Role of protein phosphatase 2A in kidney disease (Review)

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Abstract. Kidney disease affects millions of people worldwide and is a financial burden on the healthcare system. Protein phosphatase 2A (PP2A), which is involved in renal development and the function of ion-transport proteins, aquaporin-2 and podocytes, is likely to serve an important role in renal processes. PP2A is associated with the pathogenesis of a variety of different kidney diseases including podocyte injury, inflammation, tumors and chronic kidney disease. The current review aimed to discuss the structure and function of PP2A subunits in the context of kidney diseases. How dysregulation of PP2A in the kidneys causes podocyte death and the inactivation of PP2A in renal carcinoma tissues is discussed. Inhibition of PP2A activity prevents epithelial-mesenchymal transition and attenuates renal fibrosis, creating a favorable inflammatory microenvironment and promoting the initiation and progression of tumor pathogenesis. The current review also indicates that PP2A serves an important role in protection against renal inflammation. Understanding the detailed mechanisms of PP2A provides information that can be utilized in the design and application of novel therapeutics for the treatment and prevention of renal diseases.

1. Introduction

Kidney disease, which is one of the fastest-growing causes of mortality worldwide, includes acute and chronic types that damage the structure and function of renal tissue (1). Acute kidney injury (AKI) and chronic kidney disease (CKD) are associated with increased risk of adverse cardiovascular events, as well as increased morbidity and mortality (2,3). These conditions can eventually develop into end-stage renal disease (ESRD) that requires dialysis or kidney replacement (4). The global economic cost of kidney disease is vast. In 2007, the United States Medicare expenditures on CKD exceeded $60,000,000 USD, accounting for 27% of the total Medicare budget (5), while expenditures on AKI exceed $10,000,000 USD per year (6). Therefore, elucidating the pathophysiological mechanisms of kidney disease will lead to the development of promising therapeutics for multiple renal diseases, which is essential to public health.

Reversible phosphorylation and dephosphorylation of proteins serve important roles in regulating protein activities and constitute the central mechanism of signal transduction (7). Protein phosphatase 2A (PP2A) enzymes are the main members of the serine/threonine (Ser/Thr) phosphatase family and are involved in the majority of total cellular-phosphatase activities (7). PP2A, which participates in a number of key pathways during all stages of the cell cycle, has been
extensively studied in relation to tumor suppression (8). A growing body of literature suggests that PP2A is crucial in a number of aspects of renal-disease pathogenesis including AKI (9), CKD (10), aging (11) and tumorigenic processes (12). In the current review, the unique structure and function of PP2A is described and its interactions with associated signaling pathways in kidney disease are discussed. Therapeutic targeting of PP2A has demonstrated promise in enhancing the efficacy of treatments for patients with kidney disease.

2. Function of protein phosphatase in the kidneys

Protein phosphorylation and dephosphorylation are components of a vital mechanism used in the modulation of key cellular processes associated with cell proliferation, differentiation, migration and other biological behaviors involved in signaling regulation (13,14). Phosphatases are divided into four large families: i) Protein serine/threonine phosphatases [including the protein phosphatases (PPPs) and metal-dependent protein phosphatases], (2) protein tyrosine phosphatases (2), dual-specificity phosphatases (DUSP) and histidine phosphatases (3,4). As the largest of the Ser/Thr family, PPP is further subdivided into PPI, PP2A, PP2B, PP4, PPS and PP6 according to the sensitivity and specificity of the substrate to inhibitors or effectors (15,16). A number of extracellular stimuli affect the level of protein phosphorylation in the modulation of cell processes (17). These processes are involved in cellular proliferation, migration, growth, differentiation, metabolism, the immune system, cytoskeletal reorganization and muscle contraction (17). Over 50% of proteins in human cells are capable of undergoing reversible phosphorylation; Therefore, phosphorylation pathways exhibit promising potential applications in the treatment for a variety of different diseases (18).

The kidneys receive ~20% of cardiac output and consume 10% of the body oxygen to perform their main function of adjusting body-fluid constituents by glomerular filtration and renal tubular reabsorption (4). Each glomerulus consists of three main classes of cells forming the filtration layer: i) fenestrated-endothelium cells located inside the capillary, ii) mesangial cells located outside the capillary and iii) specialized epithelial cells called podocytes (19). Phosphotyrosine phosphatase is hyperactive in endothelial cells of the glomerular-mesangial-cell layer in human tissues (20). Furthermore, PTP serves a central role in podocyte homeostasis, and this has been demonstrated in a study in which treatment of podocytes with a nonspecific PTP inhibitor induced drastic morphological alterations in their actin-cytoskeleton network (21). Svennisson et al (22) demonstrated that the expression of PPI and PP2A is ubiquitous in the early metanephric kidney. The importance of kinases in kidney disease is well established; However, the roles of phosphatases are yet to be fully elucidated (10). To the best of our knowledge, there has been little research on phosphatase in the kidneys. Accumulating evidence has indicated that phosphatases are involved in normal nephron growth and renal pathological processes, and may be a promising target for therapies in patients with renal diseases (10,23).

3. Features of PP2A

In eukaryotic cells, at least 99% of protein phosphorylation is associated with Ser/Thr residues (24). PP2A, which is one of the four major cytoplasmic Ser/Thr phosphatases, acts on a number of different components within various key signal-transduction pathways (25). The function and structure of PP2A is conserved in organisms ranging from yeasts to mammals, in which PP2A regulates many important cellular functions (26). The PP2A enzyme core is made up of a 65-kDa scaffolding subunit 'A', which modulates its enzymatic properties, and a 36-kDa catalytic subunit 'C' (27). These subunits bind to the regulatory subunit 'B' (PP2A-B) to form the various heterotrimeric complexes (28). The A and C subunits have two isoforms that are encoded by genes α and β (29). While these isoforms are strongly homologous for each other, the majority of cell types predominantly express the α isoform (29). There are four categories of the B subunit, including the PR55 (B), PR61 (B'), PR72/130 (B') and the striatin family (B'). The B subunit is contained in multiple isoforms (α up to e) that are encoded by different genes. Because the structure of the B subunit varies dramatically, PP2A targets an extensive array of components involved in critical signal-transduction pathways that regulate cellular functions (29). Although the A and C subunits are widely expressed, the cellular localization and expression of the B subunit vary greatly across cell types and tissues (30-35).

PP2A dephosphorylates a number of key cellular molecules including Akt, MEK, MAPK, c-Myc, p53 and β-catenin (36). Furthermore, PP2A regulates a number of different cellular processes such as proliferation, metabolism and apoptosis (36). Aberrant PP2A regulation is commonly observed in a range of diseases such as cancer, cardiovascular pathologies and neurodegenerative disorders (29). Evidence has indicated that PP2A can act as a tumor suppressor (37). PP2A can suppress tumorigenesis via downregulation of the Akt/TSC1/TSC1/Rheb/mTOR signaling pathway, inactivation of c-Myc and antagonism of the Wnt/β-catenin pathway (38). Previous studies have also revealed that PP2A is essential in kidney organogenesis and developmental processes, and participates in kidney diseases via one of several complex mechanisms (39,40).

4. PP2A regulates ion-transport proteins and aquaporin-2 (AQP2)

Ion channels. The absorption of ions in the kidneys is regulated and controlled by multiple physiological mechanisms (41). Previous studies have indicated PP2A is responsible for the maintenance of ion channels and homeostasis (42-44). PP1 and PP2A serve an important role in the phosphorylation, surface distribution and function of Na'/Cl⁻-dependent choline transporters (43). Ang II is an important regulator of the ouabain-resistant Na⁺-ATPase from renal proximal tubule cells, which are involved in the signal cascade of Ang II receptors, protein kinase (PK)A and PKC (42,44-46). Chronic malnutrition can stimulate the activity of renal tubulointerstitial Ang II and damage the regulation of phosphorylation that is mediated by PP2A (47). These events result in excessive reabsorption of Na⁺ in proximal renal
AQP2. The targeting of AQP2 on the apical plasma membrane of renal collecting duct cells, which are used to maintain body water homeostasis in mammals, is mainly modulated via the activity of antidiuretic peptide arginine vasopressin (53). AQP2 protein has at least four vasopressin-regulated phosphorylation sites at serine residues 256, 261, 264 and 269 (54,55). Phosphorylation of these sites controls the activity of antidiuretic peptide arginine vasopressin (53). AQP2 behaves as a protein that is regulated by PP2A (51). 11,12-epoxyeicosatrienoic acid inhibits Na,K-ATPase activity at a lower dose than that of OA in renal proximal tubules. In addition, potassium channels are also regulated by these phosphatases (51). 11,12-epoxyeicosatrienoic acid dilates pregglomerular microvessels via adenosine A2A receptor mediation and activates conductance across the K+ channels in renal smooth muscles by stimulating PP2A (52). These findings reveal that PP2A functions cooperatively with this crucial regulatory mechanism in regulating the dynamics of Na+, K+ and Cl- flow (Fig. 1).

5. PP2A in renal development

PP2A serves a crucial role in embryonic development, and particularly in development and survival (40). Evidence has suggested that PP2A serves complicated stimulatory and inhibitory roles in growth- and hormone-factor signaling; especially in the extracellular signal-regulated ERK/MAPK cascade and in the activity of ubiquitous intermed дней messengers during mitosis (64). PP2A appears to be involved in controlling the activity of maturation-promoting factor (MPF) (65,66) and the modulation of MAP-ERK kinase activity (67,68). Normal kidney development, beginning at embryonic day 12 (E12) in rats and during the 5th gestational week in humans, is strictly regulated and involves several crucial steps in order to achieve a predetermined number of functioning nephrons (39). On day 15 of embryonic development, the percentage of PP2A in total Ser/Thr phosphatase activity is 78% in rat kidneys, as evaluated using a phosphatase activity assay. At the E18 and E21 stages of nephrogenesis, the expression of PP2A is limited to the nephrogenic zone, in which it is strongly expressed (39). When nephrogenesis terminates, PP2A expression is downregulated substantially (39). Svennilson et al (22) demonstrated that PP2A mRNA is strongly expressed in various cell types during early development of the kidneys. Additionally, the use of low doses of OA inhibits early (E13) embryonic kidney growth and disturbs nephron formation in E15 kidneys. Subsequently, normal PP2A activity is indispensable to metanephric development, and inhibition of this activity can induce morphological disorder and apoptosis (22).

Recent studies have highlighted the particular importance of functional PP2A in Wnt signaling due to the fact Wnt-4 serves a key role in kidney development (69,70). Overall, these studies provide novel insights into the importance of PP2A activity during renal morphogenesis and within signal-transduction pathways.

6. PP2A and podocytes

Podocytes (or visceral epithelial cells) have complicated interdigitating foot processes (FPs) that cover the external surface of the glomerular basement membrane (71). Adjacent FPs from different units are interconnected by a continuous membrane structure called the slit diaphragm (19). The slit diaphragm consists of membrane and cytoskeletal proteins, such as synaptopodin, nephrin, podocin, α-actinin-4, podoplanin and CD2 Associated Protein, as well as signaling molecules, all of which serve important roles in maintaining the basic function of the glomerular filtration barrier (GFB) (72,73). Impairments in pathways and molecular processes that regulate the function of the GFB may lead to CKD (74). Congenital or acquired podocyte damage can cause podocyte to lose certain specific markers, causing disappearance of FPs, detachment and proteinuria (75). Additionally, podocyte injury is closely associated with a number of renal diseases, including diabetic nephropathy, membrane nephritis, IgA nephropathy and focal segmental glomerulosclerosis (75). Kumar and Tikoo (20) demonstrated that selective inhibition of PP2A activity to restore insulin levels can induce the phosphorylation of Sirtuin 1 and Forkhead Box O1 and increase the activity of AKT, causing degradation of p53 and podocyte death. Kobayashi et al (76) also indicated that utilizing OA to inhibit PP2A can suppress microtubule elongation and abolish process formation in conditionally immortalized mouse podocytes. Zhu et al (77) demonstrated that podocyte-specific knockout of PP2A (Pod-PP2A-KO) in mice causes considerable weight loss, growth retardation, proteinuria, severe lethargy, and mortality in >70% mice at 15 weeks of age. Histological examination has indicated severe glomerulopathy and dramatic loss of FPs, as well as reduced expression of a number of different slit-diaphragm...
molecules and impairment of cytoskeletal rearrangement in podocytes (77).

The highly conserved Y box protein 1 (YB-1) of the cold-shock protein family has been indicated to be associated with cellular stress response and renal fibrosis (78). YB-1 is a target cellular in PP2A dephosphorylation, and fine-tuning YB-1 via post-translational modification by modulating PP2A activity may serve a role in maintaining the functional integrity of podocytes and GFB (78). Zhong et al (79) revealed that podocyte-specific PP2A deficiency aggravates diabetic glomerulopathy and accelerates diabetic kidney disease. Arctigenin (ATG) is a major component of Fructus Arctii, a traditional herbal remedy that reduces proteinuria in patients with diabetes (79). ATG administration has been revealed to attenuate proteinuria and podocyte injury in mouse models of diabetes (79). Furthermore, enhanced PP2A activity occurring via ATG ameliorates podocyte adhesion partly through T335-mediated phosphorylation of drebrin-I (DBN1). This aforementioned result reveals a novel mechanism in the regulation of podocyte cytoskeletal rearrangement (79). Selective inhibition of PP2A can improve insulin resistance, restore AKT levels, induce FOXO1 phosphorylation and rescue podocytes from cell death (20). These aforementioned data indicated that PP2A may be a potential drug target for the prevention of podocyte injury.

7. PP2A and renal carcinoma

Renal cell carcinoma (RCC) is one of the most common renal malignancies and accounts for ~2.4% of all cancers and 1.7% of total cancer-associated deaths worldwide (80). To date, therapeutics for patients with metastatic renal cancer remain limited in effectiveness and specificity (81). A number of human cancers are associated with PP2A dysfunction, such as lung cancer (82), breast cancer (83) and leukemia (84). Furthermore, downregulation of PP2A expression and its impact on cellular transformation reveals that PP2A can function as a tumor-suppressor gene in a number of different malignant cancers including leukemia, lung, breast, gastric and colon cancer (85). Increasing evidence has indicated that PP2A serves a tumor-suppressive role, but the individual roles of its subunits, which are deregulated in cancer, remain unknown (80). PP2A expression is decreased in RCC tissues, and patients with high expression of PP2A in tumor tissues exhibit improved survival compared with those exhibiting a low expression of PP2A (12). However, the mechanism of PP2A deregulation in RCC is yet to be determined. Evidence has suggested that PP2A inactivation in cancer mainly occurs via overexpression of suvar/enhancer of zeste/trithorax and cancerous inhibitor of PP2A, which are both endogenous PP2A inhibitors (86-89).

MicroRNAs (miRNA/miR) can act as oncogenes or tumor suppressor genes, depending on the function of target genes in malignant tumors (87). Additionally, miR-183 (a member of the miR-183-96-182 cluster) is expressed at higher levels in two renal cancer cell lines (ACHN and A498) and can promote the growth of renal cancer cells (87). A study has indicated that miR-183 can directly target the 3’untranslated regions of PP2A-Cα, PP2A-Cβ mRNA, as well as PP2A-B56-γ protein phosphatase subunits and inhibit their expression (81). These results confirm that miR-183 serves an oncogenic role in renal cancer cells by targeting PP2A directly (81). PP2A, Akt and McI-1 are essential in RCC malignancy and treatment resistance (90). The PP2A/Akt axis is an important substitute for aspirin-mediated induction of susceptibility to ABT-737 mediated-apoptosis in RCC cells (90). Styryllactone (R)-goniothalamin and its enantiomer (S)-goniothalamin cause apoptosis in cancer cells of human kidneys by reducing Ras expression and PP2A activity (91).

In human renal-carcinoma Caki cells, downregulation of PP2A via small-interfering RNA can significantly inhibit the upregulation of a pro-apoptotic protein Bim via the pharmacological inhibitor ZFL [cathepsin S inhibitor: Z-FL-COCHO (ZFL)] (92). Downregulation of PP2A decreases apoptosis and cleavage of poly (ADP-ribose) polymerase in ZFL- and oxaliplatin-treated Caki cells (92). Combined treatment with Raf inhibitors sorafenib and GW5074 is used to produce a two-pronged attack on renal cancer cells (93). The two inhibitors promote translocation of pC-RafS338 and pDAPKS308 from mitochondria to cytoplasm, resulting in mitochondrial dysfunction and ROS generation. Subsequently, reactive oxygen species (ROS) accelerate the PP2A-mediated dephosphorylation of pDAPKS308 to DAPK. Finally, PP2A separates from the C-Raf-DAPK complex and leads to cancer cell death (93). Luteolin also induces apoptosis in 786-o cells (94). This cytotoxicity is caused by the downregulation of Akt and consequent upregulation of Ask1, p38 and JNK activity, which is regulated by PP2A activation (94).

In summary, PP2A expression may be a useful tool that can be used in the prediction of prognosis and therapeutic outcome in patients with RCC. Further research on the molecular mechanisms of PP2A in human RCC will facilitate the identification of novel therapeutics and the development of effective treatments for patients with renal cancer.

8. PP2A in CKD

Glomerulosclerosis and tubulointerstitial fibrosis are the major pathological features of renal fibrosis, which is the final manifestation of a number of different CKDs (95). As conductors, renal microvascular endothelial cells (EC) serve important roles in kidney fibrosis (96). The association between renal fibrosis and endothelial dysfunction is well established (97). Endothelial dysfunction leads to a significant reduction in the number of peritubular capillaries in the interstitium (97). Chronic ischemia and hypoxia result in scar formation and remodeling processes in renal tissues (98). A previous study has indicated that Tyr nitration in the C subunit of PP2A decreases PP2Ac tyrosine phosphorylation and increases PP2A activity and endothelial dysfunction (99). TGF-β1-induced nitrification accelerates the nitrification of PP2Ac and increases the activity of PP2A in endothelial cells (10). Okadaic acid inhibits the activity of PP2A, weakening the effects of PP2A on EC cytoskeletal rearrangement induced by thrombin or nocodazole (100). This finding indicates that PP2A activity serves an important role in the maintenance of the EC cytoskeleton. Endothelial-mesenchymal transition (EndMT) is a major cellular behavioral mechanism that aims to increase the production of myofibroblasts (101), which are involved in
the pathogenesis and progression of renal fibrosis (102-105). Furthermore, EndMT serves a key role in the development of CKD (106,107).

PP2A activation occurs in mouse unilateral ureteral obstruction and TGF-β1-treated human umbilical vein endothelial cells (HUVECs) in vitro (10). Additionally, OA significantly inhibits the expression of α-smooth muscle actin (a fibroblast marker), which is induced by TGF-β1 and maintains the expression of VE cadherin in HUVECs (10). Furthermore, TGF-β1 decreases the abundance of phosphorylated serine and threonine residues in occludin immunoprecipitates, which is significantly inhibited by pretreatment with OA (10). Erythrocyte sphingosine 1-phosphate serves a beneficial role in CKD by promoting the activity of 2,3-BPG (an erythrocyte-specific metabolite that negatively regulates the binding affinity of hemoglobin-O2) and subsequently triggering O2 delivery to renal cells and tissues (108). These events counteract hypoxia-induced kidney damage and slow CKD progression by inhibiting PP2Ac activity (108). PP2Ac serves an important role in the dephosphorylation activity of PP2A (25), and it has been demonstrated that inhibition of PP2Ac by OA attenuates renal fibrosis by suppressing fibronectin and collagen I expression (109). These events reverse epithelial-mesenchymal transition in renal tubules, while ectopic overexpression of PP2Ac accelerates tubular extracellular matrix (ECM) accumulation in vitro (109) (Fig. 2).

Additionally, nitration of the PP2Ac tyrosine is crucial for PP2A activation during EndMT (10). Wu and Wilson (99) suggested that microvascular endothelial cells produce peroxynitrite, which nitrates PP2Ac under proinflammatory stimuli. This nitration enhances the activity of PP2A in the mediation of endothelial barrier dysfunction. Inhibition of NO and O2 production by NG-nitro-L-arginine methyl ester (an inhibitor of NO synthetases) and apocynin (APO, a specific inhibitor of NADPH oxidase) decreases the nitrification of PP2Ac and suppresses the process of EndMT via induction...
of TGF-β1 activity (99). Furthermore, tyrosine 127 (Tyr127) is essential for PP2Ac nitration, while inhibiting PP2Ac Tyr127 nitration with the peptide TAT-Y127WT effectively decreases PP2Ac nitration and ameliorates ECM deposition and capillary rarefaction (Fig. 2) (110). These results indicate that PP2Ac may be a novel drug target that could be used in anti-fibrotic therapies.

CKD is not only the main risk factor in acute myocardial infarction (AMI) but also an important factor in the reduced survival rate of patients with AMI (111-113). CKD downregulates PP2A-B55α protein expression, resulting in upregulated Akt-Thr308 phosphorylation (114). Decreased Akt activation, which is impaired by insufficient phosphorylation of ser473 during reperfusion, contributes to enlargement of myocardial infarct foci (114). These results indicate that PP2A activates the process of EndMT, while blocking PP2A signaling can inhibit this process. Therefore, inhibition of PP2A activity to prevent endothelial-mesenchymal transition is a promising strategy that could be used in anti-CKD therapies.

9. PP2A in renal inflammation

Inflammation, which is the process of detecting and eliminating harmful pathogens, is the main pathogenic mechanism of CKD and AKI (115). PP2A has been identified as an effective negative regulator of a number of different inflammatory signaling pathways (116,117), including dephosphorylation and inhibition of p65 NF-κB (118,119). An increase in PP2A activity by ATG attenuates the effects of NF-κB-mediated inflammation and enhances the stability of podocyte actin cytoskeleton via DBN1 dephosphorylation (79). The renal dopaminergic system is involved in the regulation of ROS production and the inflammatory response (120-125). A previous study indicated that dopamine D2 receptor (D2R) controls inflammation in the kidneys by modulating Akt dephosphorylation via PP2A (126). The increased PP2A activity inhibits increases in NF-κB activity, which are induced by D2R silencing (126). PP2A is also a major cellular phosphatase that can potentially contribute to NF-κB activity (127). In these events, PP2A regulates at least three different pathways, including TNF receptor-associated factor 2, IKK and MAPKs (ERK, p38, and JNK), leading to NF-κB activation (11). PP2A is also a negative regulator of TGF-β1-activated kinase 1 activation in cultured mesangial cells (129). Studies on senescence marker protein-30 (SMP30) have indicated that blocking the inactivation of PP1 and PP2A via oxidative stress leads to the activation of NF-κB in the kidneys of SMP30−/−mice (130). Therefore, PP2A regulation of NF-κB activity may provide a novel therapeutic target for the development of anti-inflammatory therapies in patients with kidney disease. Fig. 3 illustrates how PP2A regulates NF-κB by participating in a range of cellular and molecular mechanisms involved in renal inflammation.

10. Discussion

The current understanding of the structure and function of PP2A is extensive, and links between PP2A and renal diseases are becoming increasingly clear. PP2A serves diverse roles in renal pathophysiology, and normal PP2A activity is required for regulating ion channels to maintain the homeostasis of Na+, K+ and Cl- (49). PP2A also regulates the phosphorylation of AQP2 and its membrane accumulations to adjust urine...
concentration (63). Normal PP2A activity is critical not only in the formation and function of podocytes (21) but also in renal morphogenesis and development (40). It should be noted that patients with RCC who exhibit a higher PP2A expression have a higher chance of survival (12). PP2A expression may be useful in predicting patient prognosis and therapeutic outcomes in patients with RCC. PP2A has also been identified to be an antifibrotic factor and may be a promising therapeutic target in the treatment of renal fibrosis (23). In renal inflammation, PP2A is associated with a number of signaling pathways that regulate NF-kB activity (11,40,118,128). As PP2A serves numerous versatile roles in the pathogenic progression of kidney diseases, targeting PP2A in future therapeutics may improve patient outcomes. However, future studies should further examine the mechanisms of PP2A in the progression of kidney diseases.

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Authors' contributions

SW, JW and LY were involved in study conception and interpretation, writing and critically revising the manuscript. LS, YM and ZH wrote the manuscript. QF was involved with conception and design of the figures. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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