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Mitochondrial Injury in Pathogenesis of Minimal Change Disease

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Minimal change disease (MCD) is the cause of nephrotic syndrome in approximately 10% to 15% of adults and is defined by histologic glomerular abnormalities absence, other than the fusion of podocyte foot process on ultrastructural analysis using electronic microscopy. T-cell dysregulation has been proposed as a major contributor to podocytopathy and the effectiveness of B-cell depletion therapy suggests B-cells role as drivers of disease; however, MCD pathogenesis remains unknown. Although corticosteroid treatment is the first-line treatment for patients with MCD and is often effective, the mechanism is unclear and response patterns vary between patients. So far, there are no factors that could predict treatment outcomes. Since MCD current treatment is suboptimal, pathogenesis clarification and the development of biomarkers that can predict the treatment response are needed.

The kidney is an organ with high energy demand and has abundant mitochondria. Mitochondrial dysfunction is associated with the pathogenesis of several kidney diseases. Various acquired renal pathophysiological insults, including oxidative stress, renin-aldosterone-angiotensin system activation, and ischemia/hypoxia, induce mitochondrial dysfunction, which induces podocyte injury, tubular cell damage, and endothelial dysfunction. Mitochondrial damage leads to mitochondrial DNA fragmentation and it is released into the cytosol. Cytosolic mtDNA activates the cyclic GMP-AMP synthase-stimulator of interferon genes (STING) pathway, resulting in kidney damage.

We hypothesized that the MCD pathogenesis may be associated with mitochondrial injury and that STING staining signal intensity in the kidney tissue of patients with MCD at diagnosis may be a valuable biomarker for predicting treatment outcomes. We assessed the correlation with STING IHC staining signal intensity and treatment outcomes in patients with MCD. Patients with MCD were divided into high (n = 6) and low-intensity (n = 14) subgroups according to the signal intensity. Urinary mtDNA levels were elevated in the MCD groups than in the MHC group ($p < 0.001$). Time-averaged proteinuria and frequency of relapses during the follow-up period were higher in high-intensity than in low-intensity subgroup (1.18 ± 0.54 vs. 0.57 ± 0.45 g/day, p = 0.022; and 0.72 ± 0.60 vs. 0.09 ± 0.22 episodes/year, p = 0.022, respectively).

Mitochondrial injury may be associated with MCD pathogenesis, and the signal intensity of STING IHC staining at the time of diagnosis could be used as a valuable prognostic marker in MCD.