【Symposium 4-2】

Organelle stress and organelle communication

Reiko Inagi, PhD

Division of CKD Pathophysiology, the University of Tokyo Graduate School of Medicine

Our research focuses on organelle stress, particularly the maladaptive endoplasmic reticulum (ER) stress response through the unfolded protein response (UPR) pathway, which contributes to kidney cell damage in both acute and chronic kidney diseases as well as kidney aging.

ER stress associated with maladaptive UPR activation links to various kidney damage phenotypes and their progression, including oxidative stress, chronic inflammation, tubular fibrosis, and metabolic alterations involving mitochondrial stress. Recently, in diabetic kidney disease (DKD), we discovered that lipid metabolic alterations, such as lysophosphatidylcholine (LPC) accumulation in the ER, are associated with maladaptive UPR activation (ER stress) and mitochondrial morphological and functional impairment (mitochondrial stress). Notably, we found that LPC-induced organelle stress correlates with a rapid decline in kidney function, estimated by ΔeGFR (Yoshioka, et at. Kidney Int. 2022).

Recent studies highlight intra-organelle interactions, such as the mitochondria-associated ER membrane (MAM), which is crucial for lipid metabolism and calcium signaling. Our findings revealed that LPC-induced organelle stress significantly disrupted MAM formation, leading to tubular lipid metabolic alterations and lipotoxic cell death in DKD rats. Further, we further focus on the renal pathophysiological role of other types of organelle contact, such as ER-lysosome interaction, and demonstrate that the organelle-tethering factor, PDZD8, on the ER lumen plays a crucial role in maintaining mitochondrial and endosomal homeostasis during podocyte lipotoxicity. (Hasegawa, et al. JCI Insight 2024)

In my talk, I will review these findings, emphasizing the pathophysiological role of organelle stress and organelle crosstalk in kidney health and disease.