SM Journal of Nephrology and Kidney Diseases ISSN: 2576-5450

Review Article

Renal Fibrosis: A Peripheral Prionopathy?

Wen-Quan Zou*, Yirong Yang

Institute of Neurology, Jiangxi Academy of Clinical Medical Sciences, The First Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang 330006, Jiangxi Province, China

INTRODUCTION

Renal fibrosis, the common pathological endpoint of Chronic Kidney Disease (CKD), represents a global health challenge due to its high prevalence and limited therapeutic options [1]. Despite its clinical significance, the molecular mechanisms driving this process remain poorly understood. In a landmark cover study published in Science Translational Medicine, Long et al. identified a novel mechanism by which cellular prion protein (PrP^C) drives renal fibrosis through Liquid-Liquid Phase Separation (LLPS). Their work reveals that PrP^C forms pathologically active biomolecular condensates, which aberrantly activate the TBK1–IRF3 signaling axis, establishing a critical link between phase separation and fibrotic disease progression [2]. Meanwhile, the team identified Amlexanox—a clinical-stage inhibitor of TBK1-IRF3—as a promising therapeutic candidate (Figure 1). This work not only establishes PrP^C-LLPS as a key regulator of fibrosis but also proposes a translational strategy: targeting the PrP^C-TBK1-IRF3 axis could address current treatment gaps. The repurposing potential of Amlexanox may accelerate drug development for CKD.

PrP^C, a glycosylphosphatidylinositol (GPI)-anchored cell-surface glycoprotein, is best known for its role in prion diseases, fatal neurodegenerative disorders caused by its misfolded isoform, PrP^{Sc} [3]. While the physiological functions of PrP^C remain incompletely defined, emerging evidence suggests a protective role in ischemia-reperfusion injury (Figure 2). For example, wild-type mice exhibit significantly smaller infarct sizes in ischemic tissues compared to PrP gene (*PRNP*) knockout mice, attributed to PrP^C-mediated activation of ERK1/2 signaling and antioxidant responses (e.g., heme oxygenase-1 induction) [4-6]. However, it is noteworthy that its misfolded isoform PrP^{Sc}, as a nucleic acid-free infectious pathogen, has been identified as the pathogenic core of classical cerebral prion diseases, with its pathological manifestations currently observed exclusively in the central nervous system (Figure 2) [7]. The current findings from Long et al have for the first time revealed a mechanism by which the PrP^C condensate induces pathological alterations in peripheral organs through a possible non-PrP^{Sc} form (Figure 2).

This discovery raises three critical questions: 1) Subcellular localization of PrP^C condensates: In classical prion diseases, PrP^C-PrP^{Sc} conversion occurs mainly at cellular membranes [8]. However, the precise site (plasma membrane vs. cytoplasm) of PrP^C condensate formation in renal tubules remains unresolved. 2) Transmissibility of fibrosis-associated PrP^C aggregates: PrP^{Sc} aggregates in prion diseases exhibit infectivity and seeding activity in brain, cerebrospinal fluid, and skin [3,9]. Whether renal PrP^C aggregates in the kidney possess similar transmissible properties requires rigorous interdisciplinary validation. 3) Generalizability to other fibrotic disorders: It remains unclear whether PrP^C contributes to fibrosis in organs such as the liver or lungs. Addressing this could redefine fibrotic pathogenesis and introduce the concept of "peripheral-type prionopathy." By bridging prion biology and fibrotic disease mechanisms, this study opens new frontiers for understanding protein misfolding disorders and developing therapies for CKD and beyond.

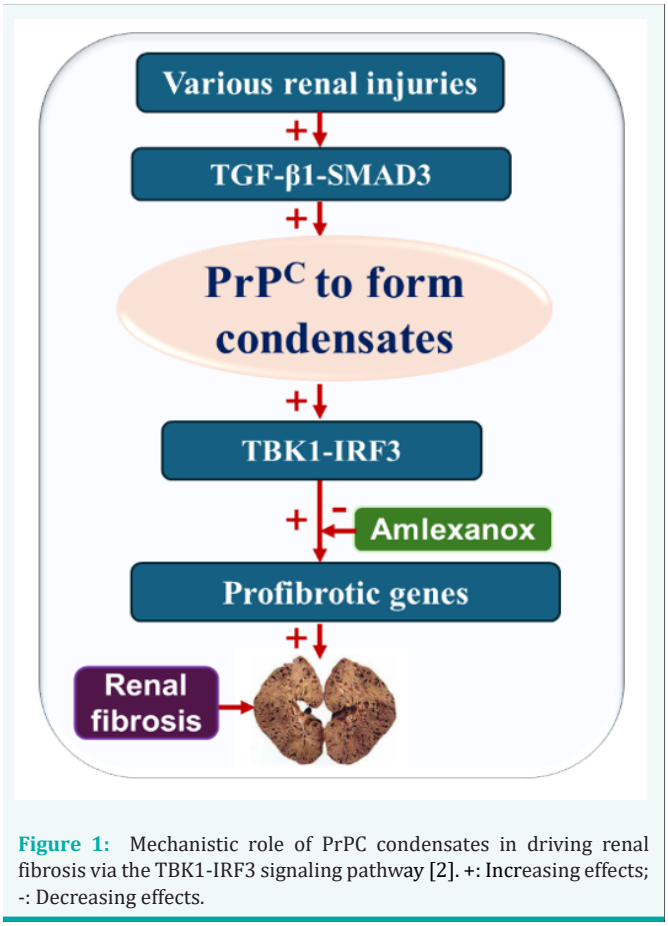

Figure 1: Mechanistic role of PrPC condensates in driving renal fibrosis via the TBK1-IRF3 signaling pathway [2]. +: Increasing effects; -: Decreasing effects.

Submitted: 23 August 2025 | **Accepted:** 24 August 2025 | **Published:** 29 August 2025

***Corresponding author:** Wen-Quan Zou, Institute of Neurology, Jiangxi Academy of Clinical Medical Sciences, The First Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi Province 330006, China.

Citation: Zou W, Yang Y (2025) Renal Fibrosis: A Peripheral Prionopathy?. J Nephrol Kidney Dis 6(1): 2.

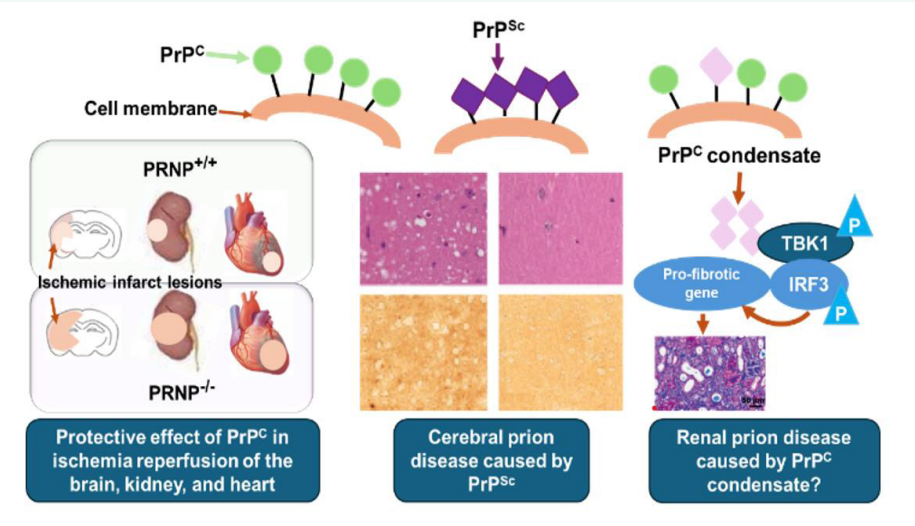

Figure 2: Schematic overview of PrP^{C}, PrP^{Sc}, and PrP^{C} condensates: dual physiological and pathophysiological roles across central and peripheral organ systems. The solid blue triangle with an enclosed 'P' denotes phosphorylation of the associated molecule.

REFERENCE

1. Abbad L, Esteve E, Chatziantoniou C. (2025). Advances and challenges in kidney fibrosis therapeutics. Nat Rev Nephrol. 21: 314-329.
2. Long T, Lu Y, Ma Y, Song Y, Yi X, et al. (2025). Condensation of cellular prion protein promotes renal fibrosis through the TBK1-IRF3 signaling axis. Sci Transl Med. 17: 794.
3. Prusiner SB. (1998). Prions. Proc Natl Acad Sci U S A. 95: 13363-83.
4. Spudich A, Frigg R, Kilic E, Kilic U, Oesch B, et al. (2005). Aggravation of ischemic brain injury by prion protein deficiency: role of ERK-1/-2 and STAT-1. Neurobiol Dis. 20: 442-449.
5. Zhang B, Cowden D, Zhang F, Yuan J, Siedlak S, et al. (2015). Prion Protein Protects against Renal Ischemia/Reperfusion Injury. PLoS One. 10: e0136923.
6. Zanetti F, Carpi A, Menabò R, Giorgio M, Schulz R, et al. (2014). The cellular prion protein counteracts cardiac oxidative stress. Cardiovasc Res. 104: 93-102.
7. Gambetti P, Kong Q, Zou W, Parchi P, Chen SG. (2003). Sporadic and familial CJD: classification and characterisation. Br Med Bull. 66: 213-239.
8. Poggiolini I, Saverioni D, Parchi P. (2013). Prion protein misfolding, strains, and neurotoxicity: an update from studies on Mammalian prions. Int J Cell Biol. 2013: 910314.
9. Orrú CD, Yuan J, Appleby BS, Li B, Li Y, et al. (2017). Prion seeding activity and infectivity in skin samples from patients with sporadic Creutzfeldt-Jakob disease. Sci Transl Med. 9: 417.