KSN SEOUL, KOREA 2023
April 27(Thu) - 30(Sun), 2023
Coex, Seoul, Korea

Abstract Type : Poster
Abstract Submission No. : 1580

Hormetic effects of phosphate in calcium-regulated podocyte filter function: Two sides of the same coin

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Objectives: The malfunction of podocytes, specialized epithelial cells for the glomerular filtration barrier, is caused by the dysregulation of intracellular Ca^{2+} signaling that interrupts the actin cytoskeleton, resulting in slit diaphragm disruption and proteinuria, an early defining feature of kidney diseases. Besides the prominent *Trpc5/6* (transient receptor potential cation channel subfamily), Orai1-mediated SOCE has emerged in preserving Ca^{2+}-dependent filter integrity related to podocyte injury. In the diabetic kidney, podocyte Ca^{2+} is elevated by reactive oxygen species (ROS). Hyperphosphatemia is a primary complication of renal damage found in advanced chronic kidney disease (CKD), which is a state of elevated oxidative stress. It remains incredulous how excessive inorganic phosphate (Pi) affects SOCE-mediated Ca^{2+} signaling in podocyte actin dynamics and filtering function, causing proteinuria in CKD.

Methods: Accordingly, our data show that the endoplasmic reticulum (ER) underwent stress due to Ca^{2+} release and SOCE activation by transient Pi-induced mitochondrial ROS production. Pi promoted Akt-dependent exocytosis of Orai1 and TRPC6, leading to their greater surface abundance.

Results: Thus, this dysregulation in cytosolic calcium or ROS itself disorganized actin cytoskeleton and diminished protein expression of synaptopodin, which temporarily altered podocyte morphology or plasticity and caused higher albumin permeability. Notably, GSK7975A (an Orai1 inhibitor) partly rescued the actin cytoskeleton disruption and synaptopodin loss. Concurrently, podocytes treated with Pi in a short-term manner generated a higher protein expression of GDF15, and FGF21, stress markers that potentiate negative feedback to hinder the fatal impact of ROS and intracellular Ca^{2+} dysregulation. However, in long-term exposure, Pi irreversibly deteriorated actin cytoskeleton and cell viability, likely resulting in loss of slit diaphragm integrity and proteinuria, subsequently.

Conclusions: Overall, our data sheds light on both the positive and negative influences of Pi in podocytes, particularly in Ca^{2+}-regulated podocyte filter function.

This study was supported by through the National Research Foundation of Korea (NRF-2017R1A5A2015369 & NRF-2022R1A2C2011079)