonstrated along with significant amelioration of proteinuria. More research is needed to fully understand how γ-Na^+/K^+/ATPase inhibition in intrarenal B cells can contribute as a targeted therapy in LN.

CONFLICT OF INTEREST STATEMENT

I.Z.: nothing to declare. M.X. discloses honoraria from GSK. L.F.Q. discloses advisory boards for GSK, Otsuka, Alexion, Novartis, Vifor; and honoraria from GSK, Otsuka, Vifor.

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