News Release

Energy Metabolism Breakdown in Podocytes Identified as Key Driver of FSGS Progression

Key Points

- Patient sera from focal segmental glomerulosclerosis (FSGS)*[1] induced podocyte*[2] injury, with the strongest cytotoxicity observed in treatment-resistant cases.
- Energy-metabolic dysfunction—particularly reduced ATP production through anaerobic glycolysis*[3]—was closely linked to the progression of podocyte damage.
- Impaired anaerobic glycolysis accelerated podocyte injury and aggravated glomerulosclerosis *in vivo*.
- Targeting metabolic abnormalities may open new avenues for therapeutic development and drug discovery in FSGS.

Summary

A research team led by Masahiro Sugimura, MD (Guest Researcher), Kayaho Maeda, MD, PhD (Assistant Professor; corresponding author), and Shoichi Maruyama, MD, PhD (Professor) of the Department of Nephrology, Nagoya University Graduate School of Medicine, together with Kenji Kadomatsu, MD, PhD (Professor) of the Institute for Glyco-core Research, and Akiyoshi Hirayama, PhD (Associate Professor) of the Institute for Advanced Biosciences, Keio University, has demonstrated that suppressed anaerobic glycolysis within podocytes is a driving force in the progression of the designated intractable disease primary nephrotic syndrome*[4], specifically FSGS.

The investigators showed that sera from FSGS patients triggered severe podocyte apoptosis, correlating with both histological severity and steroid resistance. Comprehensive metabolic analyses revealed a marked decline in glycolytic ATP production in podocytes exposed to treatment-resistant FSGS sera. Moreover, mice lacking the key glycolytic enzyme lactate dehydrogenase A (LDHA) in podocytes exhibited significantly accelerated glomerulosclerosis.

FSGS affects children and adults alike and is notable for its poor prognosis due to frequent steroid resistance. Whereas immune dysregulation has long been emphasized, the present findings highlight intracellular energy metabolism—especially glycolytic impairment—as a

pivotal pathogenic mechanism. Evaluating serum factors and cellular metabolic status may therefore aid in predicting treatment resistance, while modulating glycolytic pathways offers a promising therapeutic strategy.

The results were published online in *Kidney International Reports* on 22 June 2025.

Research Overview

1. Background

Nephrotic syndrome is a disease characterized by massive urinary protein loss. Among its subtypes, FSGS often relapses or resists therapy and can progress to end-stage kidney disease. Although immunological mechanisms have been the traditional focus, the heterogeneity of FSGS and limited understanding of refractory cases necessitate new investigative angles. While podocyte dysfunction is recognized, its link to disordered energy metabolism has been insufficiently explored.

2. Findings

- Serum cytotoxicity assay: Human cultured podocytes exposed to sera from FSGS or minimal change disease (MCD) patients revealed significantly greater apoptosis with FSGS sera. The degree of apoptosis correlated strongly with the proportion of segmental lesions and steroid resistance.
- Metabolic profiling: Metabolomics*[5] and real-time ATP flux analysis*[6] demonstrated reduced lactate (a glycolytic end-product) and diminished ATP generation in podocytes treated with FSGS sera. Anaerobic glycolytic ATP output inversely correlated with apoptosis severity.
- *In-vivo* validation: Podocyte-specific LDHA-knockout mice challenged with adriamycin developed markedly worse glomerulosclerosis than controls, underscoring LDHA's role in maintaining podocyte architecture. FSGS sera suppressed LDHA activity, decreased the expression of the cytoskeletal protein α-actinin-4, and disrupted actin-filament organization.

Collectively, these data establish a novel disease model in which suppression of podocyte anaerobic glycolysis precipitates cytoskeletal disintegration and structural collapse, driving glomerulosclerosis in FSGS.

3. Future Directions

These findings provide a foundation for new diagnostic and severity-grading tools for FSGS and may facilitate personalized medicine based on metabolic profiling. Future work will aim to translate serum and metabolite markers into clinical practice and to screen or repurpose agents that restore energy metabolism as disease-modifying therapies.

Notes

*[1] Focal segmental glomerulosclerosis (FSGS): A pathological pattern of kidney injury causing nephrotic syndrome and often leading to chronic kidney failure.

*[2] Podocyte: Specialized epithelial cells lining the glomerular basement membrane and crucial for the kidney's filtration barrier.

*[3] Anaerobic glycolysis: ATP production from glucose without oxygen, yielding lactate as an end product.

*[4] Primary nephrotic syndrome: A category of idiopathic nephrotic syndromes designated as intractable diseases in Japan.

*[5] Metabolomics: Large-scale quantitative analysis of small-molecule metabolites within cells or biofluids.

*[6] Real-time ATP flux analysis: An assay (e.g., Seahorse XF) that measures oxygen consumption and extracellular acidification to calculate ATP production pathways in living cells.

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