

Tau, a microtubule-associated protein, is upregulated and promotes kidney damage in chronic kidney disease

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Background: Tau, a microtubule-associated protein, has a well-established role in neurodegenerative disorders, but its function in the kidney and contribution to chronic kidney disease (CKD) remain unclear. Although emerging data suggest the role of tau in CKD pathogenesis, the mechanisms of tau-mediated renal injury are not well defined. In this context, we investigated tau expression in CKD and its potential link to disease progression.

Methods: Tau protein levels were measured in kidneys from CKD patients and three murine CKD models: unilateral ureteral obstruction (UUO), folic acid-induced CKD (FA-CKD), and adenine diet-induced CKD (AD-CKD). Renal functional and histological parameters were assessed. Disease progression was further evaluated in P301S tau transgenic mice. To assess potential therapeutic effects, a tau-specific antibody was administered to the AD-CKD mouse model.

Results: Expression of tau—including total, phosphorylated, and acetylated forms—was markedly elevated in the kidneys of CKD patients and across all three CKD mouse models (UUO, FA-CKD, and AD-CKD). This elevation correlated with worsening renal function, tubular injury, and kidney fibrosis. Tau was upregulated as CKD progressed, and was predominantly observed in proximal tubular epithelial cells, but was also detected in glomerular podocytes and mesangial cells. In tau transgenic mice, tau accumulation worsened renal dysfunction and pathological changes, while administering a tau-specific antibody in AD-CKD mice reduced renal tau levels and improved both tubular dilatation and fibrosis.

Conclusion: Tau is upregulated during CKD progression and contributes to tubular injury and fibrosis. Targeting tau could offer a new therapeutic approach for reducing renal injury in CKD.

Keywords: Chronic kidney disease, Microtubule-associated proteins, Tau proteins, Tubular injury, Kidney fibrosis

Introduction

In chronic kidney disease (CKD), maladaptive responses to injury, such as chronic inflammation, drive the persistent activation of proinflammatory signaling pathways. This ul-

timately leads to irreversible tissue fibrosis and organ failure. This state arises from various underlying conditions, including hypertension, diabetes mellitus, and glomerulonephritis, with oxidative stress, proinflammatory cytokines, and cellular signaling pathways playing central roles in dis-

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ease progression [1,2]. Accordingly, research efforts are focused on identifying therapeutic strategies that target these molecular mediators to mitigate CKD progression [3,4]. Despite the rising global prevalence of CKD, effective treatment options remain limited, largely due to an incomplete understanding of intermediary pathological mechanisms. Therefore, elucidating the molecular pathways underlying CKD pathophysiology is essential for developing novel therapeutic interventions.

Tau protein belongs to the microtubule-associated protein family and is evolutionarily conserved across species, with its dysfunction—particularly through hyperphosphorylation—implicated in neurodegenerative diseases [5]. It is predominantly localized in the axons of healthy neurons, where it binds to microtubules and enhances cytoskeletal stability. In humans, tau is encoded by a specific gene on chromosome 17 comprising 16 exons [6]. Through alternative splicing, six tau isoforms are generated and are predominantly expressed in the central nervous system. In contrast, a distinct, larger isoform—commonly referred to as big tau—is primarily expressed in the peripheral nervous system. To date, however, no experimental evidence has demonstrated big tau expression in kidney tissues, suggesting that tau isoform distribution in the kidney may differ fundamentally from that in neural tissues. Notably, tau undergoes phosphorylation as part of normal structural remodeling, but when this process is excessively triggered by pathological stimuli, it can promote abnormal aggregation and contribute to the development of neurodegenerative diseases or tauopathies [7,8].

Degenerative neurological diseases such as Alzheimer disease and Parkinson disease share a common trait: certain proteins undergo abnormal structural changes through cellular and molecular biological mechanisms, leading to their aggregation and formation of inclusions. While amyloid- β has been the focus of much research in neurodegenerative disease, there is currently active research on tau protein, including research on tauopathies caused by posttranslational modifications of tau protein without alterations in amyloid [9].

CKD has been increasingly recognized for its significant association with neurodegenerative diseases. By analyzing data from elderly patients who undergo hemodialysis, sourced from the United States Renal Data System, it has been discovered that one out of every nine patients will re-

ceive a dementia diagnosis within 10 years of commencing dialysis with the mortality rate more than doubling [10]. Given that amyloid- β and tau proteins have been identified as key pathological factors in neurodegenerative diseases, it has been suggested that the CKD-associated systemic environment might contribute to tau protein dysfunction within the central nervous system [11–14].

However, the role of tau protein in kidney pathology and its involvement in CKD progression remain poorly understood [15]. Therefore, this study aimed to investigate alterations in tau protein expression in injured kidneys and to determine how tau regulation influences the progression of CKD.

Methods

Human samples

This study received approval (2023-12-052) from the Institutional Review Board (IRB) of Soonchunhyang University Cheonan Hospital (Cheonan, Korea), and the requirement for obtaining informed consent was waived due to the retrospective nature of the study.

Kidney tissues were obtained from six patients who underwent nephrectomy for medical indications, with control tissues derived from non-tumorous regions of the resected kidneys. Clinical data, including age, sex, estimated glomerular filtration rate (eGFR, calculated using the CKD-EPI [Chronic Kidney Disease Epidemiology Collaboration] equation [16]), urinary specific gravity, and dipstick proteinuria, are summarized in [Supplementary Table 1](#) (available online). Tau protein expression in renal tissues was assessed by immunohistochemistry (IHC) and independently reviewed by a renal pathologist (JHL).

In addition, we analyzed a publicly available single-cell RNA sequencing dataset (GSE183276), comprising over 400,000 nuclei or cells across 51 kidney cell types from both healthy and CKD human samples [17]. As this dataset is fully de-identified and publicly accessible, no additional IRB approval was required. Data were reanalyzed and visualized using the Seurat package (version 5.3.0) in R (R Foundation for Statistical Computing), with original cell type annotations retained without modification.

Animal study

All animal procedures were approved by the Institutional Animal Care and Use Committee of Soonchunhyang University (No. SCH20-0058, SCH21-0038, SCH22-0039) and conducted in accordance with ethical guidelines.

Male C57BL/6 mice (7 weeks old) were used in three CKD models: unilateral ureteral obstruction (UUO), folic acid (FA)-induced CKD (FA-CKD), and adenine diet (AD)-induced CKD (AD-CKD). UUO was implemented by triple-ligating the left ureter, with sacrifice performed on day 6. FA-CKD mice received a single intraperitoneal (i.p.) FA injection (250 mg/kg; Sigma-Aldrich) and were sacrificed on day 7. AD-CKD mice were fed a 0.2% AD (TD.150071; 0.6% Ca, 0.36% P; Envigo) for 1, 2, or 4 weeks. Food and water intake, body weight, and urine volume (24-hour collection via metabolic cages) were monitored. Blood was collected at sacrifice, and kidneys were harvested and stored at -80°C . In this study, the term AD-CKD specifically refers to mice subjected to a 7-day AD to induce CKD, whereas mice maintained on a regular diet or fed adenine for 1, 2, or 4 weeks are described as the regular diet or AD groups, respectively.

P301S tau transgenic mice (B6; C3-Tg(Prnp-MAPT*P301S)PS19Vle/J, JAX #008169; JAX) were subjected to 7 days of adenine feeding. Although prion promoter-driven transgene expression is low in kidneys, tau expression was confirmed by IHC and western blotting.

For therapeutic evaluation, AD-CKD mice were administered an acetylated tau (ac-Tau)-specific antibody (50 mg/kg, i.p.) on days 1, 3, and 6. Control + immunoglobulin G (IgG) mice were administered an isotype control antibody (Cat# BE0083; Bio X Cell).

Blood samples were collected into serum separator tubes (BD #365967, BD), centrifuged, and stored at -80°C . Levels of blood urea nitrogen (BUN) (K024-H1; Arbor Assays), creatinine (K625-100; BioVision), cystatin C (RD291009200R; BioVendor), and tau (MBS015010; MyBioSource) were measured according to the manufacturers' protocols.

Urine samples were centrifuged and stored at -80°C before analysis for albumin (Albuwell M; Exocell), creatinine (Creatinine Companion; Exocell), neutrophil gelatinase-associated lipocalin (NGAL) (MLCN20; R&D Systems), and tau (MBS015010) using enzyme-linked immunosorbent assay (ELISA) kits. Absorbance readings were obtained ac-

cording to the manufacturers' instructions, with dilutions applied as specified.

Histopathological analysis

At sacrifice, kidney tissues were immediately fixed in 10% neutral-buffered formalin. Periodic acid-Schiff (PAS) staining was used to assess histological morphology, and Masson's trichrome (MT) and Sirius Red staining were performed to evaluate fibrosis. Fixed tissues were embedded in labeled cassettes and processed using a Myr STP120 Spin Tissue Processor for 13 hours. Paraffin-embedded samples were sectioned at 3 μm thickness (Finesse ME Microtome; Thermo Shandon), mounted, deparaffinized, and washed with distilled water. Images were captured using a Leica DMI8 microscope. Tubular injury score was assessed based on tubular dilation, atrophy, cast formation, vacuolization, degeneration, epithelial cell sloughing, brush border loss, and thickening of the tubular basement membrane. The severity of tubular injury was scored as follows: 0, no injury; 1, $\leq 10\%$ injury; 2, 11%–25%; 3, 26%–50%; 4, 51%–74%; 5, $\geq 75\%$ [18,19].

Immunostaining and image analysis

Kidney sections (3 μm thick) were deparaffinized and processed for IHC or immunofluorescence (IF) staining. For IHC, a Novolink polymer detection system (#RE7290-CE; Leica) and 3,3'-diaminobenzidine (DAB) were used, with hematoxylin for nuclear counterstaining. For IF staining, the same protocol was applied as for IHC, except that Alexa Fluor 488-conjugated secondary antibodies (Invitrogen, Thermo Fisher Scientific) were used instead of polymer. Detailed information on all primary and secondary antibodies—including host species, catalog numbers, and dilutions—is provided in [Supplementary Tables 2, 3](#) (available online). Antibody specificity was confirmed by peptide blocking using a tau peptide blocker (#MBS154000; MyBioSource). Images were acquired under consistent conditions. IHC quantification was performed using ImageJ software (National Institutes of Health) under consistent imaging conditions. DAB-positive areas were extracted using the Color Deconvolution plugin with a fixed threshold based on negative controls. For human kidneys, 10 glomerular and 10 tubular regions of interest (ROIs) per slide (20

fields/sample) were analyzed; for mouse kidneys, 5–10 representative images per mouse were evaluated. Total DAB intensity was normalized to ROI area and expressed as a fold change relative to the control mean. All analyses were performed blinded to group allocation.

Quantitative reverse transcription polymerase chain reaction

Total RNA was extracted from kidney tissues using TRIzol (Sigma-Aldrich). Complementary DNA was synthesized from 1 µg of total RNA using ReverTra Ace qPCR RT Master Mix with gDNA Remover (TOYOBO). Quantitative reverse transcription (RT) polymerase chain reaction (PCR) was performed using SYBR Green PCR Master Mix (Applied Biosystems) on ABI PRISM 7900HT (Applied Biosystems). Isoform-specific primer sequences are listed in [Supplementary Table 4](#) (available online).

Western blot

Frozen mouse kidney tissues were lysed in radioimmuno-precipitation assay buffer with protease and phosphatase inhibitors (#04-906-845-001; Roche). Protein concentrations were quantified by Bradford assay, separated by 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis, transferred to polyvinylidene fluoride membranes, blocked with 5% bovine serum albumin, and incubated overnight at 4 °C with primary antibodies. Detection was via horseradish peroxidase-conjugated secondary antibodies and enhanced chemiluminescence reagents. Antibody details are in [Supplementary Tables 2, 3](#) (available online).

Statistical analysis

Statistical data were analyzed using Microsoft Excel and GraphPad Prism software. Data are presented as mean ± standard error of the mean. Group comparisons were performed using the Student t tests or one-way analysis of variance, as appropriate, with statistical significance set at $p < 0.05$.

Results

Tau protein expression is increased in human chronic kidney disease

Kidney tissue samples from normal control (Control) and fibrosis (CKD) cases were obtained from nephrectomies. Compared with controls, CKD patients exhibited reduced eGFR and increased renal tubular dilatation ([Fig. 1A](#)) and phosphorylated tau (p-Tau) and total tau (t-Tau) expressions ([Fig. 1B, C](#)). p-Tau immunostaining showed no obvious expression in any part of the kidney, including glomeruli, proximal tubules, distal tubules, interstitium, or vascular compartment in the control group. However, in CKD compared to controls, p-Tau expression was slightly increased in all compartments, especially in the proximal tubule ([Fig. 1A, B](#)). t-Tau expression was observed in the glomeruli and proximal tubules in the control group, but there was no t-Tau expression in the distal tubules, interstitium, and vascular compartment. Meanwhile, t-Tau expression in CKD was significantly increased in both glomeruli and proximal tubules, while it remained continuously negative in distal tubules and interstitium. Although t-Tau staining was observed in blood vessels in one CKD sample, t-tau staining was negative in most blood vessels. At higher magnification, CKD kidneys showed increased p-Tau and t-Tau expression within glomerular podocytes and mesangial cells ([Fig. 1A, B](#)).

To complement these observations, we analyzed a publicly available single-cell RNA sequencing dataset (GSE183276) comprising over 400,000 nuclei across 51 kidney cell types. Tau expression was predominantly enriched in proximal tubular epithelial cells and also detected in podocytes and mesangial cells ([Supplementary Fig. 1A](#), available online). This dataset further suggested a trend toward increased expression in the interstitium and decreased expression in the vascular compartment in CKD compared to controls; however, these differences were not statistically significant, and tau-positive cells in these compartments accounted for <2% of the total, indicating overall expression was very limited. Despite minor variability among samples, tau staining intensity in proximal tubules was consistently elevated across CKD cases ([Supplementary Fig. 1B](#), available online). Quantitative analysis confirmed significantly increased tau expression in CKD

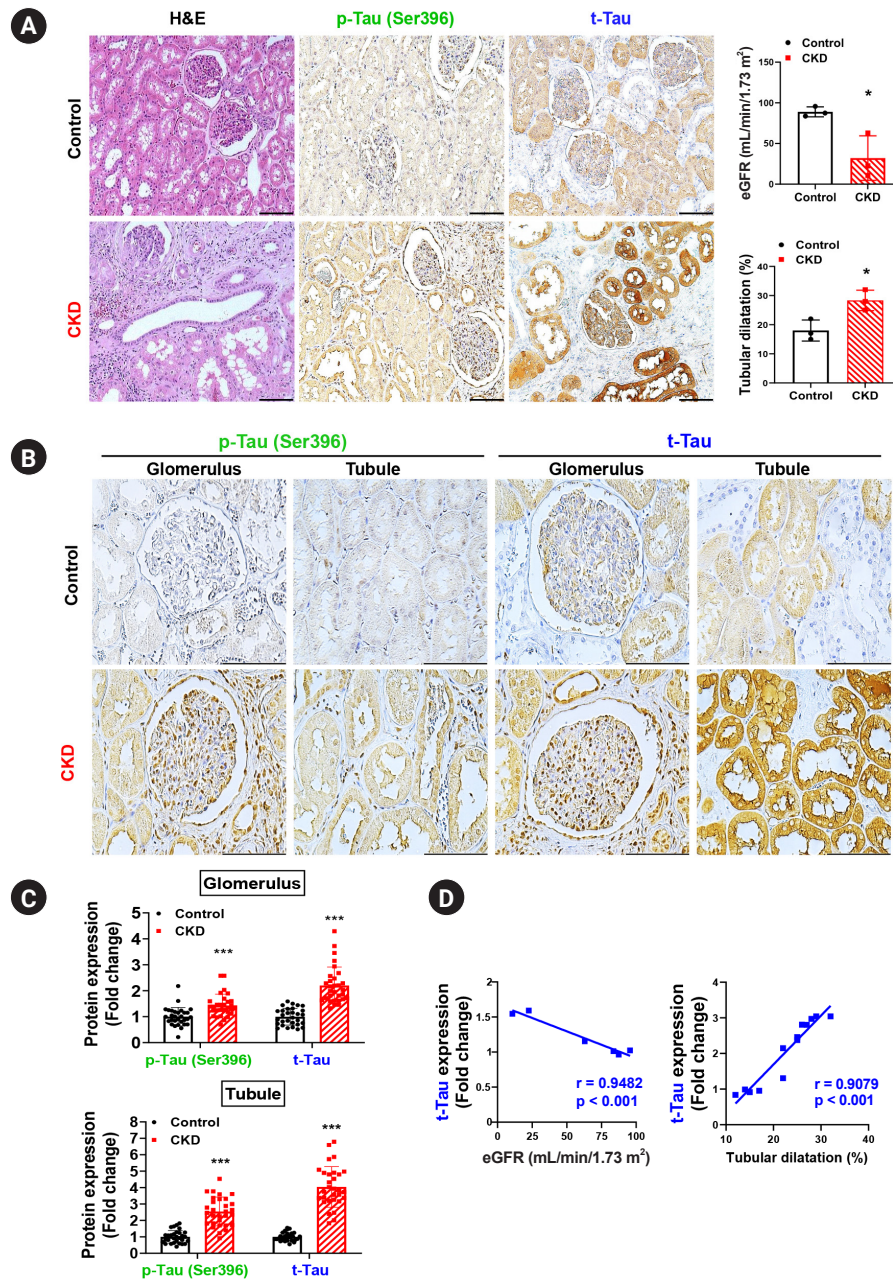


Figure 1. Renal tau expression is significantly elevated in patients with CKD. The expression of tau protein in human kidneys was confirmed by immunohistochemistry (IHC) using paraffin-embedded kidney samples from normal control (Control, $n = 3$) and fibrosis (CKD, $n = 3$) tissues obtained from nephrectomies (scale bar, 100 μ m). (A) Representative image of hematoxylin and eosin staining (H&E) showing tubular dilatation, and representative IHC staining for phosphorylated tau (p-Tau; Ser396) and total tau (t-Tau; Tau5) in kidney slides from CKD patients. (B, C) Paraffin-embedded kidney samples from normal control (Control) and fibrosis (CKD) kidney tissues were stained for p-Tau (Ser396) and t-Tau. For each sample, 10 glomeruli and 10 tubular areas were randomly selected, resulting in 30 glomeruli and 30 tubules analyzed per group. Quantification was performed using ImageJ based on 3,3'-diaminobenzidine (DAB)-positive areas. (D) Quantitative analysis revealed a negative correlation between tubular tau expression and estimated glomerular filtration rate (eGFR), and a positive correlation with the degree of tubular dilatation. Relative t-Tau intensity was quantified from IHC images using ImageJ, normalized to the control group, and expressed as fold change. Data are presented as mean $\pm$ standard error of the mean.

CKD, chronic kidney disease. * $p < 0.05$, *** $p < 0.001$ vs. Control.

kidneys, correlating negatively with eGFR and positively with tubular dilatation (Fig. 1D).

Collectively, tau expression is significantly elevated in CKD kidneys, with prominent localization in proximal tubules and glomeruli and only sparse expression in interstitial and vascular regions. These findings suggest that tau pathology is not restricted to proximal tubules but extends to multiple renal structures and may contribute more broadly to CKD progression.

Tau protein accumulates across multiple chronic kidney disease mouse models

Tau accumulation was evaluated using three CKD mouse models: UUO, FA-CKD, and AD-CKD. IHC analysis showed increased levels of p-Tau, ac-Tau, and t-Tau in kidney tissues from all CKD models compared with controls (Fig. 2A–C). The accumulation of tau was predominantly localized in tubular epithelial cells, suggesting that tau pathology is a common feature across distinct CKD models. Consistent with the findings in human kidney samples, all three CKD mouse models also showed significantly higher levels of tau proteins in the CKD groups compared with controls. In addition, correlation analyses demonstrated that p-Tau, ac-Tau, and t-Tau levels were positively associated with fibrosis area in all three CKD models (Fig. 2A–C).

Tau protein expression is increased during chronic kidney disease progression

Prior to initiating the main experimental series, we validated the specificity of the t-Tau antibody using a peptide blocking assay, which confirmed its selective recognition of t-Tau in kidney tissue without cross-reactivity (Supplementary Fig. 2A, available online). This quality control step ensured that subsequent tau detection accurately reflected true protein expression rather than nonspecific binding. To assess tau expression during CKD progression, mice were fed a 0.2% AD (AD-CKD) and sacrificed at weeks 1, 2, and 4 (Fig. 3A). Kidney function markers—including BUN, serum creatinine, and urine albumin-creatinine ratio (uACR)—were significantly elevated from week 1 (Fig. 3B). Histology revealed time-dependent increases in tubular dilation and fibrosis, assessed by PAS and MT staining (Fig. 3C). IHC and western blot analyses showed elevated p-Tau, ac-Tau,

and t-Tau from week 1, with levels rising as the disease progressed (Fig. 3C, D). t-Tau expression positively correlated with tubular dilatation and fibrosis area (Fig. 3C), and similar positive correlations were also observed for p-Tau and ac-Tau (Supplementary Fig. 3A, available online). Consistent with these findings, IF showed increased p-Tau, ac-Tau, and t-Tau in tubules, with p-Tau and ac-Tau prominently localized to the luminal membrane (Supplementary Fig. 2B, available online).

Additional characterization revealed progressive declines in body weight (Supplementary Fig. 3A, available online). ELISA detected significantly elevated urinary t-Tau levels from week 2, while serum tau levels remained unchanged (Supplementary Fig. 3B, available online). Quantitative PCR revealed upregulation of tau messenger RNA (mRNA), with four-repeat (4R)-Tau increasing more than three-repeat (3R)-Tau, and full-length Tau also markedly elevated (Supplementary Fig. 3C, available online).

Collectively, these findings demonstrate progressive increases in tau protein and transcripts, in parallel with worsening histological and functional parameters during CKD progression.

Tau protein overexpression exacerbates chronic kidney disease progression

To investigate the impact of tau overexpression on CKD progression, we induced CKD in P301S transgenic mice and compared them with wild-type (WT) controls. Mice were assigned to four groups: WT Control, WT AD-CKD, P301S Control, and P301S AD-CKD (Fig. 4A). For comparison, IHC images from 7-week-old C57BL/6 mice with or without AD were presented in Supplementary Fig. 4A (available online). P301S AD-CKD mice exhibited significantly higher BUN, cystatin C, and uACR levels compared with WT AD-CKD mice (Fig. 4B). PAS and MT staining demonstrated more severe tubular dilation and fibrosis in the kidneys of P301S AD-CKD mice (Fig. 4C). IHC analysis confirmed elevated renal expression of p-Tau, ac-Tau, and t-Tau in P301S mice, evident even under baseline conditions. Markers of EMT (α -smooth muscle actin [α -SMA]) and oxidative stress (8-hydroxy-2'-deoxyguanosine [8-OHdG]) were also significantly increased in P301S AD-CKD mice, but not under normal diet conditions (Fig. 4C).

Similarly, IHC for NGAL and kidney injury molecule 1 re-

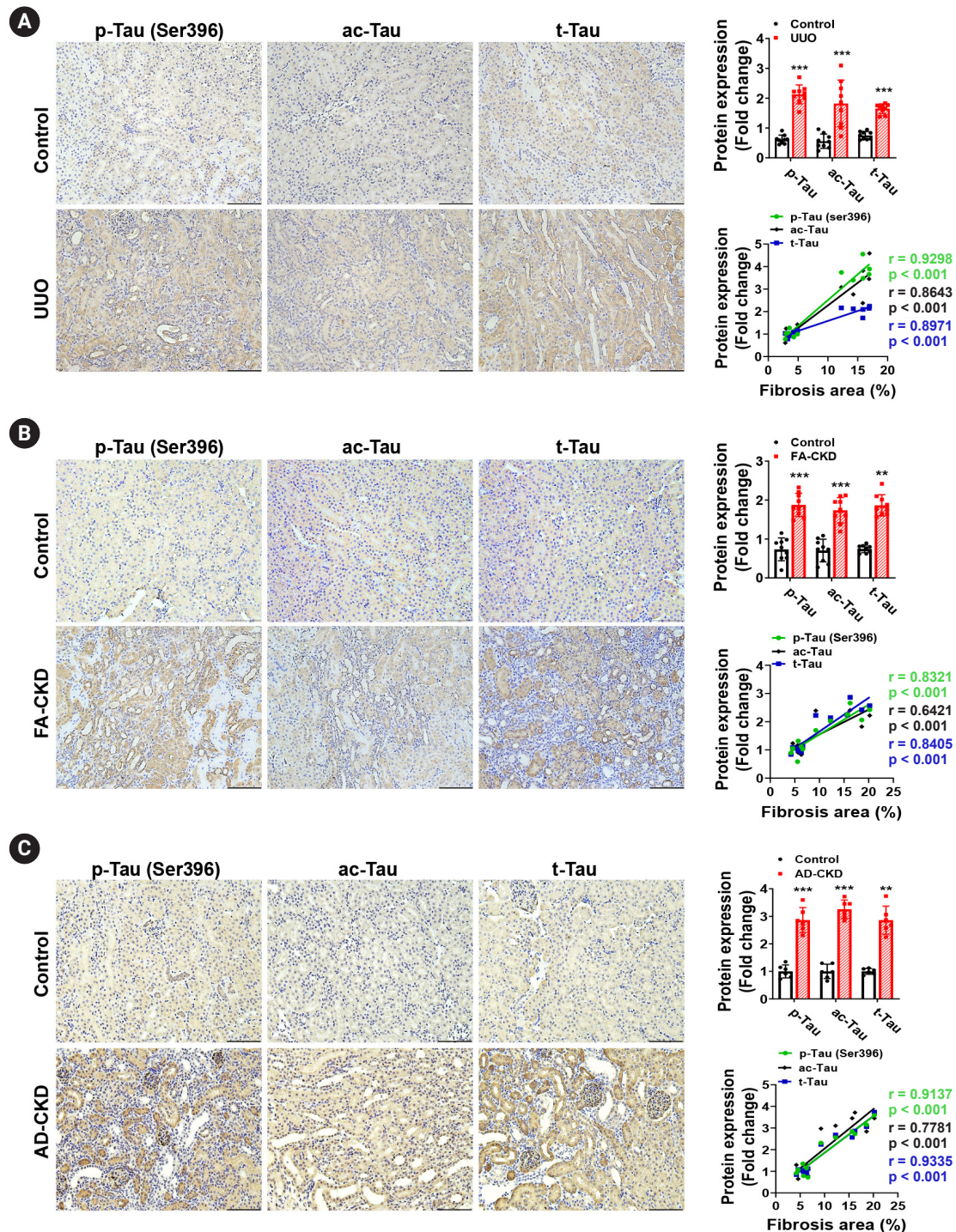


Figure 2. Renal tau protein expression is increased in multiple CKD mouse models. Representative immunohistochemistry image of tau proteins (phosphorylated tau [p-Tau], acetylated tau [ac-Tau], total tau [t-Tau]) in kidney tissues from three CKD mouse models (scale bar, 100 μ m). (A) Unilateral ureteral obstruction (UUO) model, (B) folic acid-induced CKD (FA-CKD) model, and (C) adenine diet-induced CKD (AD-CKD) model. In all models, tau protein expression was markedly increased in CKD kidneys than in respective controls. Correlation analyses between tau protein levels (p-Tau, ac-Tau, and t-Tau) and fibrotic area (%) in three CKD models: UUO, FA-CKD, and AD-CKD. All three tau protein forms showed a positive correlation with fibrosis in all models. Data are presented as mean $\pm$ standard error of the mean.

CKD, chronic kidney disease. ** $p < 0.01$, *** $p < 0.001$ vs. Control.

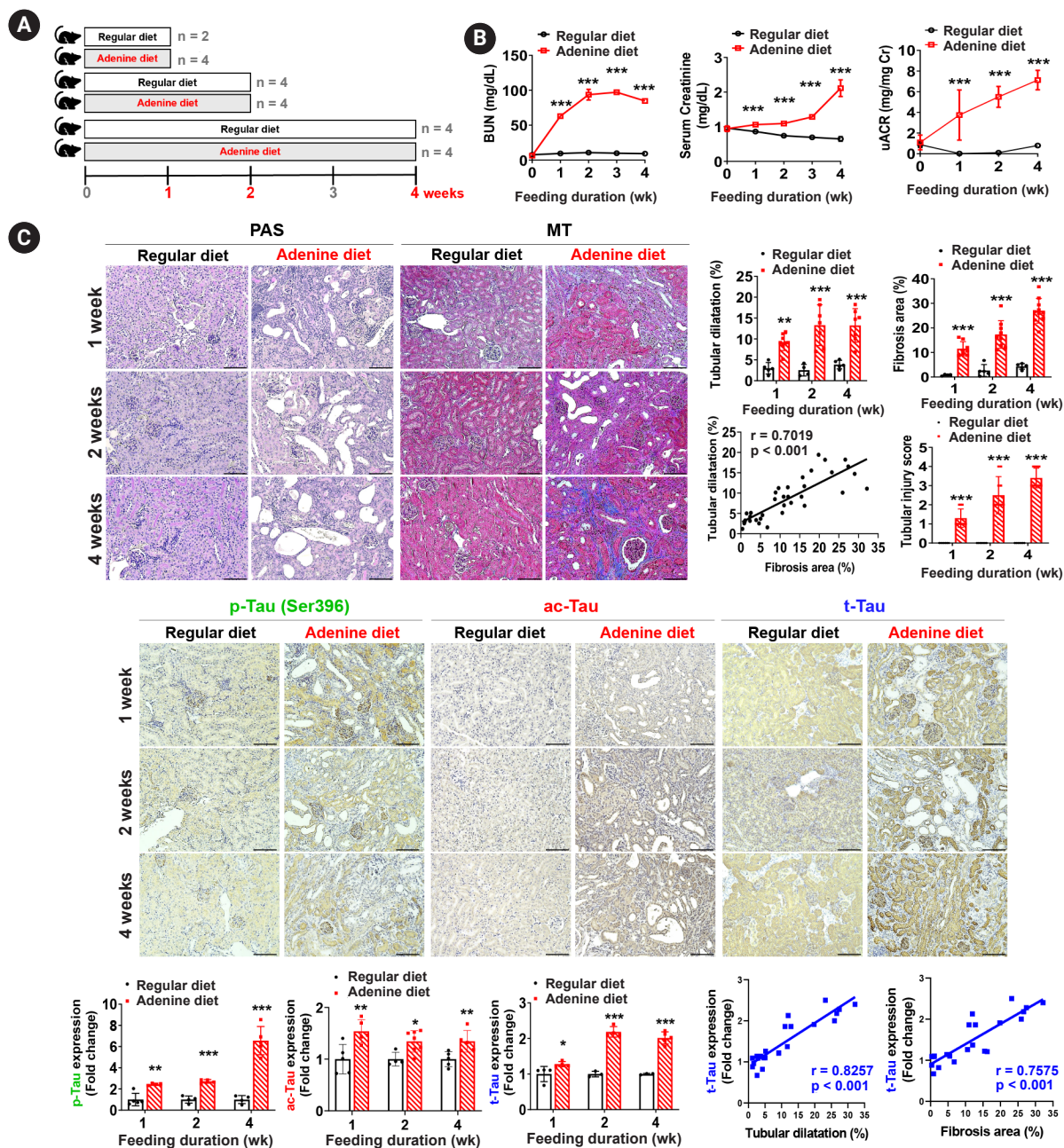


Figure 3. Kidney tau expression increases over time in the AD-induced mouse model of CKD. (A) Experimental design. Normal chow or a 0.2% adenine diet was supplied to C57BL/6 mice for 1, 2, or 4 weeks. (B) Clinical indices of kidney dysfunction (blood urea nitrogen, serum creatinine, and urinary albumin-creatinine ratio) were increased in AD mice. (C) Representative image of periodic acid-Schiff (PAS) and Masson's trichrome (MT)-stained kidney and representative images of immunohistochemistry staining for phosphorylated tau (p-Tau), acetylated tau (ac-Tau), and total tau (t-Tau). Increased tubular dilatation and fibrosis area were observed in the CKD groups. Tau protein levels increased as CKD progressed. Tubules were evaluated according to the following scoring system: 0, no tubules injured; 1, $\leq 10\%$ tubules injured; 2, 11%–25% tubules injured; 3, 26%–50% tubules injured; 4, 51%–74% tubules injured; and 5, $\geq 75\%$ tubules injured. (D) Representative western blots. Kidney expressions of p-Tau, ac-Tau, and t-Tau were significantly increased in the CKD group after different adenine feeding periods. Data are presented as mean $\pm$ standard error of the mean. Scale bar, 100 μ m.

AD, adenine diet; CKD, chronic kidney disease; GAPDH, glyceraldehyde-3-phosphate dehydrogenase. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. regular diet. (Continued to the next page)

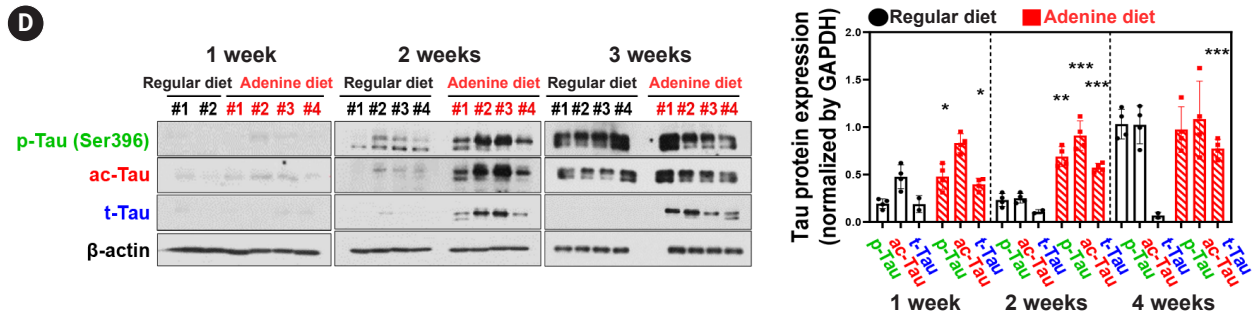


Figure 3. Continued.

vealed stronger staining in AD-CKD mice, with more pronounced changes in the P301S AD-CKD group (Fig. 4C). In contrast, urinary NGAL measured by ELISA showed only a nonsignificant increase but exhibited a trend toward higher levels in the P301S AD-CKD group. Western blot analysis further confirmed increased levels of p-Tau, ac-Tau, and t-Tau in the kidneys of P301S mice compared with WT controls (Supplementary Fig. 4B, C, available online).

Tau antibody administration ameliorates tubular injury in chronic kidney disease

To evaluate whether tau inhibition could alleviate CKD-associated kidney injury, we administered an antibody targeting ac-Tau (50 mg/kg, i.p.) to mice fed a 0.2% AD (AD-CKD) for 1 week. Experimental groups included Control, AD-CKD, AD-CKD with control IgG (AD-CKD + con IgG), and AD-CKD with ac-Tau antibody (AD-CKD + ac-Tau ab) (Fig. 5A).

IHC analysis revealed that tau protein levels (p-Tau, ac-Tau, and t-Tau), which were elevated in AD-CKD kidneys, were significantly reduced in the AD-CKD + ac-Tau ab group compared with the AD-CKD group (Fig. 5B).

In addition, PAS and Sirius Red staining demonstrated a marked reduction in tubular dilation and fibrosis area in the AD-CKD + ac-Tau ab group compared with the AD-CKD group. Consistently, expression of collagen type I α 1 (COL1A1) and α -SMA was significantly decreased in AD-CKD + ac-Tau ab group compared with the AD-CKD group. The proximal tubule marker aquaporin 1, which was diminished in AD-CKD, was restored in AD-CKD + ac-Tau ab group. For the oxidative stress marker 8-OHdG, no significant differences were observed between the AD-CKD and AD-CKD + ac-Tau ab groups, or between the AD-

CKD and AD-CKD + con IgG groups. However, a significant reduction was detected when comparing the AD-CKD + ac-Tau ab group with the AD-CKD + con IgG group (all shown in Fig. 5C).

Together, these results suggest that targeting ac-Tau reduces tau protein accumulation, attenuates tubular injury, and improves pathological features in CKD, which may support a potential role for tau in renal disease progression.

Discussion

This study uniquely identified and investigated the role of tau protein in CKD. Tau protein levels were elevated in the kidneys of CKD patients compared with controls, and this elevation correlated with renal dysfunction, as indicated by decreased eGFR [20] which is widely used for CKD staging and assessment, and increased tubular dilatation. These findings were consistently observed in multiple CKD mouse models, including UUO, FA-CKD, and AD-CKD. Moreover, tau protein overexpression aggravated tubular injury in tau transgenic mice under CKD conditions. Furthermore, antibody therapy targeting ac-Tau effectively attenuated tubular injury, highlighting its therapeutic potential. Collectively, these findings suggest that the tau protein may contribute to CKD progression under pathological conditions and support its potential as a therapeutic target.

The P301S transgenic mouse model expresses human tau (hTau) with the P301S mutation, originally identified in frontotemporal dementia. This model is driven by the prion protein promoter [21], leading to systemic hTau expression not only in the brain but also in peripheral organs including the kidney [22]. This supports the relevance of investigating tau pathology beyond the central nervous

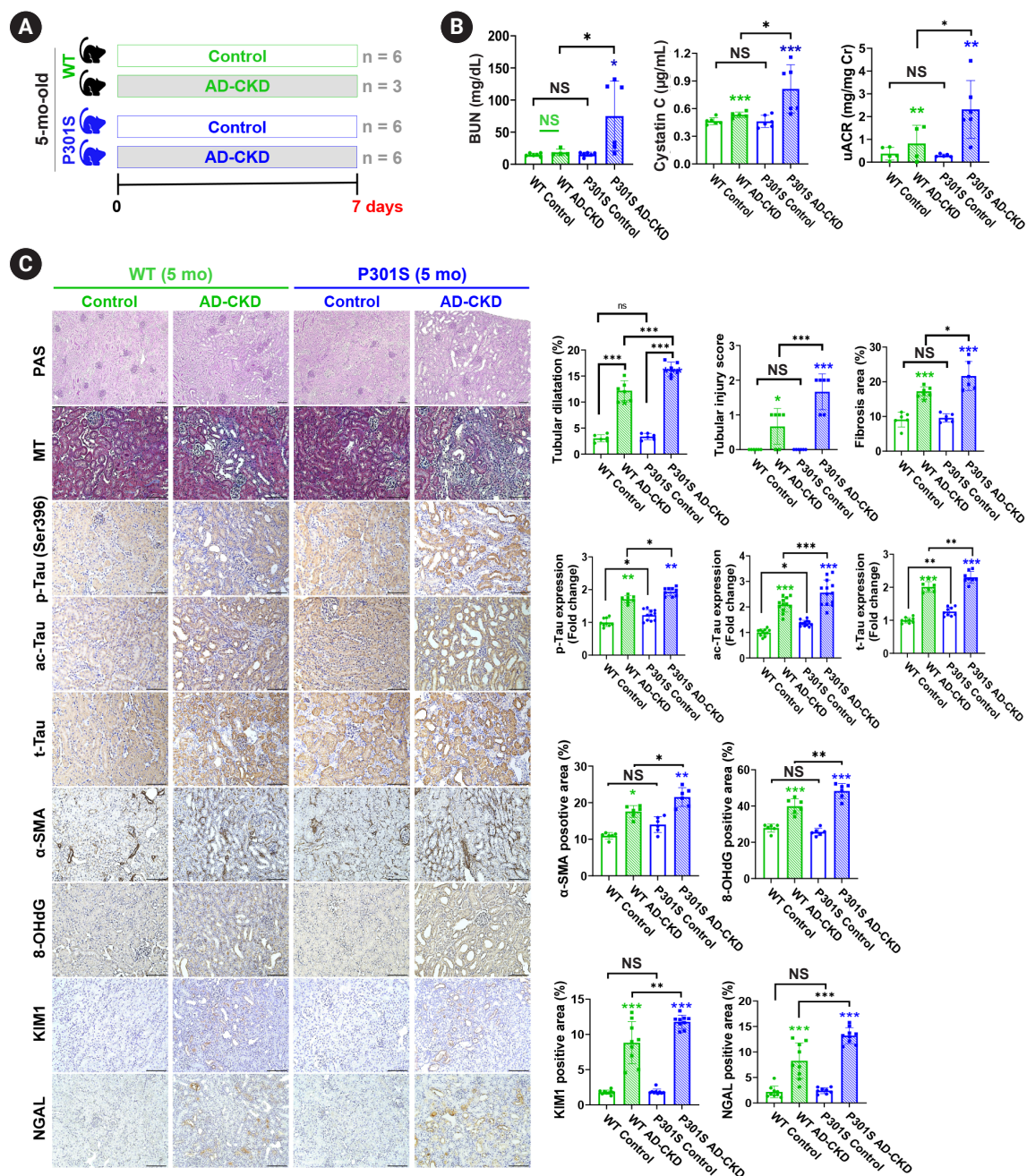


Figure 4. Tau protein overexpression worsens renal progression in AD-CKD. (A) Animal experimental design. AD-CKD was induced by a 0.2% adenine diet for 1 week using human tau mutant overexpression P301S and wild-type (WT) mouse (5 months old). (B) Kidney clinical index graph (blood urea nitrogen [BUN], cystatin C, urinary albumin-creatinine ratio [uACR]). BUN, cystatin C, and uACR on day 7 increased more in P301S AD-CKD than in WT AD-CKD. (C) Representative image of periodic acid-Schiff (PAS) and Masson's trichrome (MT)-stained kidney and image of tau protein (phosphorylated tau [p-Tau], acetylated tau [ac-Tau], total tau [t-Tau]) immunohistochemistry, α-smooth muscle actin (α-SMA), 8-hydroxy-2'-deoxyguanosine (8-OHdG), kidney injury molecule 1 (KIM1), and neutrophil gelatinase-associated lipocalin (NGAL). P301S AD-CKD had increased tubular dilatation and fibrosis area compared to WT AD-CKD. Tau proteins were more expressed in P301S. Upon induction of CKD, tau proteins were increased more in P301S Control compared to WT Control. Also, α-SMA, 8-OHdG, KIM1, and NGAL increased more in the P301S AD-CKD group than WT AD-CKD. Data are presented as mean ± standard error of the mean. Scale bar, 100 μm.

AD-CKD, adenine diet-induced chronic kidney disease; NS, not significant. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. WT Control or WT AD-CKD.

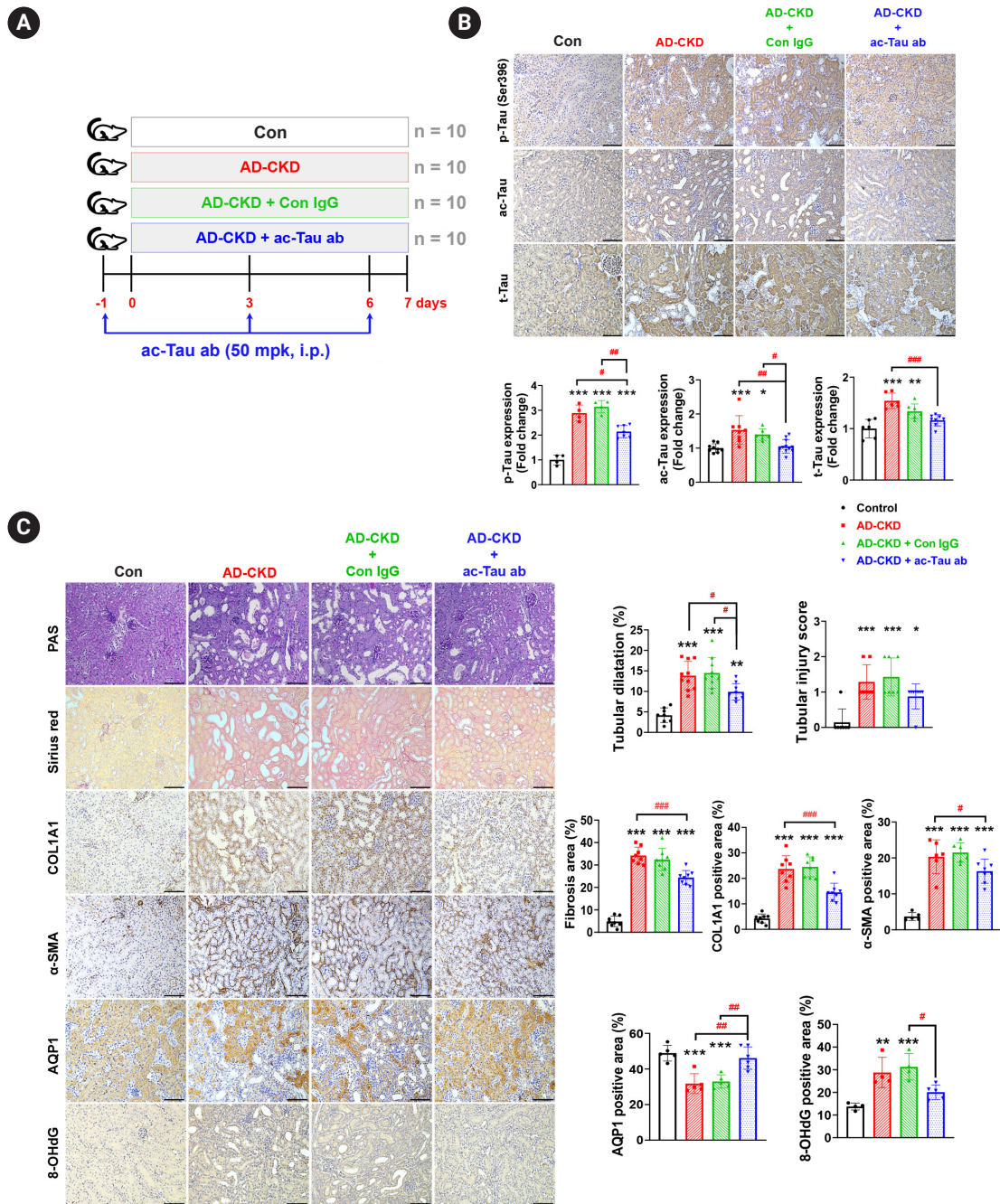


Figure 5. Inhibition of Tau decreases tubular injury and fibrosis in AD-CKD mouse kidneys. (A) Experimental design. C57BL/6 mice were fed a normal diet or a 0.2% adenine diet for 1 week. An acetylated tau (ac-Tau)-specific antibody (ac-Tau ab; 50 mg/kg [mpk], intraperitoneal injection [i.p.]) was administered 1 day before CKD induction and every 3 days thereafter, for a total of three doses. (B) Representative immunohistochemistry (IHC) images of phosphorylated tau (p-Tau), ac-Tau, and total tau (t-Tau). Antibody treatment reduced the accumulation of p-Tau, ac-Tau, and t-Tau in AD-CKD kidneys. (C) Representative images of periodic acid-Schiff (PAS), Sirius Red, and IHC for aquaporin 1 (AQP1), α -smooth muscle actin (α -SMA), collagen type I α 1 (COL1A1), and 8-hydroxy-2'-deoxyguanosine (8-OHdG). Antibody-treated mice showed reduced tubular dilatation, reduced fibrosis area, restored AQP1 expression, and reduced α -SMA and COL1A1 expression. 8-OHdG levels were also decreased compared with the AD-CKD + immunoglobulin G (IgG) group. Data are presented as mean $\pm$ standard error of the mean. Scale bar, 100 μ m.

AD-CKD, adenine diet-induced chronic kidney disease. * p < 0.05, ** p < 0.01, *** p < 0.001 vs. Control (Con). # p < 0.05, ## p < 0.01, ### p < 0.001 vs. AD-CKD or AD-CKD + IgG.

system [23], as P301S tau transgenic models have demonstrated systemic expression of human tau and associated pathology. Our IHC and single-cell RNA sequencing analyses further demonstrated that tau expression is not limited to renal tubules but also occurs in glomerular compartments such as podocytes and mesangial cells, indicating potential involvement across multiple renal structures. Interestingly, in P301S mice, tau overexpression alone did not impair kidney function or structure in the absence of CKD. However, once CKD was induced, these mice showed more rapid and severe disease progression, suggesting that tau protein may exacerbate kidney injury in the presence of CKD rather than directly initiating damage. Isoform-specific RT-PCR confirmed the presence of both 3R and 4R tau in CKD mouse kidneys, with a notable increase in 4R tau mRNA expression. This suggests functional diversity of tau beyond the previously known role in the murine kidney [15].

Posttranslational modifications of tau protein have been extensively studied in brain diseases, but to the best of our knowledge, this is the first study to investigate these modifications in both human and mouse CKD kidneys. Phosphorylation of tau has been widely studied in neuronal systems [5,24] but remains poorly characterized in kidney pathology [15]. Kinases such as glycogen synthase kinase-3 β (GSK-3 β) and p38 mitogen-activated protein kinase (MAPK), which are activated by oxidative stress and inflammation—both common in CKD—are known to promote tau phosphorylation in the central nervous system [5,9]. These kinases have also been implicated in CKD progression through tubular apoptosis, interstitial inflammation, and fibrosis [25], as shown in experimental models where pharmacologic inhibition of GSK-3 β ameliorated renal inflammation and injury. Our recent work in diabetic nephropathy models demonstrated a bidirectional relationship between tau phosphorylation and endoplasmic reticulum (ER) stress, in which ER stress promotes tau phosphorylation and phosphorylated tau aggravates ER stress [26]. This interaction was observed in both podocytes and mesangial cells, indicating that it is not restricted to a single renal cell type. Although ER stress markers were not assessed in this study, the findings suggest a plausible mechanism by which tau may contribute to tubular injury through ER stress-related signaling.

Tau acetylation has also been shown to upregulate GSK-

3 β , forming a pathogenic feedback loop in Alzheimer disease [27,28]. Conditional overexpression of GSK-3 β alone can induce Alzheimer-like pathology, which can be reversed by GSK-3 β inhibition [29]. Together with our current findings, this supports the hypothesis that CKD-associated activation of GSK-3 β and p38 MAPK may promote tau phosphorylation in renal tubules, contributing to structural damage and disease progression.

Tau is a microtubule-stabilizing protein that plays a crucial role in maintaining cell shape [30]. In renal tubules, cilia are closely associated with microtubules, and cilia-related changes have been reported in impaired kidney function [31,32]. Our observation of strong tau expression along the luminal membrane in CKD warrants further investigation into the relationship between luminal ciliary microtubule dynamics and tau. In addition, tau has been implicated in actin filament reorganization [33,34]. Previous studies in podocytes have shown that tau overexpression causes foot process effacement and nephrin loss [15]. As actin filaments are essential for podocyte structure [35–37], further studies in models with direct glomerular injury are warranted, given that the mouse model used in the present study is relatively distant from glomerular injury.

This study is significant as the first to examine tau protein in renal tubules. By elucidating the involvement of tau protein in CKD progression, our findings address a critical knowledge gap and suggest new therapeutic strategies for CKD. Inhibition of ac-Tau protein reduced not only tubular injury but also fibrotic collagen deposition in the adenine-induced CKD model. Sirius Red and COL1A1 IHC analyses revealed a statistically significant antifibrotic effect in antibody-treated mice. Future studies should extend the disease duration to confirm these effects in more advanced CKD models and further assess the therapeutic potential by optimizing antibody delivery and by targeting phosphorylated tau in addition to ac-Tau inhibition. About 10%–14% of the global population suffers from CKD [38], and the disease is accompanied by kidney fibrosis, a major pathology that eventually leads to end-stage kidney disease [39]. Therefore, our findings clearly highlight the urgency and importance of CKD research. The well-known role of tau in neurodegenerative diseases such as Alzheimer disease, together with the rising prevalence of CKD in aging populations, suggests that tau could be a promising therapeutic target, especially given the current lack of effective

antifibrotic treatments [40].

Limitations of this study include the small number of human kidney samples, which limits generalizability. Nevertheless, in the present study, tau expression was consistently elevated with minimal variability in all CKD samples. Previous small-cohort studies [13] have also yielded clinically meaningful findings when supported by complementary experimental evidence. Larger-scale validation will be needed to confirm these results.

In conclusion, our findings suggest that the tau protein may play a key role in CKD progression. Targeting tau may offer a novel therapeutic approach to reduce kidney injury and fibrosis. This work provides new insight into the molecular mechanisms of CKD and may inform the development of future therapeutic strategies to improve patient outcomes.

Conflicts of interest

All authors have no conflicts of interest to declare.

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Data sharing statement

The data presented in this study are available from the corresponding author upon reasonable request.

Authors' contributions

Conceptualization, Data Curation, Funding acquisition, Methodology: SWL, EYL

Formal analysis, Visualization; SWL, SSS, HSJ, CEM, JGL, JSK

Investigation: SWL, JGL, EYL

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