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# Induced Pluripotent Stem Cell-Derived Podocytes Reveal ER Stress-Mediated Pathogenesis in X-Linked Alport Syndrome

**Yoo Jin Shin**[1], Xianying Fang[1], Sheng Cui[1], Sun Woo Lim[1], Hanbi Lee[2], Do Hyun Na[3], Sang Hun Eum[3], Eun Jeong Ko[4], Hye Eun Yoon[2], Byung Ha Chung[2]
[1]Department of Transplantation Research Center, College of Medicine, The Catholic University of Korea, Korea, Republic of
[2]Department of Internal Medicine-Nephrology, The Catholic University of Korea Seoul St. Mary's Hospital , Korea, Republic of
[3]Department of Internal Medicine-Nephrology, Incheon St. Mary's hospital, The Catholic University of Korea, Korea, Republic of
[4]Department of Internal Medicine-Nephrology, The Catholic University of Korea Bucheon St. Mary's Hospital , Korea, Republic of

**Objectives :** X-linked Alport Syndrome (XLAS) is caused by COL4A5 mutations, leading to defective type IV collagen network in the glomerular basement membrane (GBM). Despite its genetic basis, no direct therapeutic strategy targeting collagen abnormalities is available. Induced pluripotent stem cells (iPSCs) enable patient-specific disease modeling to investigate molecular mechanisms and potential therapeutic targets. Here, we generated iPSC-derived podocytes from an XLAS patient and examined the impact of ER stress and oxidative stress on podocyte dysfunction.
**Methods :** iPSCs were established from peripheral blood mononuclear cells (PBMCs) of an XLAS patient and differentiated into podocytes. Expression levels of podocyte markers, type IV collagen genes, ER stress markers, and oxidative stress markers were analyzed using RT-qPCR or immunofluorescence. ROS levels were assessed using DCFDA fluorescence assays. Electron microscopy (EM) was used to examine ER and mitochondrial morphology, and cell viability assays were performed to assess the impact of ER and oxidative stress on podocyte survival.
**Results :** XLAS patient-derived iPSCs exhibited typical pluripotency markers, normal karyotyping, and successful tri-lineage differentiation. Compared to WT podocytes, XLAS-derived podocytes (XLAS-PCs) showed reduced expression of NPHS1 and WT1, indicating impaired differentiation. COL4A5 expression was significantly downregulated, whereas COL4A1 was upregulated, suggesting an immature extracellular matrix composition. ER stress markers were elevated, with reduced calnexin and calreticulin, confirming UPR activation. EM analysis revealed enlarged ER structures in XLAS-PCs, supporting ER stress involvement. Additionally, oxidative stress markers and ROS levels were significantly increased, with mitochondrial abnormalities in XLAS-PCs, as confirmed by DCFDA fluorescence assays. Finally, cell viability assays demonstrated that ER and oxidative stress contributed to decreased podocyte survival in XLAS-PCs.
**Conclusions :** Our findings suggest that ER stress and oxidative stress contribute to podocyte dysfunction in XLAS. UPR activation, ROS accumulation, and mitochondrial defects highlight potential therapeutic targets. This study provides insights for developing ER stress-targeting therapies in Alport Syndrome.

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