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Mfn2 Regulate High Glucose-Induced Mitochondrial Dysfunction and Apoptosis in Podocytes through PERK pathway

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Objectives: The injury and loss of podocytes are considered to be the key event in the progression of DKD.Many studies over the years have shown that, morphological and functional changes of mitochondria and endoplasmic reticulum stress（ERS）play two important roles in the process of podocyte injury.This study confirmed that reduced expression of Mfn2 in HG-induced poodocytes was accompanied by activation of PERK pathway, abnormal mitochondrial morphology and functions, and increased apoptosis.

Methods: 1.STZ was used to induce a DM mouse model,HE and PAS staining were used to observe the morphological and structural changes of glomeruli.mitochondrial morphology of podocytes were analyzed by electron microscope, and apoptosis was assaysed by Tunel staining.Mfn2 expression in podocytes was detected by Immunofluorescence.WB was performed to detect expression of Mfn2, IRE1α, ATF6β, PERK, p-PERK and CHOP in glomeruli;
2.Human podocyte(HPC) were treated with high glucose,mitochondrial morphology were evaluated .Mitochondrial membrane potential was analyzed by JC-1 staining. DCFH-DA fluorescent probe was used to analyze ROS level. Apoptosis was analyzed by flow cytometry.the interactions of Mfn2-PERK was assessed using co-immunoprecipitation.WB was performed the same as Part1;
3.HPC with Mfn2-overexpression and silence were established.WB was performed to evaluate the expression of Mfn2, PERK, p-PERK and CHOP.co-localization of Mfn2-PERK was analyzed by laser confocal microscopy.Mitochondrial membrane potential, ROS level and apoptosiwas detected the same as Part2.

Results: 1.STZ-induced DM rats exhibited renal pathological structural changes and podocyte injury ;
2.Dereased expression of Mfn2 and increased expression of ERS-related proteins was detected in glomeruli from DM rats and HG-induced HPC;
3.Mfn2 silence suppressed the Mfn2-PERK interaction, up-regulated the expression of p-PERK and CHOP, reduced mitochondrial membrane potential, increased ROS generation and HPC apoptosis;Mfn2 overexpression restored that.

Conclusions: Mfn2 is the upstream regulator of PERK and HG activates PERK pathway by down-regulating Mfn2 expression. Activated PERK pathway regulates PERK pathway-related MAMs and mitochondrial dysfuction, induces apoptosis.