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REVIEW

Glutaminolysis is a Potential Therapeutic Target for Kidney Diseases

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Abstract: Metabolic reprogramming contributes to the progression and prognosis of various kidney diseases. Glutamine is the most abundant free amino acid in the body and participates in more metabolic processes than other amino acids. Altered glutamine metabolism is a prominent feature in different kidney diseases. Glutaminolysis converts glutamine into the TCA cycle metabolite, alpha-ketoglutarate, via a cascade of enzymatic reactions. This metabolic pathway plays pivotal roles in inflammation, maladaptive repair, cell survival and proliferation, redox homeostasis, and immune regulation. Given the crucial role of glutaminolysis in bioenergetics and anaplerotic fluxes in kidney pathogenesis, studies on this cascade could provide a better understanding of kidney diseases, thus inspiring the development of potential methods for targeted therapy. Emerging evidence has shown that targeting glutaminolysis is a promising therapeutic strategy for ameliorating kidney disease. In this narrative review, equation including keywords related to glutamine, glutaminolysis and kidney are subjected to an exhaustive search on Pubmed database, we identified all relevant articles published before 1 April, 2024. Afterwards, we summarize the regulation of glutaminolysis in major kidney diseases and its underlying molecular mechanisms. Furthermore, we highlight therapeutic strategies targeting glutaminolysis and their potential clinical applications.

Keywords: glutamine, glutaminolysis, kidney diseases, therapeutic target

Introduction: Definition and General Roles

Glutamine is considered as an unessential amino acid in physiological condition, and highly utilized in kidney, intestine, and immune compartment.[1] Concentration of circulating glutamine fluctuates around 500 to 800 μM/L.[2] As a ready source in a variety of biochemical processes, glutamine plays a fundamental role in cell metabolism.

Glutaminolysis is a metabolic pathway that involves glutamine uptake and catabolism to maintain bioenergetics and replenish macromolecular biosynthesis. As illustrated in Figure 1. glutaminolysis starts with the transportation of extracellular glutamine into the cytoplasm by membrane proteins (SLC1A5, SLC38A1, SLC38A2) and subsequently into the mitochondria by SLC1A5 var. In the mitochondria, glutamine (Gln) is broken down into glutamate (Glu) and ammonia by two isoenzymes of glutaminase, designated GLS1 and GLS2, which were initially found in the kidney and liver, respectively. GLS1 and GLS2 encode two transcripts. Isozymes of Gls1 are termed kidney glutaminase A (KGA) and glutaminase C (GAC), whereas those of GLS2 include liver glutaminase A (LGA) and glutaminase B (GAB). A portion of glutamate is then converted to α-ketoglutarate (α-KG) by two different pathways: the first through the activity of glutamate dehydrogenase (GDH) and the second through the activity of a group of aminotransferases, including glutamate-oxaloacetate transaminase (GOT), glutamate-pyruvate transaminase (GPT), and phosphoserine transaminase (PSAT).[3]

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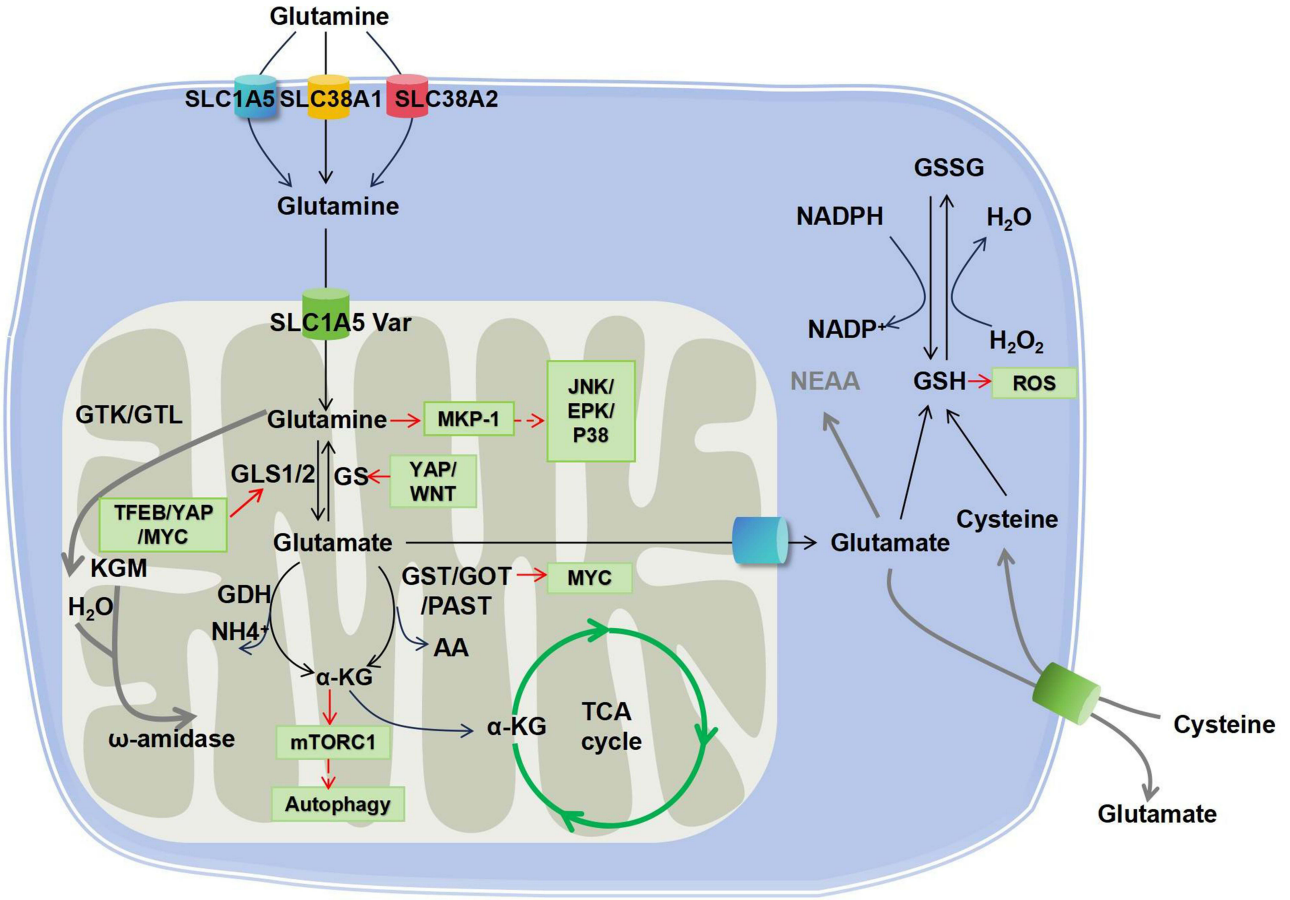


Figure 1 Glutaminolysis cascade and the interlinked signaling pathways. Glutamine is taken up into the cytosol by membrane transporters SLC1A5, SLC38A1 and SLC38A2. Afterwards, glutamine is transported to the mitochondrial matrix by SLC1A5 variants and further converted to glutamate by GLS, which is a rate-limiting reaction of glutaminolysis. Glutamate is then catalyzed by either GDH or transaminases (GOT, GST, or PAST) to generate α-KG. Besides, glutamine can also be metabolized by glutaminase II pathway mediated by enzymes including GTK (or GTL) and ω-amidase, as highlighted by the red line. Consequently, α-KG enters the TCA cycle. In addition, glutamate can be exported to the cytoplasm to participate in the glutathione metabolism (GSH/GSSG redox reaction).

Abbreviations: GLS, glutaminase; GTK, glutamine transaminase K; GLT, glutamine transaminase L; KGM, α-ketoglutaramate; GS, glutamine synthetase; GOT, glutamate-oxaloacetate transaminase; GPT, glutamate–pyruvate transaminase; PAST, phosphoserine transaminase; α-KG, α-ketoglutarate; TCA, tricarboxylic acid; GSH, Glutathione; GSSG, Glutathione oxidized; SLC1A5, Solute Carrier Family 1 Member 5; SLC38A1, Solute Carrier Family 38 member 1; SLC38A2, Solute Carrier Family 38 member 2; SLC7A11, Solute Carrier Family 7 member 11.

It is noteworthy that, while the above-described reaction is normally called the glutaminase I pathway, another cascade called the glutaminase II pathway (more recently referred to as the glutamine transaminase-ω-amidase (GTωA) pathway) also exists. In this reaction, glutamine is first transaminated to α-ketoglutaramate (KGM) by glutamine transaminase K (GTK) or glutamine transaminase L (GTL), and further hydrolyzed by ω-amidase to α-ketoglutarate.[4,5] Glutaminolysis is known for its anaplerotic role in neoplastic cell proliferation. Moreover, emerging evidence has shown that it participates in many other pathological and physiological processes, including fibrogenesis, ischemic injury, oxidative insult, and aging, as well as in cells in demand for high energy, such as kidney and corneal endothelium.[6,7]

Glutaminolysis plays a crucial role in regulating redox homeostasis by supplying glutamate for the synthesis of glutathione (GSH), which serves as a protective mechanism against oxidative stress.[8] However, it has also been reported that increased glutaminolysis can divert glutamine/glutamate from glutathione synthesis, resulting in oxidative insults.[8] Moreover, ammonia is generated during the glutaminolysis of glutamate. Free ammonia is released from the breakdown of glutamine, which plays a crucial role in maintaining renal pH homeostasis, and subsequently contributes to cellular and systemic homeostasis.[9] Glutaminolysis also plays a role in immune regulation. Inhibiting glutamine metabolism impacts the production of monocyte-derived cytokines (TNF, IL-6, and IL-1β) as well as T-cell-derived cytokines (IFN-γ and IL-22).[10] Additionally, GLS1 can modulate immune cells, and its aberrant expression may contribute to various autoimmune diseases, including SLE.[11,12] On

the other hand, glutaminolysis is closely associated with epigenetic regulation and post-translational modification. Glutamine metabolism can enhance DNA methylation and histone acetylation,[13,14] while interestingly, acetyl-CoA-mediated suppression of glutaminase activity has been observed.[15]

In conclusion, glutaminolysis plays a crucial role in maintaining the homeostasis of the body. Currently, research on glutaminolysis is mainly limited to various types of cancer, with relatively little in-depth study in kidney diseases. However, it has been reported that glutaminolysis is associated with renal fibrosis,[16] diabetic nephropathy,[17] acute kidney injury,[18] systemic lupus erythematosus,[19,20] renal cell carcinoma,[21] anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV), and nephrotic syndrome (NS)[22] as well as polycystic kidney disease.[23] Therefore, this paper will explore the current role of glutaminolysis in kidney diseases and related mechanistic studies to help develop new therapies for kidney diseases in the future.

Molecular Mechanisms: Key Factors and Signaling Pathways Related to Glutaminolysis

Upstream of Glutaminolysis

c-Myc

Myc, also known as c-Myc, serves as a transcription factor in various signaling pathways, including its involvement in glutaminolysis.[24] Previous studies demonstrated a positive correlation between c-Myc and GLS1 expression. Wise et al discovered that upon introducing an inducible Myc transgene into mouse embryonic fibroblasts (MEF), GLS1 mRNA levels were noticeably increased owing to the induction of Myc expression.[25] Similar findings have been observed in various cell lines, such as P493-6 and PC3,[26] SW620 cells,[27] U-1906 cells,[28] and Myc-induced liver tumors in mice. Furthermore, c-MYC expression exerts influence the transcriptional level of GLS1 in both colorectal cancer and liver tumors.[29]

Gao et al discovered that Myc suppressed the activity of miR-23, which targets GLS, and concurrently upregulated the expression of mitochondrial glutamine synthetase to enhance glutaminolysis during their investigation into Myc-regulated mitochondrial proteins.[26] However, they did not observe any indications of c-Myc transcriptionally regulating GLS1 despite the presence of a typical E-box sequence in its first intron.[26] Secondly, they found that MYC controlled GLS1 expression post-transcriptionally through microRNAs miR-23a and miR-23b in PC3, P493-6, human lymphoid CB33 and breast cancer MCF-7 cells.[26] In contrast, Haikala et al proposed that the impact of c-Myc on GLS1 expression was due to transcriptional regulation by binding to the promoter region near the 5'-UTR transcriptional initiation site.[30] In summary, in addition to indirectly regulating GLS1 via miR-23a/b, MYC can directly influence its expression by interacting with the promoter region of GLS1.

In addition, the current research presents conflicting findings regarding the influence of MYC on GLS2 expression. Some studies have suggested a decrease in GLS2 protein levels in renal cell carcinoma induced by MYC,[31] while an association between MYC and GLS2 has been observed in T cells.[29]

Additionally, the expression of glutamic acid dehydrogenase and glutamate-dependent aminotransferases is modulated by c-MYC. Shroff et al observed an elevation in GLUD1 protein levels in transgenic mice harboring human MYC-driven clear cell renal cell carcinoma as well as a reliance of GOT1 protein levels on MYC.[32] The precise mechanism by which MYC regulates GLUD1 and GOT1 remains elusive; however, MYC has been suggested to exert its influence at the transcriptional level on GLUD1 and GOT1 expression.[33]

YAP

The Hippo signaling pathway plays multiple roles in renal physiology, including determining cell fate, tissue regeneration, and regulating kidney size to maintain homeostasis. YAP is a necessary protein involved in the transduction of the Hippo signal.[34]

YAP and GLS1

In liver fibrosis, upregulation of glutaminolysis is observed during transdifferentiation, which is driven by the induction of GLS1 mediated by YAP.[35] The regulatory mechanism by which YAP controls GLS1 expression was investigated by Du et al who discovered that YAP collaborates with TAZ, a related transcription factor, to modulate the expression of genes containing TEAD binding sites.[35] This finding aligns with that of Bertero et al, who confirmed the presence of

TEAD/YAP-binding sites within the promoter region of GLS1 using ChIP-qPCR analysis.[36] Additionally, QPCR experiments revealed that simultaneous knockout of YAP and TAZ resulted in a reduction in GLS1 expression in PAEC and PASMC. These results suggest a cooperative role of YAP and TAZ in the regulating of GLS1.[36]

YAP and Glutamine Synthetase

Transcriptomic and metabolomic analyses revealed that YAP1 influences glutamine metabolism by upregulating the expression and activity of glutamine synthetase (GS; encoded by GLUL).[37] Moreover, GLUL activation facilitates the utilization of ammonia-bound nitrogen to produce glutamine as a precursor for nucleotide biosynthesis, thereby modulating nitrogen metabolism.[37]

YAP and GOT1

Yang et al examined the correlation between TAZ/YAP activity and genes involved in glutamine metabolism in breast cancer biopsies. They observed a robust positive association between TAZ/YAP activity and GOT1 and PSAT1 expression. Moreover, using ChIP analysis in MDA-MB-3 cells, they identified potential binding sites for YAP/TAZ and TEAD transcription factors within the enhancer region of GOT1 gene.[38]

In addition, YAP is closely related to myc signaling. For example, a recent study demonstrated that high blood glucose leads to hyperactivation of YAP, further stabilizing myc, and consequently resulting in abnormal alteration of mesangial cells in diabetic nephropathy.[39]

Wnt/β-Catenin Pathway

The Wnt/β-catenin pathway, known for its involvement in glutaminolysis[40] 34771718, plays a pivotal role in the regulation of this metabolic process.[41] Previous studies have demonstrated that transgenic mice expressing activated β-catenin in the liver exhibit increased expression of three genes involved in glutaminolysis (GS, OAT, and GLT-1).[42] These genes were specifically induced by the activation of the β-catenin pathway in the liver. Furthermore, Zhou et al discovered that during inflammatory injury, pulmonary endothelial cells release Rspondin3 to activate β-catenin signaling in pulmonary interstitial macrophages. Subsequently, this activation enhances glutaminolysis and improves the mitochondrial respiration.[43] Collectively, these findings suggest that β-catenin target genes facilitating glutaminolysis.[42] However, further research is required to elucidate the mechanisms by which Wnt signalling effectively regulates this process.

Interestingly, various studies have shown that glutamine breakdown can affect the β-catenin pathway. Wong et al discovered that glutaminolysis results in a reduction in DNA demethylation, leading to an increase in WNT signaling, stemness, and drug resistance.[44] Furthermore, depriving cancer stem cells with glutamine caused an elevation in cellular reactive oxygen species (ROS) levels by inhibiting glutathione synthesis. This subsequently impedes the β-catenin pathway by inducing phosphorylation and degradation induction.[45]

TFEB

Transcription factor EB (TFEB), a member of the MiT/TFE family of basic helix-loop-helix leucine zipper transcription factors, is widely acknowledged as a pivotal regulator of lysosomal biogenesis.[46] Research indicates that TFEB also participates in glutaminolysis. Ariano et al observed that silencing TFEB resulted in the suppression of glutaminolytic flux in melanoma tumors, as indicated by the reduced catalytic activity of GLS and the level of alpha-ketoglutarate.[47] Another study performed in pancreatic cancer reported a downregulation in GLS mRNA transcription after knockdown of TFEB, and chromatin immunoprecipitation assays further revealed the existence of seven E-box motifs within the promoter region of GLS, which is a binding motif for TFEB.[48]

Downstream of Glutaminolysis

mTORC1

As is commonly acknowledged, the mTOR pathway is significant as a pivotal signaling intersection.[49] It is currently hypothesized that mTORC1 activation is associated with glutaminolysis. Duran et al observed a decrease in mTORC1 activity when glutamine metabolism was inhibited by GLS inhibitors in U1OS and HeLa cells.[50] They suggested that

A-KG, a by-product of glutamine metabolism, activates mTORC1 and facilitates Rag-mediated GTP loading.[50] In contrast, Bodineau et al proposed an alternative perspective, stating that mTORC1 is activated by glutamine. They observed a consistent increase in ATP levels after 4 h of treatment with glutamate and leucine in amino acid-deprived cells, leading to AMPK inhibition followed by mTORC1 activation.[51] Furthermore, they investigated the impact of ASNS and GLS dual inhibition on mTORC1 using siRNA and BPTES, respectively, in U1OS cells and found that mTOR activity was inhibited only when both were present.[51] This suggests that ASNS acts as an alternative pathway for glutamine, affecting both its metabolism and the activation of mTORC1.

In summary, mTORC1 can be activated via two distinct pathways involving glutamine, necessitating further investigation to determine their potential interactions. It is important to note that the relationship between glutamine and mTORC1 is not a straightforward one-way connection. Some studies have also indicated a reciprocal association between MTORC1 and glutamine breakdown, wherein MTORC1 enhances the activity of MYC-GLS and GLUD1, thereby facilitating glutamine decomposition.[52,53]

Mkp-1

Glutamine (Gln) is a protein with immunomodulatory properties that regulates oxidative stress, inflammation, and apoptosis. MKP-1 plays a crucial role in the inhibition of inflammation by controlling phosphorylation of proteins belonging to the MAPK family. It also contributes to the negative feedback regulation and maintains cellular homeostasis during signal transduction processes.[54]

Recent research indicates that Gln positively influences MKP-1 expression. For instance, Xuan et al suggested that glutamine might exert a protective effect against neuroinflammation by downregulating MAPK signaling through increased levels of MKP-1 in rats with brain injuries.[54] Furthermore, Kim et al demonstrated that Gln modulates the MAPK pathway by upregulating MKP-1 in glutamine-deficient mice, thereby maintaining a balanced inflammatory response. This observation was also reported by Soo-Yeon Jeong[55], Otgonzaya Ayush,[56] and C-H Lee et al.[57]

There are diverse perspectives regarding the regulatory role of glutamine in MKP-1. Several studies have proposed that Gln inhibits JNK, ERK, and p38 phosphorylation by upregulating MKP-1, thereby mitigating inflammation.[54,58] Conversely, Ayush et al postulated that Gln activates the Ras-ERK-MKP-1 pathway through initial Ca2+ activation as a precise mechanism for Gln-mediated MKP-1 regulation.[56] Additionally, in their investigation of LPS-treated mice, Lee et al discovered an interaction between Gln and MKP-1 and demonstrated a physical association between MKP-1 and p-cPLA via immunoprecipitation and in situ orthogonal experiments. Further examination of various allergic asthma phenotypes revealed that Gln can directly deactivate cytosolic phospholipase a2 (cPLA2) through MKP-1-dependent cPLA2 dephosphorylation to alleviate inflammation.[57] Interestingly, two viewpoints exist regarding the mechanism of Gln-induced cPLA inactivation. First, cPLA2 dephosphorylation is indirectly achieved through mkp −1 mediated p38 inactivation, which has been extensively studied;[57,59] secondly, gln induces direct physical interaction between MKP-1 and p-cPLA2.[57]

Glutaminolysis and Autophagy

Because glutaminolysis provides metabolic and energy substrates, it is reasonable that autophagy is influenced by this reaction. However, glutaminolysis seems to regulate autophagy in both directions. Glutaminolysis activates mTORC1 and inhibits autophagy. In detail, AKG generated through glutaminolysis,[51] Noteworthy, a recent study demonstrated that glutamine could also regulate mTORC1-autophagy independent of glutaminolysis, instead, glutamine is metabolized via asparagine synthesis and the GABA shunt to produce ATP and to inhibit AMPK.

Glutaminolysis in Epigenetic and Post-Translational Modifications

Epigenetic states and post-translational modifications are closely linked to glutaminolysis. A study in colorectal cancer showed that glutaminolysis increased DNA methylation due to the accumulation of succinate and a further reduction in 5-hydroxymethylcytosine-A marker of DNA demethylation, and consequently hypermethylation at CpG sites.[44] In contrast, DNA hypermethylation repressed GLS2.[13]

In addition, since glutaminolysis yields intermediate metabolites such as acetyl-CoA, this acetyl carrier contributes to histone acetylation of RUNX2 promoters, as suggested by a study on calcific aortic valve disease suggested.[14]

Interestingly, the enzymatic activity of glutaminase is also regulated by acetylation, and enzyme oligomerization increases after acetylation, thereby inhibited activity.[15] Afterwards, α-ketoglutarate (α-KG) is produced during glutaminolysis, and it has been proven to regulate gene expression by influencing the epigenetic structure in both normal and cancer cells.[60,61] Initially, AKG acts as a cofactor for Jumonji histone demethylases (JHDMs), resulting in decreased JHDM activity when AKG levels are reduced, leading to increased histone methylation.[61] Additionally, when AKG is transformed into 2-hydroxyglutaric acid by isocitrate dehydrogenase 1 and 2 following mutation induction, it inhibits DNA demethylation enzymes and histone methylation enzymes that result in lysine residues (K) 9, 27 DNA methylation and histone methylation.[62,63]

Considering that glutaminolysis is closely related to nutritional imbalance and oxidative stress, it is not surprising that glutaminolysis also regulates phosphorylation via mTOR and other signaling pathways.[64] Interestingly, a recent study demonstrated that glutaminolysis mediates microtubule glutamylation in response to extracellular matrix stiffening in tumor microenvironment.[65] Other epigenetic modifications are also involved in glutaminolysis, including succinylation,[66] lactylation,[67] ubiquitination,[68] O-linked β-D-N-acetylglucosamine (O-GlcNAc).[69]

Other Signaling Pathways

Glutaminolysis is also involved in other signaling pathways. A study in senescent stem cells showed that JNK signaling is upstream of glutaminolysis and can upregulate GLS1 transcription.[7] However, various studies have indicated that the activation of JNK results in an increase in the accumulation of ROS, a process that is countered by activated P53. Additionally, it has been observed that mutations in the P53 gene can either hinder or enhance the expression of Nrf2.[70,71] To effectively eliminate ROS, both Nrf2 and P53 facilitate glutaminolysis, thereby providing glutamate and NADPH for GSH production.[72]

In addition, evidence has shown that glutaminolysis serves as an anti-apoptotic player. For example, in diabetes-induced podocyte injury, glutaminolysis can improve mitochondrial function and counteract apoptosis.[72] In ischemia/reperfusion-induced acute kidney injury, apoptosis of tubular epithelial cells is prevented by glutamine catabolism.[73] As indicated by the second Warburg-like effect, cancer cells rely heavily on glutaminolysis for their survival and migration. The underlying molecular pathways involve AMPK, mTOR, JNK etc.[74,75]

In summary, the upstream and downstream pathways involved in glutaminolysis are summarized in Figure 1.

Altered Glutaminolysis in Kidney Diseases

During intense periods of stress, glutamine is a conditionally essential amino acid. Alterations in glutaminolysis have frequently been reported in different kidney cell types, including podocyte,[17] tubular epithelial cells,[73,76] endothelial cells,[77] fibroblasts, and kidney immune cells,[78] etc. Generally, the effects of glutaminolysis seem context dependent.

Glutaminolysis and Fibrosis

Glutaminolysis has been frequently reported in organ fibrosis, including kidney.[16] Most studies have reported that glutaminolysis supports fibrogenesis, and that the targeted cells are mainly fibroblasts and immune cells.[6,79] Glutaminolysis regulates lysosomal function to maintain fibroblast homeostasis through the production of ammonium as a by-product.[80] This reaction is necessary for the differentiation and persistence.[81] Hence, glutaminolytic inhibitory conditions prevent the aggression of the fibrotic phenotype.

In macrophages, metabolic reprogramming to the Warburg Effect-like state, namely glutaminolysis, is critical for M1-like macrophage induction.[82] Nevertheless, another study found that when macrophages were treated with helminth-derived peptides, proinflammatory responses were significantly inhibited, whereas glutaminolysis was upregulated.[83] A similar situation was observed for the B cells. For example, several studies have suggested that glutaminolysis supports B cell proliferation and survival in a human B cell model of Burkitt lymphoma (P493) and in IL-10-expressing regulatory B cells, respectively.[84] However, another study performed in B cells of lupus-prone mice showed that glutaminolysis requirement is not B cell-intrinsic.[85]

Mechanistically, glutaminolysis can be activated by TGF-β, which further facilitates the generation of extracellular matrix (ECM) generation, such as collagen.[86]

Glutaminolysis and Aging

Previous research has established a correlation between glutaminolysis and aging progression. To date, most studies have reported that glutaminolysis is positively associated with ageing. Using an RNAi screening strategy, Johmura et al found that the glutaminolysis pathway, particularly GLS1, is pivotal for the survival of senescent cells. Consistently, they demonstrated that the elimination of senescent cells or inhibition of glutaminolysis ameliorates age-related organ dysfunction.[87] In addition, senescent cells are found to have impaired glycolysis, which leads to the use of glutamine as the primary energy source. This is accompanied by the production and accumulation of urea, which further aggravates the senescence phenotype. Debanik Choudhury et al found that blockade of GLS1 inhibited glutaminolysis and decreased urea, and significantly improved the phenotypes of senescent cells and premature aging mice. Moreover, Yangyang Zhang et al found that glutamine supplementation could attenuate the expression of aging-related proteins, inhibit aging in vivo and in vitro, and enhance autophagy.[88]

Regarding the process of aging caused by glutaminolysis, Choudhury et al put forward the hypothesized that an increase in glutamine synthetase (GLS1) activity results in a subsequent decrease in the expression of the urea transport protein SLC14A1. This leads to urea accumulation, which triggers mitochondrial dysfunction and DNA damage.[7] Furthermore, the activation of JNK in senescent cells led to an increase in GLS1 transcription, resulting in enhanced glutaminolysis.[7]

Senescence is known to accelerate kidney disease and CKD,[89] suggest possible glutaminolysis can be used as a therapeutic targets of kidney disease and chronic kidney disease (CKD). Current approaches to aging treatment involve the removal of senescent cells, but the associated soluble molecular pathways have yet to be identified. Therefore, we propose that targeting glutaminolysis and its regulatory signaling pathways, along with associated metabolites and by-products, could offer promising strategies for addressing cellular senescence.

Glutaminolysis and Diabetic Nephropathy

Recent epidemiological investigations, experimental research, and clinical trials have focused on the metabolic abnormalities associated to diabetic nephropathy. For example, a clinical epidemiological study showed that a decrease in urine glutamine is a risk factor for progression from moderate to severe albuminuria in DKD.[90]

Of particular significance is the pivotal involvement of podocyte metabolic reprogramming in driving its development.[91,92] Previous studies have indicated that glutamine (Gln) plays a crucial role in maintaining the structure and function of podocytes. Similarly, Gln supplementation effectively decreased proteinuria and enhanced glomerular health in mice treated with lipopolysaccharide (LPS).[93] Paradoxically, despite the advantages of incorporating glutamine supplements for managing oxidative stress and maintaining glucose balance, there have been reports of unfavorable reactions.[94,95] According to Tatiana Carolina Alba-Loureiro et al, diabetic rats that received glutamine supplementation exhibited elevated levels of pro-inflammatory interleukin (IL)-1 β and IL-6 in the renal cortex, along with changes indicative of glomerulosclerosis.[96]

In addition, a study conducted by Jijia Hu et al revealed that the expression of GLS2 was reduced in db/db mice, leading to impaired glutaminolysis. However, LDH-1 activation resulted in upregulation of GLS2 expression, restoring glutamine metabolism and mitochondrial function. This subsequently leads to a reduction in podocyte apoptosis and ultimately mitigates the kidney injury caused by diabetic nephropathy.[17] Unfortunately, the precise mechanism underlying the relationship between changes in glutaminolysis, and podocyte injury induced by diabetic nephropathy (DKD) remains unclear.[17]

Glutaminolysis and Acute Kidney Injury

The initial manifestation in acute kidney injury is the impairment of tubular epithelial cells, which triggers the release of inflammatory cytokines and chemotactic factors by leukocytes.[97] This results in an excessive influx of neutrophils and other immune cells into the renal system, ultimately leading to renal dysfunction. The extent of this dysfunction is directly proportional to the severity of the tubular epithelial cell damage and neutrophil infiltration.[98]

Normally, only a small portion of glutamine is consumed by the kidney, but the demand for glutamine dramatically increases during the metabolic acidosis phase of AKI, and approximately one-third of the plasma glutamine is metabolized in the kidney.[99] In line with this, a recent study found that GLS activity is upregulated in kidney T cells in ischemic AKI, and glutamine blockade by its antagonist JHU083 could ameliorate kidney injury.[18]

However, there are also reports suggesting that glutamine administration plays a protective role against AKI. A clinical trial claimed that markers of kidney damage, urinary [TIMP-2] *[IGFBP7], were significantly decreased after glutamine administration in cardiac surgery patients at a high risk for AKI.[100] Another study has suggested that glutamine enhances the synthesis of heat shock proteins (HSPs), which may serve as a defense mechanism against cellular damage.[101] Similarly, in a study conducted by Zhi-Yong Peng et al, it was observed that the administration of glutamine resulted in the upregulation of HSP70 and HSP16 expression. This leads to a reduction in inflammation and neutrophil infiltration, thereby protecting against nephrotoxic AKI.[101] Moreover, a previous investigation demonstrated that the administration of a solitary dose of glutamine following the onset of sepsis led to a decrease in the expression of mediators linked to high mobility group box-1 (HMGB1) and a decline in oxidative stress within the kidneys.[102] Kim et al discovered that glutamine mitigated tubular cell apoptosis during acute kidney injury by inhibiting c-Jun N-terminal kinase phosphorylation of 14-3-3 in an experimental rat model of myoglobinuria after intraperitoneal glutamine.[103]

Glutaminolysis and Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a long-term autoimmune disorder characterized by atypical T cell reactions to self-antigens, leading to the involvement of various organs.[104] Lee et al discovered that individuals with SLE had reduced plasma glutamine levels compared to healthy individuals, and that there was an inverse relationship between disease activity and plasma glutamine levels.[105] Shan et al discovered that Th17 cells exhibited higher levels of A-KG, suggesting increased glutaminolysis in Th17 cells.[106] Moreover, SLE progression can be slowed by impeding glutaminolysis. In a study by Zhang et al, hindering glutaminolysis resulted in decreased kidney damage in MRL/lpr mice.[107] Choi et al observed an increase in Tfh cells in individuals with SLE and lupus-prone mice. Additionally, they discovered that the utilization of DON to impede glutaminolysis resulted in a decrease in the generation of daDNA antibodies.[108]

Numerous studies have indicated the activation of the mTOR pathway in individuals diagnosed with systemic lupus erythematosus.[109,110] The initial indication of mTOR's role of mTOR in SLE was demonstrated by Warner et al, who effectively suppressed excessive T-cell activity and alleviated nephritis in rapamycin-treated lupus-prone MRL/lpr mice.[111] A study conducted by Fernandez et al revealed a notable inhibitory effect of rapamycin on T cell activation in individuals diagnosed with systemic lupus erythematosus (SLE).[112] Therefore, enhanced glutaminolysis in SLE might activate the mTOR pathway. Zhang et al discovered that when glutaminolysis was inhibited, downregulation of the mTOR/P70S6K/4EBP1 pathway was observed in MRL/lpr mice.[107] However, previous studies have indicated that glutaminolysis can affect the differentiation of T cells.[19] It has been observed that a decrease in glutamine levels or deficiency in the ASCT2 transporter can lead to a reduction in TH17 differentiation.[113] Additionally, an investigation conducted by Michihito Kono et al discovered that inhibition of glutamine synthetase 1 could impede T cell differentiation among individuals with SLE.[12]

Glutaminolysis and Renal Cell Carcinoma

Glutaminolysis is also called the second Warburg-like effect, studies have shown that the level of glutaminolysis is significantly up-regulated in various cancers, including renal cell carcinoma,[21] etc. In kidney cancer, one of the metabolic rewiring mechanisms is the significant reliance of tumor cells on glutamine.[21] Unfortunately, the effects of alterations in tumor-specific glutamine metabolism on the nearby immune microenvironment remain unknown. Furthermore, the study conducted by Sarah J Ross et al revealed a correlation between MYC activation and heightened glutamine metabolism in renal cancer cells.[114] Reinforcement of MYC triggers the upregulation of SLC1A5, leading to subsequent activation of the PI3K-Akt-mTOR signaling cascade.[115]

Other Kidney Diseases

Glutaminolysis is involved in the development of other kidney diseases. Interestingly, transcriptional profiling of kidney biopsy samples from patients showed that glutaminolysis is repressed in antineutrophil cytoplasmic antibody-associated vasculitis (AAV) and nephrotic syndrome (NS).[22] Polycystic kidney disease (PKD), an inherited disorder characterized by multiple fluid-filled cysts in the kidneys, relies on glutamine metabolism to support cellular proliferation and growth.[23]

In summary, the glutamine metabolism and kidney disease mechanisms are summarized in Figure 2.

Therapeutic Strategies: Molecules Targeting Glutamine Metabolism and Glutaminolysis

Glutamine Analogs

Glutamine analogs have been developed to combat glutamine metabolism. These antagonists include 6-diazo-5-oxo-l-norleucine (DON),[116] acivicin,[117] and azaserine,[117] 1.5-N, N′-disubstituted-2-(substituted benzenesulphonyl) glutamamides.[118] DON has long been known for its anticancer potency; however, its clinical translation is hindered by intolerable gastrointestinal toxicity. Persistent attempts have been made to optimize derivatives of DON, such as DRP-104, which is delivered specifically to tumors at much higher concentrations than to the plasma or gut[119] and JHU083.[120]

Mechanistically, these glutamine analogs competitively inhibited glutamine-utilizing enzymes in a nonselective manner. The broad inhibition of glutamine metabolism surpassed the metabolic flexibility. According to two recent

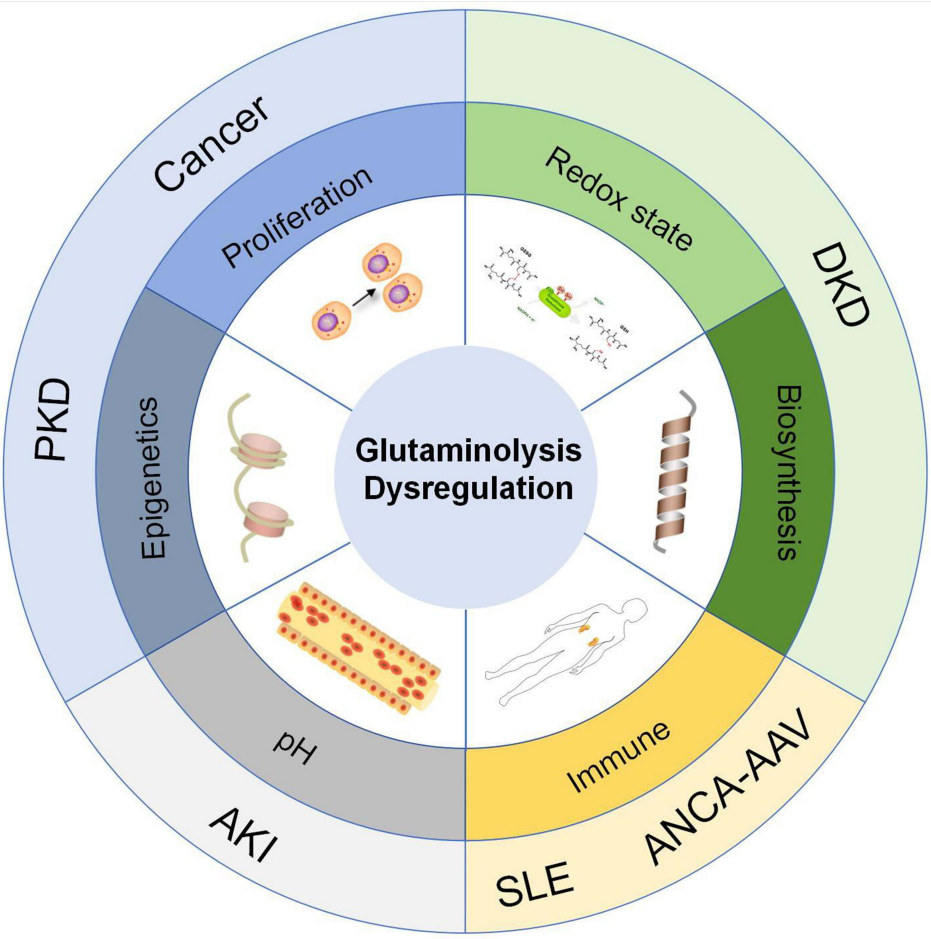


Figure 2 Glutamine metabolism and kidney disease mechanisms.
Abbreviations: PKD, polycystic kidney disease; DKD, Diabetic Kidney Disease; AKI, Acute Kidney Injury; SLE, Systemic Lupus Erythematosus; ANCA-AAV, Anti-neutrophil cytoplasmic autoantibodies- Associated vasculitis.

cancer studies, broad inhibition of glutamine metabolism with glutamine analogs seems to be a more effective strategy than the glutaminase inhibitors discussed below.[121,122] However, some studies have demonstrated that glutamine supplementation protects against AKI and attenuates tubular apoptosis.[73]

Glutamine Depletion

Glutamine depletion is another strategy to suppress glutaminolysis. One reported drug is phenylbutyrate, which has been approved by the FDA for the treatment of urea cycle disorders. Mechanistically, phenylbutyrate is converted into phenylacetate via β-oxidation. Afterwards, phenylacetate is conjugated to glutamine to produce phenylacetylglutamine, which is catalyzed by the liver enzyme phenylacetyl-CoA. An in vivo study showed that this drug resulted in a significant reduction in plasma glutamine levels.[123] Consistently, a recent study found that phenylbutyrate combined with renal injury in SLE mice.[124]

Inhibitors of Glutamine Transportes

Glutamine transporters are required in both plasma and mitochondrial membranes. Currently, the only known glutamine transporter in the mitochondrial inner membrane is SLC1A5 variant, while several exists in the plasma membrane, like SLC38A1, SLC38A2, and SLC1A5 are present in the plasma membrane. Therefore, targeting SLC1A5 variants may be an effective strategy to avoid compensation by other redundant transporters. SLC1A5 encodes the alanine-serine-cysteine transporter 2 (ASCT2). GPNA (L-γ-Glutamyl-p-nitroanilide) and V9302 (2-amino-4-bis (aryloxy benzyl) aminobutanoic acid) are potent and selective inhibitors of the glutamine (Gln) transporter ASCT2 (SLC1A5). V-9302 shows a 100-fold increase in SLC1A5 inhibitory potency over GPNA and exerts anticancer effects in various cancer cells.[125] GPNA mainly inhibits the proliferation of different lung types,[126–128] and endometrial cancers.[129] GPNA also effectively inhibits T cell differentiation in oral planus moss[130,131] and induces airway inflammation in asthma to a certain extent.[132] In addition, new SLCA5 inhibitors have been gradually identified, but further research is needed. 20k and 25e, two novel Aminobutanoic Acid-Based compounds, identified as ASCT2 inhibitors that inhibit the growth of non-small cell carcinomas.[133] 2-substituted Nγ-glutamylanilides, a novel probe of ASCT2, exhibited a stronger inhibitory effect than GPNA but lacked testing in disease models.[132] C118P, a novel ASCT2 Inhibitor, can inhibit glutamine metabolism and thus inhibit the proliferation of breast cancer cells.[134]

Interestingly, atractylenolide III, a sesquiterpenoid compound, can reduce liver fibrosis by inhibiting ASCT2-mediated glutaminolysis.[135]

Glutaminase Inhibitor

GLS-mediated deamination of glutamine to glutamate is the first rate-limiting step in glutaminolysis, making it an attractive target. The patented molecule bis-2-(5-phenylacetamido-1,2,4-thiadiazol-2-yl) ethyl sulfide (BPTES) is a potent and selective allosteric inhibitor of GLS1 and its truncated variant glutaminase C (GAC). However, owing to its poor solubility in water, great efforts on structural modifications have been made to improve its pharmacological utility without sacrificing its GLS inhibitory potency.[136] CB-839, a derivative of BPTES, is thought to be one of the best-known GLS inhibitors and has been subjected to clinical trials for various cancers, including triple-negative breast cancer and renal cell carcinoma.[137]

Compound 968 is primarily considered to be an inhibitor of GLS and GAC.[138] Further studies found that 968 also suppressed GLS2, with moderate (>3-fold) selectivity for GLS2.[139] Other inhibitors are also emerging, such as caudatan A, a novel human kidney-type glutaminase inhibitor with tetracyclic flavan, isolated from Ohwia caudata.[140]

While targeting glutaminases, one concern is that the glutaminase II pathway may provide a mechanism that bypasses GLS inhibition. Inhibition of both GLS1/2 and the glutaminase II pathway deserves consideration as a novel therapeutic strategy, which is still lacking in kidney research.[141] In addition, most studies have shown that high levels of GLS1 predict a poor prognosis of cancer, in contrast to GLS2, with more evidence suggesting a role as a tumor suppressor.[142] Therefore, strategies that target these two glutaminases should be tested separately.

Glutamate Dehydrogenase (GDH) Inhibitors

To date, compounds targeting GDH are quite limited; the first reported compound was the green tea polyphenol EGCG.[143] However, this effect is nonspecific, because EGCG inhibits a group of enzymes using NADPH as a cofactor. Additionally, it is poorly absorbed in the gut and quickly eliminated by the liver.[144]

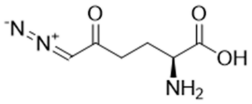
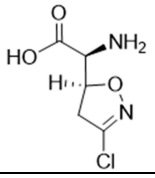
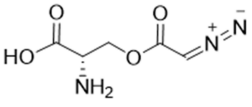
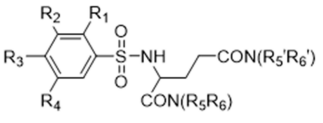
Considering these disadvantages, Kang et al screened a library of FDA-approved small molecule compounds and identified purpurin as a GDH1-selective inhibitor. Moreover, its analog, R162, is a potent and cell-permeable inhibitor.[145] Several other inhibitors, including ebselen and propylselen, have been identified. Ebselen inhibits GDH activity by binding to the catalytic site,[146] whereas propylselen inhibits GDH activity by binding to the NADP+ binding site.[147] Recently, Chang et al performed a molecular docking analysis of eight different plant-derived single compounds collected from the PubChem database to screen and select decursin (DN) and decursinol angelate (DA). DN and DA established a stable hydrogen bond interaction at the ADP activation site with the R400 and Y386 residues of GDH, thereby exerting an inhibitory effect on GDH activity.[148] However, to date, none of these compounds has been subjected to clinical trials.[149]

Aminotransferase Inhibitors

In parallel with GDH-mediated glutamate consumption, aminotransferases, such as GPT, GOT, and PSAT, mediate the conversion of glutamate into alpha-ketoglutarate. Aminooxyacetate (AOA) is an inhibitor of glutamine-utilizing transaminases.[38] Studies have shown that the suppression of glutamate transaminase by AOA is sufficient to abolish the glutaminolysis-dependent phenotype. Therefore, targeting aminotransferase and GDH levels to inhibit glutamate conversion is a potential therapeutic strategy.

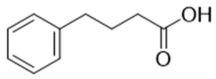
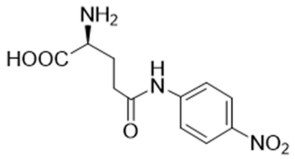
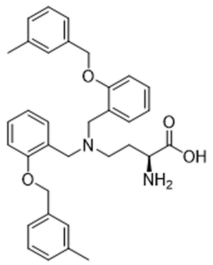
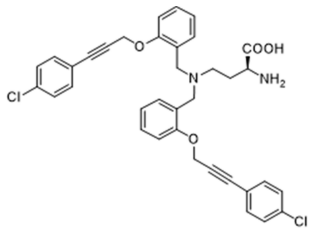
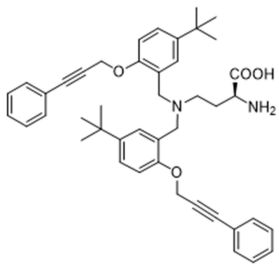
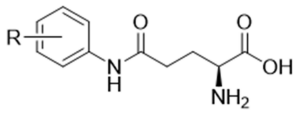
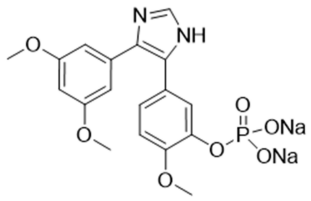
In conclusion, the molecules targeting glutamine metabolism and glutaminolysis are summarized in Table 1.

Table 1 Molecules Targeting Glutamine Metabolism and Glutaminolysis

Category	Compound	Structure	Ref.
Gln analogs	6-diazo-5-oxo-l-norleucine (DON)		[116]
	Acivicin		[117]
	Azaserine		[117]
	1,5-N, N′-disubstituted-2- (substituted benzenesulphonyl) glutamamides		[118]

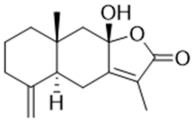
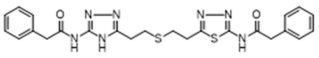
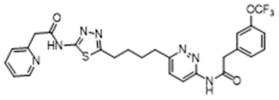
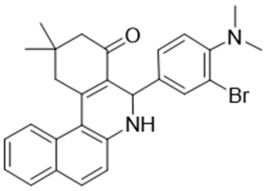
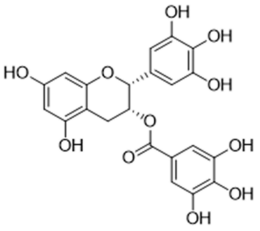
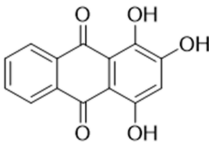
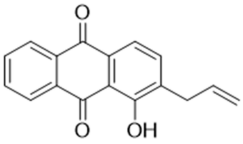
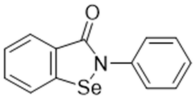
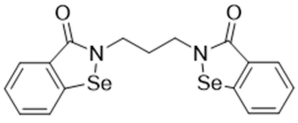
(*Continued*)

Table 1 (Continued).

Category	Compound	Structure	Ref.
Glutamine depletion	Phenylbutyrate		[123]
	GPNA (L-γ-Glutamyl-*p*-nitroanilide)		[125]
Inhibitors of glutamine transportes	V9302 (2-amino-4-bis (aryloxy benzyl) aminobutanoic acid)		[125]
	20k		[133]
	20e		[133]
	2-substituted N γ-glutamylanilides		[150]
	C118P		[134]

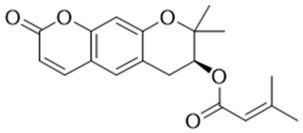
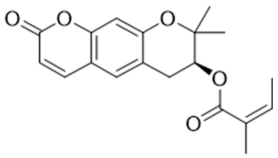
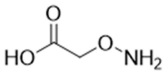
(*Continued*)

Table 1 (Continued).

Category	Compound	Structure	Ref.
	Atractylenolide III		[135]
Glutaminase inhibitor	BPTES		[136]
	CB-839		[137]
	Compound 968		[137]
Glutamate dehydrogenase (GDH) inhibitors	green tea polyphenol EGCG		[143]
	Purpurin		[145]
	Analog R162		[145]
	Ebselen		[146]
	Propylselen		[147]

(*Continued*)

Table 1 (Continued).

Category	Compound	Structure	Ref.
	Decursin (DN)		[148]
	Decursinol angelate (DA)		[148]
Aminotransferase inhibitors	Aminooxyacetate (AOA)		[38]

Conclusions and Perspectives

The development and progression of kidney disease are driven by multiple factors. Targeting metabolic pathways, particularly glutaminolysis and glutamine metabolism, has emerged as a promising therapeutic strategy. However, as reviewed above, glutaminolysis may function differently in a phase- and microenvironment-dependent manner. Therefore, further studies are urgently required to dissect its context-specific impact. In addition, while targeting glutaminolysis, metabolic flexibility should be considered as compensatory mechanisms may be induced to hamper therapeutic outcomes. Consequently, it is reasonable to combine multiple therapeutic targets to avoid metabolic adaptation, either in combination with other pathways or via the glutaminase II pathway. Besides, if glutamine supplementation is conducted in patients with reduced glutaminolysis, pharmacokinetic studies including drug delivery route, dosage need to be further evaluated. With the advance of metabolomics technology, understanding of the pleiotropic role of glutaminolysis in a specific context may be improved. At last, but not least, considering that glutaminolysis is a hallmark of cancer metabolism, so far, most of the above-mentioned molecules are investigated in cancer. Further investigations should be conducted in kidney diseases to better understand the underlying mechanisms and therapeutic efficacy.

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Disclosure

The authors report no conflicts of interest in this work.

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