INNOVAPATH™
The Premier Journal Bridging Discovery & Innovation

Letter to the Editor
https://doi.org/10.63501/w0pjbn38

Ionic Microdomains as Emerging Determinants of Compensatory Nephron Hypertrophy: A Novel Framework in Renal Cellular Signaling

Karan Chaman Lal[1,2], Ayesha Ubaid Ullah[3], Mishal Iqbal[3], Zainab Binte Tahir[3], Jepal Kumar[1]

[1]Department of Medicine, Liaquat University of Medical & Health Sciences, Jamshoro, Sindh, Pakistan.

[3]Department of Medicine, Islamic International Medical College, Rawalpindi, Punjab, Pakistan

[2]Corresponding Author Email: Karan.chaman12@gmail.com

KEYWORDS: *Ionic Microdomains, Compensatory Nephron Hypertrophy, Renal Cellular Signaling, mTOR, MAPK.*

Dear Editor,

Compensatory hypertrophy of the residual nephrons is a well-recognized physiological response following renal tissue loss or injury. This enables maintenance of overall renal function through increased tubular workload and nephron enlargement. Although these macroscopic adaptations have been described, the intracellular mechanisms that coordinate growth responses within surviving nephrons remain incompletely understood. Understanding their contribution could yield novel strategies to preserve renal function and identify early signs of maladaptive growth (1).

Ionic microdomains are regions of altered ion concentration adjacent to ion transporters or organellar membranes that modulate growth-related pathways, including mTOR (Mechanistic Target of Rapamycin) and MAPK Pathway (Mitogen-Activated Protein Kinase), through localized fluctuations in electrolytes such as calcium, phosphate, or magnesium, and serve as specialized regulators of hypertrophic cell signaling while preserving overall ionic homeostasis (2). The uncertainty whether comparable ionic microdomains exist provides a conceptual basis for further exploration.

Recent studies highlight the importance of ionic microdomains and suggest that these regions play a crucial role in cellular growth and survival by activating downstream pathways without disrupting the cell's overall ionic balance. A multi-omic approach demonstrates the significance of peroxisome proliferator-activated receptor alpha as a determinant of proximal tubule size cells (3). Calcium microdomains exist in cardiomyocytes, and, under stress, they induce cardiac cells to undergo hypertrophy by activating pathways such as CaMKI, mTOR, and MAPK (4). Drawing on this paradigm, a similar principle may operate in renal tubular cells, where ionic microdomains could locally activate phosphate- or magnesium-driven growth-related pathways, such as mTOR and MAPK, that trigger hypertrophic changes. However, while calcium-dependent microdomain signaling in renal cells is supported by emerging evidence, the involvement of phosphate- or magnesium-driven microdomains in activating growth-related pathways, such as mTOR or MAPK, remains speculative. At present, this concept should be regarded as a testable hypothesis that warrants targeted experimental validation rather than a confirmed mechanism. The study by Ning et al.

https://doi.org/10.63501/w0pjbn38

supports the relevance of calcium ionic signaling in the kidney. Calcium levels in the endoplasmic reticulum, mitochondria, and lysosomes are essential for normal cell function and survival, and their disruption leads to various renal diseases (5). Hence, these compartmentalized ionic signaling mechanisms can explain how nephrons can undergo compensatory hypertrophy when one part is damaged or removed.

Ion-sensitive fluorescence imaging and super-resolution microscopy can allow researchers to investigate ionic microdomains in renal tubular epithelial cells. Ion-sensitive fluorescence techniques allow the detection of localized ionic signaling within subcellular compartments, thereby enabling assessment of whether the proposed ionic changes occur in proximity to growth regulatory signaling nodes. In parallel, super-resolution microscopy enables nanoscale visualization of vesicle trafficking and signaling complexes that organize pathways such as mTOR and PI3K. Although ionic microdomains in the kidney have not been directly examined, earlier work has demonstrated that renal hypertrophy and kidney size are regulated by spatially organized mTOR signaling, vesicle trafficking, and PI3K pathway activity. This established compartmentalization of growth signaling provides preliminary evidence. Therefore, such techniques can help researchers understand the mechanisms of these ionic microdomains in renal tubular cells, thereby uncovering how these ionic zones may act as hidden regulators of kidney cell growth and repair.(2,6)

Microdomains are a modern concept that could revolutionize renal cellular biology, as disruptions in magnesium, phosphate, and calcium levels are linked to worse kidney outcomes. This phenomenon helps biophysicists and nephrologists by linking ionic microdomains to established growth pathways (e.g., mTOR, MAPK) and opening new avenues for inhibiting maladaptive hypertrophy in residual nephrons (7), thereby slowing the progression from adaptation to injury. At present, these insights remain largely experimental, but they provide a mechanistic foundation for future translational studies.

In conclusion, a novel approach to renal biology can be developed by identifying ionic microdomains as spatially confined regulators of hypertrophic signaling. Linking ionic gradients to growth pathways such as mTOR and MAPK, cellular biophysics, and nephrology is further corroborated. From a clinical perspective, this concept may eventually assist clinicians in earlier identification of maladaptive renal responses, although direct assessment of subcellular ionic microdomains is not yet feasible in routine practice. Future clinical translation may rely on surrogate biomarkers of tubular ion handling, molecular signatures of microdomain-related signaling, or advanced ion-sensitive imaging approaches. Importantly, a substantial gap remains between understanding subcellular ionic dynamics and developing clinically actionable tools. Future studies in the microdomain can help develop new molecular targets to prevent maladaptive hypertrophy and preserve renal function in chronic kidney disease.

Author's contributions:

Conceptualization, K.C.L.; Original Draft, K.C.L.; Literature Review, K.C.L., A.U.U., M.I., Z.B.T., J.K.; Writing - Review & Editing, K.C.L., A.U.U., M.I., Z.B.T., J.K.; Final Approval, K.C.L., A.U.U., M.I., Z.B.T., J.K.

Declaration of Interests:

The authors declare no conflict of interest.

Funding: Not applicable

https://doi.org/10.63501/w0pjbn38

Acknowledgments:

The authors declare no acknowledgments.

REFERENCES:

1. McArdle Z, Schreuder MF, Moritz KM, Denton KM, Singh RR. Physiology and Pathophysiology of Compensatory Adaptations of a Solitary Functioning Kidney. Front Physiol [Internet]. 2020 Jun 26 [cited 2025 Oct 28];11:725. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC7332829/
2. Al-Awqati Q. Kidney growth and hypertrophy: the role of mTOR and vesicle trafficking. J Clin Invest [Internet]. 2015 Jun 1 [cited 2025 Oct 28];125(6):2267. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC4497766/
3. Kikuchi H, Chou CL, Yang CR, Chen L, Jung HJ, Park E, et al. Signaling mechanisms in renal compensatory hypertrophy revealed by multi-omics. Nat Commun [Internet]. 2023 Dec 1 [cited 2025 Oct 28];14(1). Available from: https://pubmed.ncbi.nlm.nih.gov/37328470/
4. Tanaka S, Fujio Y, Nakayama H. Caveolae-specific CaMKII signaling in the regulation of voltage-dependent calcium channel and cardiac hypertrophy. Front Physiol [Internet]. 2018 Aug 7 [cited 2025 Oct 28];9(AUG):391436. Available from: https://doi.org/10.1080/15548627.2015.1052208
5. Ning B, Guo C, Kong A, Li K, Xie Y, Shi H, et al. Calcium Signaling Mediates Cell Death and Crosstalk with Autophagy in Kidney Disease. Cells 2021, Vol 10, Page 3204 [Internet]. 2021 Nov 17 [cited 2025 Oct 28];10(11):3204. Available from: https://www.mdpi.com/2073-4409/10/11/3204/htm
6. Chen JK, Nagai K, Chen J, Plieth D, Hino M, Xu J, et al. Phosphatidylinositol 3-kinase signaling determines kidney size. J Clin Invest [Internet]. 2015 Jun 1 [cited 2025 Oct 28];125(6):2429–44. Available from: https://pubmed.ncbi.nlm.nih.gov/25985273/
7. Denic A, Alexander MP, Kaushik V, Lerman LO, Lieske JC, Stegall MD, et al. Detection and Clinical Patterns of Nephron Hypertrophy and Nephrosclerosis Among Apparently Healthy Adults. Am J Kidney Dis [Internet]. 2016 Jul 1 [cited 2025 Oct 28];68(1):58. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC492125