Background Lupus nephritis is a major cause of morbidity and mortality that affects over half of the SLE population during the course of disease. Multiple factors contribute to the diverse nature of nephritis. Nevertheless, PKC-α activation, with consequent synthesis of TGF-β and matrix constituents, are common mediators of disease progression. In a murine model of antibody-mediated nephritis, nephritic nephritis (NTN), that simulates the effector phase of lupus nephritis, we investigated the role of targeted PKCα inhibition on progressive renal injury.

Materials and methods After induction of nephritis, on day 2, mice were treated with either: (1) nothing, (2) the PKCα inhibitor (Ro-32–0432) i.p., or (3) the PKCα inhibitor conjugated to F1.1, a human monoclonal α3(IV) collagen antibody that targets glomeruli. Resolution of disease was determined serologically and by histology. Comparative proteome analysis, from kidney cortices, was performed using quantitative mass spectrometry.

Results On day 7, the untreated NTN mice had severe nephritis (by BUN, proteinuria and, histology), whereas mice that received PKCα inhibitors, in either form, had minimal evidence of kidney injury: BUN was reduced to 32.29 ± 1.70 mg/dL and 36.07 ± 4.51 mg/dL in PKCα inhibitor and F1.1- PKCα inhibitor injected mice vs. 99.84 ± 0.33 mg/dL in NTN mice, and there was a parallel normalisation of histology. Serum cytokine levels confirmed reduction of systemic inflammation. To further define the role PKCα inhibition, comparative proteome analysis from kidney cortices were performed. The functional protein groups most affected by NTN were mitochondrial proteins associated with respiratory processes; proteins of all four complexes of the respiratory chain were down regulated in NTN mice. By contrast, their expression was restored by PKCα inhibition, suggesting a role for proteins that regulate oxidative phosphorylation in recovery. This hypothesis was further evaluated in glomerular endothelial cells by measuring respiration (oxygen consumption rates, OCR), and glycolytic lactic acid production (ECAR) with injury and recovery. NTS reduced OCR (225 pmol/min to 185 pmol/min) and increased ECAR (42 to 62 µH/min). PKCα inhibition normalised OCR and ECAR levels, and this was associated with restoration of cellular function.

Conclusions The results suggest that PKCα is an important mediator of glomerulonephritis. Furthermore targeted inhibition of this enzyme protects the kidneys from progressive damage associated with severe inflammation by restoring oxidative phosphorylation. This has therapeutic implications for treatment of human glomerular diseases, including lupus nephritis.

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