cells

MDPI

Review

The Interplay between Immune and Metabolic Pathways in Kidney Disease

Lili Qu [1,*,†] and Baihai Jiao [2,*,†]

[1] Division of Nephrology, Department of Medicine, School of Medicine, University of Connecticut Health Center, Farmington, CT 06030-1405, USA
[2] Department of Immunology, School of Medicine, University of Connecticut Health Center, Farmington, CT 06030-1405, USA
* Correspondence: lili@uchc.edu (L.Q.); bjiao@uchc.edu (B.J.)
† These authors have contributed equally to this work.

Abstract: Kidney disease is a significant health problem worldwide, affecting an estimated 10% of the global population. Kidney disease encompasses a diverse group of disorders that vary in their underlying pathophysiology, clinical presentation, and outcomes. These disorders include acute kidney injury (AKI), chronic kidney disease (CKD), glomerulonephritis, nephrotic syndrome, polycystic kidney disease, diabetic kidney disease, and many others. Despite their distinct etiologies, these disorders share a common feature of immune system dysregulation and metabolic disturbances. The immune system and metabolic pathways are intimately connected and interact to modulate the pathogenesis of kidney diseases. The dysregulation of immune responses in kidney diseases includes a complex interplay between various immune cell types, including resident and infiltrating immune cells, cytokines, chemokines, and complement factors. These immune factors can trigger and perpetuate kidney inflammation, causing renal tissue injury and progressive fibrosis. In addition, metabolic pathways play critical roles in the pathogenesis of kidney diseases, including glucose and lipid metabolism, oxidative stress, mitochondrial dysfunction, and altered nutrient sensing. Dysregulation of these metabolic pathways contributes to the progression of kidney disease by inducing renal tubular injury, apoptosis, and fibrosis. Recent studies have provided insights into the intricate interplay between immune and metabolic pathways in kidney diseases, revealing novel therapeutic targets for the prevention and treatment of kidney diseases. Potential therapeutic strategies include modulating immune responses through targeting key immune factors or inhibiting pro-inflammatory signaling pathways, improving mitochondrial function, and targeting nutrient-sensing pathways, such as mTOR, AMPK, and SIRT1. This review highlights the importance of the interplay between immune and metabolic pathways in kidney diseases and the potential therapeutic implications of targeting these pathways.

Keywords: immune; metabolic; inflammation; kidney disease

Citation: Qu, L.; Jiao, B. The Interplay between Immune and Metabolic Pathways in Kidney Disease. *Cells* **2023**, *12*, 1584. https://doi.org/10.3390/cells12121584

Academic Editor: Pei-Hui Lin

Received: 28 April 2023
Revised: 31 May 2023
Accepted: 6 June 2023
Published: 8 June 2023

1. Introduction

Kidney disease is a significant health problem worldwide, affecting an estimated 10% of the global population [1]. The most common forms of kidney disease include chronic kidney disease (CKD) and acute kidney injury (AKI) [2]. However, kidney disease encompasses a diverse group of disorders that vary in their underlying pathophysiology, clinical presentation, and outcomes. These disorders include tubulointerstitial, glomerulonephritis, nephrotic syndrome, polycystic kidney disease, diabetic kidney disease, vascular disease, vasculitis, and congenital kidney disease, among others.

Despite significant advances in our understanding of the pathophysiology of kidney disease, current therapies remain limited and often ineffective [3,4]. Thus, the need for new therapeutic approaches to improve outcomes in patients with kidney disease is urgent.

One promising area of research is the role of immunometabolism in the pathogenesis and progression of kidney disease [5,6].

Immunometabolism refers to the interplay between immune and metabolic pathways, which are tightly regulated in normal physiological conditions [7–10]. In pathological conditions, such as kidney disease, this delicate balance is disrupted, leading to immunometabolic dysregulation. Immunometabolic dysregulation involves various cell types, such as T cells, B cells, macrophages, and dendritic cells, as well as cytokines, chemokines, and metabolic processes, such as oxidative stress, mitochondrial dysfunction, and inflammation [8,11].

Recent studies have revealed a critical role for immunometabolic dysregulation in the pathogenesis of kidney disease [6,12,13]. Dysregulated immune responses and altered metabolic pathways interact in complex ways to contribute to the development and progression of kidney disease, regardless of the underlying etiology [8]. For instance, in CKD, chronic inflammation, oxidative stress, and altered lipid metabolism contribute to tubulointerstitial fibrosis and renal dysfunction [14–18]. Similarly, in diabetic kidney disease, hyperglycemia and dyslipidemia promote mitochondrial dysfunction and inflammation, leading to glomerular injury and renal fibrosis [19,20].

Given the profound impact of immunometabolic dysregulation on kidney disease outcomes, identifying new therapeutic targets to modulate these pathways is critical. In this review, we aim to provide a comprehensive overview of immunometabolic alterations in kidney disease, highlighting their clinical implications and potential therapeutic interventions. We discuss the most recent advancements in our understanding of the molecular mechanisms linking immunometabolism and kidney disease. Our review aims to provide insights into the critical role of immunometabolism in kidney disease, regardless of the underlying etiology, and its potential as a target for therapeutic intervention.

2. Immunometabolic Alterations in Kidney Disease

Immunometabolic alterations in kidney disease refer to the complex interplay between immune and metabolic pathways that are disrupted in pathological conditions [13,21]. These alterations involve various cell types, cytokines, chemokines, and metabolic processes, which together contribute to the pathogenesis and progression of kidney disease [8,22–24] (Figure 1).

T cells are an essential component of the adaptive immune response and play a crucial role in kidney disease [25,26]. In CKD, T-cell activation and infiltration contribute to chronic inflammation and renal fibrosis [27,28]. Activated T cells produce cytokines, such as IFN-γ and TNF-α, which promote inflammation and fibrosis in the kidney [29]. Additionally, T cells can directly induce tubular cell apoptosis and contribute to tubulointerstitial fibrosis [30,31]. In diabetic kidney disease, T cells also play a critical role in the pathogenesis of kidney disease [32,33]. T-cell infiltration in the glomerulus is associated with the development of albuminuria and renal fibrosis [16,34]. T cells in diabetic kidney disease also contribute to podocyte injury and the development of glomerular sclerosis [35,36].

B cells are another critical component of the adaptive immune response, and their role in kidney disease is becoming increasingly recognized [37]. In glomerulonephritis, autoantibodies produced by B cells play a significant role in the pathogenesis of the disease [38,39]. Autoantibodies can deposit in the glomerulus, leading to complement activation and subsequent inflammation and renal injury [40,41]. In diabetic kidney disease, B cells are also implicated in the development of the disease. B cells can produce pro-inflammatory cytokines and contribute to the infiltration of inflammatory cells in the kidney [42–44].

Macrophages are innate immune cells that play a critical role in the pathogenesis of human disease [45–50]. In CKD, macrophage infiltration in the kidney is associated with tubulointerstitial fibrosis and renal dysfunction [15,51,52]. Activated macrophages produce pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, which contribute to renal inflammation and fibrosis [53]. Macrophages can also promote renal fibrosis by producing TGF-β and promoting extracellular matrix deposition [54–56]. In diabetic kidney disease,

macrophages contribute to the development of renal injury and fibrosis [57]. Macrophages are activated by advanced glycation end products (AGEs), leading to the production of pro-inflammatory cytokines and the promotion of renal fibrosis [57,58].

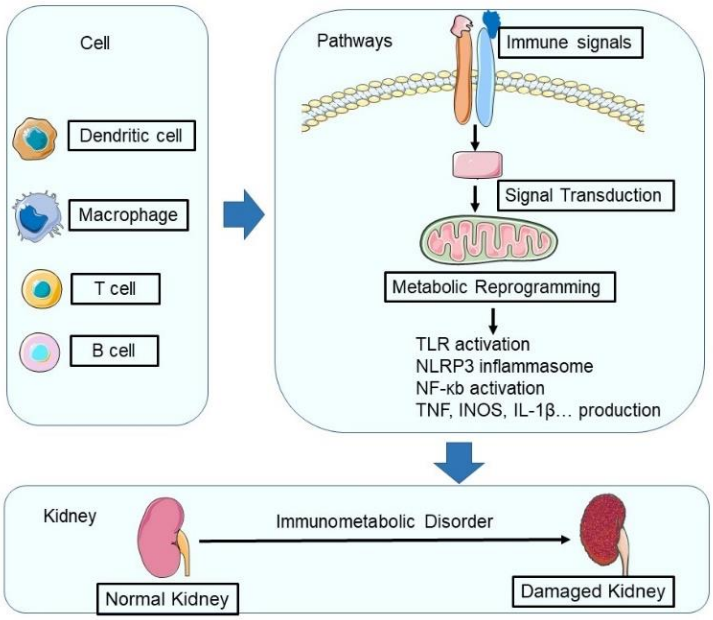

Figure 1. During renal injury, the metabolic programming of immune cells undergoes significant changes. In a healthy kidney, macrophages use α-ketoglutarate derived from glutamine to maintain their phenotypes, while both resident macrophages and T lymphocytes rely on oxidative phosphorylation (OXPHOS). However, during renal injury, hypoxia-inducible factor-1α (HIF-1α)-mediated metabolic reprogramming occurs, leading to increased glycolysis and altered amino acid metabolism in immune cells. In addition, the activation of innate pattern recognition receptors, such as Toll-like receptors (TLRs), NOD-like receptors (NLRs), and inflammasomes, triggers intracellular pathways that converge on nuclear factor κB (NF-κB), resulting in the production of pro-inflammatory cytokines (such as tumor necrosis factor (TNF) and interleukin-1β (IL-1β)) and chemokines. This complex network of metabolic and inflammatory responses ultimately contributes to the progression of renal injury and disease. Elements of some figures were produced using Servier Medical Art, https://smart.servier.com.

In addition to immune cell alterations, metabolic alterations also play a critical role in the pathogenesis of kidney disease. In CKD, oxidative stress and mitochondrial dysfunction are important metabolic alterations that contribute to renal injury and fibrosis [59,60]. Oxidative stress leads to the production of reactive oxygen species (ROS), which promote inflammation and fibrosis in the kidney [61]. Mitochondrial dysfunction can also lead to the production of ROS and promote renal fibrosis [62,63]. Additionally, altered lipid metabolism in CKD promotes tubulointerstitial fibrosis and renal dysfunction [64,65]. In diabetic kidney disease, hyperglycemia and dyslipidemia are the primary metabolic alterations that contribute to renal injury and fibrosis [65]. Hyperglycemia leads to the production of AGEs, which activate inflammatory cells and promote renal fibrosis [66,67]. Dyslipidemia leads to the accumulation of lipids in the kidney, promoting inflammation and fibrosis [68,69]. Furthermore, mitochondrial dysfunction in diabetic kidney disease contributes to the development of renal injury and fibrosis [70,71].

3. The Impact of Immunometabolic Dysregulation in Kidney Disease

3.1. Acute Kidney Injury (AKI)

Acute kidney injury (AKI) is a complex condition characterized by a rapid loss of renal function [72,73]. Immunometabolic dysregulation has been shown to play an important role in the pathogenesis of AKI [22,74]. This involves an imbalance between pro- and anti-

inflammatory cytokines, leading to the activation of innate immune cells and subsequent tissue damage.

Several genes and pathways have been linked to immunometabolic dysregulation in AKI. One of the key pathways involved in the development of AKI is the hypoxia-inducible factor 1-alpha (HIF-1α) pathway [75,76]. Under hypoxic conditions, HIF-1α is stabilized and activates the transcription of genes involved in glycolysis, angiogenesis, and inflammation [77]. Studies have shown that HIF-1α plays a critical role in the development of AKI by promoting glycolysis in immune cells and contributing to the production of pro-inflammatory cytokines [78–80]. In addition, HIF-1α can also upregulate glucose transporter 1 (GLUT1), which facilitates glucose uptake in immune cells, and its upregulation has been linked to the development of AKI [80,81]. Moreover, recent studies have suggested that epigenetic modifications, such as DNA methylation and histone modifications, can contribute to the dysregulation of HIF-1α in AKI pathogenesis [82–84]. Another important gene involved in immunometabolic dysregulation in AKI is the gene encoding for inducible nitric oxide synthase (iNOS). iNOS is an enzyme that produces nitric oxide (NO), which is a potent regulator of immune cell function [85]. Dysregulation of iNOS has been implicated in the pathogenesis of AKI, with studies showing that iNOS-mediated NO production can contribute to tissue damage in the kidney [86–88].

In addition to HIF-1α and iNOS, toll-like receptors (TLRs) are involved in the recognition of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), and their dysregulation has been linked to the development of AKI [89,90]. TLRs can activate nuclear factor kappa B (NF-κB), a transcription factor that regulates the expression of genes involved in inflammation and immune cell activation, and its dysregulation has been shown to contribute to the development of AKI [91,92]. The NLRP3 inflammasome, a multiprotein complex involved in the processing and secretion of pro-inflammatory cytokines, has also been implicated in the development of AKI. Studies have shown that NLRP3 inflammasome activation can contribute to the development of AKI by promoting the secretion of pro-inflammatory cytokines [93–95].

Furthermore, recent studies have shown that immunometabolic dysregulation in AKI also involves the dysregulation of lipid metabolism. For example, increased levels of free fatty acids (FFAs) can contribute to the development of AKI by activating inflammatory pathways in immune cells [96,97]. This process involves the activation of TLR4 and subsequent activation of NF-κB, resulting in the production of pro-inflammatory cytokines [98,99]. Moreover, dysregulation of the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), a transcriptional coactivator involved in the regulation of mitochondrial biogenesis and function [100], has been shown to contribute to the development of AKI by impairing mitochondrial function in immune cells [101–103]. Dysregulation of PGC-1α may also lead to the accumulation of ROS, which can cause oxidative stress and contribute to renal injury [104].

3.2. Chronic Kidney Disease (CKD)

Chronic kidney disease (CKD) is a progressive condition characterized by the gradual loss of kidney function over time. Dysregulation of immune cells and metabolism contribute to the accumulation of toxic metabolites, oxidative stress, and fibrosis, which are key contributors to the progression of CKD [105]. One of the key pathways involved in the development of CKD is dysregulated glucose metabolism in immune cells [106,107]. Studies have shown that this dysregulation can lead to the activation of pro-inflammatory pathways, oxidative stress, and endothelial dysfunction, all of which can contribute to the development of CKD [61]. GLUT1 and HIF-1α are two genes that have been implicated in the dysregulation of glucose metabolism in immune cells in the context of CKD [108,109]. Another important pathway involved in CKD is the activation of the NLRP3 inflammasome and subsequent cytokine production. Increased NLRP3 expression has been observed in patients with CKD, and inhibition of the NLRP3 inflammasome has been shown to ameliorate kidney damage in animal models of CKD [110]. Additionally, dysregulated

lipid metabolism has been linked to the progression of CKD. Studies have shown that increased levels of FFAs can contribute to the development of CKD by activating inflammatory pathways and inducing oxidative stress [111,112]. In addition to the above-mentioned pathways, other genes involved in immune cell dysregulation in CKD include TLRs, NF-κB, and the renin–angiotensin–aldosterone system (RAAS). TLRs are involved in the recognition of PAMPs and DAMPs, and their dysregulation has been linked to the development of CKD [113–115]. NF-κB activation in CKD can be triggered by a variety of stimuli, including oxidative stress, hypoxia, and proinflammatory cytokines, such as TNF-α and IL-1β [116,117]. Furthermore, NF-κB activation is tightly linked to NLRP3 inflammasome activation in CKD. Activation of the NLRP3 inflammasome triggers the activation of NF-κB, which, in turn, leads to the production of more proinflammatory cytokines, creating a positive feedback loop that perpetuates the inflammatory response [118,119]. The RAAS is a hormone system that regulates blood pressure and fluid balance in the body, and its dysregulation has been linked to the development of CKD through its effects on renal hemodynamics and inflammation [120–122].

Furthermore, epigenetic modifications have been suggested to play a role in the dysregulation of genes involved in CKD pathogenesis [4]. For example, studies have shown that DNA methylation and histone modifications can contribute to the dysregulation of key genes involved in CKD, such as HIF-1α and NF-κB [123–126]. In conclusion, dysregulation of immune cells and metabolism can contribute to the pathogenesis and progression of CKD through various pathways and genes. Further research in this area may provide novel insights into the mechanisms underlying the development of CKD and help identify new therapeutic targets for the treatment of this condition.

3.2.1. Lupus Nephritis

Lupus nephritis is a type of kidney inflammation that occurs as a result of systemic lupus erythematosus (SLE), an autoimmune disease [127]. Immunometabolic dysregulation is one of the key mechanisms underlying the pathogenesis of lupus nephritis [128]. Dysregulated metabolism in immune cells can contribute to the production of autoantibodies and the activation of inflammatory cells, leading to glomerular damage and renal dysfunction [129,130].

Several genes and pathways have been implicated in the dysregulated metabolism in immune cells in the context of lupus nephritis. One of the most studied pathways is the Warburg effect, which is characterized by the preferential use of glycolysis over oxidative phosphorylation in immune cells [131]. The upregulation of glycolysis is thought to be driven by various signaling pathways, including the phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway, the HIF pathway, and the JAK/STAT pathway [132,133]. These pathways have been shown to contribute to the activation of immune cells and the production of autoantibodies in lupus nephritis [133–136].

The activation of the NLRP3 inflammasome is another key pathway involved in the pathogenesis of lupus nephritis, with the subsequent production of cytokines. The NLRP3 inflammasome contribute to tissue damage in lupus nephritis [137]. Studies have shown that the NLRP3 inflammasome is upregulated in lupus nephritis patients and that its inhibition can ameliorate kidney injury in animal models of lupus nephritis [137,138]. Moreover, dysregulated lipid metabolism has also been implicated in the pathogenesis of lupus nephritis. Studies have shown that increased levels of FFAs can contribute to the activation of immune cells and the production of autoantibodies in lupus nephritis [139,140]. The dysregulation of cholesterol metabolism has also been linked to the development of lupus nephritis. In addition to the above-mentioned pathways, other genes and pathways involved in the dysregulated metabolism in immune cells in lupus nephritis include TLRs, NF-κB, and the IFN pathway. TLRs are involved in the recognition of PAMPs and DAMPs, and their dysregulation has been linked to the activation of immune cells in lupus nephritis [141–143]. NF-κB is a transcription factor that regulates the expression of

genes involved in inflammation and immune cell activation, and its dysregulation has been shown to contribute to the development of lupus nephritis [144,145]. The type I IFN pathway is another important pathway involved in the activation of immune cells in lupus nephritis, as the overexpression of type I IFN-inducible genes has been observed in lupus nephritis patients [146–148].

Furthermore, epigenetic modifications have also been suggested to play a role in the dysregulated metabolism in immune cells in lupus nephritis. For example, studies have shown that DNA methylation and histone modifications can contribute to the dysregulation of key genes involved in lupus nephritis, such as NF-κB [149]. In conclusion, immunometabolic dysregulation is a key mechanism underlying the pathogenesis of lupus nephritis.

3.2.2. Diabetic Kidney Disease

Diabetic kidney disease is a common complication of diabetes mellitus and a leading cause of end-stage renal disease [150–152]. Dysregulated metabolism and inflammation are key factors in the pathogenesis of diabetic kidney disease. Impaired glucose metabolism leads to the accumulation of AGEs in the kidneys, which contribute to renal dysfunction and fibrosis [153]. GLUT1 and HIF-1α are two genes that have been implicated in the dysregulation of glucose metabolism in immune cells in the context of diabetic kidney disease [78,154].

In addition to dysregulated glucose metabolism, dysregulated lipid metabolism in immune cells has also been implicated in the pathogenesis of diabetic kidney disease. Studies have shown that increased levels of FFAs can contribute to the development of diabetic kidney disease by activating inflammatory pathways and inducing oxidative stress [155,156]. In particular, the peroxisome proliferator-activated receptor (PPAR) family of genes, which regulates lipid metabolism, has been shown to play a role in the pathogenesis of diabetic kidney disease [157,158]. The activation of the NLRP3 inflammasome and subsequent production of pro-inflammatory cytokines have been identified as critical drivers of diabetic kidney disease. The NLRP3 inflammasome is a multiprotein complex involved in the processing and secretion of pro-inflammatory cytokines, and its activation has been implicated in the development of diabetic kidney disease [159]. The inflammasome is activated by a variety of stimuli, including high glucose levels and the accumulation of AGEs [160]. The JAK/STAT signaling pathway is involved in many biological processes, including immune responses and inflammation, and has been implicated in the pathogenesis of diabetic kidney disease [161–167]. Studies have shown that the JAK/STAT pathway is activated in response to pro-inflammatory cytokines and growth factors, and its dysregulation can contribute to the progression of diabetic kidney disease [168]. The suppressor of cytokine signaling (SOCS) family of genes, which negatively regulates JAK/STAT signaling, has been shown to play a role in the development of diabetic kidney disease [169,170].

In conclusion, dysregulated metabolism and inflammation contribute to the development and progression of diabetic kidney disease through various pathways and genes, including dysregulated glucose and lipid metabolism, activation of the NLRP3 inflammasome, and dysregulated JAK/STAT signaling. Further research in this area may provide novel insights into the mechanisms underlying the development of diabetic kidney disease and help identify new therapeutic targets for the treatment of this condition.

3.2.3. Polycystic Kidney Disease (PKD)

Immunometabolic dysfunction plays a critical role in the pathogenesis of PKD. Dysregulated metabolism in immune cells, such as the activation of the Warburg effect, has been implicated in the development and progression of PKD [171,172]. Additionally, studies have shown that immune cells in PKD exhibit increased mitochondrial stress and metabolic alterations, leading to impaired cellular energetics and increased oxidative stress [173].

One recent study has found that the inflammasome pathway, specifically the NLRP3 inflammasome, is activated in PKD, leading to the production of pro-inflammatory cy-

tokines and subsequent cyst growth [174,175]. The activation of the NLRP3 inflammasome has been linked to the accumulation of damaged mitochondria and the release of mitochondrial DNA, which can trigger an inflammatory response in the kidney [23]. Another study has shown that PKD is associated with altered immune cell metabolism and an increased production of ROS. The authors suggest that this metabolic dysfunction may contribute to the activation of the NLRP3 inflammasome and the subsequent production of pro-inflammatory cytokines in PKD [174,176]. Furthermore, recent research has also linked PKD to dysregulated lipid metabolism in immune cells [61]. One study found that PKD is associated with altered lipid metabolism in T cells, leading to increased T-cell activation and subsequent inflammation in the kidney [177].

In summary, immunometabolic dysfunction, including dysregulated metabolism in immune cells, activation of the inflammasome pathway, altered mitochondrial function, and dysregulated lipid metabolism, contributes to the pathogenesis of PKD. These findings suggest that targeting immunometabolic pathways may provide a potential therapeutic strategy for PKD.

3.2.4. Impact of Immunometabolic Dysregulation on Kidney Transplant Outcomes

Immunometabolic dysregulation has been increasingly recognized as an important contributor to kidney transplant outcomes. The immune response after kidney transplantation involves both the innate and adaptive immune systems, which interact with each other to establish a balance between tolerance and rejection [178,179]. Dysregulated metabolism and inflammation can disrupt this balance, leading to poor transplant outcomes, such as rejection, infection, and chronic allograft dysfunction [180,181].

One key pathway involved in immunometabolic dysregulation after kidney transplantation is the activation of the NLRP3 inflammasome. Studies have shown that activation of the NLRP3 inflammasome in both donor and recipient cells can contribute to the development of acute and chronic rejection [182]. Furthermore, activation of the NLRP3 inflammasome has also been implicated in the development of ischemia–reperfusion injury, a common complication during kidney transplantation [183–185]. Dysregulated metabolism in immune cells has also been implicated in poor kidney transplant outcomes. Specifically, the Warburg effect, a phenomenon where immune cells preferentially use glycolysis for energy production instead of oxidative phosphorylation, has been observed in both donor and recipient cells after kidney transplantation [186,187]. This metabolic switch has been associated with increased inflammation and oxidative stress, which can lead to allograft injury and rejection [188,189]. Finally, dysregulation of lipid metabolism in immune cells has also been implicated in poor kidney transplant outcomes [190]. Studies have shown that high levels of triglycerides and low levels of high-density lipoprotein (HDL) cholesterol are associated with an increased risk of acute rejection and chronic allograft dysfunction [191,192]. Dysregulated lipid metabolism in immune cells can also lead to the production of pro-inflammatory cytokines and the activation of the NLRP3 inflammasome [193,194].

In conclusion, immunometabolic dysregulation plays a critical role in kidney transplant outcomes. Dysregulated metabolism and inflammation can disrupt the delicate balance between tolerance and rejection, leading to poor transplant outcomes, such as rejection, infection, and chronic allograft dysfunction. Understanding the mechanisms underlying immunometabolic dysregulation in kidney transplantation may lead to the development of novel therapeutic strategies to improve transplant outcomes.

4. Potential Therapeutic Interventions Targeting Immunometabolism in Kidney Disease

Immunometabolic dysregulation is a promising target for the development of novel therapeutic interventions for kidney disease. Several current and emerging therapies targeting immunometabolism have shown promising results in preclinical and clinical studies.

One potential therapeutic intervention is targeting the NLRP3 inflammasome, a key component of the innate immune system that plays a role in the activation of pro-inflammatory cytokines. The NLRP3 inflammasome, a multimeric protein complex, acts as a key regulator of innate immunity and exhibits predominant expression within diverse renal cell populations, encompassing tubular epithelial cells, glomerular cells, and infiltrating immune cells within the kidney [195,196]. The NLRP3 inflammasome can be activated in response to different signals, such as PAMPs, DAMPs, and oxidized mitochondrial DNA fragments. Once activated, the NLRP3 inflammasome triggers the production and release of pro-inflammatory cytokines, particularly IL-1β and IL-18, leading to an amplified inflammatory response within the renal microenvironment [197,198]. The significance of NLRP3 inflammasome activation in renal diseases lies in its contribution to the pathogenesis and progression of various renal conditions [93,199]. Persistent or dysregulated activation of the NLRP3 inflammasome has been implicated in the development of glomerulonephritis, diabetic nephropathy, tubulointerstitial nephritis, and other inflammatory renal disorders. The released pro-inflammatory cytokines, IL-1β and IL-18, promote immune cell recruitment, exacerbate tissue damage, and stimulate fibrotic responses in the kidney [200–202]. Moreover, the NLRP3 inflammasome can modulate the activation and function of other inflammatory signaling pathways, such as NF-κB and mitogen-activated protein kinases (MAPKs), amplifying the inflammatory cascade in renal diseases [203]. Furthermore, the influence of the NLRP3 inflammasome extends beyond inflammation, as it has been implicated in regulating renal cell death pathways. Activation of the NLRP3 inflammasome can lead to pyroptosis, a highly inflammatory form of cell death characterized by releasing pro-inflammatory cytokines and forming membrane pores [204]. Pyroptosis of renal cells can exacerbate tissue injury and contribute to the loss of renal function [205]. Additionally, the NLRP3 inflammasome has been associated with the activation of other cell death mechanisms, including apoptosis and necroptosis, further highlighting its involvement in renal disease pathogenesis [93]. Inhibitors of the NLRP3 inflammasome, such as MCC950 and CY-09, have been shown to ameliorate renal injury and improve kidney function in various animal models of kidney disease [206–208]. However, the clinical efficacy of these inhibitors remains to be tested in human trials. Another potential therapy is the modulation of the Warburg effect, a metabolic alteration characterized by enhanced glycolysis and reduced oxidative phosphorylation. Targeting the Warburg effect in immune cells has shown potential in the treatment of kidney disease. For instance, the use of the glycolysis inhibitor 2-deoxyglucose (2-DG) has been shown to reduce renal injury and inflammation in animal models of kidney disease [171,209,210]. Additionally, several other inhibitors of glycolysis, such as dichloroacetate (DCA) and lonidamine, are currently under investigation as potential therapies for kidney disease [211,212].

In addition to targeting specific pathways, several emerging therapies aim to modulate the overall metabolic state of immune cells in kidney disease. One example is the use of metformin, a widely used drug for the treatment of diabetes, which has been shown to have immunomodulatory effects [213]. Preclinical studies have demonstrated the potential of metformin in reducing renal injury and inflammation in models of kidney disease. Similarly, the use of rapamycin, an inhibitor of the mammalian target of rapamycin (mTOR), has been shown to have immunosuppressive and renoprotective effects in various animal models of kidney disease [214]. Cyclosporine A is an immunosuppressant commonly used in renal transplant patients to prevent rejection by inhibiting immune system activity and reducing inflammatory responses and immune-mediated kidney damage. While its primary focus is on the immune system, Cyclosporine A may also have some impact on metabolic processes [215]. Glucocorticoids, such as prednisolone, possess anti-inflammatory properties and are frequently prescribed for various kidney diseases, mitigating inflammation and immune-mediated injury. They can also affect metabolism by influencing glucose metabolism and lipid metabolism [216]. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are widely employed in managing hypertension and kidney disease. In addition to their blood-pressure-lowering effects, these medications

can have an impact on metabolic processes, including the regulation of blood glucose levels and lipid metabolism [217]. It is important to consult healthcare professionals for personalized treatment decisions, taking into account the specific condition and needs of each patient.

While these immunometabolic therapies hold promise, there are also potential limitations and concerns to consider. For instance, the modulation of immune cell metabolism may have unintended consequences on other metabolic pathways and cellular functions. Additionally, the long-term safety and efficacy of these therapies in humans remain to be established. In conclusion, targeting immunometabolism represents a promising approach for the development of novel therapies for kidney disease. While several therapies have shown promise in preclinical and clinical studies, further research is needed to fully establish their safety and efficacy in humans.

5. Future Directions for Research in Immunometabolism and Kidney Disease

Despite significant progress in understanding the role of immunometabolism in kidney disease, there are still many gaps in our knowledge. Here, we outline some areas of needed research to better understand the complex interactions between immunometabolism and kidney disease.

1. Elucidating the mechanisms of immunometabolic dysregulation in kidney disease: While the role of immunometabolism in kidney disease is becoming increasingly clear, the specific molecular and cellular mechanisms underlying this dysregulation are still not fully understood. Future research should focus on elucidating these mechanisms to better understand how immunometabolic dysregulation contributes to kidney disease pathogenesis.

2. Identifying novel immunometabolic targets for therapeutic interventions: While current and emerging immunometabolic therapies for kidney disease show promise, there is a need for the identification of additional immunometabolic targets for therapeutic interventions. Innovative approaches and technologies, such as multi-omics and single-cell analysis, may help identify new targets and pathways involved in immunometabolic dysregulation.

3. Personalizing immunometabolic therapies for kidney disease: The heterogeneity of kidney disease suggests that personalized therapeutic approaches may be necessary. Future research should aim to identify specific patient subgroups that may benefit from certain immunometabolic therapies, as well as develop biomarkers to predict treatment response.

6. Conclusions

This review highlights the significant role of immunometabolic dysregulation in kidney disease. The interplay between immune and metabolic pathways affects the development and progression of various kidney diseases, including AKI, CKD, lupus nephritis, diabetic kidney disease, PKD, and kidney transplant outcomes. Potential therapeutic interventions targeting immunometabolism show promise, but further research is needed. Understanding the interactions between immune and metabolic processes is crucial for future advancements in treating kidney disease.

Author Contributions: L.Q. and B.J. arranged an overview of the content. Both of them contributed to the article and approved the submitted version. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Kovesdy, C.P. Epidemiology of chronic kidney disease: An update 2022. *Kidney Int. Suppl.* **2022**, *12*, 7–11. [CrossRef] [PubMed]
2. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990–2017: A systematic analysis for the global burden of disease study 2017. *Lancet* **2020**, *395*, 709–733. [CrossRef] [PubMed]
3. Speer, T.; Dimmeler, S.; Schunk, S.J.; Fliser, D.; Ridker, P.M. Targeting innate immunity-driven inflammation in ckd and cardiovascular disease. *Nat. Rev. Nephrol.* **2022**, *18*, 762–778. [CrossRef] [PubMed]
4. An, C.; Jiao, B.; Du, H.; Tran, M.; Song, B.; Wang, P.; Zhou, D.; Wang, Y. Jmjd3 promotes myeloid fibroblast activation and macrophage polarization in kidney fibrosis. *Br. J. Pharmacol.* **2023**. [CrossRef] [PubMed]
5. Palsson-McDermott, E.M.; O'Neill, L.A.J. Targeting immunometabolism as an anti-inflammatory strategy. *Cell Res.* **2020**, *30*, 300–314. [CrossRef] [PubMed]
6. van der Rijt, S.; Leemans, J.C.; Florquin, S.; Houtkooper, R.H.; Tammaro, A. Immunometabolic rewiring of tubular epithelial cells in kidney disease. *Nat. Rev. Nephrol.* **2022**, *18*, 588–603. [CrossRef]
7. Chi, H. Immunometabolism at the intersection of metabolic signaling, cell fate, and systems immunology. *Cell. Mol. Immunol.* **2022**, *19*, 299–302. [CrossRef]
8. Basso, P.J.; Andrade-Oliveira, V.; Camara, N.O.S. Targeting immune cell metabolism in kidney diseases. *Nat. Rev. Nephrol.* **2021**, *17*, 465–480. [CrossRef]
9. Matz, A.J.; Qu, L.; Karlinsey, K.; Vella, A.T.; Zhou, B. Capturing the multifaceted function of adipose tissue macrophages. *Front. Immunol.* **2023**, *14*, 1148188. [CrossRef]
10. Qu, L.; Matz, A.J.; Karlinsey, K.; Cao, Z.; Vella, A.T.; Zhou, B. Macrophages at the crossroad of meta-inflammation and inflammaging. *Genes* **2022**, *13*, 2074. [CrossRef]
11. Matz, A.J.; Qu, L.; Karlinsey, K.; Zhou, B. Microrna-regulated b cells in obesity. *Immunometabolism* **2022**, *4*, e00005. [CrossRef]
12. Tan, S.M.; Snelson, M.; Ostergaard, J.A.; Coughlan, M.T. The complement pathway: New insights into immunometabolic signaling in diabetic kidney disease. *Antioxid. Redox Signal.* **2022**, *37*, 781–801. [CrossRef] [PubMed]
13. Grayson, P.C.; Eddy, S.; Taroni, J.N.; Lightfoot, Y.L.; Mariani, L.; Parikh, H.; Lindenmeyer, M.T.; Ju, W.; Greene, C.S.; Godfrey, B.; et al. Metabolic pathways and immunometabolism in rare kidney diseases. *Ann. Rheum. Dis.* **2018**, *77*, 1226–1233. [CrossRef]
14. Jiao, B.; An, C.; Du, H.; Tran, M.; Wang, P.; Zhou, D.; Wang, Y. Stat6 deficiency attenuates myeloid fibroblast activation and macrophage polarization in experimental folic acid nephropathy. *Cells* **2021**, *10*, 3057. [CrossRef] [PubMed]
15. Jiao, B.; An, C.; Tran, M.; Du, H.; Wang, P.; Zhou, D.; Wang, Y. Pharmacological inhibition of stat6 ameliorates myeloid fibroblast activation and alternative macrophage polarization in renal fibrosis. *Front. Immunol.* **2021**, *12*, 735014. [CrossRef] [PubMed]
16. Yuan, Q.; Tang, B.; Zhang, C. Signaling pathways of chronic kidney diseases, implications for therapeutics. *Signal Transduct. Target. Ther.* **2022**, *7*, 182. [CrossRef] [PubMed]
17. Liu, Y.; Wang, J. Ferroptosis, a rising force against renal fibrosis. *Oxidative Med. Cell. Longev.* **2022**, *2022*, 7686956. [CrossRef]
18. Zhu, Z.; Hu, J.; Chen, Z.; Feng, J.; Yang, X.; Liang, W.; Ding, G. Transition of acute kidney injury to chronic kidney disease: Role of metabolic reprogramming. *Metab. Clin. Exp.* **2022**, *131*, 155194. [CrossRef]
19. Tuttle, K.R.; Agarwal, R.; Alpers, C.E.; Bakris, G.L.; Brosius, F.C.; Kolkhof, P.; Uribarri, J. Molecular mechanisms and therapeutic targets for diabetic kidney disease. *Kidney Int.* **2022**, *102*, 248–260. [CrossRef]
20. Mohandes, S.; Doke, T.; Hu, H.; Mukhi, D.; Dhillon, P.; Susztak, K. Molecular pathways that drive diabetic kidney disease. *J. Clin. Investig.* **2023**, *133*, e165654. [CrossRef]
21. Karlinsey, K.; Qu, L.; Matz, A.J.; Zhou, B. A novel strategy to dissect multifaceted macrophage function in human diseases. *J. Leukoc. Biol.* **2022**, *112*, 1535–1542. [CrossRef] [PubMed]
22. Han, Z.; Ma, K.; Tao, H.; Liu, H.; Zhang, J.; Sai, X.; Li, Y.; Chi, M.; Nian, Q.; Song, L.; et al. A deep insight into regulatory t cell metabolism in renal disease: Facts and perspectives. *Front. Immunol.* **2022**, *13*, 826732. [CrossRef] [PubMed]
23. Xiong, W.; Meng, X.F.; Zhang, C. Nlrp3 inflammasome in metabolic-associated kidney diseases: An update. *Front. Immunol.* **2021**, *12*, 714340. [CrossRef]
24. Karlinsey, K.; Matz, A.; Qu, L.; Zhou, B. Extracellular rnas from immune cells under obesity—A narrative review. *ExRNA* **2022**, *4*, 18. [CrossRef] [PubMed]
25. Kaminski, H.; Couzi, L.; Eberl, M. Unconventional t cells and kidney disease. *Nat. Rev. Nephrol.* **2021**, *17*, 795–813. [CrossRef]
26. Hartzell, S.; Bin, S.; Cantarelli, C.; Haverly, M.; Manrique, J.; Angeletti, A.; Manna, G.; Murphy, B.; Zhang, W.; Levitsky, J.; et al. Kidney failure associates with t cell exhaustion and imbalanced follicular helper t cells. *Front. Immunol.* **2020**, *11*, 583702. [CrossRef]
27. Winterberg, P.D.; Ford, M.L. The effect of chronic kidney disease on t cell alloimmunity. *Curr. Opin. Organ Transplant.* **2017**, *22*, 22–28. [CrossRef]
28. Sharma, R.; Kinsey, G.R. Regulatory t cells in acute and chronic kidney diseases. *Am. J. Physiol. Ren. Physiol.* **2018**, *314*, F679–F698. [CrossRef]
29. Lisowska, K.A.; Storoniak, H.; Debska-Slizien, A. T cell subpopulations and cytokine levels in hemodialysis patients. *Hum. Immunol.* **2022**, *83*, 134–143. [CrossRef]
30. Gao, M.; Wang, J.; Zang, J.; An, Y.; Dong, Y. The mechanism of cd8(+) t cells for reducing myofibroblasts accumulation during renal fibrosis. *Biomolecules* **2021**, *11*, 990. [CrossRef]

31. Xu, L.; Guo, J.; Moledina, D.G.; Cantley, L.G. Immune-mediated tubule atrophy promotes acute kidney injury to chronic kidney disease transition. *Nat. Commun.* **2022**, *13*, 4892. [CrossRef] [PubMed]
32. Liu, Y.; Lv, Y.; Zhang, T.; Huang, T.; Lang, Y.; Sheng, Q.; Liu, Y.; Kong, Z.; Gao, Y.; Lu, S.; et al. T cells and their products in diabetic kidney disease. *Front. Immunol.* **2023**, *14*, 1084448. [CrossRef] [PubMed]
33. Chiu, Y.L.; Tsai, W.C.; Hung, R.W.; Chen, I.Y.; Shu, K.H.; Pan, S.Y.; Yang, F.J.; Ting, T.T.; Jiang, J.Y.; Peng, Y.S.; et al. Emergence of t cell immunosenescence in diabetic chronic kidney disease. *Immun. Ageing* **2020**, *17*, 31. [CrossRef] [PubMed]
34. Hu, S.Y.; Jia, X.Y.; Li, J.N.; Zheng, X.; Ao, J.; Liu, G.; Cui, Z.; Zhao, M.H. T cell infiltration is associated with kidney injury in patients with anti-glomerular basement membrane disease. *Sci. China. Life Sci.* **2016**, *59*, 1282–1289. [CrossRef]
35. Lin, J.S.; Susztak, K. Podocytes: The weakest link in diabetic kidney disease? *Curr. Diabetes Rep.* **2016**, *16*, 45. [CrossRef]
36. Kuo, H.L.; Huang, C.C.; Lin, T.Y.; Lin, C.Y. Il-17 and cd40 ligand synergistically stimulate the chronicity of diabetic nephropathy. *Nephrol. Dial. Transplant. Off. Publ. Eur. Dial. Transpl. Assoc.-Eur. Ren. Assoc.* **2018**, *33*, 248–256. [CrossRef]
37. Oleinika, K.; Mauri, C.; Salama, A.D. Effector and regulatory b cells in immune-mediated kidney disease. *Nat. Rev. Nephrol.* **2019**, *15*, 11–26. [CrossRef]
38. Sosa-Hernandez, V.A.; Romero-Ramirez, S.; Cervantes-Diaz, R.; Carrillo-Vazquez, D.A.; Navarro-Hernandez, I.C.; Whittall-Garcia, L.P.; Absalon-Aguilar, A.; Vargas-Castro, A.S.; Reyes-Huerta, R.F.; Juarez-Vega, G.; et al. Cd11c(+) t-bet(+) cd21(hi) b cells are negatively associated with renal impairment in systemic lupus erythematosus and act as a marker for nephritis remission. *Front. Immunol.* **2022**, *13*, 892241. [CrossRef]
39. Hoffman, W.; Lakkis, F.G.; Chalasani, G. B cells, antibodies, and more. *Clin. J. Am. Soc. Nephrol.* **2016**, *11*, 137–154. [CrossRef]
40. Mannik, M.; Merrill, C.E.; Stamps, L.D.; Wener, M.H. Multiple autoantibodies form the glomerular immune deposits in patients with systemic lupus erythematosus. *J. Rheumatol.* **2003**, *30*, 1495–1504.
41. Hoxha, E.; Reinhard, L.; Stahl, R.A.K. Membranous nephropathy: New pathogenic mechanisms and their clinical implications. *Nat. Rev. Nephrol.* **2022**, *18*, 466–478. [CrossRef] [PubMed]
42. Smith, M.J.; Simmons, K.M.; Cambier, J.C. B cells in type 1 diabetes mellitus and diabetic kidney disease. *Nat. Rev. Nephrol.* **2017**, *13*, 712–720. [CrossRef] [PubMed]
43. Long, W.; Zhang, H.; Yuan, W.; Lan, G.; Lin, Z.; Peng, L.; Dai, H. The role of regulatory b cells in kidney diseases. *Front. Immunol.* **2021**, *12*, 683926. [CrossRef] [PubMed]
44. Kong, L.; Andrikopoulos, S.; MacIsaac, R.J.; Mackay, L.K.; Nikolic-Paterson, D.J.; Torkamani, N.; Zafari, N.; Marin, E.C.S.; Ekinci, E.I. Role of the adaptive immune system in diabetic kidney disease. *J. Diabetes Investig.* **2022**, *13*, 213–226. [CrossRef]
45. Matz, A.; Qu, L.; Karlinsey, K.; Zhou, B. Impact of microrna regulated macrophage actions on adipose tissue function in obesity. *Cells* **2022**, *11*, 1336. [CrossRef]
46. Li, C.; Qu, L.; Matz, A.J.; Murphy, P.A.; Liu, Y.; Manichaikul, A.W.; Aguiar, D.; Rich, S.S.; Herrington, D.M.; Vu, D.; et al. Atherospectrum reveals novel macrophage foam cell gene signatures associated with atherosclerotic cardiovascular disease risk. *Circulation* **2022**, *145*, 206–218. [CrossRef]
47. Li, C.; Phoon, Y.P.; Karlinsey, K.; Tian, Y.F.; Thapaliya, S.; Thongkum, A.; Qu, L.; Matz, A.J.; Cameron, M.; Cameron, C.; et al. A high oxphos cd8 t cell subset is predictive of immunotherapy resistance in melanoma patients. *J. Exp. Med.* **2022**, *219*, e20202084. [CrossRef]
48. Li, C.; Qu, L.; Farragher, C.; Vella, A.; Zhou, B. Microrna regulated macrophage activation in obesity. *J. Transl. Intern. Med.* **2019**, *7*, 46–52. [CrossRef]
49. Qu, L.L.; Yu, B.; Li, Z.; Jiang, W.X.; Jiang, J.D.; Kong, W.J. Gastrodin ameliorates oxidative stress and proinflammatory response in nonalcoholic fatty liver disease through the ampk/nrf2 pathway. *Phytother. Res. PTR* **2016**, *30*, 402–411. [CrossRef]
50. Gao, S.; Jiao, B.; Hong, W.; Cai, C.; Zhong, Y.; Quan, Z.; Chen, H.; Xu, Y. Distribution of kir/hla alleles among ethnic han chinese patients with hepatocellular carcinoma from southern china. *Chin. J. Med. Genet.* **2019**, *36*, 439–442.
51. An, C.; Jia, L.; Wen, J.; Wang, Y. Targeting bone marrow-derived fibroblasts for renal fibrosis. *Adv. Exp. Med. Biol.* **2019**, *1165*, 305–322. [PubMed]
52. An, C.; Jiao, B.; Du, H.; Tran, M.; Zhou, D.; Wang, Y. Myeloid pten deficiency aggravates renal inflammation and fibrosis in angiotensin ii-induced hypertension. *J. Cell. Physiol.* **2022**, *237*, 983–991. [CrossRef] [PubMed]
53. Mihai, S.; Codrici, E.; Popescu, I.D.; Enciu, A.M.; Albulescu, L.; Necula, L.G.; Mambet, C.; Anton, G.; Tanase, C. Inflammation-related mechanisms in chronic kidney disease prediction, progression, and outcome. *J. Immunol. Res.* **2018**, *2018*, 2180373. [CrossRef] [PubMed]
54. Wynn, T.A.; Barron, L. Macrophages: Master regulators of inflammation and fibrosis. *Semin. Liver Dis.* **2010**, *30*, 245–257. [CrossRef] [PubMed]
55. Liu, Z.; Kuang, W.; Zhou, Q.; Zhang, Y. Tgf-beta1 secreted by m2 phenotype macrophages enhances the stemness and migration of glioma cells via the smad2/3 signalling pathway. *Int. J. Mol. Med.* **2018**, *42*, 3395–3403. [PubMed]
56. Wen, J.; Jiao, B.; Tran, M.; Wang, Y. Pharmacological inhibition of s100a4 attenuates fibroblast activation and renal fibrosis. *Cells* **2022**, *11*, 2762. [CrossRef]
57. Calle, P.; Hotter, G. Macrophage phenotype and fibrosis in diabetic nephropathy. *Int. J. Mol. Sci.* **2020**, *21*, 2806. [CrossRef]
58. Watanabe, K.; Sato, E.; Mishima, E.; Miyazaki, M.; Tanaka, T. What's new in the molecular mechanisms of diabetic kidney disease: Recent advances. *Int. J. Mol. Sci.* **2022**, *24*, 570. [CrossRef]
59. Ho, H.J.; Shirakawa, H. Oxidative stress and mitochondrial dysfunction in chronic kidney disease. *Cells* **2022**, *12*, 88. [CrossRef]

60. Gamboa, J.L.; Billings, F.T.; Bojanowski, M.T.; Gilliam, L.A.; Yu, C.; Roshanravan, B.; Roberts, L.J., II; Himmelfarb, J.; Ikizler, T.A.; Brown, N.J. Mitochondrial dysfunction and oxidative stress in patients with chronic kidney disease. *Physiol. Rep.* **2016**, *4*, e12780. [CrossRef]
61. Irazabal, M.V.; Torres, V.E. Reactive oxygen species and redox signaling in chronic kidney disease. *Cells* **2020**, *9*, 1342. [CrossRef] [PubMed]
62. Bhatia, D.; Capili, A.; Choi, M.E. Mitochondrial dysfunction in kidney injury, inflammation, and disease: Potential therapeutic approaches. *Kidney Res. Clin. Pract.* **2020**, *39*, 244–258. [CrossRef] [PubMed]
63. Gyuraszova, M.; Gurecka, R.; Babickova, J.; Tothova, L. Oxidative stress in the pathophysiology of kidney disease: Implications for noninvasive monitoring and identification of biomarkers. *Oxidative Med. Cell. Longev.* **2020**, *2020*, 5478708. [CrossRef] [PubMed]
64. Bulbul, M.C.; Dagel, T.; Afsar, B.; Ulusu, N.N.; Kuwabara, M.; Covic, A.; Kanbay, M. Disorders of lipid metabolism in chronic kidney disease. *Blood Purif.* **2018**, *46*, 144–152. [CrossRef]
65. Baek, J.; He, C.; Afshinnia, F.; Michailidis, G.; Pennathur, S. Lipidomic approaches to dissect dysregulated lipid metabolism in kidney disease. *Nat. Reviews. Nephrol.* **2022**, *18*, 38–55. [CrossRef]
66. Wu, T.; Ding, L.; Andoh, V.; Zhang, J.; Chen, L. The mechanism of hyperglycemia-induced renal cell injury in diabetic nephropathy disease: An update. *Life* **2023**, *13*, 539. [CrossRef]
67. Volpe, C.M.O.; Villar-Delfino, P.H.; Dos Anjos, P.M.F.; Nogueira-Machado, J.A. Cellular death, reactive oxygen species (ros) and diabetic complications. *Cell Death Dis.* **2018**, *9*, 119. [CrossRef]
68. Khalid, M.; Petroianu, G.; Adem, A. Advanced glycation end products and diabetes mellitus: Mechanisms and perspectives. *Biomolecules* **2022**, *12*, 542. [CrossRef]
69. Chang, C.C.; Chen, C.Y.; Chang, G.D.; Chen, T.H.; Chen, W.L.; Wen, H.C.; Huang, C.Y.; Chang, C.H. Hyperglycemia and advanced glycation end products (ages) suppress the differentiation of 3t3-l1 preadipocytes. *Oncotarget* **2017**, *8*, 55039–55050. [CrossRef]
70. Yao, L.; Liang, X.; Qiao, Y.; Chen, B.; Wang, P.; Liu, Z. Mitochondrial dysfunction in diabetic tubulopathy. *Metab. Clin. Exp.* **2022**, *131*, 155195. [CrossRef]
71. Xie, Y.; Jing, E.; Cai, H.; Zhong, F.; Xiao, W.; Gordon, R.E.; Wang, L.; Zheng, Y.L.; Zhang, A.; Lee, K.; et al. Reticulon-1a mediates diabetic kidney disease progression through endoplasmic reticulum-mitochondrial contacts in tubular epithelial cells. *Kidney Int.* **2022**, *102*, 293–306. [CrossRef] [PubMed]
72. Makris, K.; Spanou, L. Acute kidney injury: Definition, pathophysiology and clinical phenotypes. *Clin. Biochemist. Rev.* **2016**, *37*, 85–98.
73. Jin, X.; An, C.; Jiao, B.; Safirstein, R.L.; Wang, Y. Amp-activated protein kinase contributes to cisplatin-induced renal epithelial cell apoptosis and acute kidney injury. *Am. J. Physiol. Ren. Physiol.* **2020**, *319*, F1073–F1080. [CrossRef] [PubMed]
74. LaFavers, K. Disruption of kidney-immune system crosstalk in sepsis with acute kidney injury: Lessons learned from animal models and their application to human health. *Int. J. Mol. Sci.* **2022**, *23*, 1702. [CrossRef] [PubMed]
75. Liu, H.; Li, Y.; Xiong, J. The role of hypoxia-inducible factor-1 alpha in renal disease. *Molecules* **2022**, *27*, 7318. [CrossRef]
76. Fu, Z.J.; Wang, Z.Y.; Xu, L.; Chen, X.H.; Li, X.X.; Liao, W.T.; Ma, H.K.; Jiang, M.D.; Xu, T.T.; Xu, J.; et al. Hif-1alpha-bnip3-mediated mitophagy in tubular cells protects against renal ischemia/reperfusion injury. *Redox Biol.* **2020**, *36*, 101671. [CrossRef]
77. McGettrick, A.F.; O'Neill, L.A.J. The role of hif in immunity and inflammation. *Cell Metab.* **2020**, *32*, 524–536. [CrossRef]
78. Shu, S.; Wang, Y.; Zheng, M.; Liu, Z.; Cai, J.; Tang, C.; Dong, Z. Hypoxia and hypoxia-inducible factors in kidney injury and repair. *Cells* **2019**, *8*, 207. [CrossRef]
79. Wang, Z.; Zhang, W. The crosstalk between hypoxia-inducible factor-1alpha and micrornas in acute kidney injury. *Exp. Biol. Med.* **2020**, *245*, 427–436. [CrossRef]
80. Taylor, C.T.; Scholz, C.C. The effect of hif on metabolism and immunity. *Nat. Rev. Nephrol.* **2022**, *18*, 573–587. [CrossRef]
81. Li, Z.L.; Ji, J.L.; Wen, Y.; Cao, J.Y.; Kharbuja, N.; Ni, W.J.; Yin, D.; Feng, S.T.; Liu, H.; Lv, L.L.; et al. Hif-1alpha is transcriptionally regulated by nf-kappab in acute kidney injury. *Am. J. Physiol. Ren. Physiol.* **2021**, *321*, F225–F235. [CrossRef] [PubMed]
82. Li, Z.; Li, N. Epigenetic modification drives acute kidney injury-to-chronic kidney disease progression. *Nephron* **2021**, *145*, 737–747. [CrossRef] [PubMed]
83. Tanemoto, F.; Mimura, I. Therapies targeting epigenetic alterations in acute kidney injury-to-chronic kidney disease transition. *Pharmaceuticals* **2022**, *15*, 123. [CrossRef] [PubMed]
84. Mimura, I.; Hirakawa, Y.; Kanki, Y.; Kushida, N.; Nakaki, R.; Suzuki, Y.; Tanaka, T.; Aburatani, H.; Nangaku, M. Novel lnc rna regulated by hif-1 inhibits apoptotic cell death in the renal tubular epithelial cells under hypoxia. *Physiol. Rep.* **2017**, *5*, e13203. [CrossRef]
85. Forstermann, U.; Sessa, W.C. Nitric oxide synthases: Regulation and function. *Eur. Heart J.* **2012**, *33*, 829–837. [CrossRef]
86. Oliveira, F.; Assreuy, J.; Sordi, R. The role of nitric oxide in sepsis-associated kidney injury. *Biosci. Rep.* **2022**, *42*, BSR20220093. [CrossRef]
87. Wang, J.; Cong, X.; Miao, M.; Yang, Y.; Zhang, J. Inhaled nitric oxide and acute kidney injury risk: A meta-analysis of randomized controlled trials. *Ren. Fail.* **2021**, *43*, 281–290. [CrossRef]
88. Carlstrom, M. Nitric oxide signalling in kidney regulation and cardiometabolic health. *Nat. Rev. Nephrol.* **2021**, *17*, 575–590. [CrossRef]

89. Ludes, P.O.; de Roquetaillade, C.; Chousterman, B.G.; Pottecher, J.; Mebazaa, A. Role of damage-associated molecular patterns in septic acute kidney injury, from injury to recovery. *Front. Immunol.* **2021**, *12*, 606622. [CrossRef]
90. Meissner, M.; Viehmann, S.F.; Kurts, C. Dampening sterile inflammation of the kidney. *Kidney Int.* **2019**, *95*, 489–491. [CrossRef]
91. Vazquez-Carballo, C.; Guerrero-Hue, M.; Garcia-Caballero, C.; Rayego-Mateos, S.; Opazo-Rios, L.; Morgado-Pascual, J.L.; Herencia-Bellido, C.; Vallejo-Mudarra, M.; Cortegano, I.; Gaspar, M.L.; et al. Toll-like receptors in acute kidney injury. *Int. J. Mol. Sci.* **2021**, *22*, 816. [CrossRef] [PubMed]
92. Liu, C.; Shen, Y.; Huang, L.; Wang, J. Tlr2/caspase-5/panx1 pathway mediates necrosis-induced nlrp3 inflammasome activation in macrophages during acute kidney injury. *Cell Death Discov.* **2022**, *8*, 232. [CrossRef]
93. Lin, Q.; Li, S.; Jiang, N.; Jin, H.; Shao, X.; Zhu, X.; Wu, J.; Zhang, M.; Zhang, Z.; Shen, J.; et al. Inhibiting nlrp3 inflammasome attenuates apoptosis in contrast-induced acute kidney injury through the upregulation of hif1a and bnip3-mediated mitophagy. *Autophagy* **2021**, *17*, 2975–2990. [CrossRef] [PubMed]
94. Akhter, J.; Khan, J.; Baghel, M.; Beg, M.M.A.; Goswami, P.; Afjal, M.A.; Ahmad, S.; Habib, H.; Najmi, A.K.; Raisuddin, S. Nlrp3 inflammasome in rosmarinic acid-afforded attenuation of acute kidney injury in mice. *Sci. Rep.* **2022**, *12*, 1313. [CrossRef] [PubMed]
95. Kim, H.J.; Lee, D.W.; Ravichandran, K.; Keys, D.O.; Akcay, A.; Nguyen, Q.; He, Z.; Jani, A.; Ljubanovic, D.; Edelstein, C.L. Nlrp3 inflammasome knockout mice are protected against ischemic but not cisplatin-induced acute kidney injury. *J. Pharmacol. Exp. Ther.* **2013**, *346*, 465–472. [CrossRef]
96. Zhang, L.; Cui, L.; Li, C.; Zhao, X.; Lai, X.; Li, J.; Lv, T. Serum free fatty acid elevation is related to acute kidney injury in primary nephrotic syndrome. *Ren. Fail.* **2022**, *44*, 1236–1242. [CrossRef]
97. Wen, L.; Li, Y.; Li, S.; Hu, X.; Wei, Q.; Dong, Z. Glucose metabolism in acute kidney injury and kidney repair. *Front. Med.* **2021**, *8*, 744122. [CrossRef] [PubMed]
98. Kumar, D.; Singla, S.K.; Puri, V.; Puri, S. The restrained expression of nf-kb in renal tissue ameliorates folic acid induced acute kidney injury in mice. *PLoS ONE* **2015**, *10*, e115947. [CrossRef]
99. Song, N.; Thaiss, F.; Guo, L. Nfkappab and kidney injury. *Front. Immunol.* **2019**, *10*, 815. [CrossRef]
100. Halling, J.F.; Pilegaard, H. Pgc-1alpha-mediated regulation of mitochondrial function and physiological implications. *Appl. Physiol. Nutr. Metab. Physiol. Appl. Nutr. Metab.* **2020**, *45*, 927–936. [CrossRef]
101. Fontecha-Barriuso, M.; Martin-Sanchez, D.; Martinez-Moreno, J.M.; Monsalve, M.; Ramos, A.M.; Sanchez-Nino, M.D.; Ruiz-Ortega, M.; Ortiz, A.; Sanz, A.B. The role of pgc-1alpha and mitochondrial biogenesis in kidney diseases. *Biomolecules* **2020**, *10*, 347. [CrossRef] [PubMed]
102. Yuan, L.; Yuan, Y.; Liu, F.; Li, L.; Liu, J.; Chen, Y.; Cheng, J.; Lu, Y. Pgc-1alpha alleviates mitochondrial dysfunction via tfeb-mediated autophagy in cisplatin-induced acute kidney injury. *Aging* **2021**, *13*, 8421–8439. [CrossRef] [PubMed]
103. Ruiz-Andres, O.; Suarez-Alvarez, B.; Sanchez-Ramos, C.; Monsalve, M.; Sanchez-Nino, M.D.; Ruiz-Ortega, M.; Egido, J.; Ortiz, A.; Sanz, A.B. The inflammatory cytokine tweak decreases pgc-1alpha expression and mitochondrial function in acute kidney injury. *Kidney Int.* **2016**, *89*, 399–410. [CrossRef]
104. Nam, B.Y.; Jhee, J.H.; Park, J.; Kim, S.; Kim, G.; Park, J.T.; Yoo, T.H.; Kang, S.W.; Yu, J.W.; Han, S.H. Pgc-1alpha inhibits the nlrp3 inflammasome via preserving mitochondrial viability to protect kidney fibrosis. *Cell Death Dis.* **2022**, *13*, 31. [CrossRef] [PubMed]
105. Li, J.; Yang, Y.; Wang, Y.; Li, Q.; He, F. Metabolic signatures of immune cells in chronic kidney disease. *Expert Rev. Mol. Med.* **2022**, *24*, e40. [CrossRef] [PubMed]
106. de Boer, I.H. Vitamin d and glucose metabolism in chronic kidney disease. *Curr. Opin. Nephrol. Hypertens.* **2008**, *17*, 566–572. [CrossRef]
107. Gupta, N.; Wish, J.B. Hypoxia-inducible factor prolyl hydroxylase inhibitors: A potential new treatment for anemia in patients with ckd. *Am. J. Kidney Dis. Off. J. Natl. Kidney Found.* **2017**, *69*, 815–826. [CrossRef]
108. Wei, X.; Hou, Y.; Long, M.; Jiang, L.; Du, Y. Molecular mechanisms underlying the role of hypoxia-inducible factor-1 alpha in metabolic reprogramming in renal fibrosis. *Front. Endocrinol.* **2022**, *13*, 927329. [CrossRef]
109. Mokas, S.; Lariviere, R.; Lamalice, L.; Gobeil, S.; Cornfield, D.N.; Agharazii, M.; Richard, D.E. Hypoxia-inducible factor-1 plays a role in phosphate-induced vascular smooth muscle cell calcification. *Kidney Int.* **2016**, *90*, 598–609. [CrossRef]
110. Vilaysane, A.; Chun, J.; Seamone, M.E.; Wang, W.; Chin, R.; Hirota, S.; Li, Y.; Clark, S.A.; Tschopp, J.; Trpkov, K.; et al. The nlrp3 inflammasome promotes renal inflammation and contributes to ckd. *J. Am. Soc. Nephrol.* **2010**, *21*, 1732–1744. [CrossRef]
111. Gai, Z.; Wang, T.; Visentin, M.; Kullak-Ublick, G.A.; Fu, X.; Wang, Z. Lipid accumulation and chronic kidney disease. *Nutrients* **2019**, *11*, 722. [CrossRef] [PubMed]
112. Pei, K.; Gui, T.; Li, C.; Zhang, Q.; Feng, H.; Li, Y.; Wu, J.; Gai, Z. Recent progress on lipid intake and chronic kidney disease. *BioMed Res. Int.* **2020**, *2020*, 3680397. [CrossRef] [PubMed]
113. Sepe, V.; Libetta, C.; Gregorini, M.; Rampino, T. The innate immune system in human kidney inflammaging. *J. Nephrol.* **2022**, *35*, 381–395. [CrossRef] [PubMed]
114. Zewinger, S.; Schumann, T.; Fliser, D.; Speer, T. Innate immunity in ckd-associated vascular diseases. *Nephrol. Dial. Transplant. Off. Publ. Eur. Dial. Transpl. Assoc.-Eur. Ren. Assoc.* **2016**, *31*, 1813–1821. [CrossRef]
115. Lee, H.; Fessler, M.B.; Qu, P.; Heymann, J.; Kopp, J.B. Macrophage polarization in innate immune responses contributing to pathogenesis of chronic kidney disease. *BMC Nephrol.* **2020**, *21*, 270. [CrossRef]
116. Zhang, H.; Sun, S.C. Nf-kappab in inflammation and renal diseases. *Cell Biosci.* **2015**, *5*, 63. [CrossRef]

117. Rangan, G.; Wang, Y.; Harris, D. Nf-kappab signalling in chronic kidney disease. *Front. Biosci.* **2009**, *14*, 3496–3522. [CrossRef]
118. Huang, G.; Zhang, Y.; Zhang, Y.; Ma, Y. Chronic kidney disease and nlrp3 inflammasome: Pathogenesis, development and targeted therapeutic strategies. *Biochem. Biophys. Rep.* **2023**, *33*, 101417. [CrossRef]
119. Zhang, H.; Wang, Z. Effect and regulation of the nlrp3 inflammasome during renal fibrosis. *Front. Cell Dev. Biol.* **2019**, *7*, 379. [CrossRef]
120. Siragy, H.M.; Carey, R.M. Role of the intrarenal renin-angiotensin-aldosterone system in chronic kidney disease. *Am. J. Nephrol.* **2010**, *31*, 541–550. [CrossRef]
121. Gaudreault-Tremblay, M.M.; Foster, B.J. Benefits of continuing raas inhibitors in advanced ckd. *Clin. J. Am. Soc. Nephrol.* **2020**, *15*, 592–593. [CrossRef] [PubMed]
122. Remuzzi, G.; Perico, N.; Macia, M.; Ruggenenti, P. The role of renin-angiotensin-aldosterone system in the progression of chronic kidney disease. *Kidney Int. Suppl.* **2005**, *68*, S57–S65. [CrossRef] [PubMed]
123. Ingrosso, D.; Perna, A.F. DNA methylation dysfunction in chronic kidney disease. *Genes* **2020**, *11*, 811. [CrossRef] [PubMed]
124. Sato, K.; Kumagai, N.; Suzuki, N. Alteration of the DNA methylation signature of renal erythropoietin-producing cells governs the sensitivity to drugs targeting the hypoxia-response pathway in kidney disease progression. *Front. Genet.* **2019**, *10*, 1134. [CrossRef]
125. Morgado-Pascual, J.L.; Marchant, V.; Rodrigues-Diez, R.; Dolade, N.; Suarez-Alvarez, B.; Kerr, B.; Valdivielso, J.M.; Ruiz-Ortega, M.; Rayego-Mateos, S. Epigenetic modification mechanisms involved in inflammation and fibrosis in renal pathology. *Mediat. Inflamm.* **2018**, *2018*, 2931049. [CrossRef]
126. Li, L.X.; Fan, L.X.; Zhou, J.X.; Grantham, J.J.; Calvet, J.P.; Sage, J.; Li, X. Lysine methyltransferase smyd2 promotes cyst growth in autosomal dominant polycystic kidney disease. *J. Clin. Investig.* **2017**, *127*, 2751–2764. [CrossRef]
127. Lazar, S.; Kahlenberg, J.M. Systemic lupus erythematosus: New diagnostic and therapeutic approaches. *Annu. Rev. Med.* **2023**, *74*, 339–352. [CrossRef]
128. Ma, L.; Roach, T.; Morel, L. Immunometabolic alterations in lupus: Where do they come from and where do we go from there? *Curr. Opin. Immunol.* **2022**, *78*, 102245. [CrossRef]
129. Liu, X.; Du, H.; Sun, Y.; Shao, L. Role of abnormal energy metabolism in the progression of chronic kidney disease and drug intervention. *Ren. Fail.* **2022**, *44*, 790–805. [CrossRef]
130. Fornoni, A.; Merscher, S. Lipid metabolism gets in a jaml during kidney disease. *Cell Metab.* **2020**, *32*, 903–905. [CrossRef]
131. Liberti, M.V.; Locasale, J.W. The warburg effect: How does it benefit cancer cells? *Trends Biochem. Sci.* **2016**, *41*, 211–218. [CrossRef] [PubMed]
132. Sun, Q.; Chen, X.; Ma, J.; Peng, H.; Wang, F.; Zha, X.; Wang, Y.; Jing, Y.; Yang, H.; Chen, R.; et al. Mammalian target of rapamycin up-regulation of pyruvate kinase isoenzyme type m2 is critical for aerobic glycolysis and tumor growth. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 4129–4134. [CrossRef] [PubMed]
133. Chen, H.; Liu, N.; Zhuang, S. Macrophages in renal injury, repair, fibrosis following acute kidney injury and targeted therapy. *Front. Immunol.* **2022**, *13*, 934299. [CrossRef] [PubMed]
134. Scuron, M.D.; Fay, B.L.; Connell, A.J.; Oliver, J.; Smith, P.A. The pi3kdelta inhibitor parsaclisib ameliorates pathology and reduces autoantibody formation in preclinical models of systemic lupus erythematosus and sjögren's syndrome. *Int. Immunopharmacol.* **2021**, *98*, 107904. [CrossRef]
135. Ripoll, E.; de Ramon, L.; Draibe Bordignon, J.; Merino, A.; Bolanos, N.; Goma, M.; Cruzado, J.M.; Grinyo, J.M.; Torras, J. Jak3-stat pathway blocking benefits in experimental lupus nephritis. *Arthritis Res. Ther.* **2016**, *18*, 134. [CrossRef] [PubMed]
136. Zhao, W.; Wu, C.; Li, L.J.; Fan, Y.G.; Pan, H.F.; Tao, J.H.; Leng, R.X.; Ye, D.Q. Rnai silencing of hif-1alpha ameliorates lupus development in mrl/lpr mice. *Inflammation* **2018**, *41*, 1717–1730. [CrossRef] [PubMed]
137. Oliveira, C.B.; Lima, C.A.D.; Vajgel, G.; Sandrin-Garcia, P. The role of nlrp3 inflammasome in lupus nephritis. *Int. J. Mol. Sci.* **2021**, *22*, 12476. [CrossRef]
138. Wu, D.; Ai, L.; Sun, Y.; Yang, B.; Chen, S.; Wang, Q.; Kuang, H. Role of nlrp3 inflammasome in lupus nephritis and therapeutic targeting by phytochemicals. *Front. Pharmacol.* **2021**, *12*, 621300. [CrossRef]
139. Pestka, J.J.; Akbari, P.; Wierenga, K.A.; Bates, M.A.; Gilley, K.N.; Wagner, J.G.; Lewandowski, R.P.; Rajasinghe, L.D.; Chauhan, P.S.; Lock, A.L.; et al. Omega-3 polyunsaturated fatty acid intervention against established autoimmunity in a murine model of toxicant-triggered lupus. *Front. Immunol.* **2021**, *12*, 653464. [CrossRef]
140. Pestka, J.J.; Vines, L.L.; Bates, M.A.; He, K.; Langohr, I. Comparative effects of n-3, n-6 and n-9 unsaturated fatty acid-rich diet consumption on lupus nephritis, autoantibody production and cd4+ t cell-related gene responses in the autoimmune nzbwf1 mouse. *PLoS ONE* **2014**, *9*, e100255. [CrossRef]
141. Wolf, S.J.; Theros, J.; Reed, T.J.; Liu, J.; Grigorova, I.L.; Martinez-Colon, G.; Jacob, C.O.; Hodgin, J.B.; Kahlenberg, J.M. Tlr7-mediated lupus nephritis is independent of type i ifn signaling. *J. Immunol.* **2018**, *201*, 393–405. [CrossRef]
142. Ding, X.; Ren, Y.; He, X. Ifn-i mediates lupus nephritis from the beginning to renal fibrosis. *Front. Immunol.* **2021**, *12*, 676082. [CrossRef]
143. Devarapu, S.K.; Anders, H.J. Toll-like receptors in lupus nephritis. *J. Biomed. Sci.* **2018**, *25*, 35. [CrossRef]
144. He, L.Y.; Niu, S.Q.; Yang, C.X.; Tang, P.; Fu, J.J.; Tan, L.; Li, Y.; Hua, Y.N.; Liu, S.J.; Guo, J.L. Cordyceps proteins alleviate lupus nephritis through modulation of the stat3/mtor/nf-small ka, cyrillicb signaling pathway. *J. Ethnopharmacol.* **2023**, *309*, 116284. [CrossRef] [PubMed]

145. Zou, L.; Sun, L.; Hua, R.; Wu, Y.; Sun, L.; Chen, T. Degradation of ubiquitin-editing enzyme a20 following autophagy activation promotes rnf168 nuclear translocation and nf-kappab activation in lupus nephritis. *J. Innate Immun.* **2023**, *15*, 428–441. [CrossRef]
146. Karasawa, T.; Sato, R.; Imaizumi, T.; Hashimoto, S.; Fujita, M.; Aizawa, T.; Tsugawa, K.; Kawaguchi, S.; Seya, K.; Terui, K.; et al. Glomerular endothelial expression of type i ifn-stimulated gene, dexd/h-box helicase 60 via toll-like receptor 3 signaling: Possible involvement in the pathogenesis of lupus nephritis. *Ren. Fail.* **2022**, *44*, 137–145. [CrossRef] [PubMed]
147. Dunlap, G.S.; Billi, A.C.; Xing, X.; Ma, F.; Maz, M.P.; Tsoi, L.C.; Wasikowski, R.; Hodgin, J.B.; Gudjonsson, J.E.; Kahlenberg, J.M.; et al. Single-cell transcriptomics reveals distinct effector profiles of infiltrating t cells in lupus skin and kidney. *JCI Insight* **2022**, *7*, e156341. [CrossRef] [PubMed]
148. Tsao, Y.P.; Tseng, F.Y.; Chao, C.W.; Chen, M.H.; Yeh, Y.C.; Abdulkareem, B.O.; Chen, S.Y.; Chuang, W.T.; Chang, P.C.; Chen, I.C.; et al. Nlrp12 is an innate immune checkpoint for repressing ifn signatures and attenuating lupus nephritis progression. *J. Clin. Investig.* **2023**, *133*, e157272. [CrossRef]
149. Zumaquero, E.; Stone, S.L.; Scharer, C.D.; Jenks, S.A.; Nellore, A.; Mousseau, B.; Rosal-Vela, A.; Botta, D.; Bradley, J.E.; Wojciechowski, W.; et al. Ifngamma induces epigenetic programming of human t-bet(hi) b cells and promotes tlr7/8 and il-21 induced differentiation. *eLife* **2019**, *8*, e41641. [CrossRef]
150. Sagoo, M.K.; Gnudi, L. Diabetic nephropathy: An overview. *Methods Mol. Biol.* **2020**, *2067*, 3–7.
151. Wang, X.; Zhao, L.; Ajay, A.K.; Jiao, B.; Zhang, X.; Wang, C.; Gao, X.; Yuan, Z.; Liu, H.; Liu, W.J. Qiditangshen granules activate renal nutrient-sensing associated autophagy in db/db mice. *Front. Physiol.* **2019**, *10*, 1224. [CrossRef] [PubMed]
152. Han, H.; Wang, L.; Du, H.; Jiang, J.; Hu, C.; Zhang, G.; Liu, S.; Zhang, X.; Liu, T.; Hu, S. Expedited biliopancreatic juice flow to the distal gut benefits the diabetes control after duodenal-jejunal bypass. *Obes. Surg.* **2015**, *25*, 1802–1809. [CrossRef] [PubMed]
153. Sanajou, D.; Ghorbani Haghjo, A.; Argani, H.; Aslani, S. Age-rage axis blockade in diabetic nephropathy: Current status and future directions. *Eur. J. Pharmacol.* **2018**, *833*, 158–164. [CrossRef] [PubMed]
154. Kobayashi, H.; Gilbert, V.; Liu, Q.; Kapitsinou, P.P.; Unger, T.L.; Rha, J.; Rivella, S.; Schlondorff, D.; Haase, V.H. Myeloid cell-derived hypoxia-inducible factor attenuates inflammation in unilateral ureteral obstruction-induced kidney injury. *J. Immunol.* **2012**, *188*, 5106–5115. [CrossRef] [PubMed]
155. Tsai, I.T.; Wu, C.C.; Hung, W.C.; Lee, T.L.; Hsuan, C.F.; Wei, C.T.; Lu, Y.C.; Yu, T.H.; Chung, F.M.; Lee, Y.J.; et al. Fabp1 and fabp2 as markers of diabetic nephropathy. *Int. J. Med. Sci.* **2020**, *17*, 2338–2345. [CrossRef]
156. Sieber, J.; Jehle, A.W. Free fatty acids and their metabolism affect function and survival of podocytes. *Front. Endocrinol.* **2014**, *5*, 186. [CrossRef]
157. Tomita, Y.; Lee, D.; Tsubota, K.; Kurihara, T. Pparalpha agonist oral therapy in diabetic retinopathy. *Biomedicines* **2020**, *8*, 433. [CrossRef]
158. Hu, Y.; Chen, Y.; Ding, L.; He, X.; Takahashi, Y.; Gao, Y.; Shen, W.; Cheng, R.; Chen, Q.; Qi, X.; et al. Pathogenic role of diabetes-induced ppar-alpha down-regulation in microvascular dysfunction. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 15401–15406. [CrossRef]
159. Ding, S.; Xu, S.; Ma, Y.; Liu, G.; Jang, H.; Fang, J. Modulatory mechanisms of the nlrp3 inflammasomes in diabetes. *Biomolecules* **2019**, *9*, 850. [CrossRef]
160. Wan, L.; Bai, X.; Zhou, Q.; Chen, C.; Wang, H.; Liu, T.; Xue, J.; Wei, C.; Xie, L. The advanced glycation end-products (ages)/ros/nlrp3 inflammasome axis contributes to delayed diabetic corneal wound healing and nerve regeneration. *Int. J. Biol. Sci.* **2022**, *18*, 809–825. [CrossRef]
161. Shi, X.; Jiao, B.; Chen, Y.; Li, S.; Chen, L. Mxa is a positive regulator of type i ifn signaling in hcv infection. *J. Med. Virol.* **2017**, *89*, 2173–2180. [CrossRef] [PubMed]
162. Chen, Y.; Jiao, B.; Yao, M.; Shi, X.; Zheng, Z.; Li, S.; Chen, L. Isg12a inhibits hcv replication and potentiates the anti-hcv activity of ifn-alpha through activation of the jak/stat signaling pathway independent of autophagy and apoptosis. *Virus Res.* **2017**, *227*, 231–239. [CrossRef] [PubMed]
163. Duan, X.; Li, S.; Holmes, J.A.; Tu, Z.; Li, Y.; Cai, D.; Liu, X.; Li, W.; Yang, C.; Jiao, B.; et al. Microrna 130a regulates both hepatitis c virus and hepatitis b virus replication through a central metabolic pathway. *J. Virol.* **2018**, *92*, e02009-17. [CrossRef] [PubMed]
164. Chen, X.; Ye, H.; Li, S.; Jiao, B.; Wu, J.; Zeng, P.; Chen, L. Severe fever with thrombocytopenia syndrome virus inhibits exogenous type i ifn signaling pathway through its nss invitro. *PLoS ONE* **2017**, *12*, e0172744.
165. Li, Y.; Li, S.; Duan, X.; Chen, Y.; Jiao, B.; Ye, H.; Yao, M.; Chen, L. Interferon-stimulated gene 15 conjugation stimulates hepatitis b virus production independent of type i interferon signaling pathway in vitro. *Mediat. Inflamm.* **2016**, *2016*, 7417648. [CrossRef]
166. Jiao, B.; Shi, X.; Chen, Y.; Ye, H.; Yao, M.; Hong, W.; Li, S.; Duan, X.; Li, Y.; Wang, Y.; et al. Insulin receptor substrate-4 interacts with ubiquitin-specific protease 18 to activate the jak/stat signaling pathway. *Oncotarget* **2017**, *8*, 105923–105935. [CrossRef]
167. Yuan, Y.; Jiao, B.; Qu, L.; Yang, D.; Liu, R. The development of covid-19 treatment. *Front. Immunol.* **2023**, *14*, 1125246. [CrossRef]
168. Chen, D.; Liu, Y.; Chen, J.; Lin, H.; Guo, H.; Wu, Y.; Xu, Y.; Zhou, Y.; Zhou, W.; Lu, R.; et al. Jak/stat pathway promotes the progression of diabetic kidney disease via autophagy in podocytes. *Eur. J. Pharmacol.* **2021**, *902*, 174121. [CrossRef]
169. Lv, L.L.; Feng, Y.; Wu, M.; Wang, B.; Li, Z.L.; Zhong, X.; Wu, W.J.; Chen, J.; Ni, H.F.; Tang, T.T.; et al. Exosomal mirna-19b-3p of tubular epithelial cells promotes m1 macrophage activation in kidney injury. *Cell Death Differ.* **2020**, *27*, 210–226. [CrossRef]
170. Zhu, M.; Wang, H.; Chen, J.; Zhu, H. Sinomenine improve diabetic nephropathy by inhibiting fibrosis and regulating the jak2/stat3/socs1 pathway in streptozotocin-induced diabetic rats. *Life Sci.* **2021**, *265*, 118855. [CrossRef]

171. Riwanto, M.; Kapoor, S.; Rodriguez, D.; Edenhofer, I.; Segerer, S.; Wuthrich, R.P. Inhibition of aerobic glycolysis attenuates disease progression in polycystic kidney disease. *PLoS ONE* **2016**, *11*, e0146654. [CrossRef]
172. Podrini, C.; Cassina, L.; Boletta, A. Metabolic reprogramming and the role of mitochondria in polycystic kidney disease. *Cell. Signal.* **2020**, *67*, 109495. [CrossRef] [PubMed]
173. Nguyen, D.T.; Kleczko, E.K.; Dwivedi, N.; Monaghan, M.T.; Gitomer, B.Y.; Chonchol, M.B.; Clambey, E.T.; Nemenoff, R.A.; Klawitter, J.; Hopp, K. The tryptophan-metabolizing enzyme indoleamine 2,3-dioxygenase 1 regulates polycystic kidney disease progression. *JCI Insight* **2023**, *8*. [CrossRef] [PubMed]
174. Swenson-Fields, K.I.; Ward, C.J.; Lopez, M.E.; Fross, S.; Heimes Dillon, A.L.; Meisenheimer, J.D.; Rabbani, A.J.; Wedlock, E.; Basu, M.K.; Jansson, K.P.; et al. Caspase-1 and the inflammasome promote polycystic kidney disease progression. *Front. Mol. Biosci.* **2022**, *9*, 971219. [CrossRef] [PubMed]
175. Raptis, V.; Loutradis, C.; Boutou, A.K.; Faitatzidou, D.; Sioulis, A.; Ferro, C.J.; Papagianni, A.; Sarafidis, P.A. Serum copeptin, nlpr3, and supar levels among patients with autosomal-dominant polycystic kidney disease with and without impaired renal function. *Cardiorenal Med.* **2020**, *10*, 440–451. [CrossRef]
176. Granata, S.; Masola, V.; Zoratti, E.; Scupoli, M.T.; Baruzzi, A.; Messa, M.; Sallustio, F.; Gesualdo, L.; Lupo, A.; Zaza, G. Nlrp3 inflammasome activation in dialyzed chronic kidney disease patients. *PLoS ONE* **2015**, *10*, e0122272. [CrossRef]
177. Kleczko, E.K.; Marsh, K.H.; Tyler, L.C.; Furgeson, S.B.; Bullock, B.L.; Altmann, C.J.; Miyazaki, M.; Gitomer, B.Y.; Harris, P.C.; Weiser-Evans, M.C.M.; et al. Cd8(+) t cells modulate autosomal dominant polycystic kidney disease progression. *Kidney Int.* **2018**, *94*, 1127–1140. [CrossRef]
178. Huang, D.L.; He, Y.R.; Liu, Y.J.; He, H.Y.; Gu, Z.Y.; Liu, Y.M.; Liu, W.J.; Luo, Z.; Ju, M.J. The immunomodulation role of th17 and treg in renal transplantation. *Front. Immunol.* **2023**, *14*, 1113560. [CrossRef]
179. Tanimine, N.; Turka, L.A.; Priyadharshini, B. Navigating t-cell immunometabolism in transplantation. *Transplantation* **2018**, *102*, 230–239. [CrossRef]
180. Tran, D.T.; Sundararaj, K.; Atkinson, C.; Nadig, S.N. T-cell immunometabolism: Therapeutic implications in organ transplantation. *Transplantation* **2021**, *105*, e191–e201. [CrossRef]
181. Kazmi, S.; Khan, M.A.; Shamma, T.; Altuhami, A.; Assiri, A.M.; Broering, D.C. Therapeutic nexus of t cell immunometabolism in improving transplantation immunotherapy. *Int. Immunopharmacol.* **2022**, *106*, 108621. [CrossRef] [PubMed]
182. Lucas-Ruiz, F.; Penin-Franch, A.; Pons, J.A.; Ramirez, P.; Pelegrin, P.; Cuevas, S.; Baroja-Mazo, A. Emerging role of nlrp3 inflammasome and pyroptosis in liver transplantation. *Int. J. Mol. Sci.* **2022**, *23*, 14396. [CrossRef]
183. Wang, M.; Pan, W.; Xu, Y.; Zhang, J.; Wan, J.; Jiang, H. Microglia-mediated neuroinflammation: A potential target for the treatment of cardiovascular diseases. *J. Inflamm. Res.* **2022**, *15*, 3083–3094. [CrossRef] [PubMed]
184. Su, X.; Liu, B.; Wang, S.; Wang, Y.; Zhang, Z.; Zhou, H.; Li, F. Nlrp3 inflammasome: A potential therapeutic target to minimize renal ischemia/reperfusion injury during transplantation. *Transpl. Immunol.* **2022**, *75*, 101718. [CrossRef] [PubMed]
185. Liu, Y.; Lei, Z.; Chai, H.; Kang, Q.; Qin, X. Salidroside alleviates hepatic ischemia-reperfusion injury during liver transplant in rat through regulating tlr-4/nf-kappab/nlrp3 inflammatory pathway. *Sci. Rep.* **2022**, *12*, 13973. [CrossRef] [PubMed]
186. Hecking, M.; Kainz, A.; Werzowa, J.; Haidinger, M.; Doller, D.; Tura, A.; Karaboyas, A.; Horl, W.H.; Wolzt, M.; Sharif, A.; et al. Glucose metabolism after renal transplantation. *Diabetes Care* **2013**, *36*, 2763–2771. [CrossRef]
187. Baker, R.J.; Marks, S.D. Management of chronic renal allograft dysfunction and when to re-transplant. *Pediatr. Nephrol.* **2019**, *34*, 599–603. [CrossRef]
188. Nafar, M.; Sahraei, Z.; Salamzadeh, J.; Samavat, S.; Vaziri, N.D. Oxidative stress in kidney transplantation: Causes, consequences, and potential treatment. *Iran. J. Kidney Dis.* **2011**, *5*, 357–372.
189. Diaz-De la Cruz, E.N.; Cerrillos-Gutierrez, J.I.; Garcia-Sanchez, A.; Andrade-Sierra, J.; Cardona-Munoz, E.G.; Rojas-Campos, E.; Gonzalez-Espinoza, E.; Miranda-Diaz, A.G. The alteration of pro-inflammatory cytokines and oxidative stress markers at six-month post-living kidney donation. *Front. Med.* **2020**, *7*, 382. [CrossRef]
190. Pandya, V.; Rao, A.; Chaudhary, K. Lipid abnormalities in kidney disease and management strategies. *World J. Nephrol.* **2015**, *4*, 83–91. [CrossRef]
191. Barn, K.; Laftavi, M.; Pierce, D.; Ying, C.; Boden, W.E.; Pankewycz, O. Low levels of high-density lipoprotein cholesterol: An independent risk factor for late adverse cardiovascular events in renal transplant recipients. *Transpl. Int. Off. J. Eur. Soc. Organ Transplant.* **2010**, *23*, 574–579. [CrossRef] [PubMed]
192. Bowe, B.; Xie, Y.; Xian, H.; Balasubramanian, S.; Al-Aly, Z. Low levels of high-density lipoprotein cholesterol increase the risk of incident kidney disease and its progression. *Kidney Int.* **2016**, *89*, 886–896. [CrossRef] [PubMed]
193. Meyers, A.K.; Zhu, X. The nlrp3 inflammasome: Metabolic regulation and contribution to inflammaging. *Cells* **2020**, *9*, 1808. [CrossRef] [PubMed]
194. Liang, J.J.; Fraser, I.D.C.; Bryant, C.E. Lipid regulation of nlrp3 inflammasome activity through organelle stress. *Trends Immunol.* **2021**, *42*, 807–823. [CrossRef] [PubMed]
195. Mangan, M.S.J.; Olhava, E.J.; Roush, W.R.; Seidel, H.M.; Glick, G.D.; Latz, E. Targeting the nlrp3 inflammasome in inflammatory diseases. *Nat. Reviews. Drug Discov.* **2018**, *17*, 588–606. [CrossRef] [PubMed]
196. Hooftman, A.; Angiari, S.; Hester, S.; Corcoran, S.E.; Runtsch, M.C.; Ling, C.; Ruzek, M.C.; Slivka, P.F.; McGettrick, A.F.; Banahan, K.; et al. The immunomodulatory metabolite itaconate modifies nlrp3 and inhibits inflammasome activation. *Cell Metab.* **2020**, *32*, 468–478. [CrossRef]

197. Zhong, Z.; Liang, S.; Sanchez-Lopez, E.; He, F.; Shalapour, S.; Lin, X.J.; Wong, J.; Ding, S.; Seki, E.; Schnabl, B.; et al. New mitochondrial DNA synthesis enables nlrp3 inflammasome activation. *Nature* **2018**, *560*, 198–203. [CrossRef]
198. Xian, H.; Watari, K.; Sanchez-Lopez, E.; Offenberger, J.; Onyuru, J.; Sampath, H.; Ying, W.; Hoffman, H.M.; Shadel, G.S.; Karin, M. Oxidized DNA fragments exit mitochondria via mptp- and vdac-dependent channels to activate nlrp3 inflammasome and interferon signaling. *Immunity* **2022**, *55*, 1370–1385. [CrossRef]
199. Zewinger, S.; Reiser, J.; Jankowski, V.; Alansary, D.; Hahm, E.; Triem, S.; Klug, M.; Schunk, S.J.; Schmit, D.; Kramann, R.; et al. Apolipoprotein c3 induces inflammation and organ damage by alternative inflammasome activation. *Nat. Immunol.* **2020**, *21*, 30–41. [CrossRef]
200. Sakai, N.; Furuichi, K.; Wada, T. Inhibition of nlrp3 inflammasome as a therapeutic intervention in crystal-induced nephropathy. *Kidney Int.* **2016**, *90*, 466–468. [CrossRef]
201. Wada, J.; Makino, H. Innate immunity in diabetes and diabetic nephropathy. *Nat. Rev. Nephrol.* **2016**, *12*, 13–26. [CrossRef] [PubMed]
202. Chi, H.H.; Hua, K.F.; Lin, Y.C.; Chu, C.L.; Hsieh, C.Y.; Hsu, Y.J.; Ka, S.M.; Tsai, Y.L.; Liu, F.C.; Chen, A. Il-36 signaling facilitates activation of the nlrp3 inflammasome and il-23/il-17 axis in renal inflammation and fibrosis. *J. Am. Soc. Nephrol.* **2017**, *28*, 2022–2037. [CrossRef] [PubMed]
203. Krishnan, S.M.; Dowling, J.K.; Ling, Y.H.; Diep, H.; Chan, C.T.; Ferens, D.; Kett, M.M.; Pinar, A.; Samuel, C.S.; Vinh, A.; et al. Inflammasome activity is essential for one kidney/deoxycorticosterone acetate/salt-induced hypertension in mice. *Br. J. Pharmacol.* **2016**, *173*, 752–765. [CrossRef] [PubMed]
204. Tan, Y.F.; Wang, M.; Chen, Z.Y.; Wang, L.; Liu, X.H. Inhibition of brd4 prevents proliferation and epithelial-mesenchymal transition in renal cell carcinoma via nlrp3 inflammasome-induced pyroptosis. *Cell Death Dis.* **2020**, *11*, 239. [CrossRef] [PubMed]
205. Hu, Y.; Shi, Y.; Chen, H.; Tao, M.; Zhou, X.; Li, J.; Ma, X.; Wang, Y.; Liu, N. Blockade of autophagy prevents the progression of hyperuricemic nephropathy through inhibiting nlrp3 inflammasome-mediated pyroptosis. *Front. Immunol.* **2022**, *13*, 858494. [CrossRef] [PubMed]
206. Ostergaard, J.A.; Jha, J.C.; Sharma, A.; Dai, A.; Choi, J.S.Y.; de Haan, J.B.; Cooper, M.E.; Jandeleit-Dahm, K. Adverse renal effects of nlrp3 inflammasome inhibition by mcc950 in an interventional model of diabetic kidney disease. *Clin. Sci.* **2022**, *136*, 167–180. [CrossRef] [PubMed]
207. Zhang, C.; Zhu, X.; Li, L.; Ma, T.; Shi, M.; Yang, Y.; Fan, Q. A small molecule inhibitor mcc950 ameliorates kidney injury in diabetic nephropathy by inhibiting nlrp3 inflammasome activation. *Diabetes Metab. Syndr. Obes. Targets Ther.* **2019**, *12*, 1297–1309. [CrossRef]
208. Liu, Z.; Chen, Y.; Niu, B.; Yin, D.; Feng, F.; Gu, S.; An, Q.; Xu, J.; An, N.; Zhang, J.; et al. Nlrp3 inflammasome of renal tubular epithelial cells induces kidney injury in acute hemolytic transfusion reactions. *Clin. Transl. Med.* **2021**, *11*, e373. [CrossRef]
209. Chiaravalli, M.; Rowe, I.; Mannella, V.; Quilici, G.; Canu, T.; Bianchi, V.; Gurgone, A.; Antunes, S.; D'Adamo, P.; Esposito, A.; et al. 2-deoxy-d-glucose ameliorates pkd progression. *J. Am. Soc. Nephrol.* **2016**, *27*, 1958–1969. [CrossRef]
210. Magistroni, R.; Boletta, A. Defective glycolysis and the use of 2-deoxy-d-glucose in polycystic kidney disease: From animal models to humans. *J. Nephrol.* **2017**, *30*, 511–519. [CrossRef]
211. Staneviciute, J.; Jukneviciene, M.; Palubinskiene, J.; Balnyte, I.; Valanciute, A.; Vosyliute, R.; Suziedelis, K.; Lesauskaite, V.; Stakisaitis, D. Sodium dichloroacetate pharmacological effect as related to na-k-2cl cotransporter inhibition in rats. *Dose-Response A Publ. Int. Hormesis Soc.* **2018**, *16*, 1559325818811522.
212. Gattone, V.H., II; Bacallao, R.L. Dichloroacetate treatment accelerates the development of pathology in rodent autosomal recessive polycystic kidney disease. *Am. J. Physiol. Ren. Physiol.* **2014**, *307*, F1144–F1148. [CrossRef] [PubMed]
213. Pernicova, I.; Korbonits, M. Metformin--mode of action and clinical implications for diabetes and cancer. *Nat. Rev. Endocrinol.* **2014**, *10*, 143–156. [CrossRef]
214. Huber, T.B.; Walz, G.; Kuehn, E.W. Mtor and rapamycin in the kidney: Signaling and therapeutic implications beyond immunosuppression. *Kidney Int.* **2011**, *79*, 502–511. [CrossRef]
215. Wu, Q.; Wang, X.; Nepovimova, E.; Wang, Y.; Yang, H.; Kuca, K. Mechanism of cyclosporine a nephrotoxicity: Oxidative stress, autophagy, and signalings. *Food Chem. Toxicol. Int. J. Publ. Br. Ind. Biol. Res. Assoc.* **2018**, *118*, 889–907. [CrossRef]
216. Walsh, M.; Merkel, P.A.; Peh, C.A.; Szpirt, W.M.; Puechal, X.; Fujimoto, S.; Hawley, C.M.; Khalidi, N.; Flossmann, O.; Wald, R.; et al. Plasma exchange and glucocorticoids in severe anca-associated vasculitis. *N. Engl. J. Med.* **2020**, *382*, 622–631. [CrossRef]
217. Thomson, S.C.; Vallon, V. Renal effects of sodium-glucose co-transporter inhibitors. *Am. J. Cardiol.* **2019**, *124* (Suppl. S1), S28–S35. [CrossRef] [PubMed]