Am J Cancer Res 2026;16(5):1847-1863
www.ajcr.us /ISSN:2156-6976/ajcr0171422

Review Article

Unravelling SLC7 family members in thyroid cancer and translational barriers

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Received January 12, 2026; Accepted March 25, 2026; Epub May 15, 2026; Published May 30, 2026

Abstract: SLC7 family transporters are an important group of membrane proteins that facilitate the transport of different amino acids across the cell membrane. They have a crucial role in oncogenic signalling pathways, cellular metabolism, and redox balance. Previous literature had revealed the functions of SLC7 in breast, liver, prostate, and lung cancers, but the role of SLC7 family members in thyroid cancer remains unclear. Therefore, this review investigated the emerging roles of SLC7, the molecular mechanisms underlying thyroid cancer progression, and strategies to improve its therapeutic delivery. In thyroid cancer, mutations in SLC7 subunits could further dysregulate amino acid metabolism and activate the PI3K/AKT, mTORC1, and MAPK/ERK signalling pathways. The activation of oncogenic signals, such as MYC, ATF4, and HIF-1α, could further enhance the SLC7 expression by promoting tumour progression, angiogenesis, and cell proliferation, impairing T-cell activation, and inhibiting the activities of natural killer cells (NK) and cytotoxic T-lymphocytes (CTLs). They also served as potential therapeutic agents, and modulating them with novel immune checkpoint inhibitors, engineered CAR-T cells, and CRISPR-edited cells represents a promising strategy for thyroid cancer treatment. The present review could explore innovative insights into the molecular mechanisms of SLC7 in thyroid cancer development, identify the novel therapeutic targets, and improve their delivery for thyroid cancer immunotherapy.

Keywords: Thyroid cancer, SLC7, transporters, MAPK/ERK, ATF4, therapeutic target

Introduction

SLC7 family transporters (solute carrier 7 family) are an important group of different membrane proteins that facilitate the transport of different amino acids, including ornithine, arginine, tyrosine, phenylalanine, serine, glycine, leucine, and lysine across the cell membranes [1]. They are classified into cationic amino acid transporters (CATs) and heteromeric amino acid transporters (HATs). They exhibit several properties due to their different roles in cellular and biochemical processes. HATs members are mostly heterodimers that readily bind to the cluster of differentiation 98 heavy chain (CD98hc), thereby mediating the transport of various amino acids. They also exhibit substrate specificity towards cationic, anionic, and neutral amino acids. They are involved in amino acid metabolism by supplying different substrates for energy production, glutathione production, nitrogen metabolism, and signalling pathways [1, 2].

Previous literature reported the role of SLC7 family members in breast, lung, prostate, and colorectal cancers. It was observed that SLC7A5 is frequently overexpressed in thyroid and breast cancer, enhancing leucine uptake and promoting the rapid tumour growth by activating the mTORC1 (mammalian target of rapamycin complex 1) pathway [3, 4]. Overexpression of SLC7A6 was observed in patients with hepatocellular carcinoma, activated the mTORC1/S6K pathway and contributes to angiogenesis and immune evasion [5]. It was observed that overexpression of SLC7A7 was significant in non-small lung cancer, where its elevated activity supported tumour growth by activating the phosphatidylinositol 3-kinase (PI3K/AKT) pathway. These findings revealed the role of SLC7 family members in various can-

https://doi.org/10.62347/PXMG2518

cers and highlighted the need to explore their function in thyroid cancer [6].

The molecular mechanisms and the role of various SLC7 family members in thyroid cancer are poorly understood [7]. SLC7A11 can activates the MAPK/ERK (mitogen-activated protein kinase/extracellular signal-regulated kinase) and phosphatidylinositol 3-kinase (PI3K/AKT) signalling pathways. It influenced the macrophages function through immunosuppression, tumour progression, and angiogenesis [8]. Moreover, SLC7A5 mediates the leucine uptake, activates the mTORC1 signalling, and enhances the release of transforming growth factor beta 1 (TGF-β) and interleukin-6 (IL-6). Excess release of these cytokines could inhibit anti-tumour responses [9]. SLC7A3 mediates the arginine uptake, thereby promoting tumour invasion. Overall, these findings highlighted the emergence of SLC7 family members in the progression of thyroid cancer [4].

SLC7 could serve as potential therapeutic agent, and its role in thyroid cancer remains unexplored. Targeting them with novel inhibitors and immunotherapy approaches, and combining therapies, could be helpful in thyroid cancer treatment [1, 10]. JPH203 is a small-molecule inhibitor of SLC7A5, that inactivated mTORC1 activity and inhibited cell proliferation [11]. It was observed that some immune checkpoint inhibitors, such as anti-PD-1/PD-L1 and anti-CTLA-4 antibodies, have shown efficacy in targeting SLC7A5 in anaplastic thyroid cancer [12]. Arginine deprivation therapies could reduce circulating arginine levels, thereby restricting substrate availability for SLC7A3, and contribute to the suppression of tumour growth in thyroid and breast cancers [13]. Different approaches, such as the design of prodrugs that mimic natural amino acid substrates, nanoparticle-based delivery, and CRISPR genome editing, could enhance their delivery to thyroid cancer cells and thereby inhibit tumour growth [14, 15].

In this review, we addressed emerging features that reveal the oncogenic signalling pathways influenced by SLC7, and identified their roles in thyroid cancer progression. This review identified the novel therapeutic targets and explored innovative strategies to improve their delivery for thyroid cancer treatment. Furthermore, emerging solutions to current challenges also addressed in reducing disease severity. Several clinical trials of SLC7 also discussed improving the treatment outcomes in the clinical management of thyroid cancer.

SLC7: properties, classification and physiological roles

They have a conserved structural framework that defines their role as amino acid transporters [2, 4]. All family members are composed of twelve α-helices with N- and C-terminal oriented towards the cytoplasm. These helices contribute to forming a substrate-binding pore responsible for amino acid transport. Based on this organization, they are classified into two groups. Cationic amino acid transporters (CATs) are comprised of four members from SLC7A1 to SLC7A4 [16]. CATs are monomers that are involved in amino acid transport, including ornithine, arginine, and lysine. Heteromeric amino acid transporters (HATs) comprising members from SLC7A5 to SLC7A11 that are involved in transport of leucine, phenylalanine, tyrosine, histidine, tryptophan, methionine. These transporters required SLC3A2 for proper functioning. SLC7 family members have important roles in amino acid homeostasis, oncogenic signalling pathways, and protein synthesis. **Table 1** summarises the major substrates, transport mode, directionality, subcellular localization, and representative inhibitors with preclinical vs. clinical status of different SLC7 family members [17].

Some structural studies revealed that HAT members exhibit the LeuT-fold arrangement [18]. In this arrangement, the extracellular domain of the heavy chain could stabilize the light chain and facilitate substrate recognition, and mediate the transport of different amino acids across cell membranes [19]. This feature allows interaction of SLC7 to CD98hc via a disulfide bridge. Xia et al. [20] reported that SLC7A5 and SLC7A11 readily form a heteromeric complex with CD98hc, which regulates the immune cell function and cellular homeostasis [20].

SLC7A1 is involved in the development of human cervical cancer through activation of hypoxia-inducible factor 1α (HIF1-α) [21]. SLC7A2 affects the cellular homeostasis in Huntington's disease [22]. The role of SLC7A3 has been observed in patients with thyroid cancers, where it activates the MAPK/ERK and

Table 1. The SLC7 transporters, major substrates, transport mode, directionality, subcellular localization, and representative inhibitors with preclinical and clinical status

SLC7 member	Major Substrates	Transport mechanism	Directionality (conventionally defined)	Subcellular localization	Inhibitors	References
SLC7A1	Arginine, lysine, ornithine	Uniport (Na^+-independent, system y^+)	Influx (depending on gradient)	Plasma membrane (monomeric)	N-ethylmaleimide (Preclinical only)	[16, 21]
SLC7A2	Arginine, lysine, ornithine	Uniport (Na^+-independent, system y^+)	Bidirectional (gradient-driven)	Plasma membrane (monomeric)	Arginine derivatives (Preclinical); N-ethylmaleimide (Preclinical)	[22]
SLC7A3	Arginine, lysine	Uniport (Na^+-independent, system y^+)	Bidirectional (symmetric passive transport)	Plasma membrane (monomeric)	No selective inhibitors reported	[16, 33]
SLC7A5	Leucine, phenylalanine, tyrosine, tryptophan, methionine	Antiport (1:1 exchange, Na^+-independent, system L)	Bidirectional (influx of essential amino acids, efflux of neutral amino acids)	Plasma membrane (heterodimer with SLC3A2)	BCH (Preclinical); Nanvuranlat (JPH203/KYT-0353, phase 1/2 clinical trials for solid tumours)	[26, 58]
SLC7A6	Cationic amino acids (arginine, lysine) and neutral amino acids (glutamine, leucine)	Antiport (Na^+-dependent, system y^+L)	Bidirectional (efflux of cationic amino acids, influx of neutral amino acids)	Plasma membrane (heterodimer with SLC3A2/CD98hc)	No selective inhibitors reported	[27]
SLC7A7	Arginine, lysine, ornithine and neutral AAs	Antiport (Na^+-independent, System y^+L)	Efflux of cationic AAs/influx of neutral AAs	Plasma membrane	No selective inhibitors reported (Preclinical only)	[6, 23]
SLC7A8	Small neutral amino acids (leucine, serine, glutamine)	Antiport (Na^+-independent, system L)	Bidirectional	Plasma membrane (heterodimer with SLC3A2/CD98hc)	BCH (Preclinical only)	[28]
SLC7A9	Cystine, cationic AAs	Antiport (Na^+-independent, system $b^{o,+}$)	Antiport, exchange of neutral and cationic AAs	Apical plasma membrane (heterodimer with SLC3A1/rBAT)	Cystine analogues (Preclinical); No clinical stage inhibitors	[29]
SLC7A10	Small neutral AAs (Serine, alanine, glycine, cystine)	Antiport (Na^+-independent, System ASC)	Bidirectional exchange	Plasma membrane	D-serine analogues (Preclinical only); No clinical stage inhibitors	[30]
SLC7A11	Cystine, glutamate	Antiport (1:1 exchange, Na^+-independent, system xc^-)	Influx of cystine, efflux of glutamate	Plasma membrane (heterodimer with SLC3A2)	Erastin (Preclinical); Sulfasalazine (Clinical, (repurposed)	[31, 71, 73]

PI3K/AKT signalling pathways [7, 23]. Shao et al. [24] investigated that male mice with obesity showed high SLC7A4 expression than control groups [24].

SLC7A5 showed substrate specificity towards leucine, tyrosine, phenylalanine, and its overexpression has been observed in thyroid and breast cancers [25, 26]. SLC7A6 is involved in nitrogen metabolism, and its overexpression was observed in patients with hepatocellular carcinoma [27]. SLC7A8 showed substrate specificity towards leucine, serine, and glutamine, and its overexpression was observed in patients with kidney diseases [28]. SLC7A9 mediates the cystine and ornithine uptake, and mutations in its subunits could contribute to the development of cystinuria [29]. SLC7A10 showed substrate specificity towards serine and glycine and promotes insulin resistance in type 2 diabetes [30]. SLC7A11 overexpression was observed in patients with thyroid cancer. These studies revealed their involvement in several cancers and diseases. However, the mechanism and roles of SLC7 family members in thyroid cancer remain unclear [31].

Mechanism and roles of SLC7 in thyroid cancer

Amino acid transport mechanisms, signalling pathways and TME interaction

Some members of the SLC7 family are involved in the progression of thyroid cancer by activating the different oncogenic signalling pathways, enhancing nutrient supply, and promoting tumour growth and metastasis [32]. The mechanism of amino acid transport and signalling pathways influenced by SLC7 is described in the following section.

Mechanism and role of SLC7A3: SLC7A3 is an important member of the SLC7 family that participates in the sodium-independent transport of arginine, and lysine [33]. It is involved in protein synthesis, nitric oxide production, and cellular metabolism. Elevated SLC7A3 activity influences the amino acid metabolism and plays a crucial role in thyroid cancer progression [34].

The role of SLC7A3 in thyroid cancer is associated with nutrient supply and metabolic changes. Overexpression of SLC7A3 was observed in patients with papillary thyroid cancer [35, 36]. This upregulation enhanced arginine uptake and accelerated the production of polyamines and nitric oxide species, which contribute to DNA damage, metastatic potential, and genomic instability that drive cancer progression. Different polyamines, including spermidine and putrescine, were elevated in thyroid cancer by promoting tumour growth [37]. Excessive production of nitric oxide species promotes angiogenesis through vascular endothelial growth factor (VEGF) signalling, facilitates tumour vascularization, and accelerates progression and metastasis (**Figure 1**). It helps thyroid cancer cells to survive in a nutrient-limited tumour microenvironment [38].

SLC7A3 also contributes to the development of thyroid cancer (**Figure 1**). It was observed that excess supply of amino acid stimulates the binding of transcription factors such as hypoxia-inducible factor 1-alpha (HIF-1α) and myelocytomatosis oncogene (MYC) to the SLC7A3 promoter and enhances its expression [4, 39]. As a result, more amino acids are utilized by thyroid cancer cells that activate the MAPK/ERK and PI3K/AKT signalling pathways. Enhanced SLC7A3-mediated arginine uptake increases substrate availability for nitric oxide production, thereby activating the MAPK/ERK pathway. It stimulated the epithelial-mesenchymal transition (EMT), thereby promoting tumour progression and metastasis [40]. It can activate the mTOR1 signalling and promote cell proliferation. The lipid messengers produced by PI3K can activate AKT, promoting cell survival and inducing resistance to apoptosis [40, 41].

SLC7A3 interacts with the tumour microenvironment and modulates the immune cell activity. Enhanced SLC7A3-mediated arginine uptake suppresses the T-cell activity [42]. It establishes the pro-tumorigenic microenvironment, characterised by tumour-associated macrophages (TAMs) and regulatory T cells (Tregs). TAMs exhibit a polarized (M2-like phenotype) and secrete immunosuppressive cytokines, such as IL-10 and TGF-β, which inhibit the activity of anti-tumour immune cells, including cytotoxic T cells and NK cells. Tregs also secrete IL-35 and IL-10, which further inhibit the anti-tumour immune responses. Therefore, this immunosuppressive effect is recognized as a

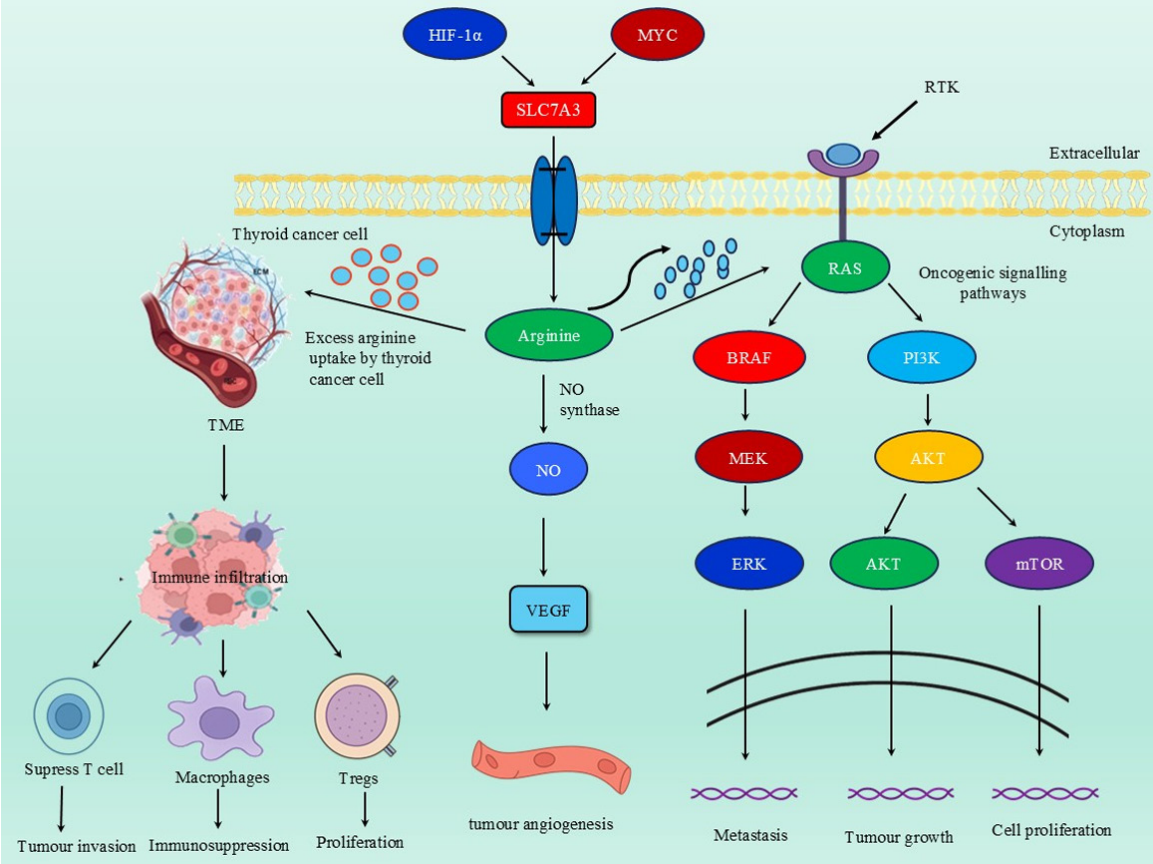

Figure 1. Mechanism and role of SLC7A3 in thyroid cancer. SLC7A3 contributes to thyroid cancer progression by activating oncogenic signalling pathways. The activated MAPK/ERK and PI3K/AKT pathways could stimulate the transcription factors HIF-1α and MYC, which bind to the SLC7A3 promoter, enhancing its expression. This overexpression stimulates arginine transport, accelerates the polyamine and nitric oxide production, and contributes to DNA damage, metastatic potential, and genomic instability that drive cancer progression. The high production of nitric oxide promotes angiogenesis via vascular endothelial growth factor (VEGF) signalling and accelerates metastasis. The enhanced uptake of arginine by thyroid cancer cells depletes extracellular arginine and suppresses T-cell function, establishing a pro-tumorigenic microenvironment characterized by regulatory T cells (Tregs) and tumour-associated macrophages (TAMs). Therefore, this immunosuppressive effect is recognised as a driver in the progression of thyroid cancer.

driver of thyroid cancer progression, as shown in **Figure 1** [16, 43, 44].

It was observed that arginine-deprivation therapies could reduce circulating arginine levels, thereby restricting substrate availability for SLC7A3 [4, 45]. These approaches could reduce arginine uptake and limit polyamine synthesis and nitric oxide production by disrupting tumour growth. Therefore, targeting of SLC7A3 could provide an effective strategy in the management of thyroid cancer [35, 36].

Mechanism and role of SLC7A5: SLC7A5 is another member of the SLC7 family that mediates sodium-independent transport of leucine, phenylalanine, tyrosine, tryptophan, and methionine [46]. SLC7A5 is readily combined with SLC3A2 by forming a heterodimer complex and mediates amino acid transport across the cell membrane. It plays an important role in nucleotide synthesis, redox balance, and protein synthesis. Its elevated activity influences the amino acid metabolism and supports the tumour growth in anaplastic thyroid cancer [47].

SLC7A5 plays an important role in thyroid cancer progression (**Figure 2**). Elevated leucine levels may stimulate MYC binding to the SLC7A5 promoter, thereby enhancing its expression. As a result, more amino acids are utilized by thyroid cancer cells, which activates the mTORC1

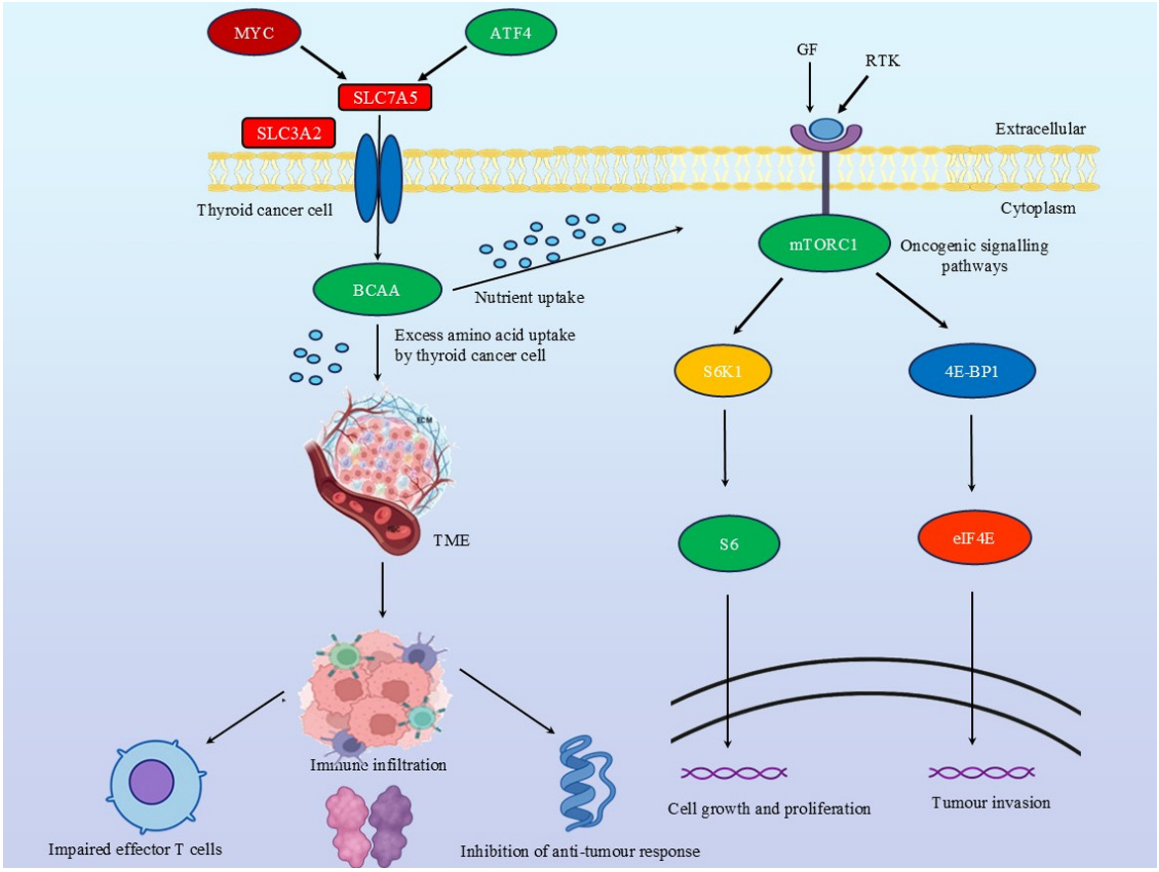

Figure 2. Mechanism and role of SLC7A5 in thyroid cancer. The excess supply of leucine stimulates the binding of MYC with the SLC7A5 promoter could enhance its expression. As a result, more amino acids are utilized by thyroid cancer cells which activates the mTORC1 pathway. Overexpression of the eukaryotic translation initiation factor 4E (eIF4E) was observed in anaplastic thyroid cancer. It promotes the translation of oncogenic mRNAs and contributes to tumour progression. Elevated eIF4E activity promotes EMT by enhancing metastasis and tumour invasion. SLC7A5 contributes to immune invasion within the TME by supporting the tumour metabolism. Thyroid cancer cells with high SLC7A5 expression can compete with immune-infiltrating T cells, such as effector T cells, for tryptophan and leucine. Excess amino acid uptake by thyroid cancer cells can impair T-cell function, cytotoxic activity, and cytokine production due to immune exhaustion. SLC7A5 also activating the mTORC1 signalling, enhancing the release of immunosuppressive cytokines TGF-β and IL-6. The excess release of these cytokines further inhibited anti-tumour responses.

pathway [48, 49]. The eukaryotic translation initiation factor 4E (eIF4E) was overexpressed in anaplastic thyroid cancer. It promoted the translation of oncogenic mRNAs and contributed to tumour progression. Elevated eIF4E activity promotes the epithelial-mesenchymal transition (EMT) by enhancing metastasis and tumour invasion [50].

SLC7A5 also influenced the cell metabolism in thyroid cancer cells. It mediates the uptake of large neutral amino acids and served as substrates for energy production and cellular metabolism. Excess availability of these amino acids could stimulate lipid synthesis and glycolytic flux [51, 52]. Moreover, SLC7A5 mediates the transport of branched-chain amino acids and stimulates glutathione production, helping thyroid cancer cells to survive in an oxidative stress environment [7, 35].

In the tumour microenvironment, SLC7A5 modulates immune cell activity [23, 53]. The elevated activity of SLC7A5 enabled thyroid cancer cells to compete with immune-infiltrating T cells and effector T cells for leucine and other large neutral amino acids uptake, thereby hindering the immune response and promoting the tumour growth [54]. Excessive uptake of these amino acids by thyroid cancer cells could impair T-cell function. Moreover, SLC7A5 also activated the mTORC1 signalling and enhanc-

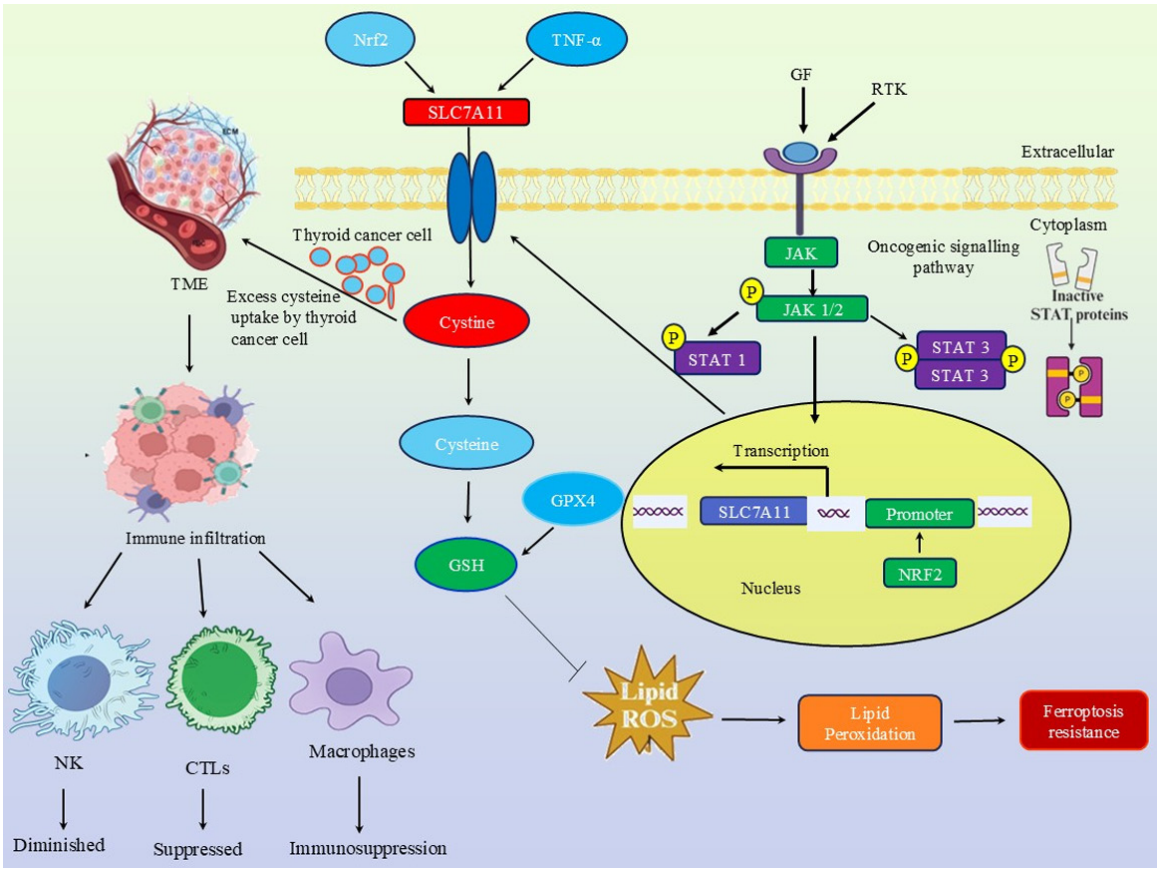

Figure 3. Mechanism and role of SLC7A11 in thyroid cancer. Under oxidative stress conditions, NRF2 is mainly translocated to the nucleus by enhancing the SLC7A11 expression. It also stimulates the cystine uptake by boosting glutathione production. This factor ultimately contributed to the ferroptosis resistance, resulting in the enhanced tumour growth and progression in thyroid cancer. Cytokine-mediated signalling through IL-6 and TNF-α activates the JAK/STAT3 and NF-κB signalling pathways. The metabolic activity of SLC7A11 alters the tumour microenvironment and suppresses the anti-tumour immunity. Excess glutamate release into the extracellular space inhibits the functions of natural killer cells (NK) and cytotoxic T lymphocytes (CTL), thereby reducing immune-mediated tumour clearance. Moreover, a glutamate-rich environment also influenced the macrophages function through immune suppression, tumour progression, and angiogenesis.

ed the release of immunosuppressive cytokines such as TGF-β and IL-6. The release of these cytokines further inhibited anti-tumour responses, as shown in **Figure 2** [55, 56].

SLC7A5 also contributes to the development of therapeutic resistance. SLC7A5 promotes the amino acid influx, enabling the thyroid cancer cells to survive under nutrient deprivation, and induces the resistance to apoptosis [57]. Its upregulation could enhance metabolic resistance, reducing the effectiveness of targeted therapies. Some studies reported that SLC7A5 can be inhibited by novel tyrosine kinase and mTOR inhibitors. Therefore, SLC7A5 targeting with novel inhibitors could represent a novel strategy to overcome resistance [58].

Mechanism and role of SLC7A11: SLC7A11 is another member of the SLC7 family that mediates sodium-independent cystine-glutamate exchange across the plasma membrane [59]. It readily forms a heterodimeric complex with SLC3A2. The light chain of SLC7A11, which contributes to substrate specificity, and the heavy chain of SLC3A2 stabilized it, ensuring proper amino transport across the cell membrane. The expression of SLC7A11 was observed in patients with papillary thyroid cancer, where it influenced the nutrient supply and promoted the tumour progression [60].

SLC7A11 influenced oncogenic signalling pathways in thyroid cancer progression (**Figure 3**). SLC7A11 was upregulated by the nuclear factor

erythroid 2-related factor 2 (NRF2). NRF2 is then translocated to the nucleus by enhancing the SLC7A11 expression [8, 61]. It contributed to ferroptosis resistance and enhanced the tumour growth. Cytokine-mediated signalling through IL-6 and TNF-α could activate the JAK/STAT3 and NF-κB signalling pathways. The activation of oncogenic signals further enhanced SLC7A11 expression by importing cystine in exchange for intracellular glutamate, boosting glutathione production and thereby protecting them from oxidative stress [62].

SLC7A11 also influenced the ferroptosis in thyroid cancer cells. Ferroptosis is a newly identified form of cell death driven by lipid peroxidation. This process is activated in the presence of iron and called ferroptosis [63, 64]. The overexpression of SLC7A11 could import cystine in exchange for intracellular glutamate, and enhance glutathione peroxidase activity (GPX-4), thereby increasing GSH synthesis. These events could eventually suppress the lipid peroxidation and protect the tumour cells from ferroptosis. Therefore, SLC7A11 induced the ferroptosis resistance, enabling thyroid cancer cells to survive under oxidative stress environment (**Figure 3**) [65, 66].

SLC7A11 also interacts with the tumour microenvironment (TME) and influences the immune cell functions. SLC7A11 is a cystine/glutamate antiporter that imports extracellular cystine in exchange for exporting intracellular glutamate, thereby promoting glutathione synthesis and protecting thyroid cancer cells from oxidative stress [67, 68]. The excess release of more nutrients into the extracellular space further inhibits the activities of natural killer cells (NK) and cytotoxic T lymphocytes (CTL). A nutrient-rich environment also influences macrophage function through immune suppression, tumour progression, and angiogenesis, as shown in **Figure 3**. Therefore, SLC7A11 could promotes immunosuppressive TME that protects thyroid cancer cells from immune attack [69].

SLC7 targeting and therapeutic implications for thyroid cancer treatment

Therapeutic roles of SLC7 and targeting approaches

SLC7 are potential therapeutic targets, and targeting them through various approaches could be helpful in the management of thyroid cancer. The mechanism of action and roles of different SLC7 inhibitors are shown in **Figure 4**. JPH203 is an inhibitor of SLC7A5, which is highly expressed in anaplastic thyroid cancer. SLC7A5 facilitates leucine uptake and drives tumour growth by activating the mTOR signalling pathway [47]. JPH203 with an IC_{50} around 1.3 μM, inhibited leucine transport in thyroid cancer cell lines (SW1736, 8505c, Hth104). It also inactivated the mTORC1 activity and inhibited cell proliferation. Moreover, clinical evaluation of JPH203 for SLC7A5 inhibition is limited to solid malignancies. Therefore, its efficacy can be evaluated in different cancers and could serve as a novel targeted therapy [70].

It was observed that SLC7A11 activity could be inhibited by different inhibitors. Sulfasalazine, an inhibitor of SLC7A11, with an IC_{50} value of 0.48 mM in differentiated thyroid cancer cell lines (FTC-133 and TPC-1), causes the depletion of intracellular glutathione [71, 72]. As a result, reactive oxygen species are produced sensitizing the tumour cells to oxidative stress. Erastin is another SLC7A11 that restrict the glutathione production. It also stimulates lipid peroxidation and ferroptosis by suppressing tumour cell survival in thyroid, lung and breast cancers [73].

Different therapeutic approaches have been employed to inhibit SLC7A3 activity. It was observed that arginine deprivation therapies could contribute to the suppression of tumour growth in thyroid and breast cancers. It disrupted the nutrient supply by limiting polyamine and nitric oxide production and inhibiting the tumour growth [42]. These inhibitors have achieved enough success in the treatment of thyroid cancer and solid malignancies. However, these inhibitors have several drawbacks, including limited specificity and off-target effects. These issues can be addressed by combining therapies and drug delivery approaches to enhance their efficacy in thyroid cancer, as discussed in the following sections [74, 75].

Immunotherapeutic roles of SLC7 and targeting approaches

SLC7 also influenced the immune cells activities in the tumour microenvironment. They establish a pro-tumorigenic microenvironment,

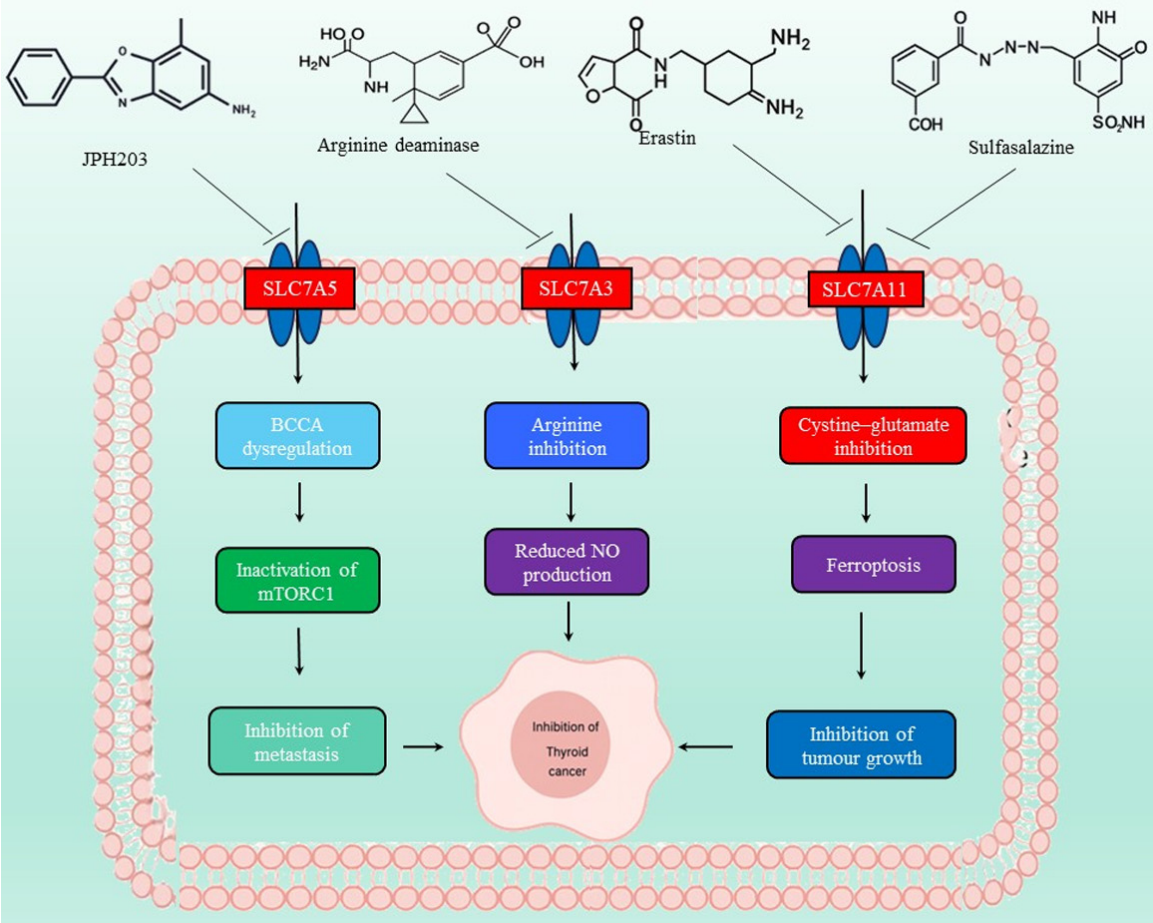

Figure 4. Therapeutic role and strategies of SLC7 targeting in thyroid cancer. JPH203 is a small-molecule inhibitor of SLC7A5 that blocks the transport of leucine in thyroid cancer cells by inactivating the mTORC1 activity. Arginine deaminase can suppress SLC7A3 activity by reducing arginine uptake, limiting polyamine and nitric oxide production, and disrupting tumour growth and cell proliferation. Sulfasalazine and erastin inhibit SLC7A11 by blocking the cystine-glutamate exchange, thereby impairing the antioxidant defence system by inhibiting glutathione production, promoting lipid peroxidation and ferroptosis, and suppressing tumour growth in thyroid cancer cells.

characterized by TAMs and Tregs that secrete immunosuppressive cytokines such as IL-10 and TGF-β, inhibiting the anti-tumour responses. They suppress T-cell activity, inhibit natural killer cell and cytotoxic T lymphocyte activities, and influence the macrophage function through immune suppression and tumour progression [23, 76]. This immunosuppressive environment protects the thyroid cancer cells from the immune attack. Immunotherapy approaches targeting SLC7 are promising avenues for thyroid cancer treatment. These therapies included the immune checkpoint inhibitors, chimeric antigen receptor (CAR)-T cell immunotherapy, cytokine therapies, and monoclonal antibodies [77]. These therapies modulate the SLC7 expression, reducing tumour invasion and improving immune cell function. These therapies have achieved enough success in the treatment of thyroid cancers and solid malignancies [4, 78].

CAR-T cell therapy is a type of immunotherapy in which patient-derived T cells are engineered to express specific receptors for tumour antigens [79]. Modulating the SLC7 expression in CAR-T cells could improve the efficacy of these therapies. CAR-T cells inhibited the SLC7A5 activity, thereby reducing tumour growth. Moreover, CAR-T cells exhibit cytotoxic activity, specifically target thyroid cancer cells, and destroy them effectively [76].

Another approach is the immune checkpoint inhibitors, which influence the activity of immune cells in the tumour microenvironment.

Some immune checkpoint inhibitors such as anti-PD-1/PD-L1, and anti-CTLA-4 antibodies showed efficacy in SLC7A5 targeting in anaplastic thyroid cancer [23, 80]. Immune checkpoint inhibitors work by blocking the interaction between tumour cells and immune checkpoints on T-cells, thereby stimulating the immune system to attack tumour cells more effectively. Therefore, these inhibitors could help to improve the antitumor immunity [12, 81].

Tumour-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) have crucial roles in the immunosuppressive environment [82]. The elevated SLC7A11 activity promotes ferroptosis resistance in thyroid cancer cells. It was observed that SLC7A11 activity could be inhibited by sulfasalazine and sorafenib. These inhibitors induced the ferroptosis in tumour cells. Combining these inhibitors with immune checkpoint inhibitors further inhibits SLC7A11 activity, decreasing the activities of TAMs and MDSCs, reducing immune invasion, enhance the effectiveness of T-cell-mediated immunity, and stimulating T-cell activation. Therefore, activated T cells effectively respond to tumour cells [82, 83].

Strategies for improving the therapeutic delivery of SLC7

Recent studies have shown that SLC7 are promising gateway for targeted drug delivery in the treatment of thyroid cancer. Different approaches, such as the design of novel drugs that mimic natural amino acid substrates, nanoparticle-based delivery, and gene-based interventions, could help for enhancing their delivery in thyroid cancer cells by inhibiting tumour cell growth, as shown in **Figure 5** [84, 85].

The first approach is the development of prodrugs that are selectively recognized and transported effectively to targeted tissues. Conjugation of cytotoxic agents to amino acid-like moieties could facilitate entry into tumour tissues via SLC7A3 and SLC7A5. The development of such drugs could inhibit tumour growth and cell proliferation, improve bioavailability, and ensure activation occurs in the tumour microenvironment. This strategy has several advantages over conventional therapies, as it reduces toxicity while delivering the maximum concentration to the tumour site [4, 86].

Gene-based intervention is another effective approach for improving drug delivery in thyroid cancer. The clustered regularly interspaced short palindromic repeats system (CRISPR/Cas9), and RNA interference are useful for modulating SLC7 expression [87]. These tools help upregulate the SLC7 expression and silence genes that promote tumour growth and cell proliferation in thyroid cancer cells. Targeted silencing of SLC7A11, through CRISPR/Cas9 gene editing or siRNA-mediated knockdown, has been shown to reduce cystine uptake in thyroid cancer cells, thereby weaken the antioxidant system and making tumour cells more vulnerable to oxidative stress. Therefore, such genetic modifications could improve the drug delivery and therapeutic response [88].

Another approach is the design of nanoparticle-based delivery systems [89]. Liposomes coated with amino acid ligands and transporter-targeted peptides enhance their binding to SLC7A5, and SLC7A11 could promote the efficient delivery of CRISPR constructs and chemotherapeutics. This strategy enables the co-delivery of multiple therapeutic agents into thyroid cancer cells while reducing off-target effects. For example, combinations of redox modulators and chemotherapy stimulate their accumulation in tumour tissues by disrupting glutathione production, and sensitizing tumour cells to oxidative stress [90, 91].

Theranostics is another advanced technology that integrates therapy and diagnostic imaging into a single platform to assess thyroid cancer progression and drug delivery treatment [92]. Radiolabelled amino acid analogues showed binding to SLC7A5. These analogues selectively entered tumour tissues, thus enabling tumour visualization. Using this technique, cytotoxic nucleotides can be delivered to thyroid malignant tissues. This dual function could help monitor therapeutic response and enhance treatment precision [36, 93].

Clinical trials in SLC7

Several trials are recruiting to investigate the role of SLC7, monitor patient response to therapy, improve treatment outcomes, and assess clinical relevance [94, 95]. The clinical trial NCT00062348 was conducted by the European Centre of Cancer that utilized the sodium borocaptate and boronophenylalanine fructose

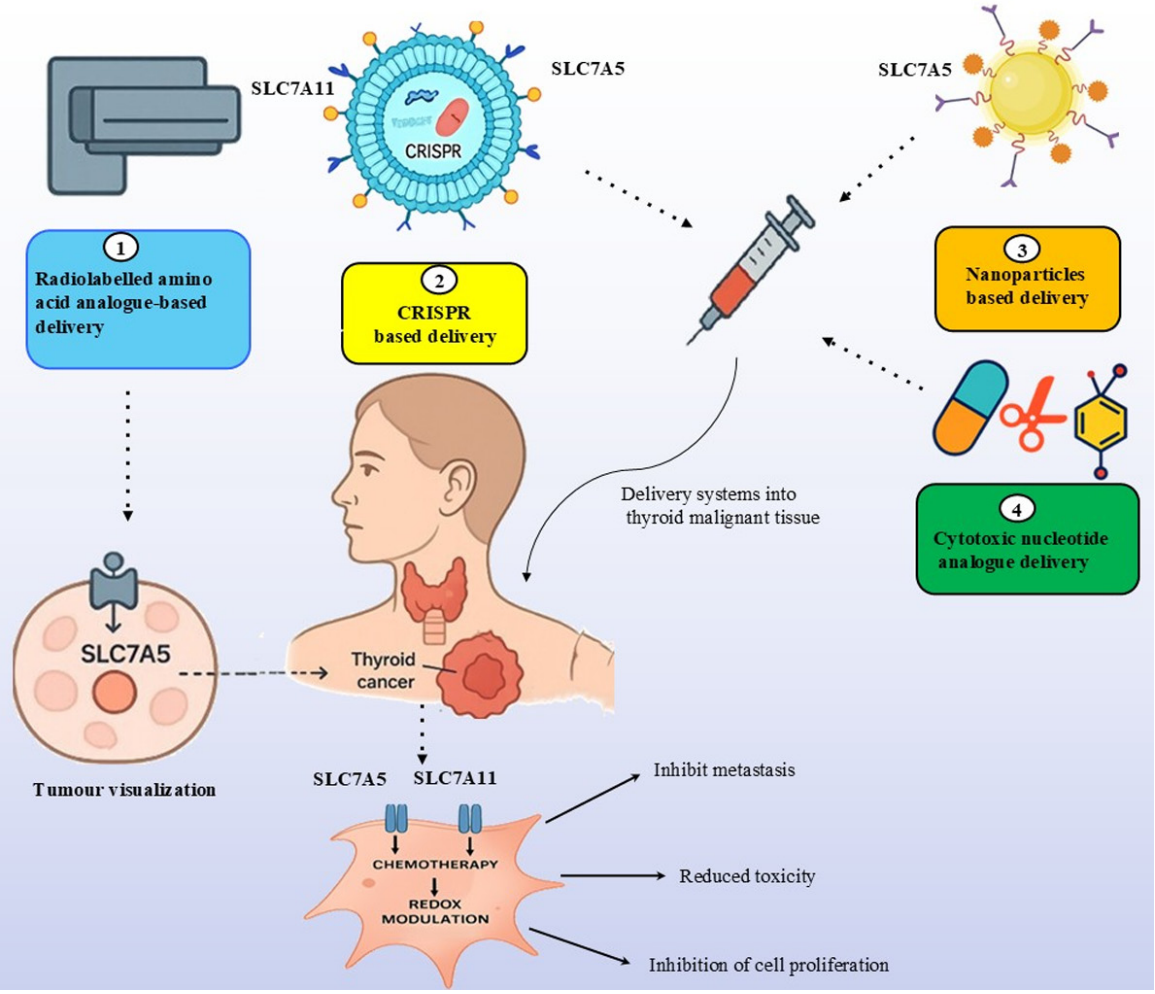

Figure 5. Strategies for improving the therapeutic delivery of SLC7 into thyroid cancer cells. (1) The radiolabelled amino acid analogues that selectively enter the thyroid cancer cells and enable the tumour visualization. (2) CRISPR technology is employed for the regulation of SLC7 expression and silencing the genes that promote tumour growth and proliferation. (3) Nanoparticles are coated with amino acid ligands to improve the targeted delivery of chemotherapeutics. (4) Cytotoxic nucleotides are delivered into the thyroid malignant tissues for monitoring the therapeutic response and enhancing the treatment precision. Overall, these approaches help improve targeted drug delivery to cells by inhibiting tumour growth, metastasis, and cell proliferation.

complex in the diagnosis of solid malignancies. The presence of these compounds in tumour tissues aiding to monitor the disease severity. Another trial, NCT01830504, was conducted to investigate the effects of BKM120 in patients with thyroid cancer. The findings of this trial revealed that BKM120 inhibited the PI3K activity by modulating SLC7 expression and offered therapeutic benefits in thyroid cancer management. The trial NCT06791005 showed carbon nanoparticles delivered via SLC7A5 could be helpful for diagnostic imaging in thyroid cancer patients. The clinical trial NCT04670068 was conducted by the Lineberger Cancer Centre to design the novel autologous CAR-T cells for cancer immunotherapy. This trial revealed that CAR-T cells could target the B7-H3 antigen, showing potential for treating solid malignancies. Another trial, NCT03264456, was conducted by the University of Alabama to evaluate the efficacy of 18F-FSPG. This trial revealed the behaviour of proliferating cells by inhibiting the SLC7A11 expression.

Current challenges and future implications to SLC7 in thyroid cancer management

Despite the physiological and therapeutic significance of SLC7, several challenges still exist that limit its translational application in thyroid

cancer management. Firstly, heterogeneity in expression patterns across thyroid cancer subtypes complicates clinical data interpretation [4, 96]. The upregulation of SLC7A5 was observed in the anaplastic thyroid cancer, but its expression remains variable in differentiated thyroid cancer, making it more difficult to establish a more standard diagnostic platform. Multi-omics approaches, such as integrating transcriptomic and proteomic data, could help identify more suitable biomarkers for specific thyroid cancer subtypes. Moreover, machine learning models can be used to explore molecular expression signatures for each subtype [36, 97].

Other challenges included the development of therapeutic resistance and limited drug selectivity [98]. SLC7A11 plays an important role in ferroptosis resistance via cystine-glutamate exchange, thereby limiting the clinical efficacy of redox-targeted therapies. Combining immunotherapies could overcome ferroptosis resistance by targeting of SLC7A11 and resensitizing the tumour cells to checkpoint inhibitors, including anti-PD-1/PD-L1 and anti-CTLA-4 antibodies. These approaches could help stimulate the immune system to attack thyroid cancer cells [68, 99].

Several therapeutic agents are used to inhibit SLC7A11 activity. However, off-target toxicity issues still exist, highlighting the need for more selective, safe, and effective therapeutic strategies. Moreover, targeting SLC7A5 and SLC7A11 with available small-molecule inhibitors may encounter selectivity issues that remain a barrier to clinical treatment [100]. These issues can be overcome by designing selective inhibitors and targeted delivery systems. Nanoparticle delivery system that enables efficient delivery into tumour tissues while minimising off-target toxicity. Moreover, the development of a prodrug is currently under clinical investigation to exploit the LAT-1 mediated delivery in solid tumours and could be extended to thyroid cancer [26, 101].

The lack of metabolic network data obtained through traditional methods is another hurdle in exploration of SLC7 as a robust diagnostic biomarkers [4, 102]. Integrated approaches combining transcriptomics, metabolomics, and genomics reveal the metabolic network associated with SLC7 data in thyroid cancer and solid malignancies. These approaches are helpful to identify tumour subtypes and biomarkers, thereby enabling therapeutic interventions [103, 104].

Most thyroid cancer studies are limited to cancer cell lines and animal models and fail to explore the complex tumour microenvironment [105]. For example, SLC7A11 can exacerbate oxidative stress and exhibit antitumor effects in mouse xenograft models, but clinical validation in thyroid cancer patients remains lacking. Clinical trials and cohort studies are limited in their ability to show a correlation between SLC7 family members and survival outcomes. In future, prospective studies are needed to validate therapeutic agents in thyroid cancer treatment [106, 107].

Conclusion

This review explored the emerging roles of SLC7 family members, the molecular mechanisms by which they influence thyroid cancer development, highlighted current challenges, and innovative strategies for targeting them as a promising avenue in thyroid cancer treatment. They are involved in amino acid metabolism, tumour growth, and immune cell function. However, dysregulated amino acid metabolism was observed in thyroid cancer, leading to activation of oncogenic signalling pathways, stimulating cell proliferation, and conferring resistance to ferroptosis. The heterodimeric complex formed by SLC3A2 with SLC7A5 and SLC7A11 could enhance amino acid uptake in thyroid cancer cells, promoting tumour growth. They are used as promising therapeutic agents, and targeting them through the design of immune checkpoint inhibitors, engineered CAR-T cells, and CRISPR-edited cells could represent promising strategies in clinical oncology. These approaches may target SLC7 and inhibit their activity by disrupting the nutrient supply to thyroid cancer cells. Further research is needed to explore their mechanisms of regulation, their interactions in the tumour microenvironment across different cancers, and to develop new therapeutic approaches to improve cancer patient outcomes.

Acknowledgements

This work was supported by the grants from the Shenzhen Science and Technology Program (JCYJ20240813144032042).

Disclosure of conflict of interest

None.

Abbreviations

SLC7, solute carrier 7 family; PI3K/AKT, phosphatidylinositol 3-kinase; IL-6, Interleukin 6; JPH203, LAT1 inhibitor; PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein 1; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; HIF-1α, hypoxia-inducible factor 1-alpha; MYC, myelocytomatosis oncogene; TAMs, tumour associated macrophages; Tregs, regulatory T-cells; GPX-4, glutathione peroxidase 4; CAR-T, chimeric antigen receptor; TGF-β, Transforming growth factor beta; CD98hc, cluster of differentiation 98 heavy chain; mTORC1, mammalian target of rapamycin complex 1; NRF2, nuclear factor erythroid 2-related factor 2; MAPK/ERK, mitogen-activated protein kinase/extracellular signal-regulated kinase; JAK/STAT3, Janus kinase-signal transducer and activator of transcription.

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