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Review

The Regulation and Function of the Amino Acid Transporters LAT1, ASCT2, xCT in Urological Cancers

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Abstract: Amino acid transporters play pivotal roles in cancer biology, including in urological cancers. Among them, L-type amino acid transporter 1 (LAT1), alanine-serine-cysteine transporter 2 (ASCT2), and cystine-glutamate transporter (xCT) have garnered significant attention due to their involvement in various aspects of tumor progression and response to therapy. This review focuses on elucidating the regulation and functions of these amino acid transporters in urological cancers, including prostate, bladder, and renal cancers. Understanding the intricate regulatory mechanisms governing these amino acid transporters is essential for developing effective therapeutic strategies. Furthermore, exploring their interactions with signaling pathways and microenvironmental cues in the context of urological cancers may uncover novel therapeutic vulnerabilities. This comprehensive overview highlights the importance of amino acid transporters, particularly LAT1, ASCT2, and xCT, in urological cancers and underscores the potential of their inhibitors as therapeutic targets for improving patient outcomes.

Keywords: amino acid transporters; LAT1; ASCT2; xCT; urological cancer; inhibitor

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1. Introduction

Urological cancers, including kidney, bladder, and prostate cancers, are some of the most common malignant tumors in the world and pose a serious threat to human health [1]. According to statistics, millions of people are diagnosed with urinary system tumors every year, and these diseases not only lead to reduced quality of life for patients, but are also a major contributor to cancer-related causes of death [1]. Therefore, it is of great clinical significance to deeply understand the pathogenesis and therapeutic targets of urological cancers.

Cancer cells differ from normal cells in that they extensively reprogram their metabolic pathways to support increased synthesis and energy requirements. One of the common mechanisms by which cancer cells undergo metabolic reprogramming is to increase the uptake of nutrients that are critical to cancer cell proliferation and energy processes, including amino acids such as leucine (Leu) and glutamine (Gln) [2,3]. Amino acids are an important basis for cell growth and metabolism [4], and play an important role in regulating the growth and metastasis of tumor cells [5]. In the tumor microenvironment, amino acid metabolism is abnormally increased, and tumor cells continuously take up foreign amino acids to meet their growth and energy needs, which are regulated by a variety of factors [6]. For years, the research community has focused on three transporters: LAT1 (Large Neutral Amino Acid Transporters, Solute Carrier Family (SLC)7A5), ASCT2 (Alanine, Serine, Cysteine Transporter 2, SLC1A5), and xCT (Cystine/Glutamate Transporter, SLC7A11). Recent studies have shown that these three amino acid transporters play an important role

in cancers, and their expression levels are closely related to the occurrence, development, and prognosis of tumors [7–9].

Cancer cells accomplish the reprogramming of their metabolic pathways primarily by upregulating various transporters that mediate glucose and amino acid uptake. LAT1 is a large neutral amino acid transporter, which is responsible for the transport of large neutral amino acids under normal physiological conditions [10]. ASCT2 (Alanine, Serine, Cysteine Transporter 2) is a specific amino acid transporter, mainly transporting amino acids such as alanine, serine, and cysteine, as reflected in its name [11]. xCT is a cysteine/glutamate transporter that plays an important role in regulating cysteine levels inside and outside cells [12]. Recent studies have found that the expression level of these amino acid transporters in urological cancers is significantly increased, and this is closely related to the biological behavior of tumor growth, metastasis, and chemotherapy resistance [13–16].

In this review, we will focus on the role and significance of LAT1, ASCT2, and xCT in urological cancers. Based on the existing literature, we will discuss the expression level, functional regulation, and clinical significance of these transporters in urinary tumors, to provide a theoretical basis and clinical guidance for further study of these transporters as therapeutic targets.

2. Basic Features and Functions of LAT1, ASCT2 and xCT

2.1. LAT1 Complex

LAT transporters facilitate the absorption of branched-chain amino acids (BCAAs) and aromatic amino acids without sodium dependency and comprise four subtypes (LAT1, LAT2, LAT3, LAT4). LAT1 serves as a vital amino acid exchanger, facilitating the transport of Leu, isoleucine, valine, phenylalanine, methionine, tyrosine, histidine, and tryptophan into cells. In our review, we emphasize LAT1 due to its broader involvement in cancer compared to other LAT transporters [17].

LAT1 binds with 4F2hc (SLC3A2, CD98) heavy chain protein to form a transmembrane complex, facilitated by the glycoprotein 4F2hc acting as a molecular chaperone, ensuring LAT1's positioning on the cell membrane [18]. A previous study by the author underscores the necessity of 4F2hc for LAT1 transportation to the plasma membrane, with LAT1 influencing the transport properties of heterodimers. Notably, elevated 4F2hc expression correlates with poorer prognosis in various cancers [19–22].

The LAT1 complex is predominantly expressed in human cells serving as inter-tissue barriers in normal human physiology [23]. This complex provides BCAAs, particularly Leu, to the mammalian target of rapamycin complex 1 (mTORC1), regulating cell proliferation through downstream effectors involved in gene expression and metabolism [24].

Many malignancies, including prostate cancer (PCa), exhibit heightened LAT1 expression [25–30] alongside upregulated 4F2hc expression [19,21,31,32], correlating with increased cell proliferation, metastasis, and reduced survival rates [33]. Knockout of LAT1 or 4F2hc in cancer cells inhibits Leu uptake and cell proliferation, rendering the LAT1 complex a potential therapeutic target for impeding cancer cell growth and proliferation [34,35].

2.2. ASCT2

The SLC1 family comprises seven members grouped into excitatory amino acid transporters (EAATs) and ASCTs, sharing similar 3D structures. EAAT includes high-affinity glutamate transporters, while ASCT1 (SLC1A4) and ASCT2 (SLC1A5) transport neutral amino acids across cell membranes (Figure 1) [36]. ASCT1 primarily maintains brain homeostasis by transporting D-serine, a glial transmitter, whereas ASCT2 is predominantly located on the plasma membrane and widely distributed in various human tissues [37–40]. Electron microscopy structural analysis revealed that ASCT2 forms a homotrimeric complex, with each subunit consisting of a transport domain and a scaffold domain. Compared to EAAT and other members of the SLC1 family, the transport domain of ASCT2 is notably separated from the central scaffold domain on the cytoplasmic side, a separation that may be required for substrate binding and release [41]. It is evident that ASCT2, rather than

ASCT1, possesses the ability to transport glutamine [11], a fact further substantiated by the research conducted by Scopelliti et al. [42]. Two residues present in the substrate-binding site of ASCT2 are essential for glutamine binding and transport, while these residues are absent in ASCT1. Mutation of these residues to the ASCT2 sequence confers glutamine transport capability to ASCT1 [42]. Moreover, there may be an indirect effect of ASCT2 and LAT1 on substance transport, as research has shown that ASCT2 shRNA leads to a reduction in Leu transport, despite Leu not being a substrate of ASCT2 [43]. This study suggests that since LAT1 functions as an amino acid exchanger for glutamine and Leu, and that the reduction in intracellular glutamine levels caused by ASCT2 knockdown may result in decreased Leu uptake/exchange via LAT1. ASCT2 exhibits elevated expression in many cancer types compared to ASCT1 and is implicated in tumorigenesis and malignant outcomes [44]. High ASCT2 expression correlates with poorer overall and recurrence-free survival in gastric cancer [45], hepatocellular carcinoma [46], colorectal cancer [47], non-small cell lung cancer [48,49], clear cell renal cell carcinoma [50], ovarian cancer [51], breast cancer [52], and adrenal pheochromocytomas [53].

Current research has confirmed the mechanisms by which cellular Myc (c-Myc), Ring Finger Protein 5 (RNF5), and microRNA-137 regulate ASCT2. The regulatory mechanisms of ASCT2 activity are still under investigation. Overexpression of oncogenes such as c-Myc can lead to "glutamine addiction" in cancer cells, thereby promoting proliferation and survival. c-Myc directly upregulates ASCT2 and SLC7A6, leading to increased amino acid uptake and activation of the mammalian target of the rapamycin complex 1 (mTORC1) signaling pathway. Recently, ASCT2 has been identified as a key downstream effector of miR-137, revealing a molecular link between DNA methylation, microRNAs, and tumor metabolism. Additionally, RNF5, an endoplasmic reticulum-associated E3 ubiquitin ligase, regulates protein stability and clearance in various cellular processes. Increased RNF5 expression is associated with advanced breast cancer. Researchers have demonstrated that paclitaxel-induced endoplasmic reticulum stress in breast cancer cells promotes the ubiquitination and degradation of ASCT2 and SLC38A2 through RNF5 binding. In summary, RNF5-mediated control of glutamine uptake underlies breast cancer's response to chemotherapeutic agents. Studies on human leukocyte antigen (HLA) ligands also suggest that ASCT2 may be a therapeutic target in renal cell carcinoma [54].

2.3. xCT

The xCT system is a sodium-independent reverse transporter that outputs intracellular glutamate and inputs extracellular cystine in a 1:1 ratio [55,56]. Like LAT1, it forms dimers with 4F2hc via disulfide bonds, which maintain the stability and proper membrane localization of the SLC7A11 protein [56,57]. The amino acid transporter xCT is mainly responsible for transporting two substances, cysteine and glutathione. Cysteine is an important component of protein synthesis and is also a precursor to glutathione. Glutathione has an antioxidant effect within cells, helping to clear free radicals and protect cells from oxidative damage. Therefore, the function of the amino acid transporter xCT is essential for cellular metabolism, antioxidant activity, and immune regulation [58] (Figure 1).

In a 2012 study, inhibition of xCT-mediated cystine uptake using compounds like erastin was found to trigger ferroptosis, a novel form of cell death [59]. Cells employ diverse defense mechanisms against toxic lipid peroxides, notably glutathione peroxidase 4 (GPX4) from the GPX family. GPX4 utilizes reduced glutathione (GSH) to detoxify lipid peroxides into lipid alcohols, thus thwarting ferroptosis [60,61]. Since cysteine is essential for the synthesis of glutathione (GSH), intracellular cysteine is mainly obtained through xCT-mediated cystine uptake. When cystine is depleted or xCT is inhibited either genetically or pharmacologically, it induces strong ferroptosis in many cancer cells. On the other hand, the upregulation of xCT in cancer cells boosts GSH production, providing resistance to ferroptosis [59,62,63].

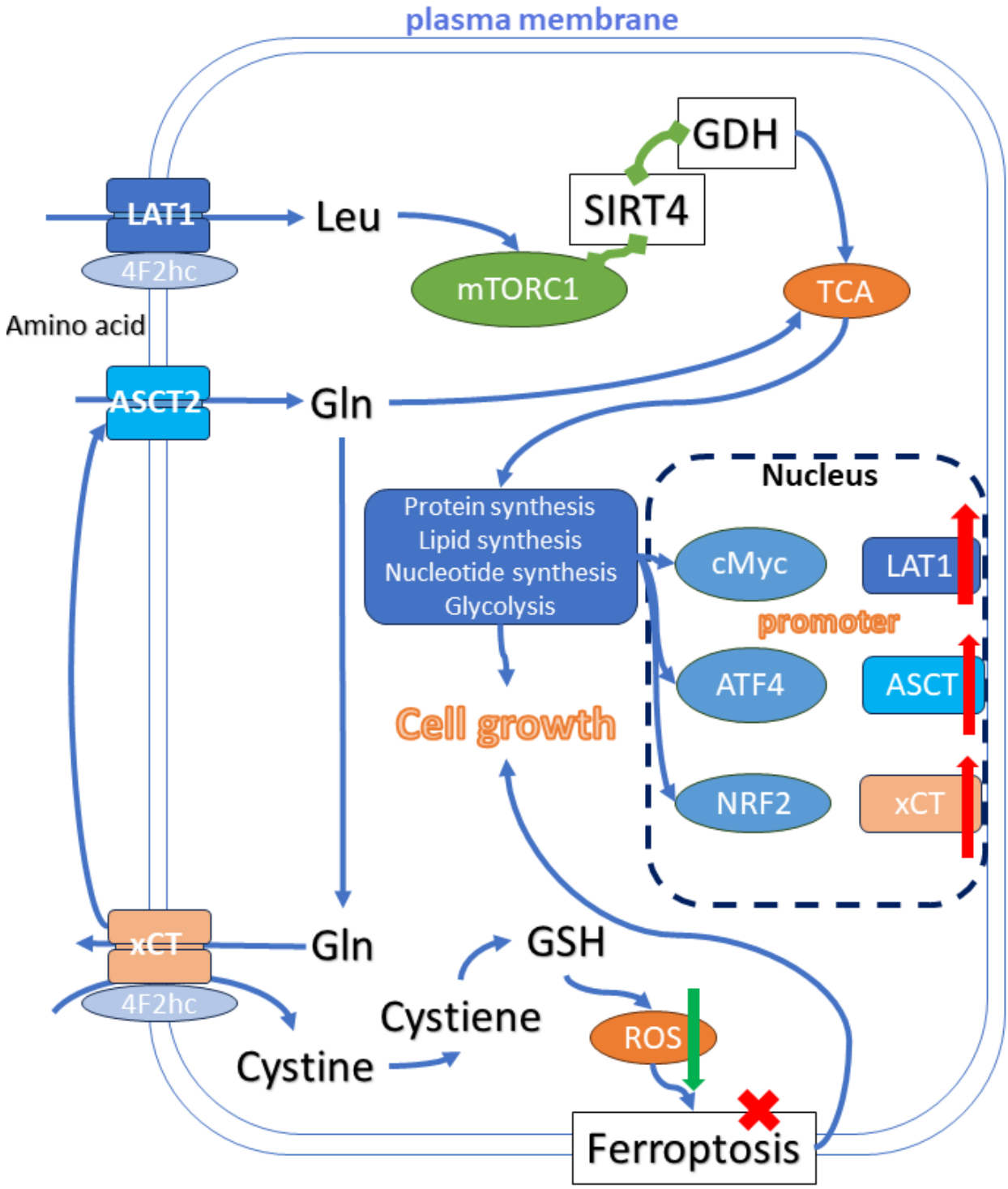

Figure 1. LAT1, ASCT2, and xCT as key transporters responsible for substance transport. They supply branched-chain amino acids (BCAAs) to the mammalian target of rapamycin complex 1 (mTORC1), fueling the tricarboxylic acid (TCA) cycle for energy production and fatty acid metabolism, thereby enhancing cell proliferation. Conversely, the nuclear expression of LAT1, ASCT2, and xCT is modulated by mTORC1 downstream factors. Gln = Glutamine; cMyc = cellular Myc; ATF4 = Activating Transcription Factor 4; NRF2 = Nuclear Factor Erythroid 2-Related Factor 2; SIRT4 = Sirtuin 4; GDH = glutamate dehydrogenase; Leu = Leucine; GSH = Glutathione. Upregulation: red upward arrow; Downregulation: green downward arrow; Inhibition: red "×" symbol; Inverse correlation between the expression of the former and the latter: green curve.

Of course, it is important to understand that these three transporters are not completely isolated; there is extensive synergy and interconnection among them. For example, the mammalian target of rapamycin (mTOR) kinase integrates signals from growth factors (via Phosphoinositide 3-Kinase and Akt) and energy metabolism via AMP-dependent protein kinase (AMPK) and nutrients, particularly amino acids, to regulate protein synthesis and cell growth. Both LAT1 and ASCT2 are linked to the mTOR signaling pathway [24]. In the induction of ferroptosis, ASCT2 and xCT can establish a synergistic relationship via Yes-Associated Protein 1 (YAP1). YAP1 is highly expressed in castration-resistant prostate cancer (CRPC) tissues and positively correlates with ASCT2 levels. By promoting extracellular glutamine uptake and subsequent glutamate and GSH production, YAP1 increases GPX4 activity. Therefore, inhibiting ASCT2 activity can attenuate YAP1's antagonistic effect on xCT-induced ferroptosis in CRPC cells [64]. A study on bladder cancer revealed that interfering with 4F2hc led to increased levels of reactive oxygen species (ROS), lipid peroxidation, and ferrous ions (Fe^{2+}) in cells, accompanied by the downregulation of xCT and GPX4, and the upregulation of acyl-CoA synthetase long-chain family member 4 (ACSL4) and transferrin receptor 1 (TFR1). The findings suggest that interfering with 4F2hc can inhibit bladder cancer cell growth and the polarization of tumor-associated macrophages by promoting ferroptosis in bladder cancer cells [65]. These examples sufficiently demonstrate that the aforementioned amino acid transporters are part of a larger amino acid metabolism system, rather than functioning in isolation. The regulation of one amino acid transporter may trigger varying feedback responses in other transporters.

3. The Role of LAT1, ASCT2, and xCT in Urological Cancers

3.1. Prostate Cancer

3.1.1. LAT1 Complex in PCa

The LAT1 complex plays a pivotal role in the survival, growth, and invasion of PCa cells. Increased LAT1 expression in PCa serves as an independent and highly malignant biomarker, complementing the Gleason score for prognosis estimation [26]. The amino acid positron emission tomography (PET) tracer, anti-[^{18}F]-Fluciclovine (anti-[^{18}F]-FACBC), approved by the US Food and Drug Administration (FDA) and the European Commission (EC), targets LAT1, aiding in PCa visualization, particularly in patients with elevated PSA post-treatment [66–68].

Studies demonstrate that LAT inhibition hampers M-phase cell cycle genes controlled by E2F transcription factors, pivotal in castration-resistant PCa regulation. In vivo, LAT1 knockdown curtails tumor development, cell cycle progression, and spontaneous metastasis in xenografts [13]. Si4F2hc impedes cell growth, migration, and invasion. Both 4F2hc and LAT1 expression levels correlate with prognosis across various tumors [19].

Upregulation of LAT1 during antiandrogen therapy promotes PCa progression, while LAT1 knockdown curtails proliferation, migration, and invasion in cell models. Elevated LAT1 expression during androgen deprivation therapy signifies significantly shorter prostate-specific antigen relapse-free survival [29].

Androgen Receptor Splice Variant 7 (AR-V7), a key feature of castration-resistant prostate cancer (CRPC), inversely regulates LAT1 complex expression during PCa progression from hormone-sensitive to castration-resistant stages. AR-V7 upregulation post-treatment correlates with heightened 4F2hc expression in clinical samples, implicating AR-V7 in 4F2hc activation. Harmonic regulation of LAT1 complex expression during PCa progression underscores its significance in disease advancement [69].

3.1.2. ASCT2 in PCa

Similarly, owing to its elevated expression in tumor cells and affinity for radio-labeled PET tracers of amino acids, ASCT2 serves as a potential PET detection target for PCa, contributing to its diagnostic capabilities [70–74]. Li's research reveals ASCT2's cytoplasmic localization in normal prostate, benign prostatic hyperplasia (BPH), and PCa epithelial cells. ASCT2 plays a crucial role in glutamine metabolism across non-malignant and malignant

prostate tissues. Compared to BPH (25.8%) or PCa (25.3%), ASCT2 expression levels are significantly higher in normal tissue (49%) ($p < 0.001$). However, ASCT2-positive PCa correlates with aggressive biological behavior and tumor progression [75]. Inhibition of LAT activity, as indicated by Wang, upregulates ASCT2 and 4F2hc expression, mediated by transcription factor 4 and regulated by androgen receptors [13]. Studies have found that following chronic androgen deprivation therapy (ADT), the expression levels of LAT1 and 4F2hc are relatively higher in 22Rv1 castration-resistant orthotopic tumors, while ASCT2 expression is elevated in CWR22Res tumors following acute androgen deprivation therapy (ADT) [76].

Targeting ASCT2-mediated glutamine uptake inhibits PCa growth and tumor development. Inhibition of ASCT2 function reduces glutamine uptake, cell cycle progression via E2F transcription factors, mTORC1 pathway activation, and cell growth. Chemical inhibition also decreases basal oxygen consumption and fatty acid synthesis, indicating that downstream metabolic functions depend on ASCT2-mediated glutamine uptake [15,77,78].

As mentioned above, ASCT2 is regulated by androgens [13]. This finding was reinforced by examining mRNA expression in patient samples before and after ADT, showing a significant decrease in ASCT2 expression following ADT. However, Western blot analysis demonstrated an upregulation of ASCT2 protein expression after dihydrotestosterone treatment, highlighting the complexity of ASCT2 regulation [13,79]. Androgens enhance glutamine metabolism in PCa cells, a process that is crucial for cell growth under serum starvation conditions. Mechanistically, androgen receptor (AR) signaling promotes glutamine metabolism by increasing ASCT2 expression, and the gene expression profile associated with AR activity correlates with ASCT2 mRNA levels in clinical cohorts [80].

In vitro experiments have demonstrated that ASCT2 inhibition suppressed the growth of Castration-Sensitive Prostate Cancer (CSPC) cells. In LNCaP cells, combined treatment with ASCT2 siRNA and enzalutamide resulted in an approximately 50% greater reduction in cell growth compared to treatment with enzalutamide alone or ASCT2 siRNA transfection alone [77]. This suggests a potential synergistic effect between ASCT2 inhibition and enzalutamide treatment, consistent with previous findings that AR signaling can stimulate processes such as aerobic glycolysis and lipid metabolism, acting as a key metabolic regulator.

At the CRPC stage, ASCT2 inhibition was also found to suppress the growth of androgen receptor variant 7 (AR-V7)-positive 22Rv1 and LNCaP cells, further supporting the role of ASCT2 in PCa progression. Although ASCT2 inhibition does not affect AR expression, it may independently inhibit PCa cell growth through AR-independent mechanisms [77].

Additionally, c-Myc, a prototypical oncogene in PCa, regulates ASCT2 expression levels via PTEN. In contrast, rapamycin reduces androgen-mediated ASCT2 expression independently of phosphatase and tensin homolog (PTEN) status, indicating that mTORC1 is essential for maximal AR-mediated glutamine uptake and PCa cell growth. Collectively, these data suggest that the three established oncogenic drivers (AR, c-Myc, and mTOR) converge to increase ASCT2 protein expression, thereby promoting glutamine uptake and subsequent PCa cell growth [80].

Furthermore, ASCT2 has been identified as an EGFR-related protein that sensitizes cancer cells to ROS-induced apoptosis when co-targeted with cetuximab. The study demonstrated that cetuximab-mediated epidermal growth factor receptor (EGFR) endocytosis reduces ASCT2 in an EGFR expression-dependent manner, leading to decreased intracellular glutamine uptake and reduced glutathione levels [81]. Given the close relationship between EGFR and prostate cancer, targeting ASCT2 could regulate the progression of prostate cancer through the EGFR pathway [14].

3.1.3. xCT in PCa

Similarly to LAT1's relationship with anti-[^{18}F]-FACBC, (4S)-4-(3-[^{18}F] fluoropropyl)-L-glutamate ([^{18}F]-FSPG) serves as a radiopharmaceutical for xCT-active PET imaging,

showing upregulation in PCa. This enables the diagnosis of new or recurrent PCa using this radiopharmaceutical [82].

Destruction of xCT significantly impedes the growth of various cancers, including lymphoma, glioma, PCa, and breast cancer [83]. In PCa cells, ferroptosis induced by the drug erastin is closely associated with xCT. Erastin inhibits xCT expression in LNCaP and PC3 cells, which correlates with a significant increase in intracellular malondialdehyde (MDA) and Fe^{2+}, along with a marked decrease in GSH and oxidized glutathione (GSSG). In androgen-dependent cell lines (LNCaP and VCaP), knockdown of transmembrane protein with EGF-like and two FXYD Domains 2 (TMEFF2) leads to suppressed xCT expression and reduced cell viability, whereas no significant effect is observed in androgen-independent cell lines (PC3 and C4-2) [84].

Shi's study reported that antimony (Sb), a typical environmental pollutant, leads to increased GSH levels, elevated GPX4 expression, and reduced Fe^{2+} levels under low-dose exposure. Since GPX4 and Fe^{2+} are critical molecular markers in the ferroptosis mechanism, low-dose antimony exposure can inhibit RSL3-induced ferroptosis and promote PCa proliferation through the activation of the Nuclear Factor Erythroid 2-Related Factor 2 (NRF2)–xCT–GPX4 pathway [85].

Zhong's research highlights the role of extracellular superoxide dismutase (ECSOD) and cysteine/glutamate transporter (Cys)/(xCT) in regulating the redox state of the tumor microenvironment (TME). Altered expression of ECSOD and xCT can disrupt TME redox balance. In PCa tissues, xCT protein expression is markedly increased while ECSOD protein expression is decreased. Simultaneous overexpression of ECSOD and knockdown of xCT exhibit has been shown to enhance inhibition of PCa cell invasion as compared to individual interventions [86].

Hagiwara's findings reveal that the carcinogenic protein Mucin 1-C-terminal (MUC1-C) forms a complex with NRF2 and Polybromo 1 (PBRM1) on the NRF2 target gene xCT, encoding the xCT cystine-glutamate reverse transporter. This complex enhances chromatin accessibility and induces xCT expression, contributing to PCa progression by integrating Polybromo-Associated Brg1-Associated Factor (PBAF) and BRG1/BRM-Associated Factor (BAF) pathways [87].

3.2. Bladder Cancer (Urothelial Carcinoma)

3.2.1. LAT1 Complex in Bladder Cancer

Kyung's study characterized L-system amino acid transporters in T24 cells, revealing LAT1 as the primary mediator of [^{14}C] L-Leu uptake [88]. Maimaiti investigated LAT1's expression profile and functional role in bladder cancer, identifying high LAT1 expression as an independent predictor of overall survival (OS). Elevated LAT1 and Insulin-like Growth Factor Binding Protein 5 (IGFBP-5) expression correlated with poorer overall survival, while LAT1 levels correlated with pathological stage, Lactate Dehydrogenase (LDH), and Neutrophil-to-Lymphocyte Ratio (NLR). Inhibition of LAT1 hindered cell proliferation, migration, and invasion in vitro, with IGFBP-5 expression associated with a favorable prognosis in aggressive bladder cancer cases [89].

3.2.2. ASCT2 in Bladder Cancer

The association between arsenic and ASCT2 in bladder cancer has been documented, showing increased ASCT2 and β-catenin expression levels both in vivo and in vitro. Arsenic exposure increases the risk of bladder cancer in humans, but the mechanisms behind it are unclear. Up-regulation of ASCT2 promotes the uptake of glutamine by cancer cells, which is a key factor in cancer cell proliferation and survival. The increase in ASCT2 further activates the β-catenin signaling pathway, which plays a key role in cell proliferation, self-renewal, and maintenance of tumor stem cell properties. By maintaining a balance of GSH/ROS, ASCT2 supports low levels of ROS, which is necessary for the stability and activity of beta-catenin. Thus, ASCT2 promotes cell proliferation and self-renewal by activating

beta-catenin, crucial for maintaining GSH/ROS homeostasis. ASCT2 emerges as a potential therapeutic target for arsenic-induced urothelial cell proliferation and self-renewal [90,91].

It has been reported that a traditional Chinese medicine, Qici Sanling (QCSL), significantly inhibits the viability of T24 cells and increases apoptosis in a dose-dependent manner. QCSL is capable of suppressing glutamine consumption and reducing the expression levels of Glutaminase 1 (GLS1), ASCT2, and c-Myc. In a nude mouse model, QCSL inhibited tumor growth and decreased the levels of GLS1, ASCT2, and c-Myc in tumor tissues [92]. Additionally, the level of ASCT2 in urine may have the potential to serve as a screening marker for urothelial carcinoma [93].

Studies have also shown that in prostate and bladder cancers, the increased expression of ASCT2 is associated with an increase in tumor-associated macrophages (TAMs) with immunosuppressive properties [94]. JHU083 is a prodrug of a glutamine antagonist, which inhibits tumor growth by blocking glutamine metabolism. In prostate and bladder cancer models, JHU083 significantly inhibits tumor growth and alters immune cells within the tumor microenvironment, particularly TAMs. JHU083 suppresses glutamine utilization, promoting a shift in TAMs from the immunosuppressive M2 type to the inflammatory M1 type. This shift increases TAMs' phagocytic activity and reduces their pro-angiogenic capabilities, disrupting tumor cell metabolic pathways, including glycolysis, the TCA cycle, and purine metabolism. This metabolic disruption in tumor cells may ultimately lead to apoptosis. In prostate and bladder cancer models, JHU083 as a monotherapy can significantly inhibit tumor growth, and this effect is not entirely dependent on T cells. As a novel glutamine antagonist, JHU083 offers a potential therapeutic strategy for tumors rich in immunosuppressive TAMs, especially for tumor types that respond poorly to immune checkpoint blockade therapy [94].

3.2.3. xCT in Bladder Cancer

Ye's study revealed the upregulation of stress-inducing transcription factors NRF2 and Activating Transcription Factor 4 (ATF4) upon proteasome inhibition, synergistically enhancing human xCT gene expression. Knockdown or pharmacological inhibition of xCT sensitized T24 cells to proteasomal inhibition, suggesting the therapeutic potential of simultaneous proteasome and xCT inhibition in bladder cancer treatment [95]. Related studies showed increases in the expression of p53, which in turn leads to the downregulation of xCT and GPX4, thereby increasing the sensitivity of bladder cancer cells to ferroptosis [96,97].

Cluster of differentiation 44 variant (CD44v)8–10 upstream molecules of xCT possess the molecular mechanism which confers cisplatin resistance in urothelial carcinoma. CD44v8–10 promote oxidative stress defense associated with chemoresistance by enhancing the function of xCT, which regulates glutathione synthesis [98]. Additionally, a Chinese study demonstrated that astragalus polysaccharides (APS) inhibited urothelial carcinoma cell proliferation and reduced GPX4 expression. APS promoted the formation of the Beclin 1 (BECN1)-xCT complex via AMP-Activated Protein Kinase (AMPK)/BECN1 signaling, inhibiting xCT activity, inducing ferroptosis, and inhibiting urothelial carcinoma progression [16].

3.3. Renal Cancer

3.3.1. LAT1 Complex in Renal Cancer

Hironori investigated LAT1 and 4F2hc mRNA expression in clear cell renal cell carcinoma (ccRCC) tissues, finding significantly higher LAT1 mRNA levels in tumor tissue compared to non-tumor tissue. Increased LAT1 mRNA expression correlated with poorly differentiated tumors, local invasion, microvascular invasion, and metastasis, with higher blood LAT1 mRNA levels predicting shorter overall survival. Phosphorylated S6 ribosomal protein levels positively correlated with LAT1 mRNA expression and metastatic potential in primary cancer [25].

Higuchi's review revealed LAT1 expression in 92% of RCC tissues, with high expression associated with reduced overall survival and progression-free survival [99].

3.3.2. ASCT2 in Renal Cancer

Research has found that ASCT2 expression is significantly increased in sunitinib-resistant RCC cells, which leads to the upregulation of glutamine uptake and glycolysis, along with enhanced antioxidant activity, and suggests a close association between ASCT2 and sunitinib resistance in RCC cells [100].

Kawakami's loss-of-function experiments using the ASCT2 inhibitor (V9302) in human ccRCC cell lines (A498 and Caki1) demonstrated that ASCT2 inhibition significantly suppressed tumor growth, invasion, and migration. Similar results were observed in xenograft mouse models. The antitumor effects of SLC1A5 inhibition are associated with mechanisms of cellular senescence [101].

Alyssa's study demonstrated ASCT2's impact on PET tracer uptake and its inhibition by V-9302 in a ccRCC mouse model, where tumor cell glutamine uptake was significantly higher than in normal renal cells. Treatment with V-9302 reduced tracer uptake by 20–50% [102].

Liu found that elevated ASCT2 expression correlated with advanced TNM stage, higher Fuhrman grade, and shorter overall survival in ccRCC patients, serving as an independent predictor of overall survival [50].

3.3.3. xCT in Renal Cancer

Ye reported upregulation of Six-Transmembrane Epithelial Antigen of the Prostate 3 (STEAP3) in renal cell carcinoma tissues and cell lines, associated with poor survival and prognosis. Knocking out STEAP3 increased kidney cancer cell susceptibility to ferroptosis via the p53/xCT pathway, rendering cell lines with reduced STEAP3 expression more sensitive to ferroptosis [103]. In collecting duct carcinoma (CDC) of the kidney, overexpression of the cisplatin resistance-associated gene xCT was observed in four out of five CDC tumors (80%) compared to matched non-tumor tissue [104]. Furthermore, xCT is a prognostic gene associated with ferroptosis in chromophobe renal cell carcinoma (ChRCC). High xCT expression in ChRCC is correlated with reduced immune cell infiltration and lower levels of MHC and immune checkpoint molecule expression within the tumor microenvironment. Additionally, elevated xCT expression is significantly associated with advanced tumor stages and poorer cancer-specific survival rates [105,106] Knockdown of xCT promotes cell growth and lipid peroxidation, increases ferroptosis levels, and significantly inhibits the growth of tumor xenografts. This effect persists even in cell lines resistant to neoadjuvant tyrosine kinase inhibitor (TKI) therapy [107].

A study on immunogenic cell death (ICD)-related features in kidney renal clear cell carcinoma (KIRC) explored the relationship between ICD and KIRC, aiming to identify potential biomarkers that could provide new insights into personalized immunotherapy for KIRC. The researchers identified 73 key ICD-related genes, including xCT, through the GeneCards database and the relevant literature. Using consensus clustering analysis, two ICD subtypes were identified, which exhibited significant differences in clinical outcomes, genomic alterations, and the tumor immune microenvironment. The differential expression of xCT, as one of the ICD-related genes, across the subtypes may be linked to these clinical and immunological characteristics. The researchers developed an ICD prognostic signature based on multiple genes, including xCT, to assess patient prognosis. Through risk scoring, patients could be stratified into high-risk and low-risk groups, with the high-risk group demonstrating significantly poorer outcomes. The study also investigated the relationship between the ICD risk score and various immune cell subtypes in the tumor immune microenvironment. While the paper did not explicitly emphasize a direct association between xCT and specific immune cells, the overall ICD risk score was correlated with the infiltration levels of multiple immune cell types, potentially indicating an important role of xCT in modulating the tumor immune microenvironment [108]. In damaged kidneys, M2-like macrophages promote renal cancer progression and induce resistance to anti-PD1 antibodies through their tumor-promoting functions and suppression of CD8+ T cell infiltration. RNA sequencing revealed that xCT is upregulated in M2-like

macrophages. Inhibition of xCT with sulfasalazine can suppress the tumor-promoting functions of M2-like macrophages and synergize with anti-programmed cell death protein 1 (PD1) antibodies. Furthermore, xCT-positive macrophages are associated with poor prognosis in renal cancer patients [109]. Overall, these studies elucidate the mechanisms by which xCT drives renal cancer progression and resistance to PD1 antibody therapy in an impaired kidney or immune environment. By modulating the immune microenvironment, these insights provide a promising therapeutic approach for ICD, targeting anti-PD1 antibodies, and macrophages.

4. Prospect of Treatment of Urological Cancers Based on Amino Acid Transporters (Inhibitors and Targeted Therapies)

4.1. Inhibitors and Targeted Therapies of LAT1 Complex

Inhibitors targeting transporters include both substrate-like compounds and non-transporters acting as blockers or exerting inhibitory effects on steroids. In pharmacology, the prevailing notion is that non-transport compounds are preferable to transport compounds due to their lack of cellular accumulation and high affinity. While 2-aminobicyclo-(2,2,2,1)-heptane-2-carboxylic acid (BCH) serves as a metabolic Leu analog and a sodium-independent L system inhibitor, its clinical utility is limited by its substrate delivery, low specificity, and affinity for LAT1 [13,110,111].

The first specific LAT1 inhibitor reported was triiodothyronine (T3), which, being nearly non-transportable, inspired the development of LAT1 inhibitors [112]. JPH203 (KYT-0353) emerged in 2009 as a non-delivery LAT1-specific inhibitor, sharing structural similarities with T3 [113]. JPH203 exhibits high affinity and specificity for LAT1 without affecting LAT2. It interferes with mTORC1 and Akt activation, reduces c-Myc expression, and induces CHOP-mediated cell death [114]. Clinical studies have shown promising results of JPH203 in treating biliary tract cancer, with a disease control rate of approximately 60% [115]. Additionally, JPH203 demonstrates inhibitory effects on the growth, migration, and invasion of CRPC cells in vitro and inhibits CRPC cell proliferation in vivo, suggesting LAT1 as a promising therapeutic target for CRPC [116].

The SKN series of LAT1 inhibitors, similar to JPH203, have been developed by Japanese researchers [117,118]. Moreover, the OKY series, led by Professor Kanai at Osaka University, has produced OKY-034 with high inhibitory efficacy and specificity on LAT1. Clinical trials evaluating the safety and efficacy of OKY-034 in pancreatic cancer patients are underway (UMIN000036395), with potential applications in PCa treatment on the horizon [110].

4.2. Inhibitors and Targeted Therapies of ASCT2

To date, no clinically approved drugs specifically target ASCT2 due to challenges related to potency or specificity. One reason for the poor selectivity is the highly conserved binding sites among SLC1 family members. Recent research has focused on developing compounds that combine hydrophobicity with polar groups in the amino acid side chains [119]. The polar groups around the serine backbone may interact with polar residues within the binding site, thereby conferring the necessary selectivity for ASCT2. Experimental results indicate that these compounds selectively block the anion conductance of ASCT2, rather than that of other closely related SLC1A family members. This research provides a clear direction for the pharmacological development of ASCT2-specific inhibitors [119].

4.2.1. L-γ-Glutamyl-p-Nitroanilide (GPNA)

As a glutamine structural analog, GPNA inhibits Na^+-dependent amino acid transporters, including ASCT2, albeit its usage is limited to basic research due to toxicity. GPNA therapy downregulates BCAAs in most cancer cell lines and inhibits mTORC1 [120].

4.2.2. V-9302

Schulte's team introduced V-9302 in 2018 as the first potent small molecule inhibitor of ASCT2, demonstrating a half-maximal inhibitory concentration (IC50) three times higher

than GPNA. This inhibitor effectively suppresses tumor growth, invasion, migration, and metastasis, as verified both in colon cancer cells [121] and in human ccRCC cells [101]. Results were also observed in xenograft mouse models.

4.2.3. 1,2,3-Dithiazole Compounds

Oppalesano's group designed 1,2,3-dithiazole compounds as ASCT2 inhibitors, showing over 50% inhibition of glutamine antiport in rat liver transporter recombinant liposomes [122].

4.2.4. Anti-ASCT2 Monoclonal Antibody

Suzuki's team is actively developing monoclonal antibodies targeting ASCT2. Monoclonal antibodies (KM series) inhibit the proliferation of glutamine-dependent colon cancer cells in vitro. Additionally, the optimized antibody KM8094 exhibits enhanced anti-tumor efficacy [123,124]. These findings offer promising strategies for monoclonal antibody application in cancer therapy.

In addition, Tubulin inhibitor C118P also has a good inhibitory effect on ASCT2 [125]. In various breast cancer cell lines, C118P inhibits ASCT2-mediated glutamine metabolism, reduces adenosine triphosphate (ATP) production, suppresses oxidative phosphorylation (OXPHOS), and decreases glutamine uptake. It also inhibits tumor growth by inducing apoptosis, G2/M phase arrest, and autophagy. Similar results were observed in a co-culture model of adipocytes and breast cancer cells. Adipocyte-derived interleukin-6 (IL-6) enhances breast cancer cell proliferation via ASCT2: IL-6 promotes proliferation by upregulating ASCT2-mediated glutamine metabolism, whereas C118P inhibits the IL-6 effect in the co-culture system [125]. Benzylserine, an inhibitor of LAT1, can also inhibit the activity of ASCT2, resulting in dual inhibition of both LAT1 and ASCT2 [74]. Good results have been obtained in studies on controlling breast cancer cells [74,125]. There are reports that the United States has approved phase I clinical trials of ASCT2 inhibitors in hematological tumors (NCT03102468). Additionally, some researchers have conducted combination therapy studies for PCa using high-throughput screening of natural compound libraries. In vivo administration of ursolic acid, curcumin, and resveratrol, either individually or in combination, was found to reduce ASCT2 protein levels in HMVP2 cells. In a mouse xenograft PCa model, all combinations of these natural compounds exhibited a synergistic effect on tumor size and weight, suggesting that these compounds may influence glutamine metabolism in PCa cells by modulating ASCT2 [126]. However, the effects of these compounds are more oriented towards altering tumor cell metabolism compared to ASCT2 inhibitors [127].

4.3. Inhibitors and Targeted Therapies of xCT

Blocking the xCT pathway to induce iron death is a hot research topic, which has been confirmed in liver cancer [128], ovarian cancer [129], breast cancer [130,131], and adrenocortical carcinoma (ACC) [132].

4.3.1. Sulfasalazine (SAS)

SAS is an xCT inhibitor that suppresses cellular GSH biosynthesis, thereby enhancing the anticancer activity of vitamin C (VC), which may lead to increased accumulation of ROS. The synergy between SAS and VC results in a significant depletion of cellular GSH, leading to elevated ROS levels. This synergy can be reversed by the antioxidant N-acetyl-L-cysteine (NAC). The synergistic effect of SAS and VC is also evident in PCa xenografts and correlates with immunohistochemical findings [133].

4.3.2. PSMA-Targeted Arsenic Nanosheets

Wang designed a novel nanomaterial, the PSMA-targeted arsenic nanosheet (PMAN), which differs from existing metal-based inducers of ferroptosis. This inorganic, metal-free material simultaneously increases GSH depletion, inhibits the expression of xCT and GPX4,

and promotes the production of ROS and lipid peroxides (LPO). PMAN effectively facilitates the delivery of doxorubicin (DOX) to PCa cells for synergistic therapy. Additionally, it sensitizes PCa cells to DOX by downregulating the expression of the ataxia-telangiectasia mutated (ATM) gene, further enhancing the GPX4 downregulation-mediated ferroptotic tumoricidal effect [134].

4.3.3. Modulators of Upstream Factors

The phosphoglycerate dehydrogenase (PHGDH) targeting inhibitor NCT-502, a key molecule in serine metabolism, can knock down PHGDH, further downregulating xCT expression. PHGDH binds to the RNA-binding protein PCBP2 and inhibits its ubiquitination and degradation. In turn, PCBP2 stabilizes xCT mRNA and increases its expression. NCT-502 promotes ferroptosis and delays the malignant progression of bladder cancer by inhibiting PHGDH and downregulating xCT expression through interaction with PCBP2 [135]. Similar results were also confirmed in studies on enzalutamide-resistant CRPC cells. The combination of ferroptosis inducers with targeted inhibition of the upstream xCT regulator PHGDH may represent a potential therapeutic strategy for bladder cancer and PCa [136].

Fenbendazole, an FDA-approved anthelmintic, induces the expression of p53, partially leading to G2/M phase cell cycle arrest, and results in the transcriptional repression of xCT, thereby downregulating the ferroptosis-related gene GPX4. Additionally, fenbendazole exhibits a synergistic effect with 5-fluorouracil (5-FU) in chemotherapy for CRPC. As a p53 inducer, fenbendazole has potential new applications in CRPC neoadjuvant chemotherapy by impeding cell cycle progression and activating ferroptosis, thus exerting anti-proliferative and pro-apoptotic effects [137].

4.3.4. Certain Plant-Derived Compounds

Brusatol, extracted from the dried mature fruits of Brucea javanica, inhibits bladder cancer growth and induces ferroptosis by upregulating ChaC glutathione-specific γ-glutamylcyclotransferase (Chac1) expression while downregulating xCT and NRF2 expression in bladder cancer cells [138]. Cephaeline is a natural product isolated from ipecac (Cephaelis ipecacuanha [Brot.] A. Rich. [Rubiaceae]). Cephaeline can downregulate the expression of xCT and NRF2 in lung cancer cell lines, inducing ferroptosis in these cells [139]. Icariin-curcumol can reduce the levels of xCT, GPX4, and GSH, as well as the levels of NRF2 and heme oxygenase-1 (HO-1) in PCa cells. Icariin-curcumol induces ferroptosis in PCa cells by inhibiting the NRF2/HO-1 signaling pathway [140].

We have summarized the relationship between amino acid transporters and cancers and inhibitors in Table 1 below.

Table 1. The relationship between amino acid transporters and cancers and inhibitors.

Amino Acid Transporter	Cancer	Inhibitor	Outcome	Main Reference
LAT1-4F2hc	CRPC	JPH203	Inhibits growth, migration, and invasion of CRPC cells in vitro and in vivo	[116]
	Pancreatic cancer	OKY-034	High inhibitory effect and specificity on LAT1; Phase I/IIa trial ongoing	[110]
	Biliary tract cancer	JPH203	Disease control rate of approximately 60%	[115]
ASCT2	PCa	GPNA	Down-regulates branched-chain amino acids and inhibits mTORC1	[120]
	Colorectal cancer ccRCC	V-9302	Inhibits tumor growth, invasion, migration, and metastasis	[101,121]

Table 1. *Cont.*

Amino Acid Transporter	Cancer	Inhibitor	Outcome	Main Reference
ASCT2	PCa Bladder cancer	JHU083	Acts as a glutamine antagonist that inhibits tumor growth by disrupting glutamine metabolism, reprogramming tumor-associated macrophages from an immunosuppressive to an inflammatory state, and causing metabolic disruption in tumor cells.	[94]
	Breast cancer	C118P	Inhibits ASCT2-mediated glutamine metabolism, reduces ATP production, suppresses OXPHOS, and decreases glutamine uptake	[125]
	PCa	Ursolic acid, Curcumin, Resveratrol	Reduce ASCT2 protein levels in HMVP2 cells and exhibit a synergistic effect on tumor size and weight	[126]
xCT	PCa	Sulfasalazine	Suppresses cellular GSH biosynthesis, enhances anticancer activity of VC, leading to increased ROS	[133]
	ACC	PSMA-targeted arsenic nanosheets (PMAN)	Increases GSH depletion, inhibits xCT and GPX4, promotes ROS and LPO production	[134]
	Bladder cancer PCa	NCT-502	Knocks down PHGDH, downregulates xCT expression, promotes ferroptosis	[135,136]
	CRPC	Fenbendazole	Induces p53 expression, downregulates xCT and GPX4, exhibits synergistic effect with 5-FU	[137]
	Bladder cancer	Brustalol	Inhibits bladder cancer growth by upregulating ChaC1 and downregulating xCT and NRF2	[138]

PCa = Prostate cancer; CRPC = Castration-resistant prostate cancer; GPNA = L-γ-Glutamyl-p-nitroanilide; ccRCC= Clear cell renal cell carcinoma; ATP = Adenosine triphosphate; OXPHOS = Oxidative phosphorylation; GSH = Glutathione; ROS = Reactive Oxygen Species; VC = Vitamin C; GPX4 = Glutathione Peroxidase 4; LPO = Lipid Peroxidation; PHGDH = Phosphoglycerate Dehydrogenase; 5-FU = 5-Fluorouracil; ChaC1 = ChaC Glutathione Specific Gamma-Glutamylcyclotransferase 1; NRF2 = Nuclear Factor Erythroid 2-Related Factor 2.

5. Future Development of Amino Acid Transporter Inhibitors: Mechanisms and Research Directions

5.1. Combined Inhibition of the mTORC1 Signaling Pathway

LAT1 and ASCT2 facilitate amino acid uptake, particularly Leu and glutamine, which activates the mTORC1 signaling pathway, driving cell proliferation and growth. By inhibiting the upstream activators of mTORC1, the oncogenic effects of LAT1 and ASCT2 can be mitigated. Alternatively, mTOR inhibitors (e.g., rapamycin and its derivatives) directly inhibit mTORC1 activity. Combining these with LAT1 and ASCT2 inhibitors reduces amino acid uptake, further weakening mTORC1 signaling.

5.2. Induction of Ferroptosis

xCT mediates cystine uptake, essential for glutathione synthesis, which protects cells from oxidative stress and ferroptosis. Inhibiting xCT reduces glutathione production, increases ROS accumulation, and induces ferroptosis. xCT inhibitors like sulfasalazine can block cystine uptake, while ROS-inducing drugs such as erastin can accelerate ferroptosis. Combining these with mTOR inhibitors can overcome cancer cells' resistance mechanisms and enhance therapeutic efficacy.

5.3. Multi-Target Protein Degradation

Designing PROTACs (Proteolysis Targeting Chimeras) or similar technologies can target LAT1, ASCT2, and xCT, inducing their ubiquitination and degradation. This reduces the expression of these transporters at the root level. PROTAC molecules can be developed to specifically bind LAT1, ASCT2, and xCT, leading to their degradation. This approach not only blocks transporter functions but also decreases their cellular levels, resulting in a more sustained inhibitory effect. By simultaneously reducing the expression of multiple transporters, this strategy could inhibit cancer cell amino acid uptake and weaken antioxidant defenses, leading to cell death or growth inhibition.

These strategies, which include combined inhibition of key signaling pathways (such as mTORC1), induction of ferroptosis, multi-target protein degradation, and pathway interference, hold the potential for effectively countering the cancer-promoting roles of LAT1, ASCT2, and xCT. They may offer a more robust anticancer approach, especially for treatment-resistant cancers.

6. Conclusions

Amino acid transporters (LAT1, ASCT2, xCT) are usually highly expressed in tumor cells, which is related to the enhanced dependence of tumor cells on nutrients and the promotion of tumor growth. Therefore, amino acid transporters (LAT1, ASCT2, xCT) play an important role in the diagnosis, treatment, and prognosis of urological cancers. Moreover, inhibitors targeting amino acid transporters are being investigated as potential anticancer therapeutics. They show great potential and application prospects in inhibiting tumor growth, increasing drug sensitivity, and reducing tumor invasion and metastasis.

In urological cancers, inhibitors of the amino acid transporter LAT1 (such as JPH203) may have broader clinical applications, having been demonstrated in CRPC. However, for specific types of urinary cancers, such as bladder and kidney cancers, further research is needed to determine the therapeutic efficacy and safety of LAT1 inhibitors. Although there is no precedent for the clinical application of ASCT2 and xCT inhibitors, with the development of technology and a deeper understanding of the biological functions of ASCT2 and xCT, it is expected that these inhibitors will become one of the important components of cancer therapy in the future.

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