Cellular and Molecular Life Sciences (2023) 80:115
https://doi.org/10.1007/s00018-023-04749-0

COMMENTARY

circPTPN14 promotes renal fibrosis through its interaction with FUBP1 to enhance *MYC* transcription

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Received: 1 February 2023 / Accepted: 6 March 2023 / Published online: 4 April 2023

Abstract

CircRNAs are a class of single-stranded molecules with tissue/development-specific expression patterns. Increasing evidence demonstrates that circRNAs play important roles in physiological or pathological conditions. Here, we provide a brief discussion of circRNA in renal fibrosis.

Keywords Circular RNA · Renal fibrosis · MYC · FUBP1

Renal fibrosis is a chronic and progressive process and the common consequence of almost all chronic kidney diseases, causing structural and functional impairment of the kidney. However, there are currently no therapeutic approaches that can slow or reverse renal fibrosis. Therefore, understanding its underlying mechanisms is of great importance to delay the progression and protect renal function in patients with renal fibrosis. A recent study by Nie et al. discovered the crucial role of circular RNA (circRNA) in renal fibrosis [1], providing new insights into the diagnosis and treatment of chronic kidney diseases.

Renal fibrosis is characterized by excessive deposition of extracellular matrix (ECM) components, such as collagen and fibronectin, leading to sclerosis of the kidney and loss of renal function. Increasing investigations demonstrate that multiple signaling pathways including transforming growth factor (TGF)-β and Wnt participate in renal fibrosis through regulating expression of protein-encoding genes and non-coding RNAs (ncRNAs) [2]. CircRNAs are a class of ncRNA molecules with a covalently closed loop structure formed by back-splicing, which lack the 5′ and 3′ ends and are resistant to RNA exonucleases. Therefore, circRNAs are more stable than linear RNAs and can serve as novel diagnostic and prognostic biomarkers [3]. Numerous studies indicate that circRNAs regulate gene expression at transcriptional and/or post-transcriptional levels through binding to proteins/miRNAs or encoding small functional peptides. This study by Nie et al. employed two well-recognized mouse models for renal fibrosis (induced by ischemia–reperfusion (IR) or unilateral ureteral obstruction (UUO)) and performed high-throughput RNA-seq to identify that circPTPN14 (circbase ID: mmu_circ_0000130, hsa_circ_0007015) was significantly elevated in both renal fibrosis models. Moreover, such upregulation was further confirmed by fluorescence in situ hybridization (FISH) assays in TGFβ1-stimulated renal tubular epithelial cells (TECs) and human kidneys with biopsy-proved chronic interstitial fibrosis, suggesting that circPTPN14 could exacerbate renal fibrosis and serve as a therapeutic target.

To test this, the authors designed short hairpin RNA (shRNA) for circPTPN14 and packed it into AAV9 for in vivo delivery. The results demonstrate that interference of circPTPN14 significantly decreased the expression of pro-fibrotic genes (α-SMA, collagen I and fibronectin) and dramatically ameliorated IR or UUO-induced kidney injury and fibrosis in mice, confirming the essential role of circPTPN14

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This letter refers to the article available at https://doi.org/10.1007/s00018-022-04603-9.

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in renal fibrosis and highlighting the potential of targeting circPTPN14 for fibrosis therapy. Moreover, in human kidney cells, knockdown of circPTPN14 significantly reduced TGFβ1-induced expression of pro-fibrotic genes while circPTPN14 overexpression exhibited the opposite effects, indicating that circPTPN14 promotes TGFβ1-induced fibrosis in TECs. Taken together, circPTPN14 aggravates renal fibrosis through activating expression of pro-fibrotic genes.

The transcription factor MYC was reported to be significantly upregulated during renal fibrosis and promotes the development of fibrosis through activation of TGF-β signaling [4]. However, the molecular mechanism underlying MYC regulation in fibrosis remains unclear. This study by Nie et al. revealed how circPTPN14 positively regulates MYC expression [1]. circPTPN14 was found to bind to both KH3 and KH4 domains of the far upstream element (FUSE) binding protein 1 (FUBP1), a protein regulating *MYC* transcription through binding to the FUSE domain in the upstream of *MYC* promoter [5]. Furthermore, circPTPN14 binds to FUBP1 to enhance the interaction between FUBP1 and FUSE, thus promoting *MYC* transcription, which in turn exacerbates renal fibrosis. Probably, binding of circPTPN14 to FUBP1 confers a favorable protein conformation of FUBP1 to interact with FUSE. But this issue needs more investigation to prove it. Notably, the positive correlation between circPTPN14 and MYC expression was validated in the pathogenesis of renal fibrosis in mice models and human clinical samples, confirming the important role of circPTPN14-MYC axis during renal fibrosis progression in vivo.

There are some open questions worthy of intensive study. For example, what is the role of circPTPN14 in liver fibrosis and lung fibrosis? Although the kidney, liver and lung are greatly different in terms of structure and function, fibrosis in these organs has similar pathological mechanisms, such as activation of TGF-β and abnormal deposition of ECM [6]. Moreover, circBNC2 was reported to alleviate extracellular matrix deposition in both kidney fibrosis and liver fibrosis [7]. Therefore, circPTPN14 could exert similar functions in epithelial organ fibrosis. In addition, what is the potential of circPTPN14 as a liquid biopsy marker? Liquid biopsy is a non-invasive diagnostic method to analyze the components of body fluids (e.g., blood and urine) and exhibits promising applications in the detection of diseases such as cancer [8] and fibrosis [9]. CircRNA was found to be enriched and stable in exosomes, becoming an attractive biomarker for liquid biopsy [10]. We previously reported that F-circEA derived from the *EML4-ALK* fusion gene specifically exists in the plasma of lung cancer patients harboring this fusion gene, and could be a liquid biopsy marker for the diagnosis of *EML4-ALK*-positive lung cancer patients [11]. Kidney biopsy is currently the gold standard for assessment of renal fibrosis. However, traditional tissue biopsies are accompanied by potential problems such as bleeding and infection. Since circPTPN14 was highly expressed in biopsy-proven renal fibrosis samples, it is worth investigating whether or not circPTPN14 exists in blood or urine. If so, whether the circPTPN14 level in blood or urine elevates during renal fibrosis. Thus, the development of blood- and urine-based liquid biopsy techniques is of great clinical significance for the diagnosis of renal fibrosis.

In summary, the work by Nie et al. identified the essential role of circPTPN14 in the process of renal fibrosis, elucidated the molecular mechanism by which circPTPN14 promotes renal fibrosis through enhancing *MYC* transcription, revealed the potential of circPTPN14 as a molecular target for renal fibrosis treatment. What is more, the authors demonstrated that the interaction of circPTPN14 and FUBP1 enhances the binding of FUBP1 to FUSE domain, leading to increased *MYC* transcription. Therefore, this study provides new insights of how circRNA transcriptionally regulates gene expression.

Acknowledgements This work was supported by Science and Technology Program of Sichuan Province (2022NSFSC0761, 2022ZYD0128, 2022YFS0046 and 2021YJ0444), Chengdu Medical College Research Foundation (KYPY22-02), and the 1.3.5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (ZYGD20008).

Author contributions JKZ and JL wrote the manuscript, and YP revised the manuscript.

Funding Funding was supported by Sichuan Province Science and Technology Support Program (2022NSFSC0761, 2022ZYD0128, 2022YFS0046, 2021YJ0444), Chengdu Medical College Research Foundation (KYPY22-02), West China Hospital, Sichuan University (ZYGD20008).

Availability of data and materials Not applicable.

Declarations

Conflict of interest The author declares that there is no conflict of interest.

Consent for publication We give our consent for the publication.

Ethics approval and consent to participate Not applicable. This study does not involve experiments on humans and animals.

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