Session Title: Precision Nephrology

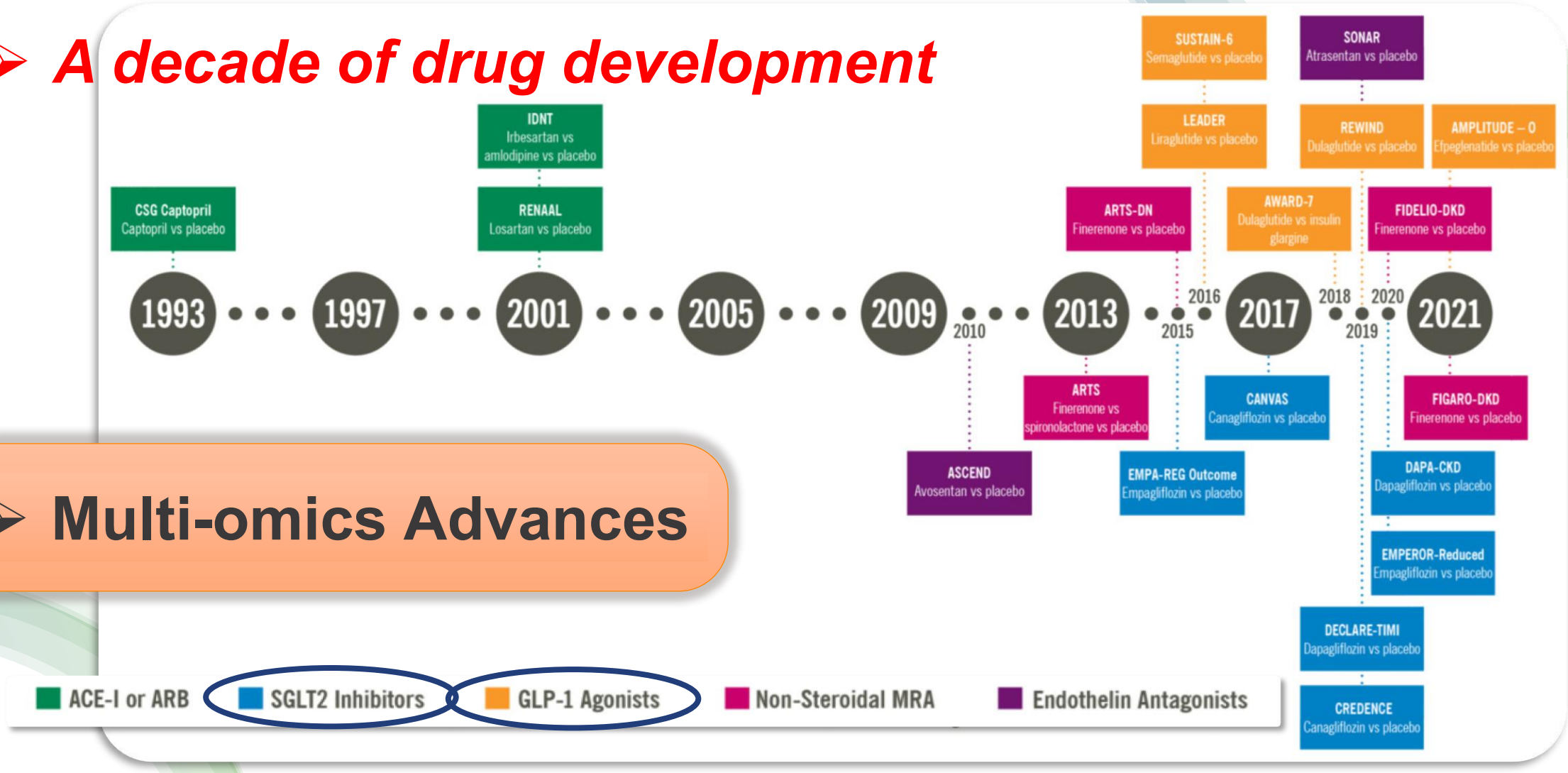
Organelle Dynamics in Kidney Diseases

Reiko Inagi, PhD

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

Renaissance of Nephrology

➢ *A decade of drug development*



➢ **Multi-omics Advances**

Sawaf H. J Clin Med 2022

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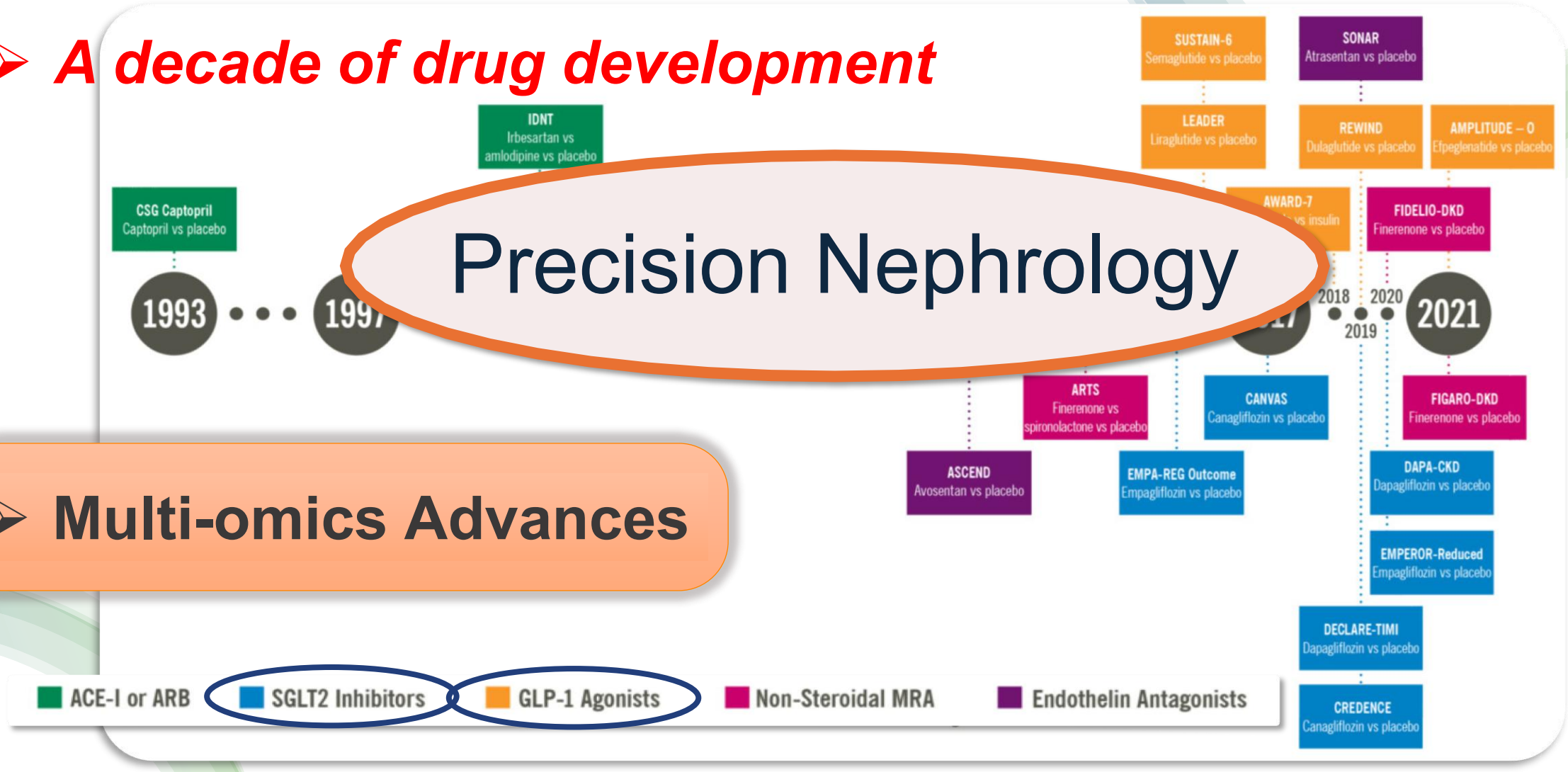
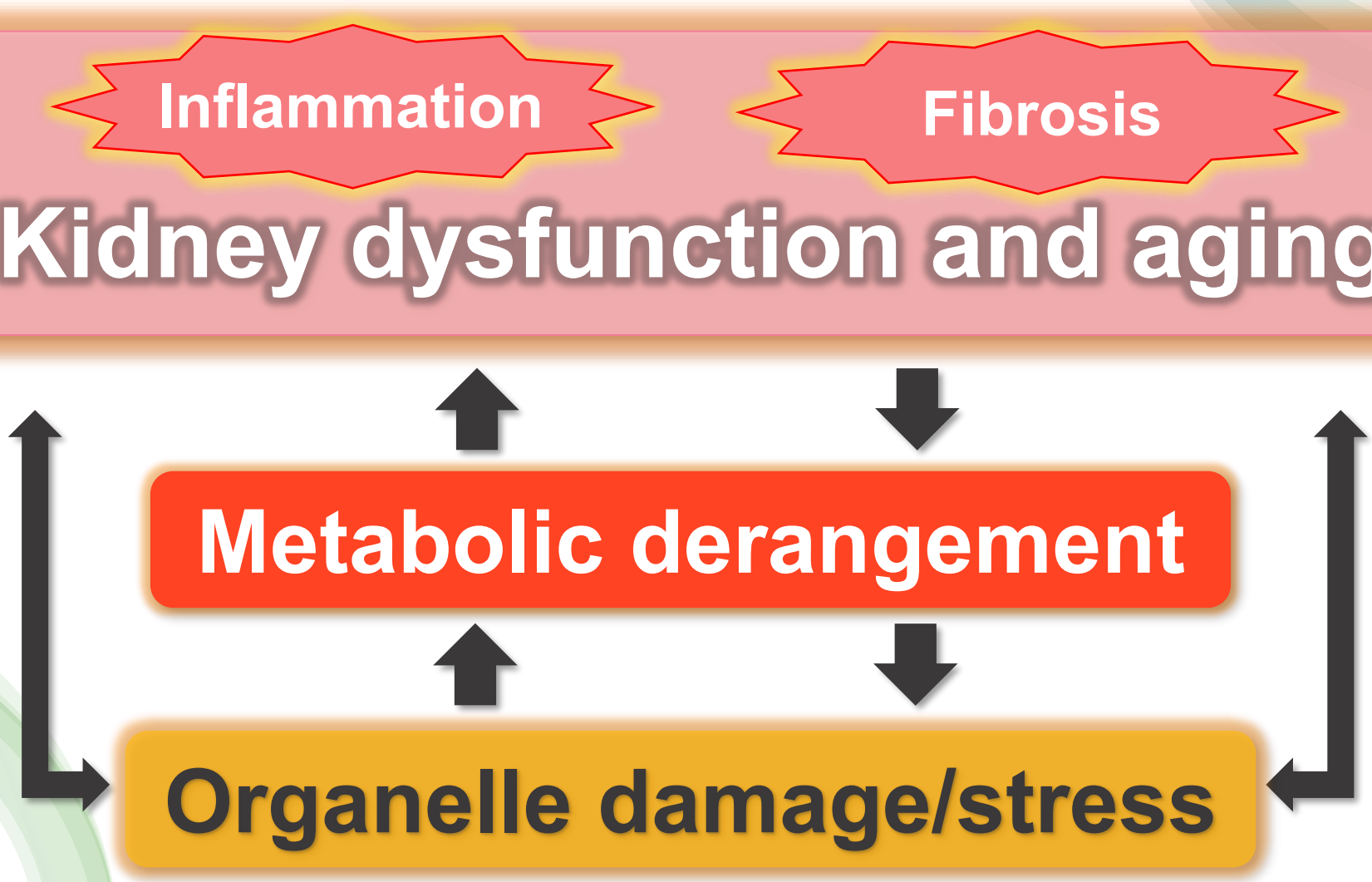


➢ **Multi-omics Advances**

Sawaf H. J Clin Med 2022

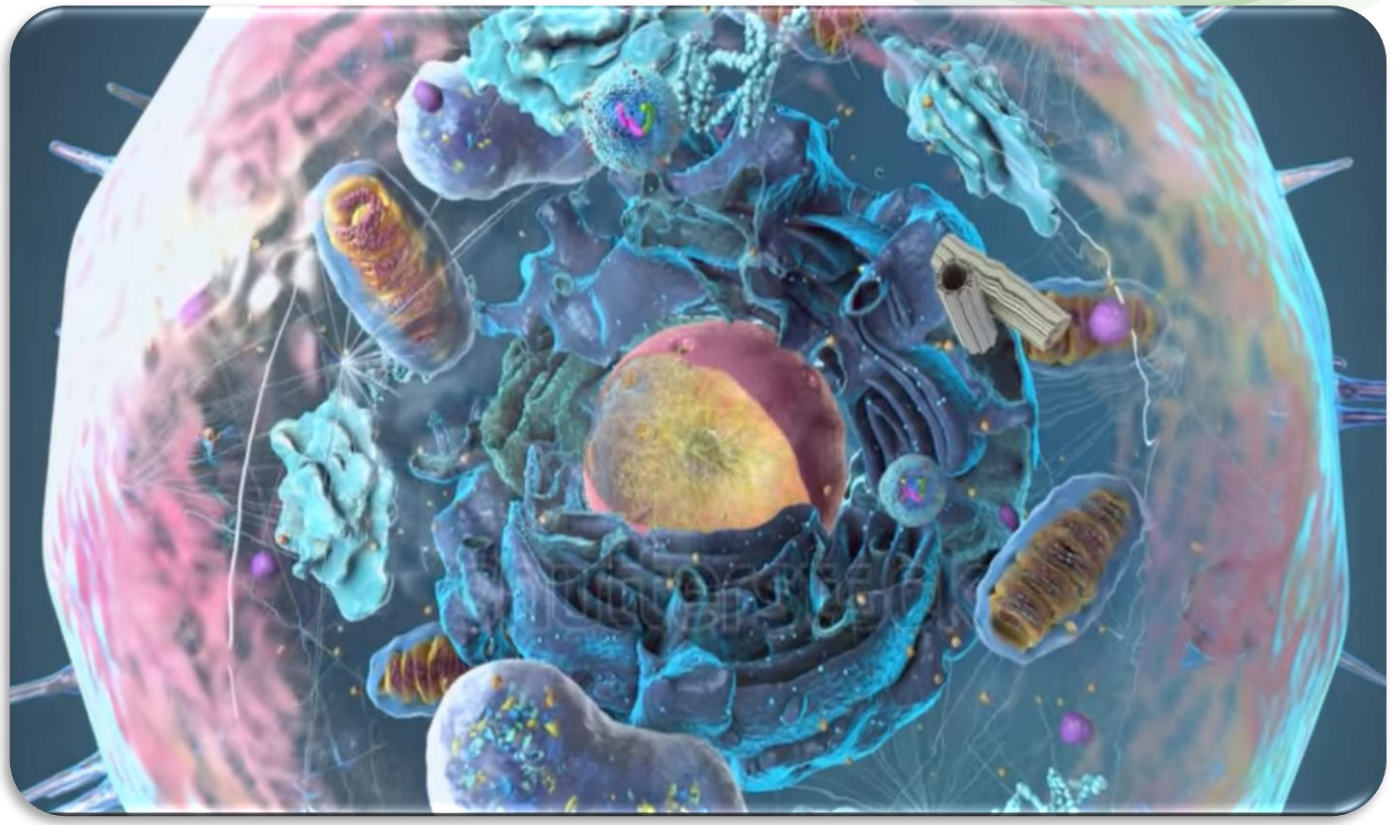
Pathophysiology of CKD

- Key Molecular Mechanisms in Spotlight -



From Organelle Stress to Metabolic Derangement in CKD

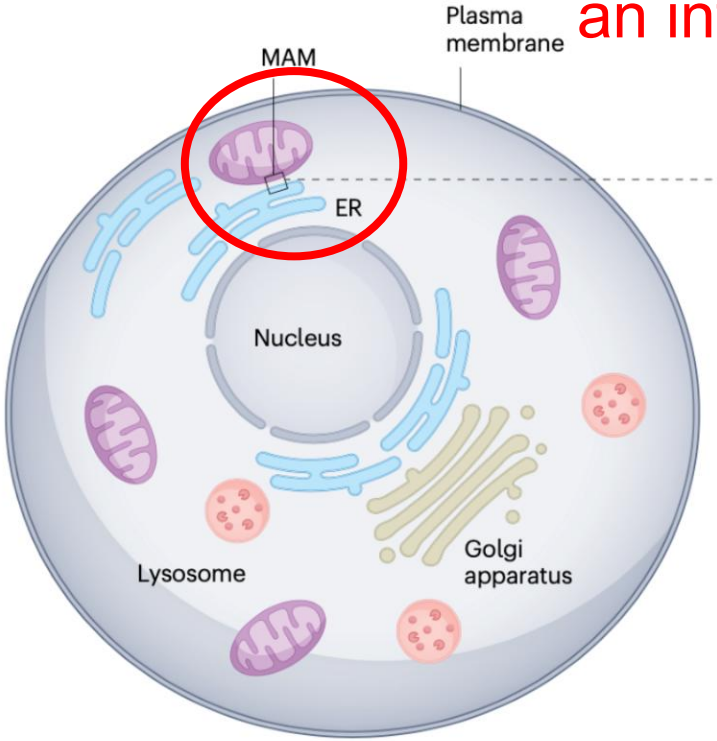
- ER stress
  - ↓ Proteostasis
  - ↓ ER-mito lipid transfer
- Mitochondrial stress
  - ↓ OXPHOS, ATP
  - ↓ FA β-oxidation

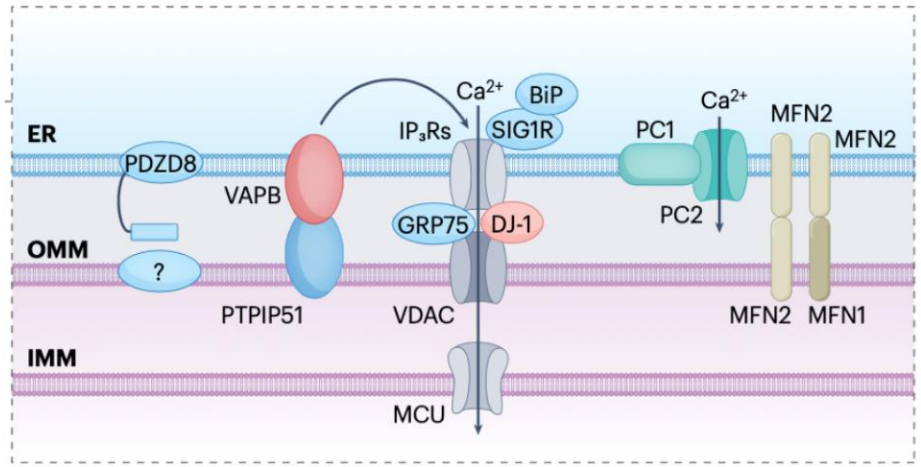


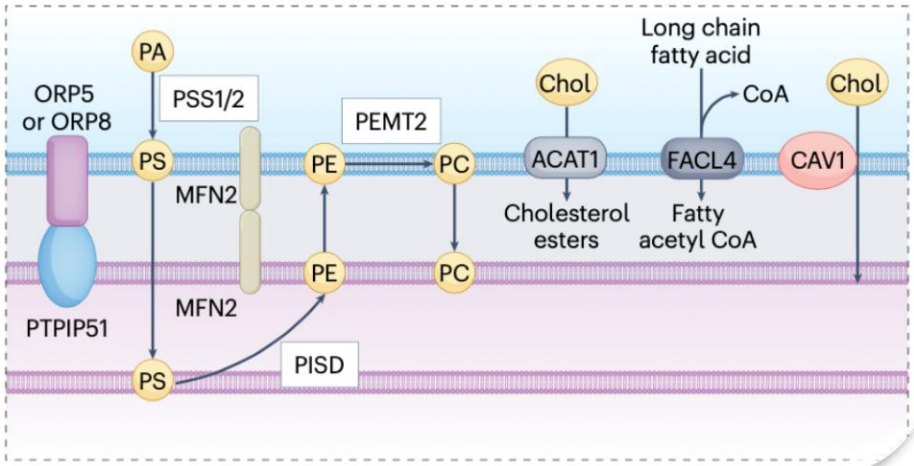
https://www.shutterstock.com/video/clip-1110802575-organelles-inside-eukaryote-eukaryotic-cell-focus-on

Inter-organelle communication orchestrated by organelle zones

MAM (mitochondria-associated ER membrane):
an inter-organelle hub for lipid synthesis and remodeling







Hong, YA. Inagi, R.
Nat Rev Nephrol, 2025

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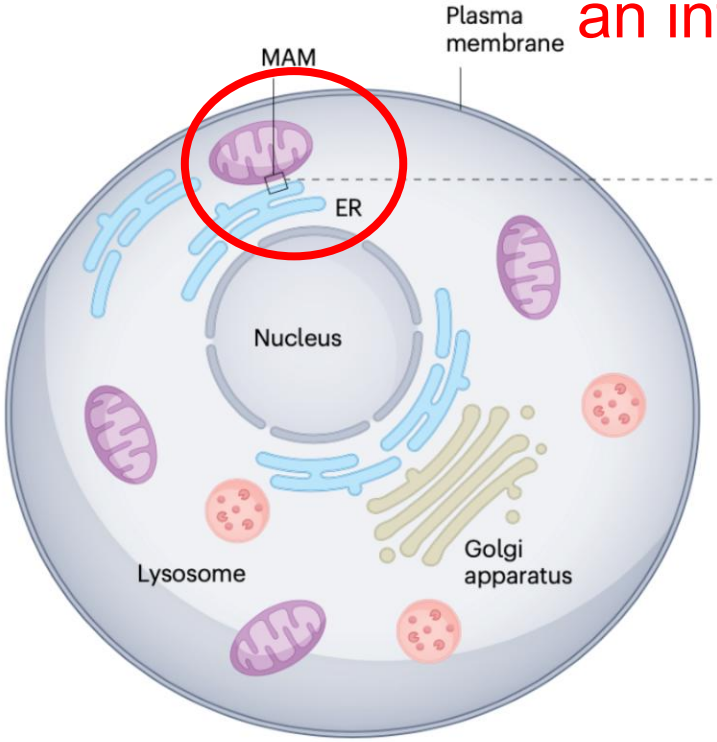
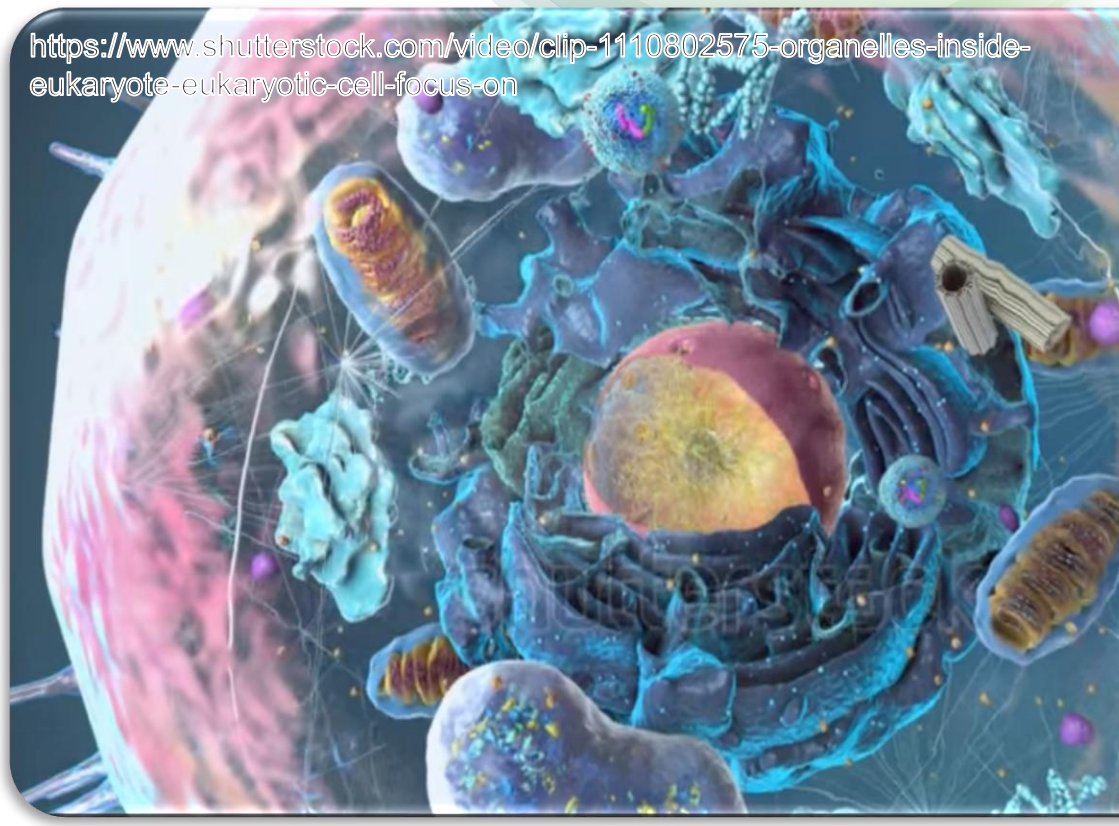


Hong, YA. Inagi, R.
Nat Rev Nephrol, 2025

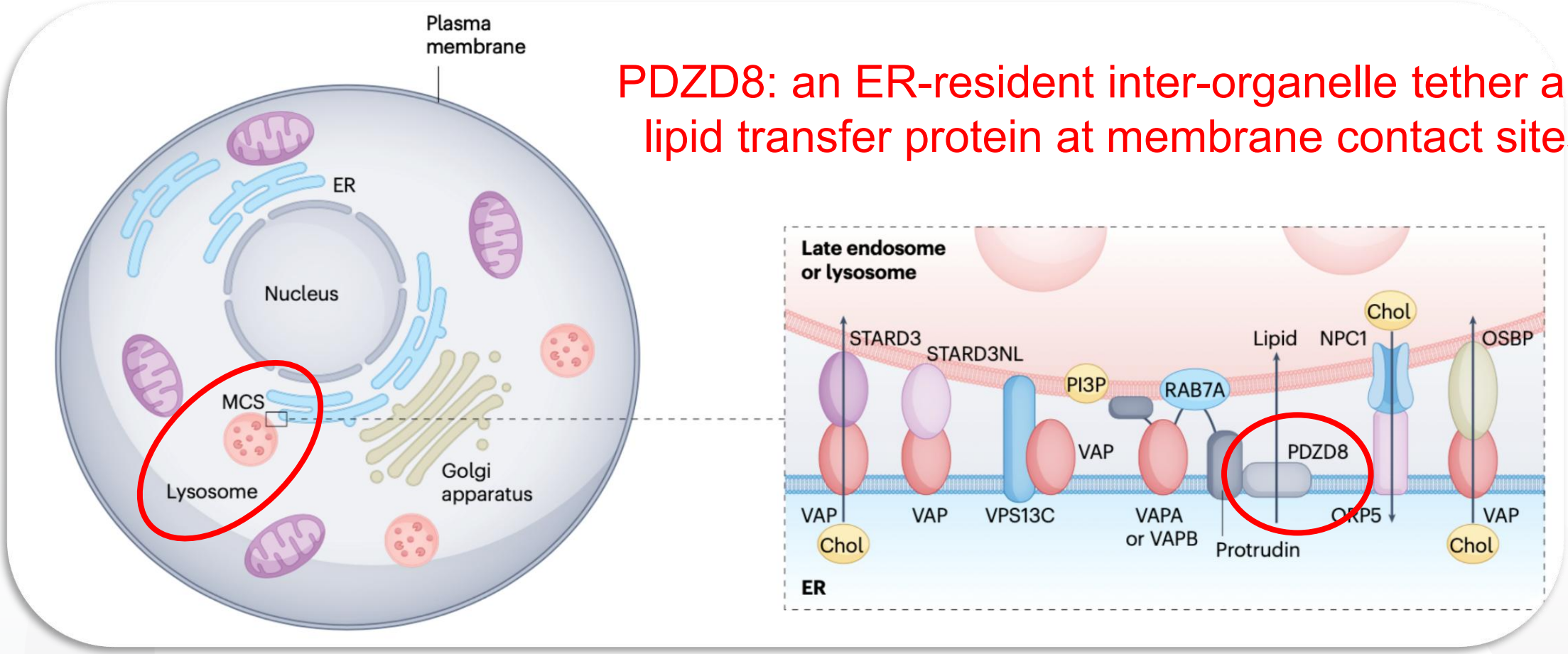
NO.	Oral 1-2
Title	IP3R2 Orchestrates Calcium-Independent ER-Mitochondrial Signalling to Protect Proximal Tubular Cells from Anoxia–Reoxygenation
Room	Room 7 (703)
Presentation Time	Dec. 5 (Fri.) 16:19-16:28
Oral Communications	AKI
First Author	Midori Sakashita

From Organelle Stress to Metabolic Derangement in CKD

- lysosome stress
  - ↓ Degradation & recycling (Autophagic/mitophagic flux)
  - ↓ Tubular handling of filtered proteins and lipids
  - ↓ Nutrient sensing (mTORC1) & metabolic adaptation
  - ↑ Tubular lipotoxicity → Pro-fibrotic & inflammatory signaling



Inter-organelle communication orchestrated by organelle zones

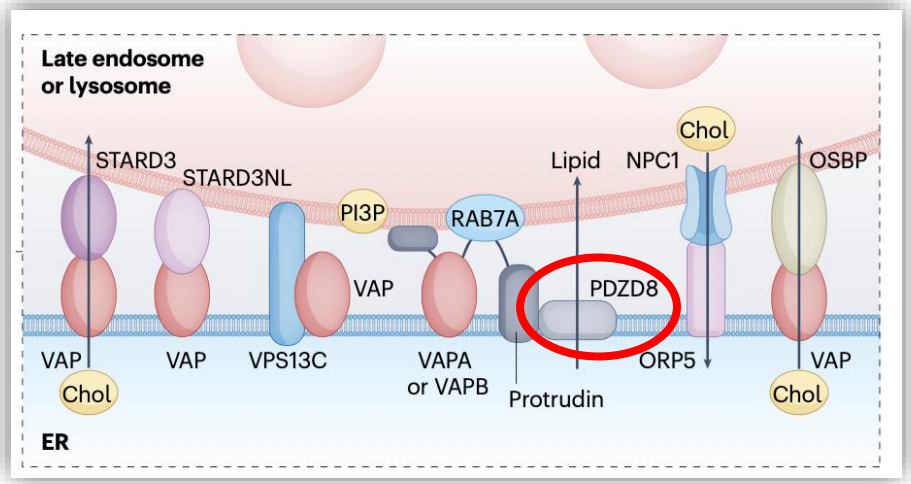


PDZD8: an ER-resident inter-organelle tether and lipid transfer protein at membrane contact sites

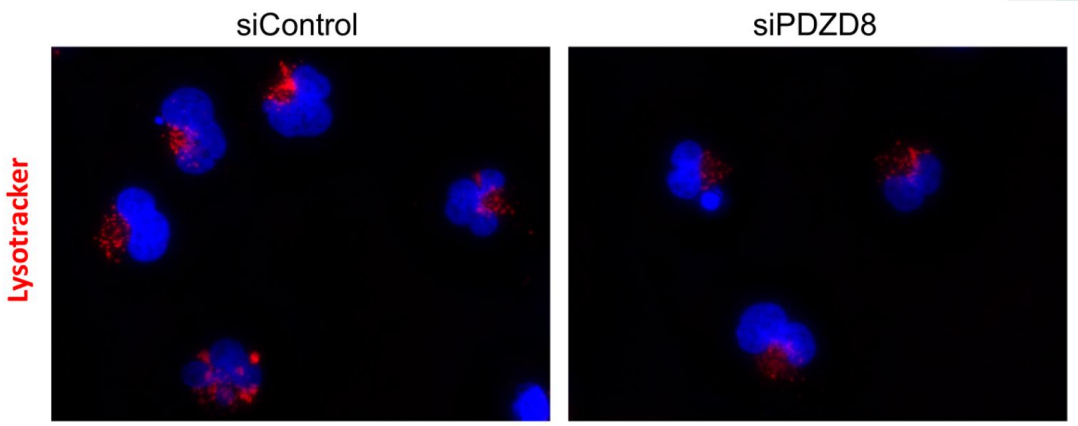
Hong, YA. Inagi, R. Nat Rev Nephrol, 2025

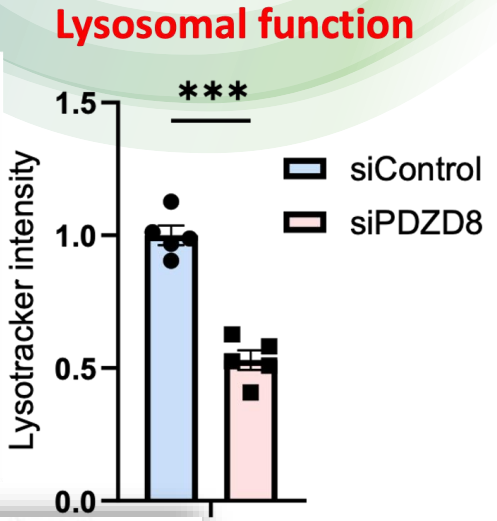
KIDNEY WEEK 2025

PDZD8, a tethering protein of ER-lysosome interaction, regulates endolysosomal maturation and TLR9-NF-κB signaling in cisplatin-induced AKI

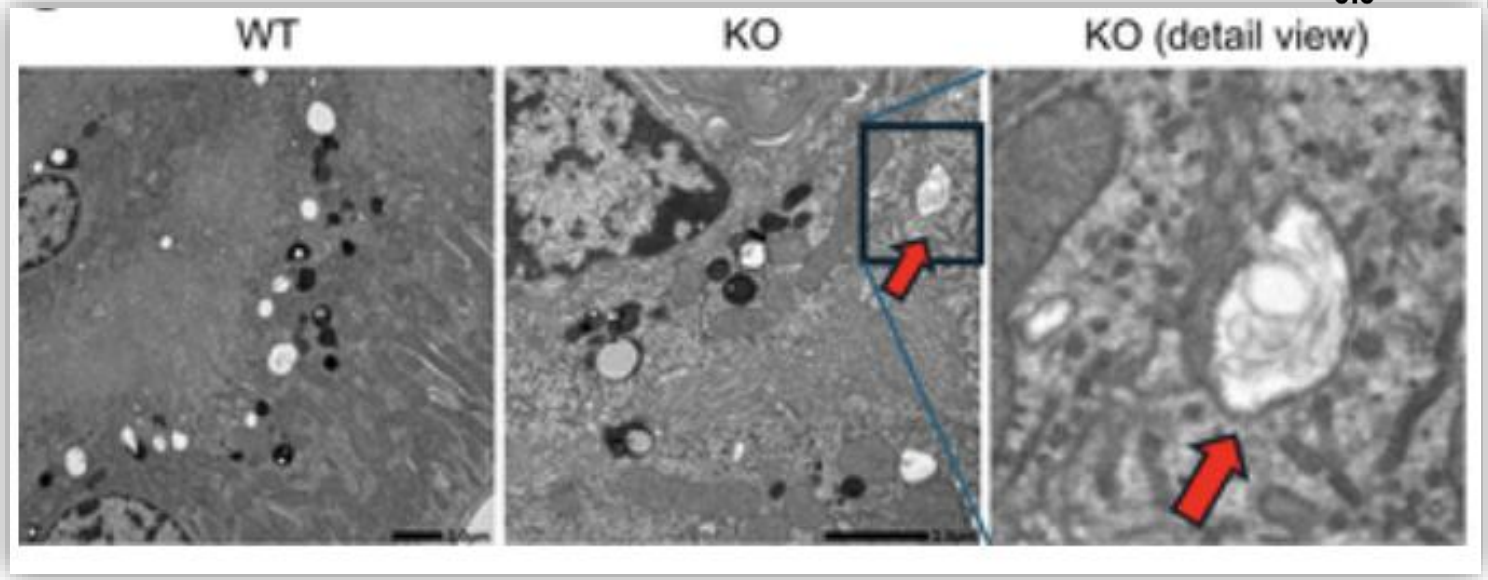


- **PDZD8 regulates lysosomal homeostasis in human proximal tubular cells**





Yuto Takenaka
AJP-Renal, 2025



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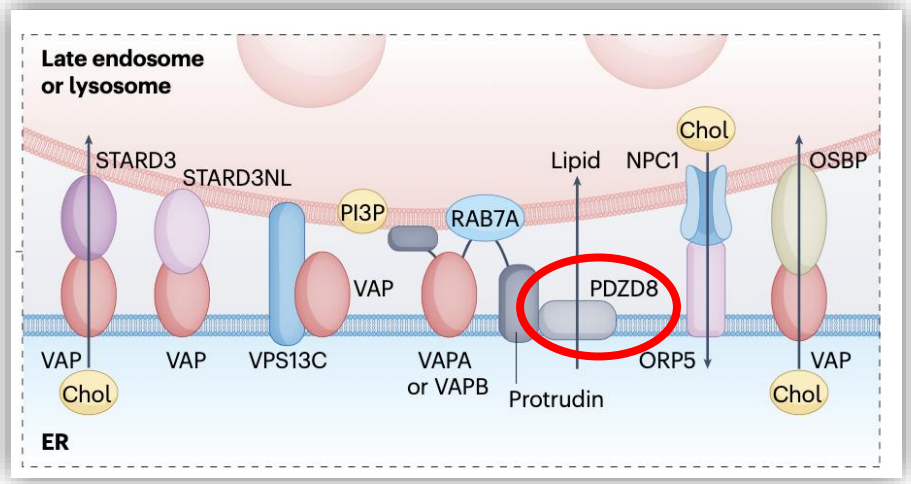

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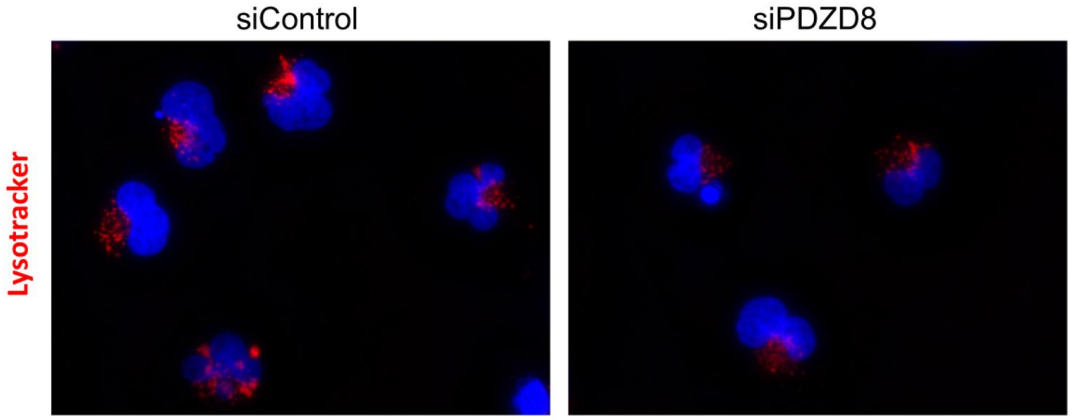

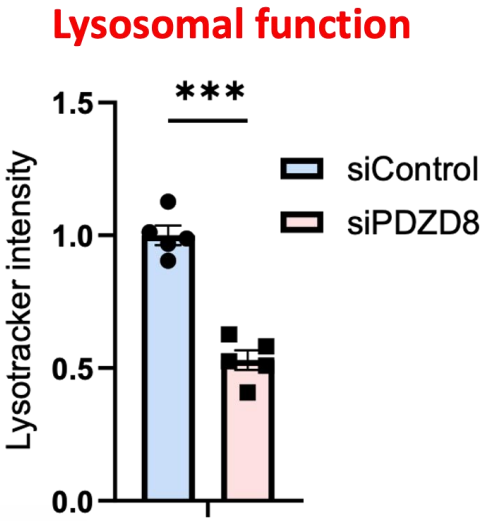

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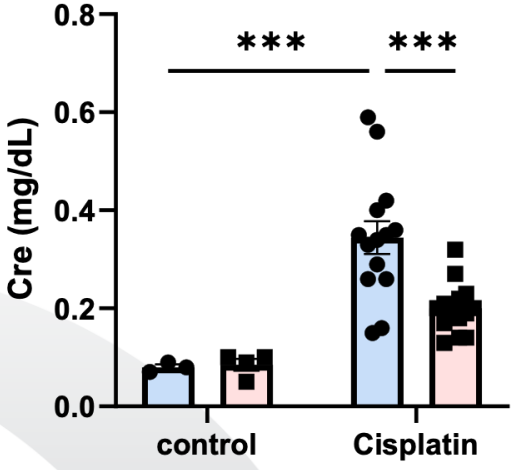
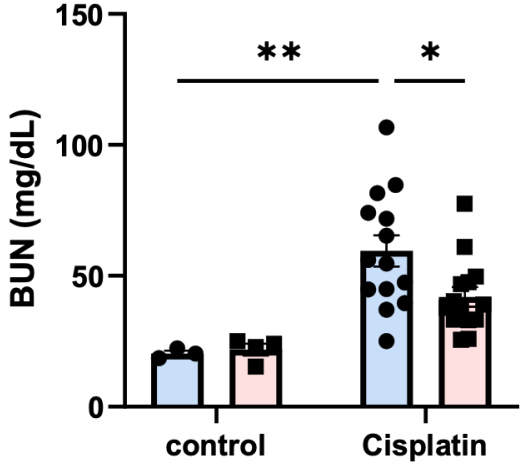
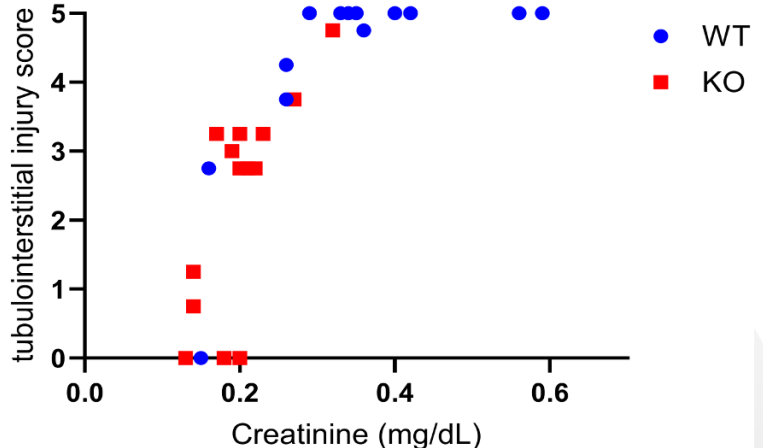
➢ **Pdzd8 KO improves kidney function and tubular injury in cisplatin-AKI**







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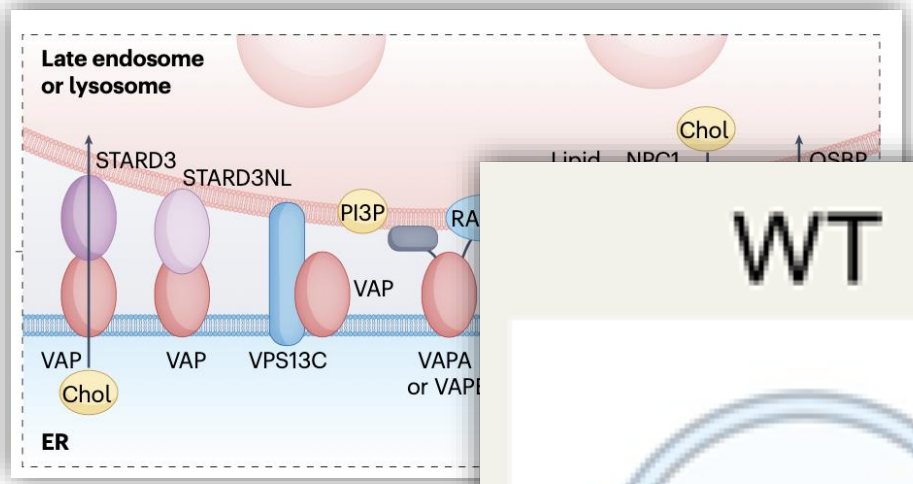

➢ **PDZD8 regulates lysosomal homeostasis in human proximal tubular cells.**

Lysosomal function

Yuto Takenaka
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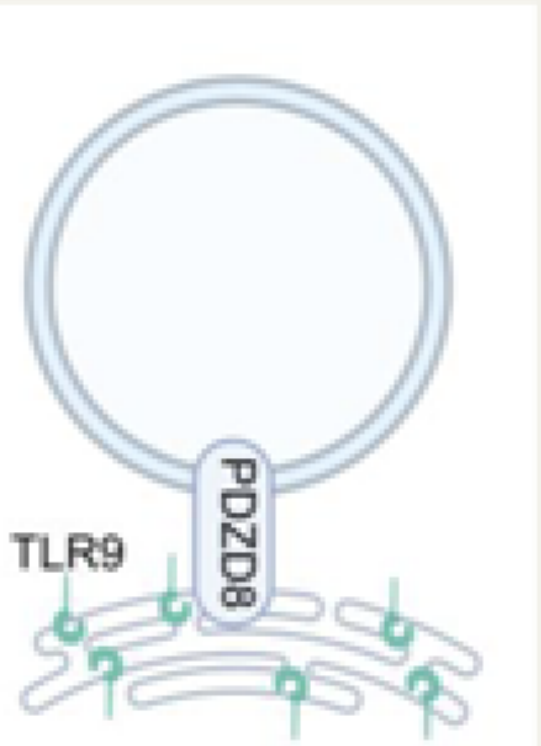
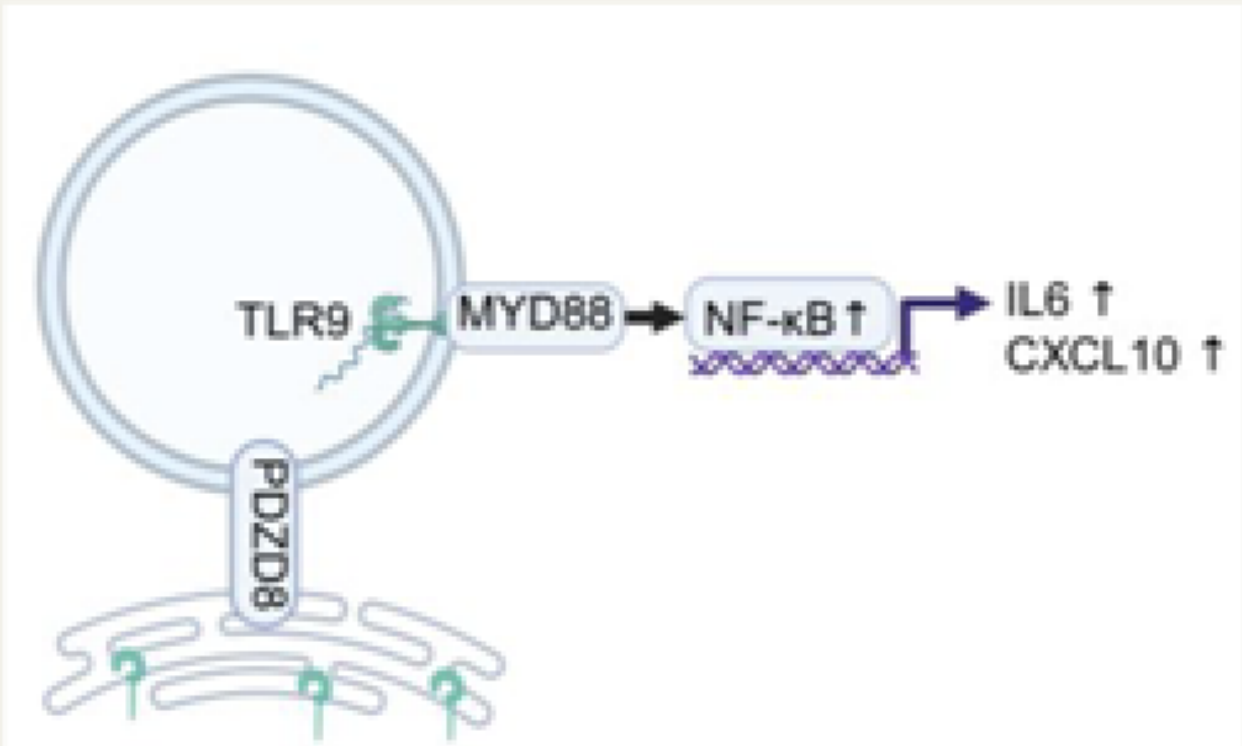
➢

siControl siPDZD8

WT



Cisplatin - WT



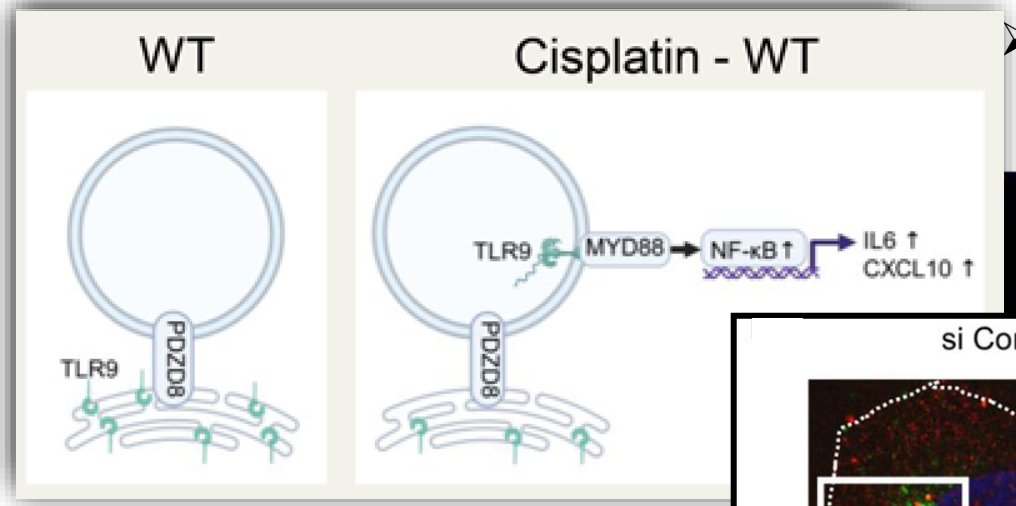
control Cisplatin control Cisplatin

ontrol
DZD8

WT
KO

Creatinine (mg/dL)

PDZD8, a tethering protein of ER-lysosome interaction, regulates endolysosomal maturation and TLR9-NF-κB signaling in cisplatin-induced AKI



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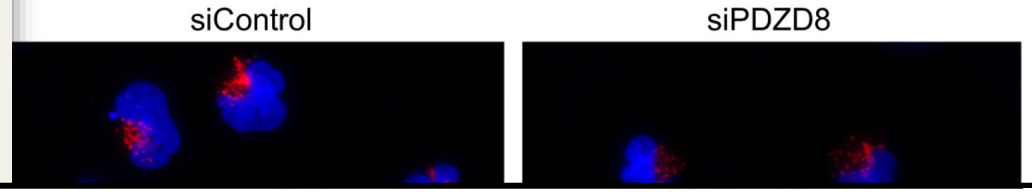
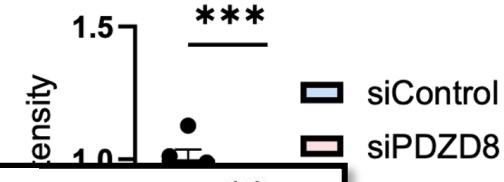
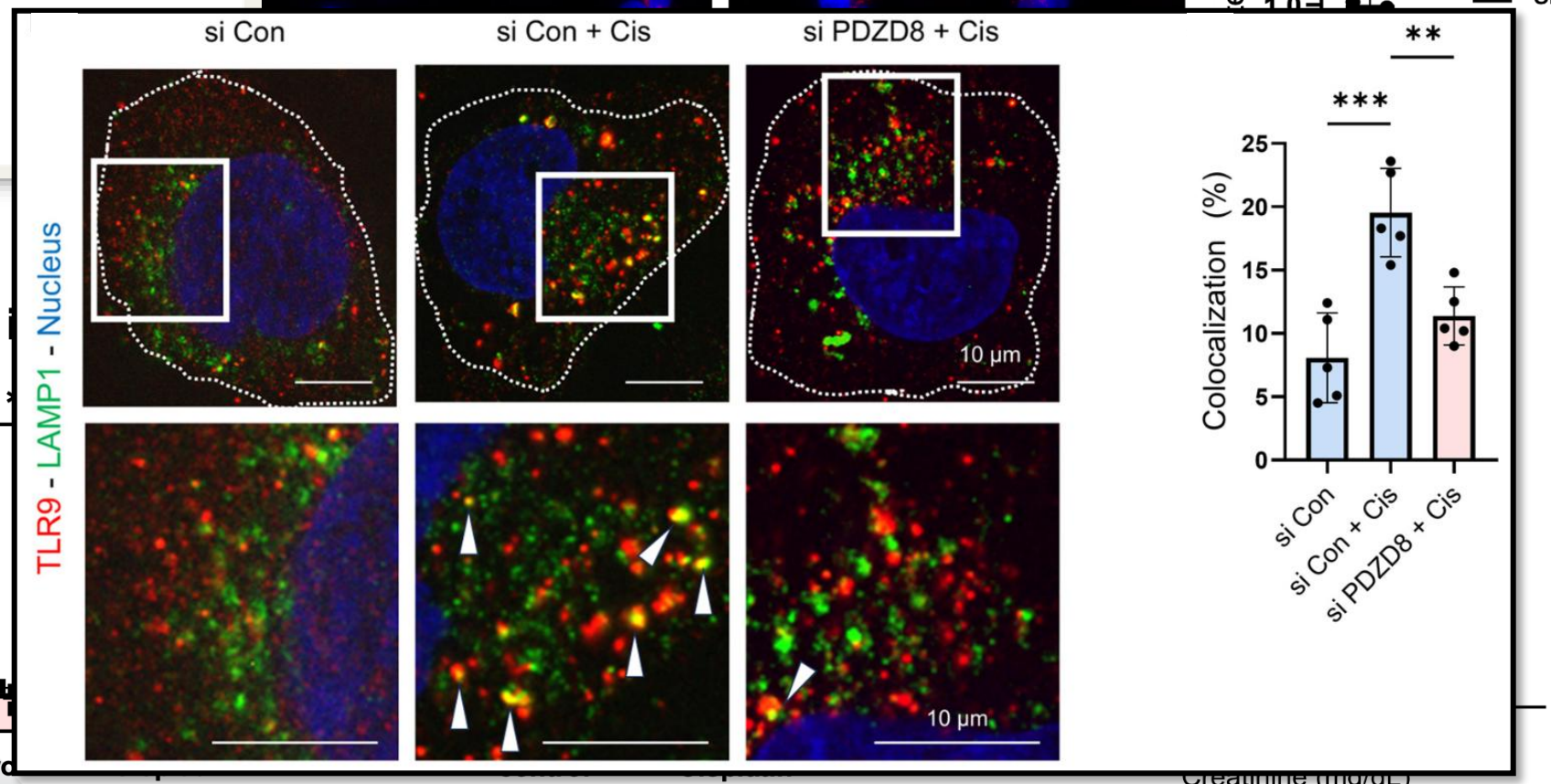


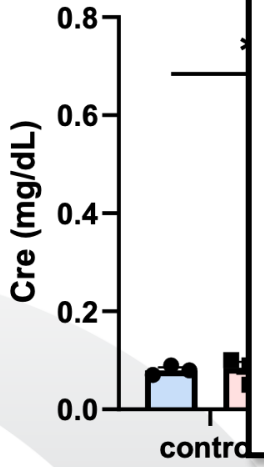
Lysosomal function





Yuto Takenaka
AJP-Renal, 2025

➢ **Pdzd8 KO i**



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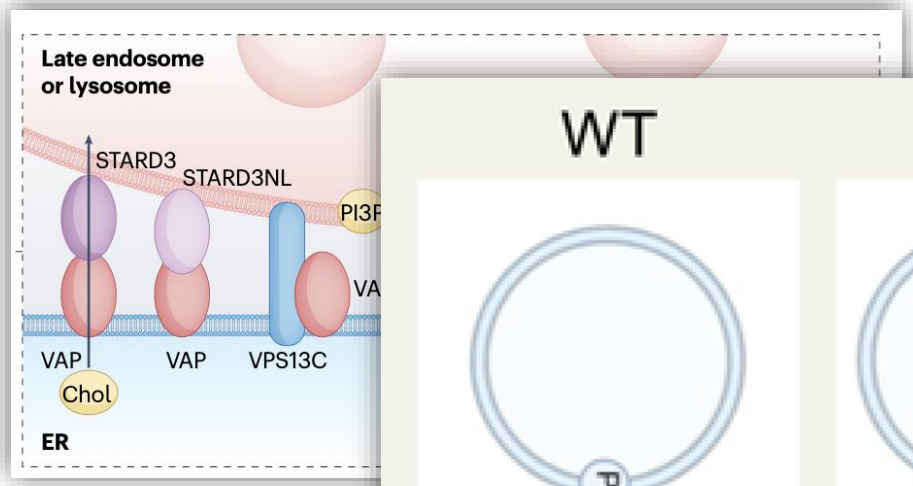

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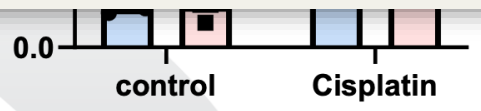
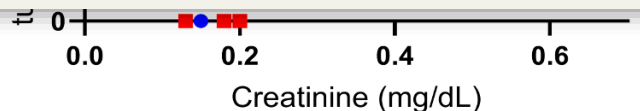
➢ **PDZD8 regulates lysosomal homeostasis**

- Pdzd8 knockout reduces NF-κB activation and mitigates cisplatin-AKI.
- PDZD8 knockdown in proximal tubule cells impedes endolysosomal maturation and suppresses TLR9–MyD88–NF-κB signaling, reducing *IL-6* and *CXCL10* expression.

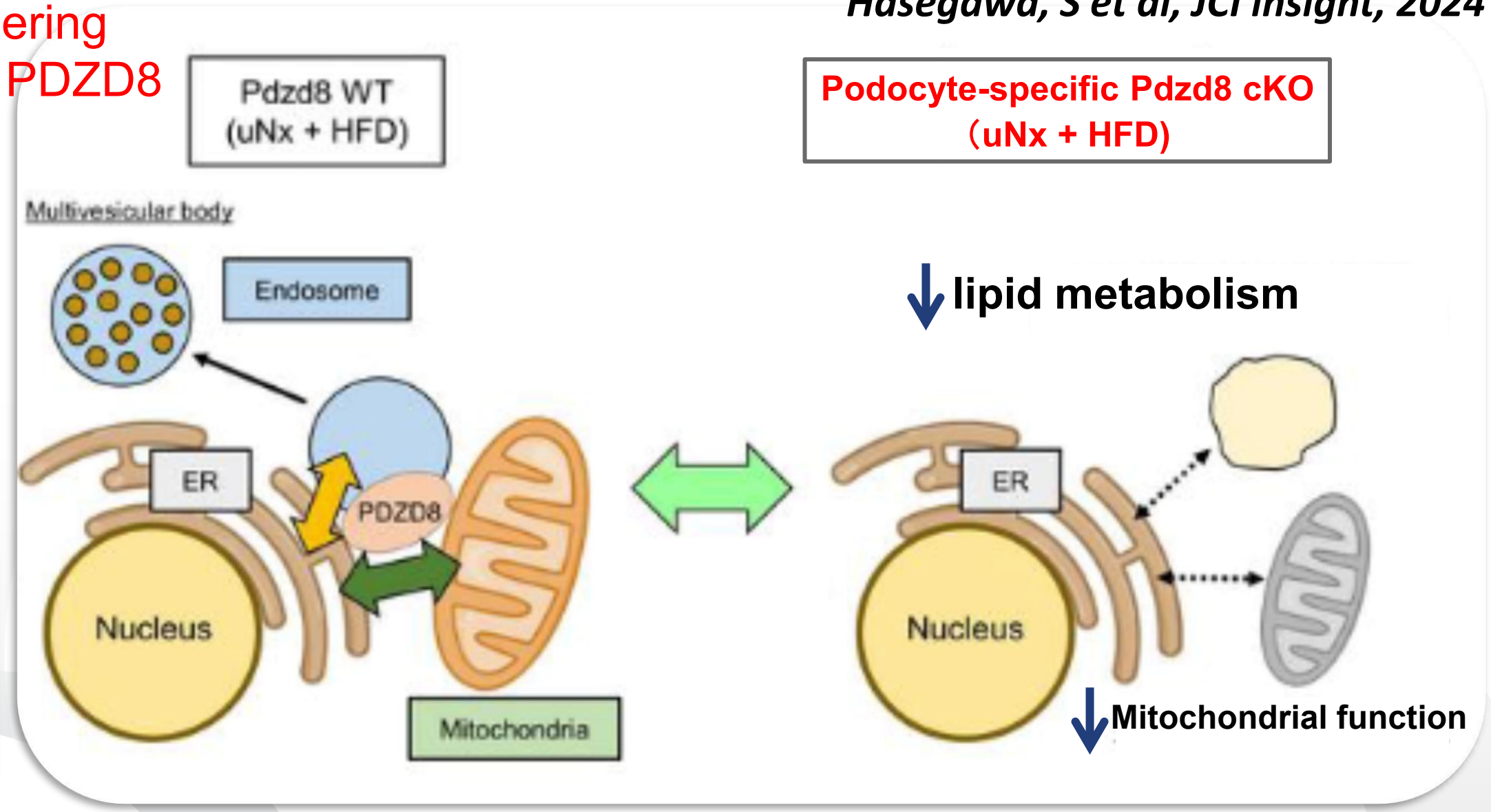




Organelle communication maintains mitochondrial and endosomal homeostasis during podocyte lipotoxicity

Hasegawa, S et al, JCI insight, 2024

◆ER tethering protein PDZD8



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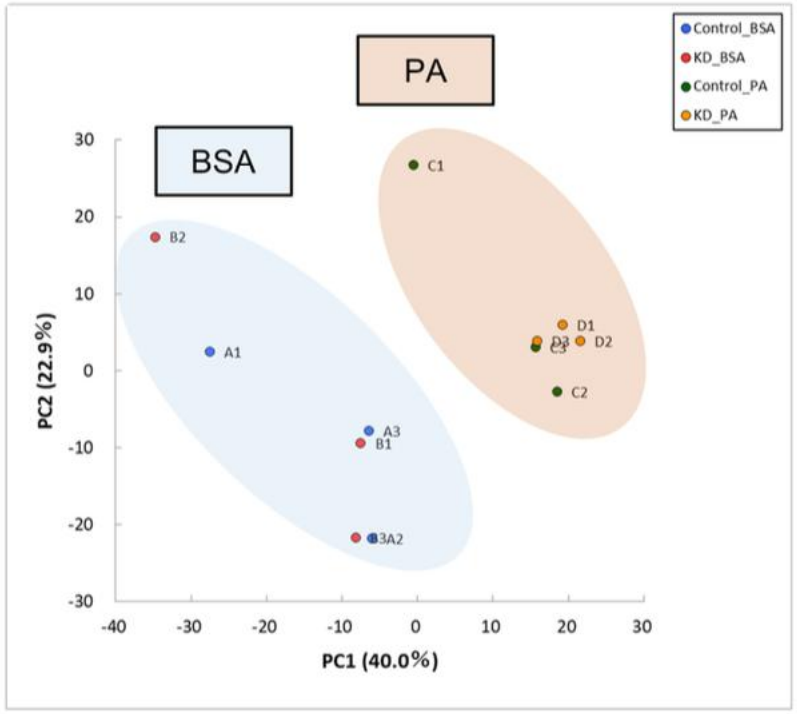
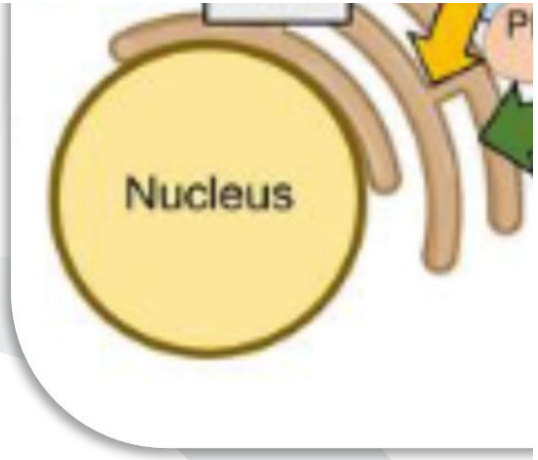


siControl_BSA siPdzd8_BSA siControl_PA siPdzd8_PA

Line	LipidMolec	Standardized Relative Area §											
		A1	A2	A3	B1	B2	B3	C1	C2	C3	D1	D2	D3
14	Hex1Cer(d18:2_24:0)	-1.499	-1.018	-0.270	0.988	1.675	0.582	-0.962	-0.529	-0.627	1.188	0.685	-0.211
15	GM3(d34:1)	-0.860	-0.614	-0.017	0.341	2.304	0.077	-1.522	-0.980	-0.403	0.336	0.602	0.736
16	Hex1Cer(d18:1_24:0)	0.070	-0.976	-1.049	0.992	2.065	0.162	-0.486	-1.269	-1.013	0.651	0.363	0.489
17	Hex1Cer(d18:1_22:0)	-0.701	-1.326	-0.694	1.043	1.476	0.017	-0.158	-1.162	-1.074	0.658	0.647	1.274
18	Hex1Cer(d17:1_24:0)	-0.424	-0.816	-1.038	1.391	1.126	0.248	-0.946	-1.319	-0.737	1.299	0.287	0.929
19	GM3(d42:2)	-0.686	-0.052	0.089	1.366	1.476	0.599	-1.800	-1.045	-1.053	0.056	0.277	0.771
20	GM3(d40:1)	-0.237	0.078	0.018	1.626	1.151	0.896	-2.018	-0.892	-1.090	0.100	0.311	0.058
21	Hex1Cer(d18:1_16:0)	-0.977	-0.707	-0.436	1.781	0.459	0.551	-1.271	-0.901	-0.991	0.656	0.656	1.182
22	Hex1Cer(d18:2_24:1)	-1.241	-1.138	-1.299	0.317	1.090	0.164	-0.131	-0.661	-0.670	1.173	1.120	1.275
23	Hex1Cer(d18:2_22:0)	-1.349	-1.417	-0.942	0.800	0.485	-0.122	-0.418	-0.272	-0.307	1.943	0.819	0.779
24	Hex1Cer(d18:1_20:0)	-0.426	-1.282	-0.324	-0.359	0.324	-0.171	-0.757	-0.767	-0.219	2.522	0.441	1.019
25	SPH(d18:2)	-0.150	-0.894	-0.618	1.493	-1.038	0.199	-1.280	-0.427	-0.352	1.132	1.789	0.147
26	DG(16:1_20:4)	-0.824	-0.937	-0.781	1.713	0.271	0.042	-0.251	-0.331	-1.187	1.885	0.750	-0.352
27	FA(26:0)	1.308	-0.743	-1.770	1.322	0.106	0.090	-0.607	-0.197	-1.111	1.033	0.980	-0.411
28	DG(14:0_14:0)	-1.481	0.649	0.706	0.396	-1.458	-0.190	-1.716	0.713	0.175	0.617	1.265	0.324

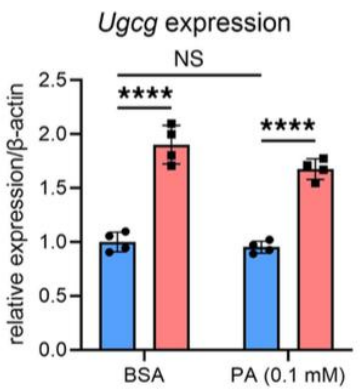


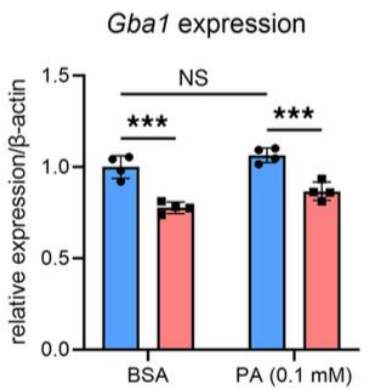
Glucosylceramide (Hex1Cer)

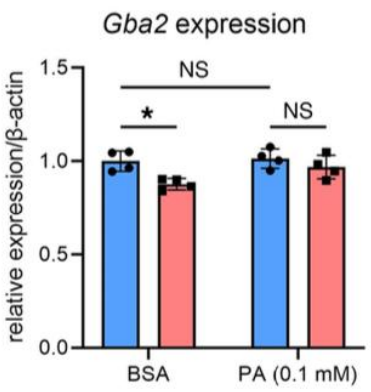
Glucosylceramide synthase (Ugcg)

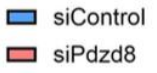
Glucocerebrosidase (Gba)

Ceramide









Take-home messages

- **Kidney cell phenotypic changes** are associated with metabolic dysregulation.
- **Organelle stress** alters metabolic homeostasis, contributing to kidney cell dysfunction.
- **Inter-organelle communication**, such as ER-mitochondria and ER-lysosome interactions, modulates kidney injury.
- **Targeting kidney metabolism** through organelle dynamics offers new strategies to combat kidney damage.

Acknowledgements

★The University of Tokyo

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Masaomi Nangaku
Hiroshi Nishi
Yosuke Hirakawa
Yoichiro Ikeda
Imari Mimura
Mai Sugahara
Shinji Tanaka

Cell Biology and Anatomy
Nobutaka Hirokawa
Yosuke Tanaka

Diabetes and Metabolic Diseases
Takashi Kadowaki
Naoto Kubota

Clinical Laboratory
Yutaka Yatomi
Makoto Kurano

Graduate School of Pharmaceutical Sciences
Junken Aoki
Kuniyuki Kano

★ Kyoto University
Kazutoshi Mori

★ Tohoku University
Masayuki Yamamoto
Norio Suzuki

東京大学 THE UNIVERSITY OF TOKYO
科研費 KAKENHI
COI STREAM
AMED

JSN welcomes back WCN after 1990 !!

Stay tuned !