biomolecules

MDPI

Review

Inspiring Tactics with the Improvement of Mitophagy and Redox Balance for the Development of Innovative Treatment against Polycystic Kidney Disease

Moeka Nakashima, Naoko Suga, Yuka Ikeda, Sayuri Yoshikawa and Satoru Matsuda *

Department of Food Science and Nutrition, Nara Women's University, Kita-Uoya Nishimachi, Nara 630-8506, Japan
* Correspondence: smatsuda@cc.nara-wu.ac.jp

Abstract: Polycystic kidney disease (PKD) is the most common genetic form of chronic kidney disease (CKD), and it involves the development of multiple kidney cysts. Not enough medical breakthroughs have been made against PKD, a condition which features regional hypoxia and activation of the hypoxia-inducible factor (HIF) pathway. The following pathology of CKD can severely instigate kidney damage and/or renal failure. Significant evidence verifies an imperative role for mitophagy in normal kidney physiology and the pathology of CKD and/or PKD. Mitophagy serves as important component of mitochondrial quality control by removing impaired/dysfunctional mitochondria from the cell to warrant redox homeostasis and sustain cell viability. Interestingly, treatment with the peroxisome proliferator-activated receptor-α (PPAR-α) agonist could reduce the pathology of PDK and might improve the renal function of the disease via the modulation of mitophagy, as well as the condition of gut microbiome. Suitable modulation of mitophagy might be a favorable tactic for the prevention and/or treatment of kidney diseases such as PKD and CKD.

Keywords: polycystic kidney disease; chronic kidney disease; autophagy; mitophagy; mitochondria; hypoxia; adenosine monophosphate-activated protein kinase; gut microbiome

check for updates

Citation: Nakashima, M.; Suga, N.; Ikeda, Y.; Yoshikawa, S.; Matsuda, S. Inspiring Tactics with the Improvement of Mitophagy and Redox Balance for the Development of Innovative Treatment against Polycystic Kidney Disease. *Biomolecules* **2024**, *14*, 207. https://doi.org/10.3390/biom14020207

Academic Editor: Liang-Jun Yan

Received: 21 December 2023
Revised: 31 January 2024
Accepted: 8 February 2024
Published: 9 February 2024

Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

Polycystic kidney disease (PKD) is the most familiar genetic type of CKD. The condition is characterized by the development of multiple kidney cysts, and it could subsequently instigate kidney damage and/or renal failure [1]. This disease may be triggered by mutations in *PKD1* or *PKD2* genes, which encode the integral membrane proteins polycystin-1 and polycystin-2, respectively [2]. Interestingly, these PKD proteins are associated with decreased autophagy [2,3]. Autophagy has been found to be impaired in the epithelial cells of the kidneys in animal models of PKD, as well as in patients with PKD, suggesting that this impairment might contribute to the development and/or progression of PKD [4,5]. In addition, several agents, such as rapamycin, could protect against PKD, which might restore the autophagy in animal models [6]. Mechanistically, aberrant activation of the mammalian target of rapamycin (mTOR), a target molecule of rapamycin, has been shown to be linked to the impaired autophagy as well as the pathology of PKD [7]. Cyst enlargement in PKD kidneys may result in restricted areas of hypoxia [8]. Hypoxic stimuli may then increase the hypoxia-inducible factor-1α (HIF-1α) protein by preventing its degradation by the proteasome. Under hypoxic conditions, the phosphatidylinositol 3-kinase (PI3K) and the mTOR pathway might activate the expression of HIF-1α [9]. (Figure 1) Hypoxia-related events have been revealed to be linked with cyst formation [10,11]. HIF-1α has been found to be also highly expressed in dendritic cells, and its expression is relatively higher in radicular cysts than in odontogenic tumors [12]. In PKD, HIF-1α may not disturb initial cyst formation, but it is important for cyst progression and expansion in later stages of the disease [13]. Conversely, it has also been shown that HIF-1α inhibition could reduce

cystic growth [14]. Signaling pathways being related to the activation of HIF-1α during hypoxia could be contributing to cyst expansion in PKD [15]. Reactive oxygen species (ROS) have been also shown to stimulate cyst development in PKD. In addition, several tissues of PKD may exhibit elevated ROS levels that are positively interrelated with disease severity [15,16]. Peroxidation of phospholipids in animal and human kidneys may be caused by high amounts of ROS [17,18]. Cultured renal cysts and MDCK cell cysts in a three-dimensional setup have confirmed a relationship between lipid peroxidation and increased cyst size [14,19]. It is well-known that damaged mitochondria could induce the generation of ROS and may bring about an increase in membrane lipid peroxidation. Therefore, autophagy, mitochondria, hypoxia and/or ROS might be important administrators in the progression in PKD. Undoubtedly, these hypotheses need further investigation. In addition, despite remarkable efforts to clarify all features of PKD through wide-ranging translational research, there is still an unmet clinical requirement for biomarkers and/or prognosticators that may possibly predict the speed of disease progression [20–22]. A better comprehending of the pathophysiology of cystic expansion may lead to the advancement of potential therapies to slow cyst development and/or expansion. The development of innovative treatments that may act synergistically or have fewer side effects might considerably improve the treatment consequences.

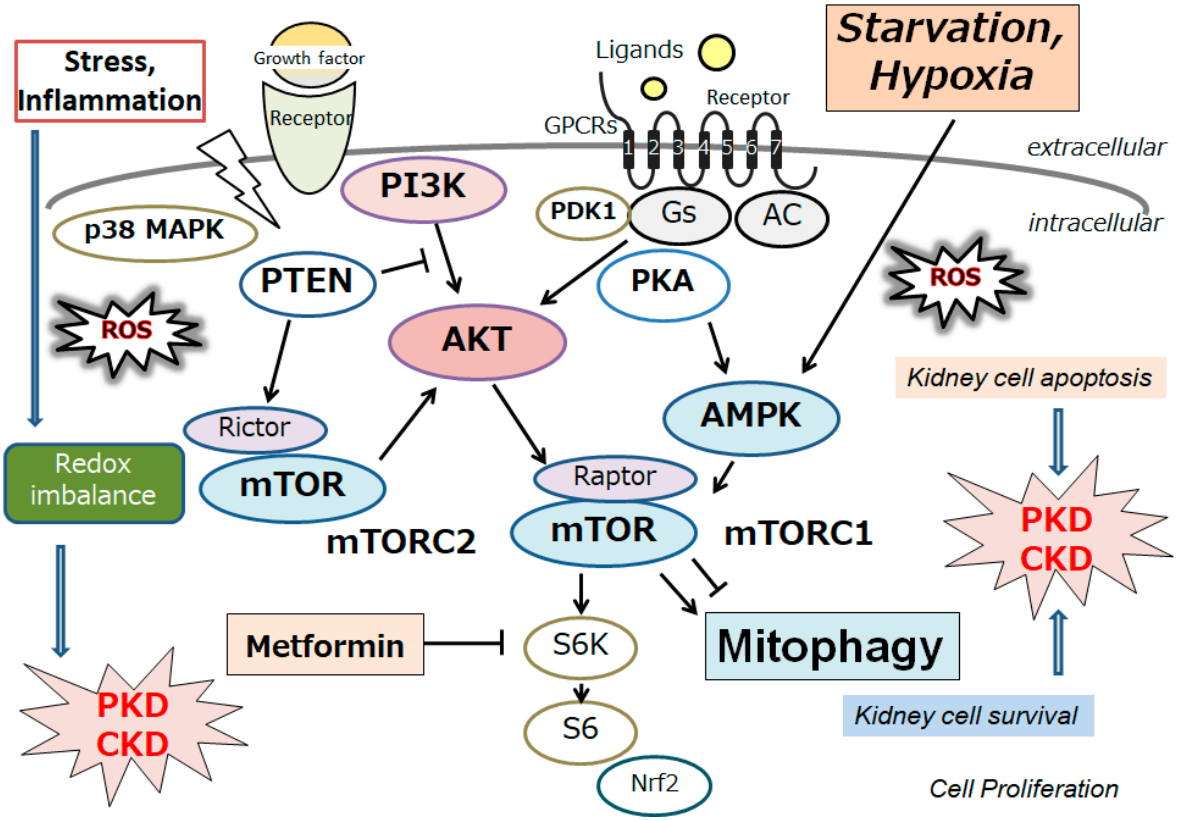

Figure 1. Schematic representation of the relevant signaling pathway potentially being involved in the pathogenesis of polycystic kidney disease (PKD) and/or chronic kidney disease (CKD). Several modulator molecules linked to the PI3K/AKT/mTOR/mTORC1 signaling pathway are demonstrated. Examples of compound metformin, as well as hypoxia and/or starvation, known to act on the AMPK/mTOR and/or mitophagy signaling, are also shown. Arrowhead indicates stimulation, whereas hammerhead shows inhibition. Note that several important activities, such as cytokine-induction and/or inflammatory reactions, have been omitted for clarity. Abbreviation: mTOR, mammalian/mechanistic target of rapamycin; PI3K, phosphoinositide-3 kinase; ROS, reactive oxygen species.

2. Autophagy/Mitophagy and Redox Imbalance in the Homeostasis of Kidney Cells

Substantial evidence has supported an imperative role for autophagy in kidney pathophysiology. Autophagy is firmly regulated to support cells to get used to and/or decrease cellular stress. Some studies have emphasized an intricate signaling system that could detect alterations in energy and/or nutrient condition to either activate or prevent autophagy. Intracellular stresses, which can be brought from ROS, hypoxia, stress of endoplasmic reticulum, several DNA damages and/or inflammatory immune signaling have been revealed as potential stimulators of autophagy [23]. Interestingly, autophagy has been defined as a HIF-1α-dependent response [24]. Autophagy describes the process by which cytoplasmic materials, including organelles, access the lysosomes for hydrolytic degeneration [25], which is also a course of cell repair that may frequently convey the apoptosis termed "self-killing" of cells [26]. Dying cells may frequently exhibit an accumulation of autophagosomes and hence adopt a morphology known as autophagic cell death [26]. Consequently, autophagic cell death might cause cell death with autophagy rather than cell death by autophagy. Hypoxia can regulate the mTOR complex 1 (mTORC1) [27]. Therefore, hypoxia and/or mTOR signaling may be modulators of autophagy [27]. (Figure 1) Mitochondria are particularly sensitive to hypoxa, which might result in both functional and morphological impairments. Mitophagy is an arrangement of autophagy that eliminates surplus mitochondria, facilitates reconstruction of mitochondria, and prevents the accumulation of impaired mitochondria [28]. Therefore, mitophagy might be a key mechanism for preserving the quality of mitochondria by eliminating damaged mitochondria. In response to hypoxia, the PTEN-induced putative kinase 1 (PINK1) may be activated as a regulator of mitophagy, confirming the suitable functioning of the total mitochondrial network [29]. Various stressors, such as hypoxia, ischemia, ageing, and oxidative stress, may lead to an increase in ROS and damages to mitochondria, which may trigger the PINK1 mediated mitophagy [30]. (Figure 2) There is evidence for weakened mitophagy in the renal cells of diabetic mice with reduced expressions of mitochondrial PINK1 [31]. A working mitophagy system may act as a scavenger of damaged mitochondria, and thereby maintain a decent mitochondrial homeostasis.

Mitophagy is principally facilitated by microtubule-associated protein 1 light chain 3 (LC3)-linked receptors. Ubiquitin-dependent mitophagy may include the mitochondrial serine/threonine protein kinase PINK1 and E3 ubiquitin protein ligase Parkin; it also may include the Parkin/PINK1 pathways [32]. Conclusions of the experiment in primary human renal epithelial cells have demonstrated that mitochondrial quality control could be disturbed by mitophagy mediated via PINK/Parkin signaling [33]. PINK1 accumulates on the outer mitochondrial membrane (OMM) after loss of mitochondrial membrane potential, where it recruits and then phosphorylates Parkin to add phosphor-ubiquitin chains on OMM proteins. Interestingly, mitophagy could inhibit oxidative stress via the upregulation of the PINK1-parkin pathway, which could delay kidney senescence in mice [34]. Autophagy receptors, including optineurin, calcium-binding and coiled-coil domain-containing protein 2, also called nuclear dot protein 52 kDa (NDP52), which comprise both ubiquitin binding domains and LC3-interacting regions, could link the ubiquitylated mitochondria to LC3-associated membranes for appropriation [35]. PINK1-mediated phosphorylation of ubiquitin can employ optineurin and/or NDP52 to induce mitophagy without Parkin. By attaching to LC3 at their cytosolic N-terminus, mitophagy receptors could connect impaired mitochondria directly to autophagosomes. (Figure 2) After ubiquitination, impaired mitochondria might be consequently recognized by adapter proteins to be eaten by autophagosomes. Too much mitophagy might result in cellular energy depletion. Therefore, mitophagy may positively or negatively regulate apoptosis, which is a double-edged sword in the pathogenesis of several diseases. For example, a high or low level of mitophagy activity may occasionally induce podocyte apoptosis, which is the collective pathological base for the progression of several kidney diseases [36]. In general, mitophagy may be induced as a protection mechanism for keeping a population of well mitochondria and thus safeguarding cell survival. Although mitophagy may be

dispensable for kidney development [37], mitophagy seems to be essential for maintaining kidney integrity and normal physiology in adult kidney cells [38]. Clearance of damaged mitochondria via mitophagy is valuable to the protective effect of impaired kidney cells [39].

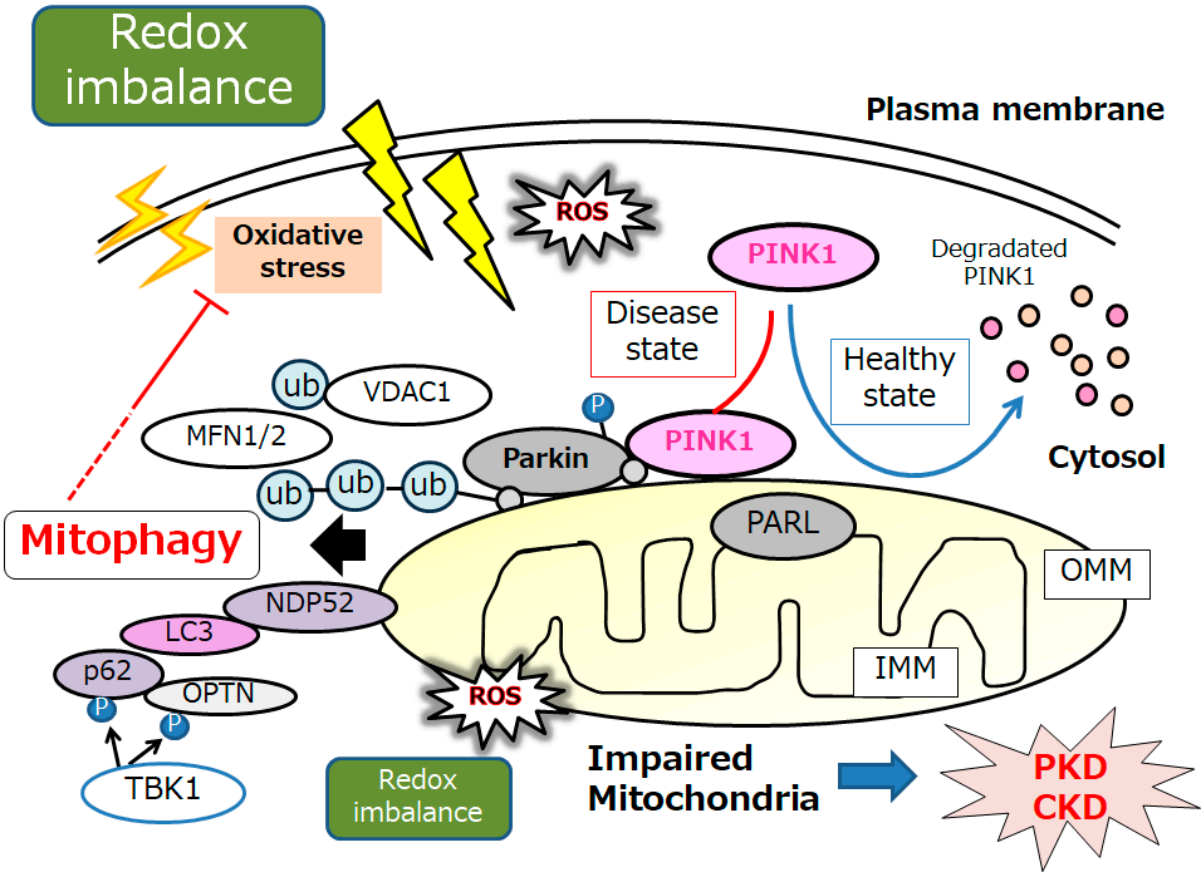

Figure 2. An illustrative representation and overview of PINK1, Parkin, and related molecules in the regulatory pathway for mitophagy. Under the healthy and steady state of cells, PINK1 is despoiled within the surface of mitochondria, which may be reduced by mitochondrial damage due to oxidative stress and/or redox imbalance, resulting in PINK1 and Parkin increases in the outer membrane of mitochondria. Mainly, the PINK1 could phosphorylate ubiquitin to activate the ubiquitin ligase activity for Parkin, where the Parkin is expected to be phosphorylated and ubiquitinated, resulting in the induction of mitophagy. OMM, outer mitochondrial membrane; IMM, inner mitochondrial membrane; MARK2, microtubule affinity regulating kinase 2; MFN1, mitofusin 1; MFN2, mitofusin 2; NDP52, nuclear dot protein 52; PARL, presenilin-associated rhomboid-like; OPTN, optineurin; PINK1, PTEN-induced kinase 1; ROS, reactive oxygen species; VDAC1, voltage-dependent anion channel 1; Ub, ubiquitin.

3. Autophagy/Mitophagy Involved in the Pathogenesis of Several Kidney Diseases, including Polycystic Kidney

Collecting evidence relates the impaired mitophagy with disease pathogenesis/progression in several pathological situations, including kidney diseases [40]. Acute kidney injury (AKI) may be categorized by a rapid weakening of kidney function, which typically results from renal ischemia, sepsis, and nephrotoxic agents [41]. Mitophagy induction might act as a mutual mechanism to kidney tubular cell protection in many models of AKI [42]. The mitophagy-mediated removal of injured mitochondria might inhibit excessive ROS accumulation, as well as prevent the release of damage-associated molecular arrays which might indorse inflammation during AKI. As renal tissue has massive mitochondrial content, mitophagy and/or mitochondrial biogenesis may be critical to overwhelming stressful illnesses, including AKI [42,43]. Mitophagy might enable compromised cells to persist

during kidney interstitial fibrosis, which is a feature of maladaptive restoration in the transition from AKI to chronic kidney disease (CKD) [44]. Mitophagy being induced in distal tubules and pericytes could protect against renal interstitial fibrosis by suppressing the inflammasome of the tumor growth factor β (TGFβ) and the NLR family pyrin domain containing 3 (NLRP3) signaling [45]. Therefore, mitophagy might be a pharmacological target for the management of interstitial fibrosis in kidneys, particularly in regard to offering new concepts for more efficient anti-fibrosis and delaying the development of CKD [46]. It has been shown that mitophagy activation may protect against renal fibrosis via the downregulation of TGF-β1/Smad signaling, improving mitochondrial fitness and alleviating inflammatory infiltration in kidneys [47]. Focal segmental glomerulosclerosis may be one of the fibrotic diseases in kidneys that is characterized by glomerular lesions with podocytes [48]. It has been revealed that podocyte mitophagy could have an imperative role in the development of the focal segmental glomerulosclerosis [48]. In addition, modifications of the apolipoprotein L1 (*APOL1*) gene have known links with the focal segmental glomerulosclerosis, which may affect endosomal trafficking and/or block mitophagic flux, eventually leading to podocyte injury [49]. Therefore, podocyte mitophagy could counteract the development of the focal segmental glomerulosclerosis [50]. A decrease in podocyte mitophagy may underlie the conceivable progression of podocytopathies, including the focal segmental glomerulosclerosis [51]. Interestingly, activation of mTORC1 has been detected in glomeruli from patients with the focal segmental glomerulosclerosis [52]. Hyperglycemia may inhibit mitophagy in kidney tubules of diabetic patients with diabetes mellitus [53]. It seems that mitophagy has been impaired in the diabetic kidneys of patients with diabetic kidney disease [53]. Defective mitophagy induced by high glucose levels may accelerate the senescence of tubular cells [54]. Treatment with the mitochondria-targeted antioxidant may ameliorate tubular injury in diabetic mice by restoring mitophagy, which might be mediated by an elevation in PINK1 expression provoked by nuclear factor erythroid 2-related factor 2 [53,54]. Therefore, mitophagy in kidney tubules might be helpful for diabetic kidney disease.

Autosomal-dominant polycystic kidney disease is a popular heritable human disease featuring the final development of renal failure, which is caused by mutations in either *PKD1* or *PKD2* genes. These gene product polycystins (PC1 and PC2) might play crucial roles in ensuring proper mitophagic processes. In fact, PKD is one of the most common ciliopathies that may be associated with decreased mitophagy [3,55]. The existence of cilia may to be essential in the activation of mitophagy [56]. Accordingly, impairment of mitophagy might suppress ciliagenesis [56]. At present, effective treatment seems to be lacking, while inhibition of mTOR may slow cyst expansion in animal models. Several agents that may protect against PKD in animal models could also restore mitophagy, suggesting that mitophagy might be associated with a pathogenic role in PKD [6,57]. Interestingly, abnormal mTOR activation could be connected to the impaired mitophagy and/or defective cilia in PKD [7,58].

4. Autophagy/Mitophagy as a Target of Treatment against Polycystic Kidney Disease

A number of studies have emphasized the dysregulation of mitophagy in PKD, representing both the augmented and diminished activities of mitophagy. Impaired mitophagy could lead to the accumulation of damaged mitochondria and cyst formation, while increased mitophagy might exacerbate the cyst growth. Therefore, treatment with chemical autophagy activators, including mTOR-dependent rapamycin, could slightly but noticeably attenuate cyst formation and repair the kidney function [59]. It has been shown that the *PKD1* gene, which encodes the polycystin-1 (PC1) protein, is responsible for 85% of cases of autosomal-dominant polycystic kidney disease [60]. The PC1 could regulate the function of calcium-dependent calpain proteases, which may preserve lysosomal integrity [61]. In addition, failure of PC1 function might be associated with the development of renal cysts and/or weakened kidney function. The polycystin-2 (PC2) constructs a complex with beclin-1, which might exert a key role involved in the formation of autophagic vac-

uole [62,63]. Therefore, PC2 is a critical mediator of mitophagy initiation [63,64]. Basal autophagy may be boosted in PC1-deficient cells, implying that PC1 might promote autophagic cell survival [65]. Interestingly, it has been shown that steviol, a metabolite of the sweetening chemical compound stevioside, could decelerate the cyst development in renal epithelial cells by increasing PC1 expression and by stimulating lysosomal degradation of β-catenin in animal models of PKD [66]. In addition, the stevioside metabolite could enhance the autophagy via the stimulation of an adenosine monophosphate-activated protein kinase (AMPK) pathway [67]. Trehalose is also a natural, nonreducing disaccharide comprising two glucose molecules linked by an α, α-1,1-glucosidic bond that has been shown to enhance autophagy. Trehalose is found in microorganisms, plants, insects, and invertebrates, but not in mammals [68]. Trehalose could defend the integrity of cells against several damages, including oxidation and/or hypoxia, by decreasing protein denaturation via the protein–trehalose interaction [69], which has been utilized in the preservation of food but also applied to deal with medical diseases because of its ability to augment autophagy. In adults, oral trehalose supplements may improve the vascular function by increasing redox balance [70]. Furthermore, trehalose may exert cytoprotective effects in podocytes and in proximal tubular cells by inducing autophagy [71,72].

In general, autophagy could be stimulated by nutrient and/or energy deprivation, which may be regulated by signaling pathways with AMPK and/or mTOR. The mTOR could construct the rapamycin-sensitive mTORC1 and the rapamycin-insensitive mTORC2, which might be key regulators of autophagy [73]. Under nutrient-rich conditions, however, mTORC1 suppresses autophagy by phosphorylating the unc-51-like autophagy activating kinase 1 (ULK1) and the autophagy related 13 (ATG13) [74]. Active mTORC1 could also stimulate ribosome biogenesis and mRNA translation by phosphorylating p70 ribosomal protein S6 kinase (p70S6K), as well as the eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1) [75]. Well-known inhibitors of mTORC1 include rapamycin and rapamycin analogues [76]. In hunger situations, mTORC1 is repressed and detaches from the ULK1–ULK2 complex, permitting ULK1 to be triggered by AMPK to induce autophagy [77]. Sirtuins, from SIRT1 to SIRT7, are nicotinamide adenine dinucleotide (NAD^+)-dependent class III histone deacetylases. In the conditions of energy depletion, SIRT1 Is stimulated by increased NAD^+ levels. Dynamic SIRT1 could activate autophagy through the deacetylation of ATG proteins and/or of the transcription factor forkhead box protein O1 (FOXO1) and forkhead box protein O3a (FOXO3a), which can transactivate autophagy genes [78–80]. Moreover, crosstalks of Sirtuin-1 (SIRT1) with the mTOR and AMPK pathway may control cell survival and/or autophagy by adjusting diverse mechanisms involved in energy metabolism [81,82]. Interestingly, resveratrol could appropriately activate SIRT1 [83], which might attenuate the oxidative stress and/or the mitochondrial dysfunction partly via the mitophagy [84]. SIRT1 is upregulated in the autosomal-dominant polycystic kidney disease and accelerates disease progression by deacetylating the p53 tumor suppressor. Niacinamide, also known as nicotinamide, is a dietary supplement and a non-competitive inhibitor of sirtuins that can reduce proliferation and augment apoptosis of cystic epithelial cells by preventing the deacetylation of p53 [85]. Long-term calorie restriction could restore the autophagic activity via the activation of SIRT1, which may protect from mitochondrial damages in the kidney induced by oxidative stress [86]. In addition, calorie restriction might also enhance the autophagy in podocytes and in proximal tubules [87]. Metformin could affect cells via the activation of AMPK [88,89], which is a key regulator of several pathways involved in energy, glucose, and lipid metabolism, as mentioned above. The blockade of AMPK signaling could considerably influence the efficiency of metformin for the type-2 diabetes mellitus and/or atherosclerosis [90,91]. Also, metformin plays roles in altering the pathogenesis of diseases by restoring the redox balance and influencing mitochondrial function [92,93]. Moreover, metformin can improve mitochondrial bioenergetics by increasing autophagy [94,95].

5. Another Tactic Regarding the Alteration of Gut Microbiome for the Treatment of Polycystic Kidney

Decreased fatty acid oxidation and/or a dysregulated lipid metabolism have been recognized as key PKD features [96]. Remarkably, treatment with the peroxisome proliferator-activated receptor-α (PPAR-α) agonist could enhance the fatty acid oxidation and reduce cystic disease in PKD models [97]. Peroxisome proliferator-activated receptors (PPARs) are categorized as members of the nuclear receptor family of transcription factors, which may be activated by several fatty acids and their derivatives [98]. It is well-known that some fatty acids may modulate the autophagy. In addition, gut microbiota may play crucial roles in some pathological processes through controlling several metabolic factors, including certain fatty acids [99]. Therefore, reciprocal interactions have been observed between PPARs and the gut microbiota in both healthy and diseased conditions, indicating that the nuclear receptors might be good targets for treatment of various diseases through the crosstalk with the gut microbiota [99]. The discovery of the gut–kidney axis may also establish the relationship between the disruption of gut homeostasis and CKD onset and/or progression, which may be regulated by the gut microbiota and/or immune cells [100,101]. Autosomal-dominant polycystic kidney disease may be the prominent cause of inherited kidney disease, with significant contributions to CKD [102]. Hence, treatment against CKD might be also beneficial for the treatment of polycystic kidney disease. The relationship between CKD and gut dysbiosis is also bidirectional. For example, gut-derived metabolites and/or toxins could influence the progression of CKD, and the uremic situation might also affect the gut microbiota [103]. Intestinal dysbiosis may contribute to the compromised intestinal barrier function, which could facilitate the translocation of uremic metabolites from the gut to the blood, contributing to the elevation of oxidative stress and CKD progression [104]. With increased permeability of the colon-intestinal epithelium, pathogens and/or antigens could come into systemic circulation, which may also lead to CKD progression. Remarkably, it has been shown that *Bifidobacterium* and *Lactobacilli* sp. in the gut may be negatively correlated with CKD progression and long-term survival [105]. In addition, the presence of *Roseburia*, *Faecalibacterium prausnitzii*, and/or *Prevotella* may be also negatively correlated with uremic toxin accumulation and disease progression [105]. The colon–intestinal tract might be protected by a huge number of immune cells and structures for the appropriate homeostasis. Several infections may be common factors in critical exacerbations of CKD, which may be resulting from immune and inflammatory responses [106,107]. Alterations in the gut microbiota might be sometimes beneficial for the CKD regression via the metabolic changes, immune modification, and/or reduced inflammation. Therefore, using prebiotics, probiotics, and/or fecal microbiota transplantation (FMT) to regulate the gut ecology may alleviate oxidative stress as well as improve kidney function [108]. (Figure 3) Remarkably, it has been reported that oral supplementation of short chain fatty acid may amend kidney functions in rats, possibly by enhancing autophagy/mitophagy via the AMPK/mTOR pathway [109]. Lastly, there is some evidence that the gut microbiome is possibly altered in patients with CKD and polycystic kidney disease [110].

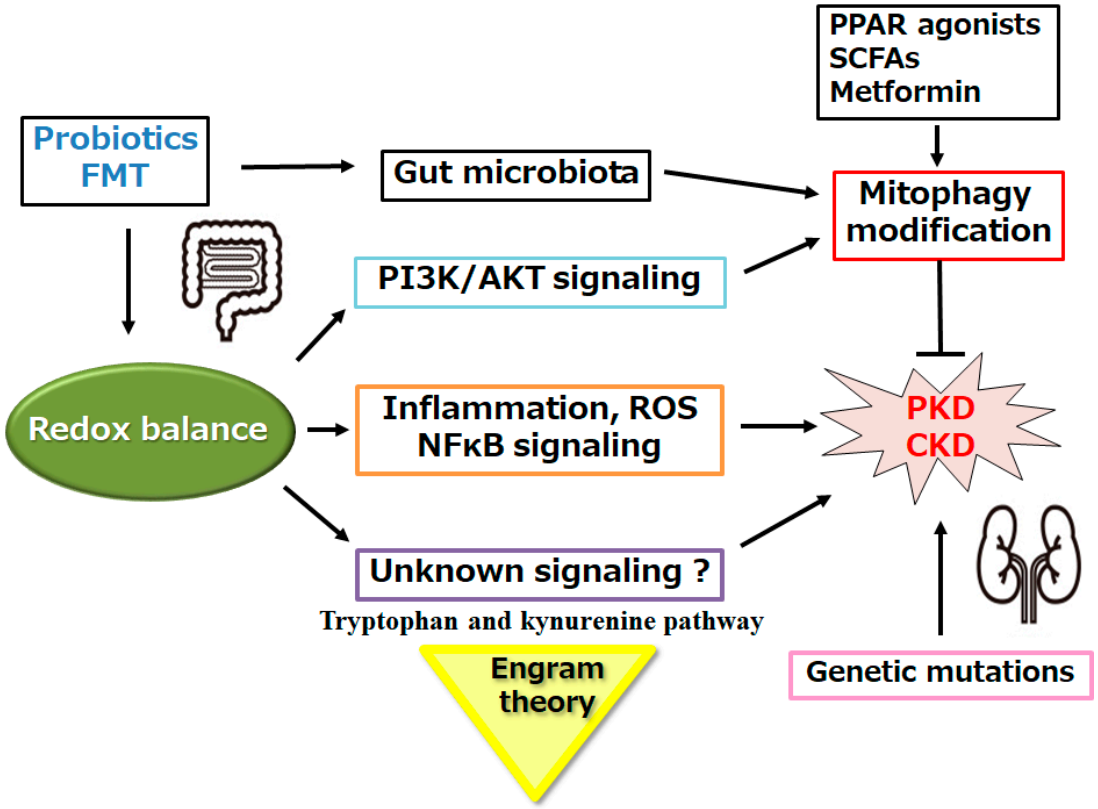

Figure 3. Schematic demonstration of the potential strategies against the pathogenesis of various kidney diseases, including polycystic kidney disease (PKD) and chronic kidney disease (CKD). Some kinds of probiotics and/or fecal microbiota transplantation (FMT) might assist the alteration of the gut microbiome for the modification of mitophagy, which might be advantageous in the treatment of several kidney diseases, including polycystic kidney disease (PKD) and chronic kidney disease (CKD). Note that some important activities, such as autophagy initiation, inflammatory reaction, and reactive oxygen species (ROS) production, have been misplaced for clarity. "?" represents author speculation. PPAR: peroxisome proliferator-activated receptor. SCFAs: short chain fatty acids.

6. Future Perspectives

Given the vital role of mitophagy in the development of various kidney diseases, suitable modulation of mitophagy might be a promising tactic for the prevention and/or treatment of kidney diseases, including polycystic kidney disease. In addition, pharmacological modulation of autophagy has been useful in some experimental models of AKI and chronic kidney injury (CKI). However, the precise advantageous function of mitophagy in kidney cells remains controversial. Although many signaling pathways may participate in the regulation of mitophagy in various organs, their detailed mechanisms also remain mostly unknown and/or complicated. Furthermore, signaling of mitophagy might interact with other cellular routes to influence the development of other renal diseases. Among them, CKD might be a major public health concern affecting more than 10% of the global population [111]. In general, dietary restrictions have been used to treat the CKD. Additionally, interventions such as synbiotics, prebiotics, and probiotics may improve the balance of the gut microbiota and enhance gut barrier function, which may also contribute to the amelioration of the kidney function.

Against the polycystic kidney diseases, however, those interventions with probiotics/prebiotics may be somewhat inadequate in regard to the improvement of the kidney function [109,110]. What are the additional factors/signaling required? Firstly, some antioxidants and/or redox balance might be valuable, as mentioned in the previous section. For example, significant studies have suggested that metformin exerts its favorable

effect by various mechanisms, including affecting mitochondrial function, restoring of redox balance, and modulating the gut microbiome, which may be apart from the AMPK-dependent mechanism [112]. Preceding studies have shown the inhibition of nuclear factor (erythroid-derived 2)-like 2 (Nrf2), which is involved in regulating the expression of antioxidant proteins such as heme-oxygenase 1(HO-1) and/or catalase in animal models of chronic kidney disease (CKD), and it also may increase the inflammation and oxidative stress [113]. Resveratrol may be favorable for saving the redox balance, which is a polyphenolic chemical compound isolated from *Veratrum grandiflorum* with a diversity of biological activities, including antioxidant and/or anti-inflammatory properties [114]. In fact, resveratrol administration could inhibit HIF-1α expression, which may reduce the production of hypoxia-induced reactive oxygen species (ROS) [115]. Secondly, some factors involved in the tryptophan and kynurenine pathway might also be conceivable, which has been shown to be associated with immune-related diseases [116]. Several studies have described abnormal expression of the genes-encoding factors of the immune response in autosomal-dominant polycystic kidney disease, in which the immune system and/or infiltration of immune cells may be mostly stimulated [117]. The events associated with inflammation and/or activation of the immune system might promote the pathology of PKD [118]. Therefore, both polycystic kidney and autosomal-dominant polycystic kidney disease may be also categorized as immune-related diseases. Shaped by repetitive inflammatory conditions, an "engram" might commit to a mild progression of several immune-related diseases [116]. If that is the case in PKD, a certain "engram" modulation with the modification of gut microbiome might be beneficial for a superior treatment tactic against PKD [116]. (Figure 3) Additionally, a substantial proportion of PKD patients may experience hypertension prior to kidney dysfunction [119]. Remarkably, a significant proportion of PKD patients with normal kidney function may also progress to hypertension prior to the development of polycysts, suggesting that PKD2 channels can regulate blood pressure, probably through an extrarenal mechanism [120]. Hypertension is an important prognosticator of the disease progression, which might be the most frequent cause of death in patients with autosomal-dominant polycystic kidney disease. Angiotensin-converting enzyme inhibitors may be used as therapeutic agents in the treatment of hypertension in autosomal-dominant polycystic kidney disease [121]. The therapeutic benefit of using angiotensin-converting enzyme inhibitors may contribute to treating hypertension, as well as to diminishing renal cyst growth in the autosomal-dominant polycystic kidney disease [122].

7. Conclusions

Mitophagy may play an imperative role in the pathology of various kidney diseases, including PKD, CKD and/or AKI. Appropriate mitophagy might be firmly regulated to enable cells to lessen cellular stress, probably via sustaining the redox balance. Prior research has indicated that those kidney diseases might be also related with gut dysbiosis, which may lead to the development and/or progression of kidney diseases. Superior modification of mitophagy in kidneys via the modulation of the gut microbiome may contribute to the development of prevention/treatment tactic for several kidney diseases, including PKD.

Author Contributions: Conceptualization, M.N., N.S., Y.I. and S.M.; original draft preparation and editing, M.N., N.S., Y.I., S.Y. and S.M.; visualization, M.N., N.S., Y.I. and S.M.; supervision, S.M. Each author (M.N., N.S., Y.I., S.Y. and S.M.) has participated sufficiently in the work of drafting the article and/or revising the article for important rational content. Then, all authors gave final approval of the version to be submitted. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare that they have no competing financial interests.

Abbreviations

AKI	Acute kidney injury
AMPK	adenosine monophosphate-activated protein kinase
APOL1	apolipoprotein L1
ATG13	autophagy related 13
CKD	chronic kidney disease
4E-BP1	eukaryotic translation initiation factor 4E-binding protein 1
eIF3	eukaryotic initiation factor 3
FMT	fecal microbiota transplantation
FOXO1	forkhead box protein O1
FOXO3a	forkhead box protein O3a
HIF-1α	hypoxia inducible factor-1α
HO-1	heme-oxygenase 1
LC3	microtubule-associated protein 1 light chain 3
mRNAs	messenger RNAs
mTOR	mechanistic/mammalian target of rapamycin
mTORC1	mTOR complex 1
mTORC2	mTOR complex 2
NAD+	nicotinamide adenine dinucleotide
NDP52	nuclear dot protein 52 kDa
NLRP3	NLR family pyrin domain containing 3
Nrf2	nuclear factor (erythroid-derived 2)-like 2
ORF	open reading framework
p70S6K	p70 ribosomal protein S6 kinase
PC1	polycystin-1
PC2	polycystin-2
PINK1	PTEN-induced putative kinase 1
PKD	Polycystic kidney disease
PPAR-α	peroxisome proliferator-activated receptor-α
PPARs	Peroxisome proliferator-activated receptors
SIRT1	Sirtuin-1
TGFβ	tumor growth factor β
ULK1	unc-51-like autophagy activating kinase 1
ULK2	unc-51-like autophagy activating kinase 2

References

1. Torres, V.E.; Harris, P.C. Progress in the understanding of polycystic kidney disease. *Nat. Rev. Nephrol.* **2019**, *15*, 70–72. [CrossRef]
2. Harris, P.C.; Rossetti, S. Molecular diagnostics for autosomal dominant polycystic kidney disease. *Nat. Rev. Nephrol.* **2010**, *6*, 197–206. [CrossRef] [PubMed]
3. Anvarian, Z.; Mykytyn, K.; Mukhopadhyay, S.; Pedersen, L.B.; Christensen, S.T. Cellular signalling by primary cilia in development, organ function and disease. *Nat. Rev. Nephrol.* **2019**, *15*, 199–219. [CrossRef] [PubMed]
4. Belibi, F.; Zafar, I.; Ravichandran, K.; Segvic, A.B.; Jani, A.; Ljubanovic, D.G.; Edelstein, C.L. Hypoxia-inducible factor-1α (HIF-1α) and autophagy in polycystic kidney disease (PKD). *Am. J. Physiol. Renal Physiol.* **2011**, *300*, F1235–F1243. [CrossRef] [PubMed]
5. Nowak, K.L.; Edelstein, C.L. Apoptosis and autophagy in polycystic kidney disease (PKD). *Cell. Signal.* **2020**, *68*, 109518. [CrossRef] [PubMed]
6. Li, A.; Fan, S.; Xu, Y.; Meng, J.; Shen, X.; Mao, J.; Zhang, L.; Zhang, X.; Moeckel, G.; Wu, D.; et al. Rapamycin treatment dose-dependently improves the cystic kidney in a new ADPKD mouse model via the mTORC1 and cell-cycle-associated CDK1/cyclin axis. *J. Cell. Mol. Med.* **2017**, *21*, 1619–1635. [CrossRef] [PubMed]
7. Kou, P.; Wei, S.; Xiong, F. Recent advances of mTOR inhibitors use in autosomal dominant polycystic kidney disease: Is the road still open? *Curr. Med. Chem.* **2019**, *26*, 2962–2973. [CrossRef] [PubMed]
8. Zeier, M.; Jones, E.; Ritz, E. Autosomal dominant polycystic kidney disease—The patient on renal replacement therapy. *Nephrol. Dial. Transplant.* **1996**, *11* (Suppl. S6), 18–20. [CrossRef] [PubMed]
9. Dery, M.C.; Michaud, M.D.; Richard, D.E. Hypoxia-inducible factor 1: Regulation by hypoxic and non-hypoxic activators. *Int. J. Biochem. Cell Biol.* **2005**, *37*, 535–540. [CrossRef]
10. De Mendonça, R.P.; Balbinot, K.M.; Martins, B.V.; da Silva Kataoka, M.S.; Mesquita, R.A.; de Jesus Viana Pinheiro, J.; de Melo Alves Júnior, S. Hypoxia and proangiogenic proteins in human ameloblastoma. *Sci. Rep.* **2020**, *10*, 17567. [CrossRef]

11. Pereira-Prado, V.; Vigil-Bastitta, G.; Sánchez-Romero, C.; Arocena, M.; Molina-Frechero, N.; González-González, R.; Meleti, M.; Bologna-Molina, R. Immunoexpression of galectin-3 and its potential relation to hypoxia-inducible factor-1α in ameloblastomas. *Biotech. Histochem.* **2021**, *96*, 296–301. [CrossRef] [PubMed]
12. Da Costa, N.M.M.; de Siqueira, A.S.; Ribeiro, A.L.R.; da Silva Kataoka, M.S.; Jaeger, R.G.; de Alves-Júnior, S.M.; Smith, A.M.; de Jesus Viana Pinheiro, J. Role of HIF-1α and CASPASE-3 in cystogenesis of odontogenic cysts and tumors. *Clin. Oral. Investig.* **2018**, *22*, 141–149. [CrossRef]
13. Buchholz, B.; Eckardt, K.U. Role of oxygen and the HIF-pathway in polycystic kidney disease. *Cell. Signal.* **2020**, *69*, 109524. [CrossRef] [PubMed]
14. Buchholz, B.; Schley, G.; Faria, D.; Kroening, S.; Willam, C.; Schreiber, R.; Klanke, B.; Burzlaff, N.; Jantsch, J.; Kunzelmann, K.; et al. Hypoxia-inducible factor-1α causes renal cyst expansion through calcium-activated chloride secretion. *J. Am. Soc. Nephrol.* **2014**, *25*, 465–474. [CrossRef] [PubMed]
15. Li, Z.L.; Ding, L.; Ma, R.X.; Zhang, Y.; Zhang, Y.L.; Ni, W.J.; Tang, T.T.; Wang, G.H.; Wang, B.; Lv, L.L.; et al. Activation of HIF-1α C-terminal transactivation domain protects against hypoxia-induced kidney injury through hexokinase 2-mediated mitophagy. *Cell Death Dis.* **2023**, *14*, 339. [CrossRef] [PubMed]
16. Schreiber, R.; Buchholz, B.; Kraus, A.; Schley, G.; Scholz, J.; Ousingsawat, J.; Kunzelmann, K. Lipid peroxidation drives renal cyst growth in vitro through activation of TMEM16A. *J. Am. Soc. Nephrol.* **2019**, *30*, 228–242. [CrossRef] [PubMed]
17. Jiang, W.; Liu, J.; Cui, J.; Su, J.; Xu, W.; Zhang, F.; Ding, Y. Ferroptosis plays a crucial role in lung cell damage caused by ventilation stretch. *Free Radic. Biol. Med.* **2023**, *209 Pt 1*, 84–95. [CrossRef] [PubMed]
18. Zhang, X.; Li, L.X.; Ding, H.; Torres, V.E.; Yu, C.; Li, X. Ferroptosis Promotes Cyst Growth in Autosomal Dominant Polycystic Kidney Disease Mouse Models. *J. Am. Soc. Nephrol.* **2021**, *32*, 2759–2776. [CrossRef]
19. Falchook, G.S.; Wheler, J.J.; Naing, A.; Jackson, E.F.; Janku, F.; Hong, D.; Ng, C.S.; Tannir, N.M.; Lawhorn, K.N.; Huang, M.; et al. Targeting hypoxia-inducible factor-1α (HIF-1α) in combination with antiangiogenic therapy: A phase I trial of bortezomib plus bevacizumab. *Oncotarget* **2014**, *5*, 10280–10292. [CrossRef]
20. Gregory, A.V.; Chebib, F.T.; Poudyal, B.; Holmes, H.L.; Yu, A.S.L.; Landsittel, D.P.; Bae, K.T.; Chapman, A.B.; Frederic, R.O.; Mrug, M.; et al. Utility of new image-derived biomarkers for autosomal dominant polycystic kidney disease prognosis using automated instance cyst segmentation. *Kidney Int.* **2023**, *104*, 334–342. [CrossRef]
21. Kim, Y.; Tao, C.; Kim, H.; Oh, G.Y.; Ko, J.; Bae, K.T. A Deep Learning Approach for Automated Segmentation of Kidneys and Exophytic Cysts in Individuals with Autosomal Dominant Polycystic Kidney Disease. *J. Am. Soc. Nephrol.* **2022**, *33*, 1581–1589. [CrossRef] [PubMed]
22. Raj, A.; Tollens, F.; Hansen, L.; Golla, A.K.; Schad, L.R.; Nörenberg, D.; Zöllner, F.G. Deep Learning-Based Total Kidney Volume Segmentation in Autosomal Dominant Polycystic Kidney Disease Using Attention, Cosine Loss, and Sharpness Aware Minimization. *Diagnostics* **2022**, *12*, 1159. [CrossRef] [PubMed]
23. Kroemer, G.; Marino, G.; Levine, B. Autophagy and the integrated stress response. *Mol. Cell* **2010**, *40*, 280–293. [CrossRef]
24. Zhang, H.; Bosch-Marce, M.; Shimoda, L.A.; Tan, Y.S.; Baek, J.H.; Wesley, J.B.; Gonzalez, F.J.; Semenza, G.L. Mitochondrial autophagy is an HIF-1α-dependent adaptive metabolic response to hypoxia. *J. Biol. Chem.* **2008**, *283*, 10892–10903. [PubMed]
25. Mizushima, N.; Yoshimori, T.; Levine, B. Methods in mammalian autophagy research. *Cell* **2010**, *140*, 313–326. [CrossRef] [PubMed]
26. Kroemer, G.; Levine, B. Autophagic cell death: The story of a misnomer. *Nat. Rev. Mol. Cell Biol.* **2008**, *9*, 1004–1010. [CrossRef]
27. Jung, C.H.; Ro, S.H.; Cao, J.; Otto, N.M.; Kim, D.H. mTOR regulation of autophagy. *FEBS Lett.* **2010**, *584*, 1287–1295. [CrossRef]
28. Li, A.; Gao, M.; Liu, B.; Qin, Y.; Chen, L.; Liu, H.; Wu, H.; Gong, G. Mitochondrial autophagy: Molecular mechanisms and implications for cardiovascular disease. *Cell Death Dis.* **2022**, *13*, 444. [CrossRef]
29. Chen, M.; Wang, W.; Fu, X.; Yi, Y.; Wang, K.; Wang, M. Role of Pink1-mediated mitophagy in adenomyosis. *PeerJ* **2023**, *11*, e16497. [CrossRef]
30. Ji, Y.; Leng, Y.; Lei, S.; Qiu, Z.; Ming, H.; Zhang, Y.; Zhang, A.; Wu, Y.; Xia, Z. The mitochondria-targeted antioxidant MitoQ ameliorates myocardial ischemia-reperfusion injury by enhancing PINK1/Parkin-mediated mitophagy in type 2 diabetic rats. *Cell Stress Chaperones* **2022**, *27*, 353–367. [CrossRef]
31. Feng, J.; Lu, C.; Dai, Q.; Sheng, J.; Xu, M. SIRT3 Facilitates Amniotic Fluid Stem Cells to Repair Diabetic Nephropathy through Protecting Mitochondrial Homeostasis by Modulation of Mitophagy. *Cell. Physiol. Biochem.* **2018**, *46*, 1508–1524. [CrossRef]
32. Tang, C.; Livingston, M.J.; Liu, Z.; Dong, Z. Autophagy in kidney homeostasis and disease. *Nat. Rev. Nephrol.* **2020**, *16*, 489–508. [CrossRef]
33. Chen, K.; Chen, J.; Wang, L.; Yang, J.; Xiao, F.; Wang, X.; Yuan, J.; Wang, L.; He, Y. Parkin Ubiquitinates GATA4 and Attenuates the GATA4/GAS1 Signaling and Detrimental Effects on Diabetic Nephropathy. *FASEB J.* **2020**, *34*, 8858–8875. [CrossRef]
34. E, Y.; Lin, Y.; Yan, G.; Yang, J.; Jiao, L.; Wu, R.; Yan, Q.; Chen, Y.; Chen, Y.; Yan, X.; et al. Exogenous H_2**S** alleviates senescence of glomerular mesangial cells through up-regulating mitophagy by activation of AMPK-ULK1-PINK1-parkin pathway in mice. *Biochim. Biophys. Acta Mol. Cell Res.* **2023**, *1870*, 119568. [CrossRef] [PubMed]
35. Saha, B.; Olsvik, H.; Williams, G.L.; Oh, S.; Evjen, G.; Sjøttem, E.; Mandell, M.A. TBK1 is ubiquitinated by TRIM5α to assemble mitophagy machinery. *bioRxiv* **2023**. [CrossRef]
36. Gao, X.; Liu, Y.; Wang, L.; Sai, N.; Liu, Y.; Ni, J. Morroniside Inhibits H_2O_2-Induced Podocyte Apoptosis by Down-Regulating NOX4 Expression Controlled by Autophagy In Vitro. *Front. Pharmacol.* **2020**, *11*, 533809. [CrossRef] [PubMed]

37. Liu, S.; Hartleben, B.; Kretz, O.; Wiech, T.; Igarashi, P.; Mizushima, N.; Walz, G.; Huber, T.B. Autophagy plays a critical role in kidney tubule maintenance, aging and ischemia-reperfusion injury. *Autophagy* **2012**, *8*, 826–837. [CrossRef] [PubMed]
38. Forbes, M.S.; Thornhill, B.A.; Chevalier, R.L. Proximal tubular injury and rapid formation of atubular glomeruli in mice with unilateral ureteral obstruction: A new look at an old model. *Am. J. Physiol. Renal Physiol.* **2011**, *301*, F110–F117. [CrossRef] [PubMed]
39. Livingston, M.J.; Wang, J.; Zhou, J.; Wu, G.; Ganley, I.G.; Hill, J.A.; Yin, X.M.; Dong, Z. Clearance of damaged mitochondria via mitophagy is important to the protective effect of ischemic preconditioning in kidneys. *Autophagy* **2019**, *15*, 2142–2162. [CrossRef] [PubMed]
40. Su, L.; Zhang, J.; Gomez, H.; Kellum, J.A.; Peng, Z. Mitochondria ROS and mitophagy in acute kidney injury. *Autophagy* **2023**, *19*, 401–414. [CrossRef] [PubMed]
41. Su, L.; Zhang, J.; Wang, J.; Wang, X.; Cao, E.; Yang, C.; Sun, Q.; Sivakumar, R.; Peng, Z. Pannexin 1 targets mitophagy to mediate renal ischemia/reperfusion injury. *Commun. Biol.* **2023**, *6*, 889. [CrossRef]
42. Wang, Y.; Cai, J.; Tang, C.; Dong, Z. Mitophagy in acute kidney injury and kidney repair. *Cells* **2020**, *9*, 338. [CrossRef]
43. Bhatia, D.; Choi, M.E. The emerging role of mitophagy in kidney diseases. *J. Life Sci.* **2019**, *1*, 13–22. [CrossRef]
44. Baisantry, A.; Bhayana, S.; Rong, S.; Ermeling, E.; Wrede, C.; Hegermann, J.; Pennekamp, P.; Sörensen-Zender, I.; Haller, H.; Melk, A.; et al. Autophagy induces prosenescent changes in proximal tubular S3 segments. *J. Am. Soc. Nephrol.* **2016**, *27*, 1609–1616. [CrossRef] [PubMed]
45. Nam, S.A.; Kim, W.Y.; Kim, J.W.; Kang, M.G.; Park, S.H.; Lee, M.S.; Kim, H.W.; Yang, C.W.; Kim, J.; Kim, Y.K. Autophagy in FOXD1 stroma-derived cells regulates renal fibrosis through TGF-beta and NLRP3 inflammasome pathway. *Biochem. Biophys. Res. Commun.* **2019**, *508*, 965–972. [CrossRef] [PubMed]
46. Sun, J.; Liu, C.; Liu, Y.Y.; Guo, Z.A. Mitophagy in renal interstitial fibrosis. *Int. Urol. Nephrol.* **2023**, *56*, 167–179. [CrossRef] [PubMed]
47. Jin, L.; Yu, B.; Liu, G.; Nie, W.; Wang, J.; Chen, J.; Xiao, L.; Xia, H.; Han, F.; Yang, Y. Mitophagy induced by UMI-77 preserves mitochondrial fitness in renal tubular epithelial cells and alleviates renal fibrosis. *FASEB J.* **2022**, *36*, e22342. [CrossRef]
48. 48 Rosenberg, A.Z.; Kopp, J.B. Focal Segmental Glomerulosclerosis. *Clin. J. Am. Soc. Nephrol.* **2017**, *12*, 502–517. [CrossRef]
49. Kumar, V.; Ayasolla, K.; Jha, A.; Mishra, A.; Vashistha, H.; Lan, X.; Qayyum, M.; Chinnapaka, S.; Purohit, R.; Mikulak, J.; et al. Disrupted apolipoprotein L1-miR193a axis dedifferentiates podocytes through autophagy blockade in an APOL1 risk milieu. *Am. J. Physiol. Cell Physiol.* **2019**, *317*, C209–C225. [CrossRef]
50. Asanuma, K.; Tanida, I.; Shirato, I.; Ueno, T.; Takahara, H.; Nishitani, T.; Kominami, E.; Tomino, Y. MAP-LC3, a promising autophagosomal marker, is processed during the differentiation and recovery of podocytes from PAN nephrosis. *FASEB J.* **2003**, *17*, 1165–1167. [CrossRef]
51. Zeng, C.; Fan, Y.; Wu, J.; Shi, S.; Chen, Z.; Zhong, Y.; Zhang, C.; Zen, K.; Liu, Z. Podocyte autophagic activity plays a protective role in renal injury and delays the progression of podocytopathies. *J. Pathol.* **2014**, *234*, 203–213. [CrossRef]
52. Zschiedrich, S.; Bork, T.; Liang, W.; Wanner, N.; Eulenbruch, K.; Munder, S.; Hartleben, B.; Kretz, O.; Gerber, S.; Simons, M.; et al. Targeting mTOR signaling can prevent the progression of FSGS. *J. Am. Soc. Nephrol.* **2017**, *28*, 2144–2157. [CrossRef]
53. Ma, Z.; Li, L.; Livingston, M.J.; Zhang, D.; Mi, Q.; Zhang, M.; Ding, H.F.; Huo, Y.; Mei, C.; Dong, Z. p53/microRNA-214/ULK1 axis impairs renal tubular autophagy in diabetic kidney disease. *J. Clin. Investig.* **2020**, *130*, 5011–5026. [CrossRef]
54. Chen, K.; Dai, H.; Yuan, J.; Chen, J.; Lin, L.; Zhang, W.; Wang, L.; Zhang, J.; Li, K.; He, Y. Optineurin-mediated mitophagy protects renal tubular epithelial cells against accelerated senescence in diabetic nephropathy. *Cell Death Dis.* **2018**, *9*, 105. [CrossRef] [PubMed]
55. Kim, Y.; Li, C.; Gu, C.; Fang, Y.; Tycksen, E.; Puri, A.; Pietka, T.A.; Sivapackiam, J.; Kidd, K.; Park, S.J.; et al. MANF stimulates autophagy and restores mitochondrial homeostasis to treat autosomal dominant tubulointerstitial kidney disease in mice. *Nat. Commun.* **2023**, *14*, 6493. [CrossRef] [PubMed]
56. Pampliega, O.; Cuervo, A.M. Autophagy and primary cilia: Dual interplay. *Curr. Opin. Cell Biol.* **2016**, *39*, 1–7. [CrossRef] [PubMed]
57. Ramírez-Sagredo, A.; Quiroga, C.; Garrido-Moreno, V.; López-Crisosto, C.; Leiva-Navarrete, S.; Norambuena-Soto, I.; Ortiz-Quintero, J.; Díaz-Vesga, M.C.; Perez, W.; Hendrickson, T.; et al. Polycystin-1 regulates cardiomyocyte mitophagy. *FASEB J.* **2021**, *35*, e21796. [CrossRef] [PubMed]
58. Santoni, M.; Piva, F.; Cimadamore, A.; Giulietti, M.; Battelli, N.; Montironi, R.; Cosmai, L.; Porta, C. Exploring the Spectrum of Kidney Ciliopathies. *Diagnostics* **2020**, *10*, 1099. [CrossRef] [PubMed]
59. Zhu, P.; Sieben, C.J.; Xu, X.; Harris, P.C.; Lin, X. Autophagy activators suppress cystogenesis in an autosomal dominant polycystic kidney disease model. *Hum. Mol. Genet.* **2017**, *26*, 158–172. [CrossRef] [PubMed]
60. Lea, W.A.; Winklhofer, T.; Zelenchuk, L.; Sharma, M.; Rossol-Allison, J.; Fields, T.A.; Reif, G.; Calvet, J.P.; Bakeberg, J.L.; Wallace, D.P.; et al. Polycystin-1 Interacting Protein-1 (CU062) Interacts with the Ectodomain of Polycystin-1 (PC1). *Cells* **2023**, *12*, 2166. [CrossRef] [PubMed]
61. Peintner, L.; Venkatraman, A.; Waeldin, A.; Hofherr, A.; Busch, T.; Voronov, A.; Viau, A.; Kuehn, E.W.; Köttgen, M.; Borner, C. Loss of PKD1/Polycystin-1 Impairs Lysosomal Activity in a CAPN (Calpain)-Dependent Manner. *Autophagy* **2021**, *17*, 2384–2400. [CrossRef]

62. Peña-Oyarzun, D.; Rodriguez-Peña, M.; Burgos-Bravo, F.; Vergara, A.; Kretschmar, C.; Sotomayor-Flores, C.; Ramirez-Sarmiento, C.A.; De Smedt, H.; Reyes, M.; Perez, W.; et al. PKD2/Polycystin-2 Induces Autophagy by Forming a Complex with BECN1. *Autophagy* **2021**, *17*, 1714–1728. [CrossRef]
63. Pan, F.; Bu, L.; Wu, K.; Wang, A.; Xu, X. PKD2/polycystin-2 inhibits LPS-induced acute lung injury in vitro and in vivo by activating autophagy. *BMC Pulm. Med.* **2023**, *23*, 171. [CrossRef]
64. Criollo, A.; Altamirano, F.; Pedrozo, Z.; Schiattarella, G.G.; Li, D.L.; Rivera-Mejías, P.; Sotomayor-Flores, C.; Parra, V.; Villalobos, E.; Battiprolu, P.K.; et al. Polycystin-2-Dependent Control of Cardiomyocyte Autophagy. *J. Mol. Cell. Cardiol.* **2018**, *118*, 110–121. [CrossRef]
65. Decuypere, J.-P.; Ceulemans, L.J.; Agostinis, P.; Monbaliu, D.; Naesens, M.; Pirenne, J.; Jochmans, I. Autophagy and the Kidney: Implications for Ischemia-Reperfusion Injury and Therapy. *Am. J. Kidney Dis.* **2015**, *66*, 699–709. [CrossRef]
66. Yuajit, C.; Muanprasat, C.; Homvisasevongsa, S.; Chatsudthipong, V. Steviol Stabilizes Polycystin 1 Expression and Promotes Lysosomal Degradation of CFTR and β-Catenin Proteins in Renal Epithelial Cells. *Biomed. Pharmacother.* **2017**, *94*, 820–826. [CrossRef]
67. Mei, Y.; Hu, H.; Deng, L.; Sun, X.; Tan, W. Therapeutic effects of isosteviol sodium on non-alcoholic fatty liver disease by regulating autophagy via Sirt1/AMPK pathway. *Sci. Rep.* **2022**, *12*, 12857. [CrossRef]
68. Collins, J.; Robinson, C.; Danhof, H.; Knetsch, C.W.; van Leeuwen, H.C.; Lawley, T.D.; Auchtung, J.M.; Britton, R.A. Dietary trehalose enhances virulence of epidemic Clostridium difficile. *Nature* **2018**, *553*, 291–294. [CrossRef] [PubMed]
69. Chen, Q.; Haddad, G.G. Role of trehalose phosphate synthase and trehalose during hypoxia: From flies to mammals. *J. Exp. Biol.* **2004**, *207 Pt 18*, 3125–3129. [CrossRef] [PubMed]
70. Kaplon, R.E.; Hill, S.D.; Bispham, N.Z.; Santos-Parker, J.R.; Nowlan, M.J.; Snyder, L.L.; Chonchol, M.; LaRocca, T.J.; McQueen, M.B.; Seals, D.R. Oral trehalose supplementation improves resistance artery endothelial function in healthy middle-aged and older adults. *Aging* **2016**, *8*, 1167–1183. [CrossRef] [PubMed]
71. Kang, Y.L.; Saleem, M.A.; Chan, K.W.; Yung, B.Y.; Law, H.K. Trehalose, an mTOR independent autophagy inducer, alleviates human podocyte injury after puromycin aminonucleoside treatment. *PLoS ONE* **2014**, *9*, e113520. [CrossRef] [PubMed]
72. Wang, X.Y.; Yang, H.; Wang, M.G.; Yang, D.B.; Wang, Z.Y.; Wang, L. Trehalose protects against cadmium-induced cytotoxicity in primary rat proximal tubular cells via inhibiting apoptosis and restoring autophagic flux. *Cell Death Dis.* **2017**, *8*, e3099. [CrossRef] [PubMed]
73. Liu, G.Y.; Sabatini, D.M. mTOR at the nexus of nutrition, growth, ageing and disease. *Nat. Rev. Mol. Cell Biol.* **2020**, *21*, 183–203. [CrossRef] [PubMed]
74. Woo, M.; Choi, H.I.; Park, S.H.; Ahn, J.; Jang, Y.J.; Ha, T.Y.; Lee, D.H.; Seo, H.D.; Jung, C.H. The unc-51 like autophagy activating kinase 1-autophagy related 13 complex has distinct functions in tunicamycin-treated cells. *Biochem. Biophys. Res. Commun.* **2020**, *524*, 744–749. [CrossRef] [PubMed]
75. Kim, J.; Kundu, M.; Viollet, B.; Guan, K.L. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. *Nat. Cell Biol.* **2011**, *13*, 132–141. [CrossRef]
76. Galluzzi, L.; Bravo-San Pedro, J.M.; Levine, B.; Green, D.R.; Kroemer, G. Pharmacological modulation of autophagy: Therapeutic potential and persisting obstacles. *Nat. Rev. Drug Discov.* **2017**, *16*, 487–511. [CrossRef]
77. Hosokawa, N.; Hara, T.; Kaizuka, T.; Kishi, C.; Takamura, A.; Miura, Y.; Iemura, S.; Natsume, T.; Takehana, K.; Yamada, N.; et al. Nutrient-dependent mTORC1 association with the ULK1-Atg13-FIP200 complex required for autophagy. *Mol. Biol. Cell* **2009**, *20*, 1981–1991. [CrossRef]
78. Lee, I.H.; Cao, L.; Mostoslavsky, R.; Lombard, D.B.; Liu, J.; Bruns, N.E.; Tsokos, M.; Alt, F.W.; Finkel, T. A role for the NAD-dependent deacetylase Sirt1 in the regulation of autophagy. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 3374–3379. [CrossRef]
79. Huang, R.; Xu, Y.; Wan, W.; Shou, X.; Qian, J.; You, Z.; Liu, B.; Chang, C.; Zhou, T.; Lippincott-Schwartz, J.; et al. Deacetylation of nuclear LC3 drives autophagy initiation under starvation. *Mol. Cell* **2015**, *57*, 456–466. [CrossRef]
80. Hariharan, N.; Maejima, Y.; Nakae, J.; Paik, J.; Depinho, R.A.; Sadoshima, J. Deacetylation of FoxO by Sirt1 plays an essential role in mediating starvation-induced autophagy in cardiac myocytes. *Circ. Res.* **2010**, *107*, 1470–1482. [CrossRef]
81. Lan, F.; Cacicedo, J.M.; Ruderman, N.; Ido, Y. SIRT1 modulation of the acetylation status, cytosolic localization, and activity of LKB1. Possible role in AMP-activated protein kinase activation. *J. Biol. Chem.* **2008**, *283*, 27628–27635. [CrossRef]
82. Ghosh, H.S.; McBurney, M.; Robbins, P.D. SIRT1 negatively regulates the mammalian target of rapamycin. *PLoS ONE* **2010**, *5*, e9199. [CrossRef] [PubMed]
83. Dai, H.; Sinclair, D.A.; Ellis, J.L.; Steegborn, C. Sirtuin activators and inhibitors: Promises, achievements, and challenges. *Pharmacol. Ther.* **2018**, *188*, 140–154. [CrossRef]
84. Tabassum, S.; Misrani, A.; Huang, H.X.; Zhang, Z.Y.; Li, Q.W.; Long, C. Resveratrol Attenuates Chronic Unpredictable Mild Stress-Induced Alterations in the SIRT1/PGC1α/SIRT3 Pathway and Associated Mitochondrial Dysfunction in Mice. *Mol. Neurobiol.* **2023**, *60*, 5102–5116. [CrossRef]
85. El Ters, M.; Zhou, X.; Lepping, R.J.; Lu, P.; Karcher, R.T.; Mahnken, J.D.; Brooks, W.M.; Winklhofer, F.T.; Li, X.; Alan, S.L. Biological Efficacy and Safety of Niacinamide in Patients with ADPKD. *Kidney Int. Rep.* **2020**, *5*, 1271–1279. [CrossRef]
86. Lempiäinen, J.; Finckenberg, P.; Mervaala, E.E.; Sankari, S.; Levijoki, J.; Mervaala, E.M. Caloric restriction ameliorates kidney ischaemia/reperfusion injury through PGC-1α-eNOS pathway and enhanced autophagy. *Acta Physiol.* **2013**, *208*, 410–421. [CrossRef] [PubMed]

87. Calvo-Rubio, M.; Burón, M.I.; López-Lluch, G.; Navas, P.; de Cabo, R.; Ramsey, J.J.; Villalba, J.M.; González-Reyes, J.A. Dietary fat composition influences glomerular and proximal convoluted tubule cell structure and autophagic processes in kidneys from calorie-restricted mice. *Aging Cell.* **2016**, *15*, 477–487. [CrossRef] [PubMed]
88. Zhou, G.; Myers, R.; Li, Y.; Chen, Y.; Shen, X.; Fenyk-Melody, J.; Wu, M.; Ventre, J.; Doebber, T.; Fujii, N.; et al. Role of AMP-activated protein kinase in mechanism of metformin action. *J. Clin. Investig.* **2001**, *108*, 1167–1174. [CrossRef]
89. Duca, F.A.; Côté, C.D.; Rasmussen, B.A.; Zadeh-Tahmasebi, M.; Rutter, G.A.; Filippi, B.M.; Lam, T.K. Metformin activates a duodenal Ampk–dependent pathway to lower hepatic glucose production in rats. *Nat. Med.* **2015**, *21*, 506–511. [CrossRef]
90. Vasamsetti, S.B.; Karnewar, S.; Kanugula, A.K.; Thatipalli, A.R.; Kumar, J.M.; Kotamraju, S. Metformin inhibits monocyte-to-macrophage differentiation via AMPK-mediated inhibition of STAT3 activation: Potential role in atherosclerosis. *Diabetes* **2015**, *64*, 2028–2041. [CrossRef]
91. Musi, N.; Hirshman, M.F.; Nygren, J.; Svanfeldt, M.; Bavenholm, P.; Rooyackers, O.; Zhou, G.; Williamson, J.M.; Ljunqvist, O.; Efendic, S.; et al. Metformin increases AMP-activated protein kinase activity in skeletal muscle of subjects with type 2 diabetes. *Diabetes* **2002**, *51*, 2074–2081. [CrossRef]
92. Batandier, C.; Guigas, B.; Detaille, D.; El-Mir, M.; Fontaine, E.; Rigoulet, M.; Leverve, X.M. The ROS production induced by a reverse-electron flux at respiratory-chain complex 1 is hampered by metformin. *J. Bioenerg. Biomembr.* **2006**, *38*, 33–42. [CrossRef] [PubMed]
93. Chakraborty, A.; Chowdhury, S.; Bhattacharyya, M. Effect of metformin on oxidative stress, nitrosative stress and inflammatory biomarkers in type 2 diabetes patients. *Diabetes Res. Clin. Pract.* **2011**, *93*, 56–62. [CrossRef] [PubMed]
94. Bharath, L.P.; Agrawal, M.; McCambridge, G.; Nicholas, D.A.; Hasturk, H.; Liu, J.; Jiang, K.; Liu, R.; Guo, Z.; Deeney, J.; et al. Metformin Enhances Autophagy and Normalizes Mitochondrial Function to Alleviate Aging-Associated Inflammation. *Cell Metab.* **2020**, *32*, 44–55.e6. [CrossRef] [PubMed]
95. Liao, H.H.; Ding, W.; Zhang, N.; Zhou, Z.Y.; Ling, Z.; Li, W.J.; Chen, S.; Tang, Q.Z. Activation of AMPKα2 attenuated doxorubicin-induced cardiotoxicity via inhibiting lipid peroxidation associated ferroptosis. *Free Radic. Biol. Med.* **2023**, *205*, 275–290. [CrossRef] [PubMed]
96. Padovano, V.; Podrini, C.; Boletta, A.; Caplan, M.J. Metabolism and mitochondria in polycystic kidney disease research and therapy. *Nat. Rev. Nephrol.* **2018**, *14*, 678–687. [CrossRef] [PubMed]
97. Lakhia, R.; Yheskel, M.; Flaten, A.; Quittner-Strom, E.B.; Holland, W.L.; Patel, V. PPARα agonist fenofibrate enhances fatty acid β-oxidation and attenuates polycystic kidney and liver disease in mice. *Am. J. Physiol. Renal Physiol.* **2018**, *314*, F122–F131. [CrossRef] [PubMed]
98. Manickam, R.; Duszka, K.; Wahli, W. PPARs and Microbiota in Skeletal Muscle Health and Wasting. *Int. J. Mol. Sci.* **2020**, *21*, 8056. [CrossRef] [PubMed]
99. Wang, Z.; Chen, W.D.; Wang, Y.D. Nuclear receptors: A bridge linking the gut microbiome and the host. *Mol. Med.* **2021**, *27*, 144. [CrossRef]
100. Frąk, W.; Kućmierz, J.; Szlagor, M.; Młynarska, E.; Rysz, J.; Franczyk, B. New Insights into Molecular Mechanisms of Chronic Kidney Disease. *Biomedicines* **2022**, *10*, 2846. [CrossRef]
101. Yang, T.; Richards, E.M.; Pepine, C.J.; Raizada, M.K. The gut microbiota and the brain-gut-kidney axis in hypertension and chronic kidney disease. *Nat. Rev. Nephrol.* **2018**, *14*, 442–456. [CrossRef]
102. Gulati, A.; Watnick, T. Vascular Complications in Autosomal Dominant Polycystic Kidney Disease: Perspectives, Paradigms, and Current State of Play. *Adv. Kidney Dis. Health* **2023**, *30*, 429–439. [CrossRef]
103. Wehedy, E.; Shatat, I.F.; Al Khodor, S. The Human Microbiome in Chronic Kidney Disease: A Double-Edged Sword. *Front. Med.* **2022**, *8*, 790783. [CrossRef] [PubMed]
104. Noce, A.; Marchetti, M.; Marrone, G.; Di Renzo, L.; Di Lauro, M.; Di Daniele, F.; Albanese, M.; Di Daniele, N.; De Lorenzo, A. Link between Gut Microbiota Dysbiosis and Chronic Kidney Disease. *Eur. Rev. Med. Pharmacol. Sci.* **2022**, *26*, 2057–2074. [PubMed]
105. Wang, X.; Yang, S.; Li, S.; Zhao, L.; Hao, Y.; Qin, J.; Zhang, L.; Zhang, C.; Bian, W.; Zuo, L.; et al. Aberrant gut microbiota alters host metabolome and impacts renal failure in humans and rodents. *Gut* **2020**, *69*, 2131–2142. [CrossRef] [PubMed]
106. Xu, H.; Gasparini, A.; Ishigami, J.; Mzayen, K.; Su, G.; Barany, P.; Ärnlöv, J.; Lindholm, B.; Elinder, C.G.; Matsushita, K.; et al. eGFR and the risk of community-acquired infections. *Clin. J. Am. Soc. Nephrol.* **2017**, *12*, 1399–1408. [CrossRef] [PubMed]
107. Su, G.; Trevisan, M.; Ishigami, J.; Matsushita, K.; Stålsby Lundborg, C.; Carrero, J.J. Short-and long-term outcomes after incident pneumonia in adults with chronic kidney disease: A time-dependent analysis from the stockholm creatinine measurement project. *Nephrol. Dial. Transplant.* **2020**, *35*, 1894–1900. [CrossRef] [PubMed]
108. Liu, X.; Wang, X.; Zhang, P.; Fang, Y.; Liu, Y.; Ding, Y.; Zhang, W. Intestinal homeostasis in the gut-lung-kidney axis: A prospective therapeutic target in immune-related chronic kidney diseases. *Front. Immunol.* **2023**, *14*, 1266792. [CrossRef]
109. Cooper, T.E.; Khalid, R.; Chan, S.; Craig, J.C.; Hawley, C.M.; Howell, M.; Johnson, D.W.; Jaure, A.; Teixeira-Pinto, A.; Wong, G. Synbiotics, prebiotics and probiotics for people with chronic kidney disease. *Cochrane Database Syst. Rev.* **2023**, *10*, CD013631.
110. Yacoub, R.; Nadkarni, G.N.; McSkimming, D.I.; Chaves, L.D.; Abyad, S.; Bryniarski, M.A.; Honan, A.M.; Thomas, S.A.; Gowda, M.; He, J.C.; et al. Fecal microbiota analysis of polycystic kidney disease patients according to renal function: A pilot study. *Exp. Biol. Med.* **2019**, *244*, 505–513. [CrossRef]

111. Mancin, S.; Mazzoleni, B.; Reggiani, F.; Calatroni, M.; Alterchi, E.; Donizzetti, D.; Finazzi, S.; Soekeland, F.; Sguanci, M.; Badalamenti, S. Integrated protocol for the prevention and treatment of skin ulcers in patients with end-stage renal disease. *MethodsX* **2023**, *11*, 102482. [CrossRef]
112. Du, Y.; Zhu, Y.J.; Zhou, Y.X.; Ding, J.; Liu, J.Y. Metformin in therapeutic applications in human diseases: Its mechanism of action and clinical study. *Mol. Biomed.* **2022**, *3*, 41. [CrossRef]
113. Aminzadeh, M.A.; Nicholas, S.B.; Norris, K.C.; Vaziri, N.D. Role of impaired Nrf2 activation in the pathogenesis of oxidative stress and inflammation in chronic tubulo-interstitial nephropathy. *Nephrol. Dial. Transplant.* **2013**, *28*, 2038–2045. [CrossRef]
114. Galiniak, S.; Aebisher, D.; Bartusik-Aebisher, D. Health benefits of resveratrol administration. *Acta Biochim. Pol.* **2019**, *66*, 13–21. [CrossRef]
115. Xu, D.; Li, Y.; Zhang, B.; Wang, Y.; Liu, Y.; Luo, Y.; Niu, W.; Dong, M.; Liu, M.; Dong, H.; et al. Resveratrol alleviate hypoxic pulmonary hypertension via anti-inflammation and anti-oxidant pathways in rats. *Int. J. Med. Sci.* **2016**, *13*, 942–954. [CrossRef]
116. Tsuji, A.; Ikeda, Y.; Yoshikawa, S.; Taniguchi, K.; Sawamura, H.; Morikawa, S.; Nakashima, M.; Asai, T.; Matsuda, S. The Tryptophan and Kynurenine Pathway Involved in the Development of Immune-Related Diseases. *Int. J. Mol. Sci.* **2023**, *24*, 5742. [CrossRef]
117. De Almeida, R.M.; Clendenon, S.G.; Richards, W.G.; Boedigheimer, M.; Damore, M.; Rossetti, S.; Harris, P.C.; Herbert, B.S.; Xu, W.M.; Wandinger-Ness, A.; et al. Transcriptome analysis reveals manifold mechanisms of cyst development in ADPKD. *Hum. Genomics* **2016**, *10*, 37. [CrossRef] [PubMed]
118. Swenson-Fields, K.I.; Vivian, C.J.; Salah, S.M.; Peda, J.D.; Davis, B.M.; van Rooijen, N.; Wallace, D.P.; Fields, T.A. Macrophages promote polycystic kidney disease progression. *Kidney Int.* **2013**, *83*, 855–864. [CrossRef] [PubMed]
119. Bulley, S.; Fernández-Peña, C.; Hasan, R.; Leo, M.D.; Muralidharan, P.; Mackay, C.E.; Evanson, K.W.; Moreira-Junior, L.; Mata-Daboin, A.; Burris, S.K.; et al. Arterial smooth muscle cell PKD2 (TRPP1) channels regulate systemic blood pressure. *Elife* **2018**, *7*, e42628. [CrossRef] [PubMed]
120. Hasan, R.; Leo, M.D.; Muralidharan, P.; Mata-Daboin, A.; Yin, W.; Bulley, S.; Fernandez-Peña, C.; MacKay, C.E.; Jaggar, J.H. SUMO1 modification of PKD2 channels regulates arterial contractility. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 27095–27104. [CrossRef] [PubMed]
121. Clark, L.A.; Whitmire, S.; Patton, S.; Clark, C.; Blanchette, C.M.; Howden, R. Cost-effectiveness of angiotensin-converting enzyme inhibitors versus angiotensin II receptor blockers as first-line treatment in autosomal dominant polycystic kidney disease. *J. Med. Econ.* **2017**, *20*, 715–722. [CrossRef] [PubMed]
122. Schrier, R.W. ACE inhibitors, left ventricular mass and renal cyst growth in ADPKD. *Pharmacol. Res.* **2016**, *114*, 166–168. [CrossRef] [PubMed]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.