先端医療開発研究クラスター

Advanced Medical Development Research Cluster

講座名　慢性腎臓病（CKD）病態生理学講座

英文講座名　Division of CKD Pathophysiology

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Emerging CKD Pathophysiology in the Renal Renaissance: From Organelle Stress to Contact-Site Biology in Metabolic Kidney Disease

腎ルネッサンスにおける新しいCKD病態生理：オルガネラ・ストレスからコンタクトサイト生物学へ代謝性腎疾患を紐解く

- Why CKD matters: Kidney disease affects more than 850 million people worldwide, and is projected to become the 5th leading cause of years of life lost (YLL) by 2040. In Japan, approximately one in eight adults (about 13.3 million people) has chronic kidney disease (CKD), which reduces quality of life and productivity and constitutes a major risk factor for cardiovascular disease and frailty. Moreover, disruption of kidney-centered inter-organ communication is closely linked to systemic homeostasis and, ultimately, to aging.

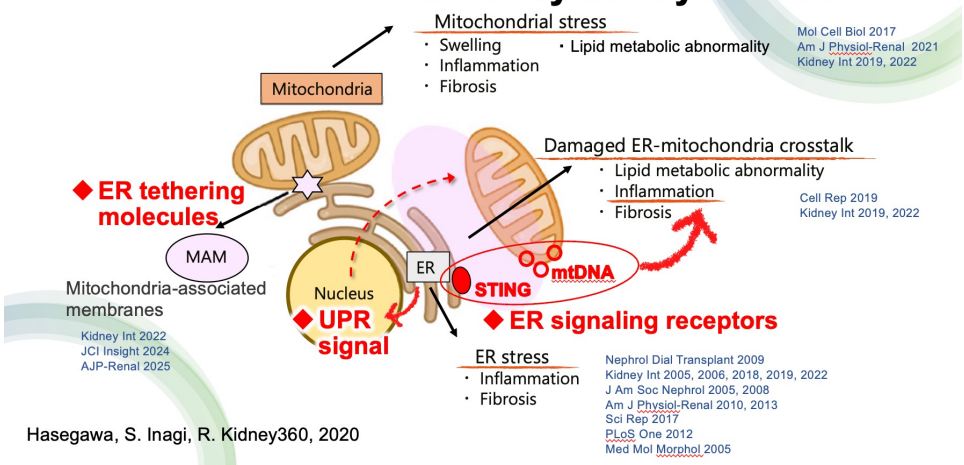
なぜ今、CKD？ CKDは腎臓だけの問題ではなく、心血管イベント、フレイルに直結する全身疾患です。腎障害が進むほど、腎臓を起点とする“臓器間コミュニケーション”が破綻し、代謝・免疫・神経系の恒常性が連鎖的に崩れ、老化の加速にもつながります。だからこそ、CKDを「臓器ネットワークの破綻」として捉え直す視点が必要です。

- What we learn from organelle biology: Recent advances, from successful clinical trials (including SGLT2 inhibitors and complement inhibitors) to single-cell and spatial multi-omics, have highlighted that kidney injury is underpinned by metabolic reprogramming, disrupted lipid homeostasis, and organelle stress that are tightly interconnected. Building on our long-standing work demonstrating that dysregulation of endoplasmic reticulum (ER) stress signaling, particularly the unfolded protein response (UPR), contributes to diverse renal pathologies affecting both glomeruli and tubules, we have more recently focused on organelle contact sites, including ER-mitochondria and ER-lysosome interfaces. We have shown that disruption of these contact sites induces organelle dysfunction in both glomerular and tubular compartments, thereby leading to inflammation, fibrosis, and metabolic remodeling.

腎臓とオルガネラバイオロジー：小胞体ストレス／UPR、ミトコンドリア障害、リソソーム機能不全は、別々の出来事ではなく相互増幅する一連の病態です。代謝障害や脂質恒常性の破綻が引き金となり、オルガネラ品質管理が追いつかなくなることで、腎臓の機能低下や炎症・線維化が加速します。病態の核心は「単一オルガネラ障害」ではなく、オルガネラ間相互作用の障害、破綻が連鎖する悪循環にあります。

- Where we are headed: We are entering an organelle renaissance in nephrology. Our next goal is to identify the molecular “switches” at organelle contact sites that convert adaptive crosstalk into chronic injury, and to develop strategies to restore organelle communication and protect renal function.

Organelle stress and organelle crosstalk link to kidney cell dysfunction



Selected publications: (2022-2025)

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2. Hong YA, Inagi R. Endoplasmic reticulum-mediated organelle crosstalk in kidney disease. **Nat Rev Nephrol.** 2025;21(11):736-755.
3. Li Q, Shang J, Inagi R. Control of Mitochondrial Quality: A Promising Target for Diabetic Kidney Disease Treatment. **Kidney Int Rep.** 2024;10(4):994-1010.
4. Hasegawa S, et al. Organelle communication maintains mitochondrial and endosomal homeostasis during podocyte lipotoxicity. **JCI Insight.** 2024;9(18):e182534.
5. Hasegawa S, Inagi R. Molecular mechanisms of kidney crosstalk with distantborgans. **Nat Rev Nephrol.** 2023;19(2):75-76.
6. Yoshioka K, et al. Lysophosphatidylcholine mediates fast decline in kidney function in diabetic kidney disease. **Kidney Int.** 2022;101(3):510-526.