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REVIEW ARTICLE

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Amino acid transporters as emerging therapeutic targets in cancer

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Abstract

Amino acids are indispensable nutrients for both normal and cancer cells. Cancer cells are unable to synthesize essential amino acids as well as some non-essential amino acids adequately to support rapid proliferation, and must take up amino acids from the surroundings. To meet the increased demand for the amino acid needed for proliferation, high levels of amino acid transporters are expressed on the surface of cancer cells. Cancer cells utilize amino acids to synthesize proteins and nucleotides, as well as to obtain energy. In addition, amino acids are known to play pathological roles in cancer cells. Interestingly, breast cancer cells limit the use of amino acids for cell proliferation based on amino acid availability, which depends on estrogen receptor status. Here, we present a summarized literature review of novel amino acid functions in cancer cells. This review organizes the available knowledge on 2 amino acid transporters, SLC7A5 and SLC7A11, which are considered essential for breast cancer cell growth in a cell-dependent manner. In particular, we propose the glutamine recycling model to clarify the mechanism underlying aberrant SLC7A5 activation. Finally, we overview the pathological significances of SLC7A5 and SLC7A11 in cancer tissues.

KEYWORDS
amino acid transporter, breast cancer, cell proliferation, cystine uptake, leucine uptake

1 | INTRODUCTION

Metabolic reprogramming, which is a hallmark of cancer, enables cancer cells to continue growing under severe environmental conditions, such as those involving a lack of nutrients.[1] One aspect of metabolic reprogramming observed in cancer cells is deregulated amino acid uptake. Amino acids are indispensable nutrients for both normal and cancer cells. Cancer cells use amino acids to synthesize proteins and nucleotides, as well as to obtain energy.[2] Interestingly, recent studies have revealed that some amino acids are specifically used to promote cancer cell growth. Therefore, the biological role of amino acids may vary unexpectedly in a tumor-specific or oncogene-dependent manner. Therefore, amino acids that exhibit tumor- or oncogene-dependent functions have attracted attention as therapeutic targets.

Essential amino acids are taken in from extracellular sources. Therefore, amino acid transporters in tumor cells are frequently found to be aberrantly expressed. Overexpression of amino acid transporters in breast cancer tissues is strongly associated with amino acid dependency.

Here, we review the current understanding of newly discovered biological characteristics of amino acids in cancer cells. Furthermore,

Abbreviations: ARE, Antioxidant response element; CASTOR1/2, Cellular arginine sensor for mTORC1; ER, Estrogen receptor; GATOR2, GAP activity toward Rag GTPases2; KEAP1, Kelch-like ECH-associated protein 1; LAT1, L-type amino acid transporter 1; L-DOPA, L-3,4-dihydroxyphenylalanine; LLGL2, Lethal giant larvae; mTORC1, Mechanistic targets of rapamycin complex 1; SNARE, Soluble NSF attachment protein receptor.

we summarize the role played by amino acid transporters, SLC7A5 and SLC7A11, in breast cancer cell growth. We briefly explain the new systemic flow "glutamine recycling" model to clarify the aberrant activation of SLC7A5 in addition to the reported SLC7A11 activation model. Finally, we present an overview of the pathological roles played by SLC7A5 and SLC7A11 in other cancer tissues.

2 | THE PATHOLOGICAL ROLES OF AMINO ACID IN CANCER

Diversity in amino acid metabolism among tumors has been observed at the same time in various cancers. Recent studies have shown that some amino acids are preferentially used by cancer cells to promote cellular growth or metastasis. For instance, pancreatic cancer cells, in which alanine functions as a carbon source, utilize autophagic alanine secretion from stellate cells to promote pancreatic tumor growth.[3] Leucine depletion from culture media reportedly induced apoptosis in RAS-MEK-activated melanoma cells.[4] Restriction of dietary methionine significantly improved the therapeutic response in KRAS-mutated colorectal cancer cells.[5] Asparagine was indispensable for forming metastases in metastatic triple-negative breast cancer cell models.[6] These reports suggested that amino acids exert a cell–context-dependent effect to regulate cell proliferation or metastasis in cancer cells. However, the molecular mechanisms underlying the regulation of cancer cell growth by amino acids remain unclear.

3 | AMINO ACIDS DIRECTLY AFFECT PROTEIN FUNCTION AS AN EFFECTOR MOLECULE

Amino acid-derived metabolites exhibit numerous tumorigenic functions. However, regulation of cell proliferation or metastasis in cancer cells by amino acid-derived metabolites is beyond the scope of this review. Instead, we focus on the functions of amino acids as effector molecules.

Leucine, arginine, and cysteine, in particular, modulate the activities of mTORC1, which is a master regulator that responds to environmental inputs such as nutrients. Leucine, arginine, and cysteine bind directly to amino acid sensor proteins. These sensor proteins control mTORC1 activity to regulate cell growth.[7] Sestrin2 is a cytosolic leucine sensor, while CASTOR1/2 is a cytosolic arginine sensor. Intracellular leucine binds to Sestrin2, a negative regulator of mTORC1, and dissociates Sestrin2 from GATOR2, a positive regulator of mTORC1 activity (Figure 1A).[8] The CASTOR1/2 protein binds to GATOR2 under arginine-deprived conditions. Arginine binding to CASTOR disrupts the interaction between CASTOR and GATOR2, resulting in the activation of mTORC1 (Figure 1B).[9]

Furthermore, cysteine is sensed by EglN1 (also known as PHD), which regulates the accumulation of the HIF transcription factor. Decreased intracellular cysteine levels inactivate EglN1, resulting in the stabilization of HIF-1 α.[10] Therefore, intracellular amino acids function as effector molecules that modulate growth signals in cancer cells.

4 | PATHOLOGICAL ROLES OF AMINO ACID IN BREAST CANCER

Amino acids in cancer cells may function in a tissue-dependent or oncogene-dependent manner. Next, we outline amino acid utilization in breast cancer cells. Breast cancer is characterized based on the aberrant gene expression status of ER, progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2).[11] Based on gene expression patterns, breast cancer is roughly classified into 3 subclasses: ER-positive (corresponding to luminal type); HER2-positive; and basal (also known as triple-negative type or ER-negative) breast cancer. In breast cancer cells, the amount of amino acids required for cell proliferation differs according to ER status. ER+ breast cancer cells require leucine for growth, whereas ER-negative (ER−) breast cancer cells require cystine. However, there have been no reports on the amino acid requirements for cell proliferation in HER2-positive breast cancer cells.

The key amino acids involved in breast cancer cell proliferation are leucine and cystine. ER+ breast cancer cells use leucine, whereas ER− breast cancer cells need cystine for growth. These 2 amino acids are taken in from the extracellular environment by amino acid transporters. The amino acid transporter SLC7A5 (LAT1) plays a central role in leucine uptake by ER+ breast cancer cells, while SLC7A11 (also known as xCT and system X_c^-) is used for cystine uptake in ER− breast cancer cells. Both SLC7A5 and SLC7A11 are members of the heteromeric amino acid transporter group. In the following section, we summarize the characteristics of these 2 transporters with particular reference to the

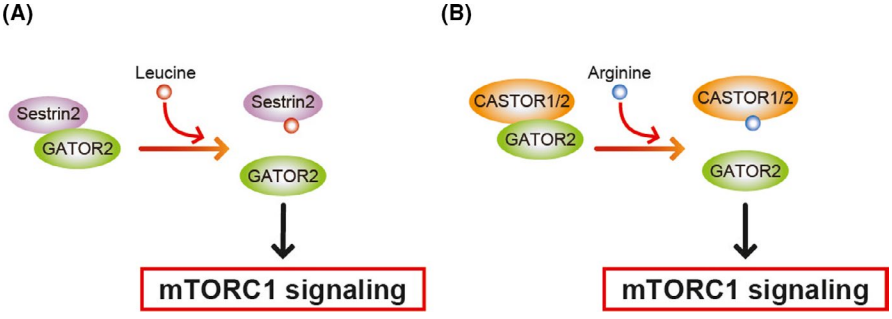

FIGURE 1 Schematic of mTORC1 regulation by amino acids. A, Leucine-binding to Sestrin2 causes dissociation of GATOR2 from Sestrin2. B, Arginine binding to CASTOR leads to disruption of the CASTOR/GATOR2 interaction, leading to the activation of mTORC1 signaling

involvement of these in therapeutic developments in breast and other tumor cells.

5 | SLC7A5 IN BREAST CANCER CELLS

SLC7A5 is a bidirectional amino acid transporter that localizes at the plasma membrane (Figure 2). Phenylalanine, tryptophan, leucine, tyrosine, valine, histidine, methionine, isoleucine, and L-DOPA are substrates of SLC7A5.[12] SLC7A5 functions together with SLC3A2 (also known as 4F2hc or CD98hc), as a heterodimeric complex at the plasma membrane. Notably, complex formation with SLC3A2 is indispensable for the transport activity and substrate specificity of SLC7A5.[13,14] Structural analysis indicated that SLC7A5, which contains 12 transmembrane domains, interacts with SLC3A2 through a disulfide bond and hydrophobic interaction at their protein surface.[14,15]

SLC7A5 is an antiporter that exports intracellular glutamine to facilitate uptake of its substrate leucine. The growth of ER+ breast cancer cells depends highly on intracellular leucine and SLC7A5, as mentioned below. Therefore, intracellular glutamine must be aberrantly excreted from the cell to allow leucine-dependent cell proliferation to take place in ER+ breast cancer cells. Curiously, the SLC7A5/SLC3A2 heterodimeric complex contains SLC1A5, a glutamine transporter that regulates glutamine uptake into cells.[16,17] Overexpression of SLC1A5 is frequently observed in breast cancer tissues. Therefore, we believe that "glutamine recycling" between SLC7A5 and SLC1A5, enables aberrant leucine uptake into ER+ breast cancer cells (Figure 2).

SLC7A5 functions at the plasma membrane in cancer cells. Membrane localization of SLC7A5 is modulated by the polarity protein LLGL2 (mammalian orthologue *lgl*, *lethal giant larvae*), and the trafficking protein YKT6, a SNARE protein. Briefly, LLGL2 shuttles SLC7A5 from the cytosol to the plasma membrane, whereupon the LLGL2-SLC7A5 complex interacts with YKT6 at the plasma membrane, resulting in the translocation of SLC7A5 to the plasma membrane.

The cellular surface protein level of SLC7A5 is higher in ER+ breast cancer cells compared with that in ER− breast cancer cells. In addition, treatment with a low dose of leucine/glutamine culture medium or a SLC7A5 inhibitor suppresses cell proliferation in ER+ breast cancer cells, whereas this treatment does not affect cell proliferation in ER− breast cancer cells. These results indicated that, although ER+ breast cancer cells rely on leucine uptake by SLC7A5 to proliferate, ER− breast cancer cell growth is less affected by leucine uptake by SLC7A5.[18] LLGL2 and SLC7A5 are direct transcriptional targets of the ER in ER+ breast cancer cells.[19] Furthermore, SLC7A5 expression is a marker of the Mammostat test that predicts clinical outcomes for ER+ breast cancer patients.[20] Considering that ER+ breast cancer cells depend significantly on leucine uptake to grow, the LLGL2-SLC7A5 pathway plays an important role in the growth of ER+ breast cancer cells, and therefore SLC7A5 presents a potential target for cancer therapy in ER+ breast cancer.

6 | SLC7A5 IN CANCER TISSUES

The pathological relevance of SLC7A5 to tumorigenesis is not restricted to ER+ breast cancer cells. Overexpression of SLC7A5 is broadly observed in many cancer tissues, and high SLC7A5 mRNA expression levels are known to be correlated with poor clinical prognoses for ER+ breast cancer, as well as a variety of other cancer types (Table 1). Therefore, inhibitors targeting SLC7A5 in these cancer cells are extensively evaluated for the purpose of

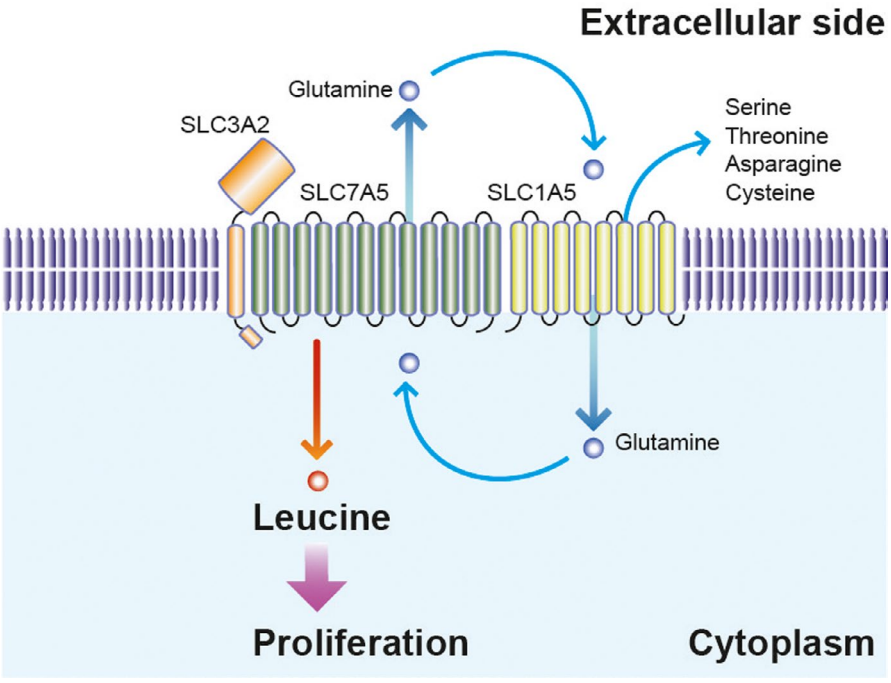

FIGURE 2 Schematic of amino acid flux by SLC7A5/SLC3A2 in ER+ breast cancer cells. The bidirectional amino acid transporter, SLC7A5, interacts with SLC3A2 and SLC1A5 on the plasma membrane. In ER+ breast cancer cells, leucine uptake by SLC7A5 accelerates cell proliferation. The glutamine cycle model supports the view that high consumption of glutamine, due to the activation of SLC7A5, is retrieved by SLC1A5

TABLE 1 Summary of SLC7A5 involvement in cancer tissues

Tissue	Type of cancer cells	SLC7A5 inhibitors used in	Patient data (IHC or K-M plot)	Relationship to therapeutic resistance	References
Breast	Estrogen receptor (ER)-positive breast cancer	BCH, JPH203	Yes	Yes	[16]
	Luminal type of breast cancer	-	Yes	Yes	[29]
	Luminal type of breast cancer	-	Yes	-	[30]
	Endocrine therapy-treated patients	-	Yes	Yes	[31]
Lung	NSCLC	-	Yes	-	[32]
	NSCLC	BCH	-	-	[33]
Prostate	Prostate cancer	-	Yes	Yes	[34]
Biliary tract	Cholangiocarcinoma	BCH	Yes	-	[35]
	Cholangiocarcinoma	JPH203	-	-	[36]
	Biliary tract cancer	-	Yes	-	[37]
Gastrointestinal cells	Gastric cancer cell line/colon cancer cell line	JPH203	-	-	[38]
	Gastric cancer cell line	Knockdown	Yes	-	[39]
	Esophageal squamous cell carcinoma	-	Yes	-	[40]
Colon	KRAS-mutant CRC	-	-	-	[41]
Pancreas	Pancreatic ductal adenocarcinoma	-	Yes	-	[42]
	Pancreatic ductal adenocarcinoma	-	Yes	Yes	[43]
	Pancreatic ductal adenocarcinoma	-	Yes	-	[44]
Skin	Basal cell carcinoma	-	Yes	-	[45]
	Melanoma	-	Yes	-	[46]
Ovary	Ovarian cancer	-	Yes	Yes	[47]
	Ovarian cancer	BCH	-	-	[48]
Uterine	Endometrioid carcinoma	-	Yes	Yes	[49]
	Endometrioid carcinoma	BCH	Yes	-	[50]
Thyroid	Anaplastic thyroid cancer	JPH203	Yes	-	[51]
	Anaplastic thyroid cancer	JPH203	Yes	-	[52]
	Papillary thyroid cancer	-	Yes	-	[53]
Liver	hepatocellular carcinoma	-	Yes	-	[54]
Neuroendocrine tissue	Pheochromocytoma/medullary thyroid carcinoma	-	Yes	-	[55]
	Medulloblastoma	JPH203	-	-	[56]
Blood	T-cell acute lymphoblastic leukemia/T-cell lymphoblastic lymphoma	BCH, JPH203	Yes	-	[57]
Kidney	Renal cell carcinoma	JPH203	Yes	-	[58]
Bone	Rhabdomyosarcoma, synovial sarcoma, Ewing sarcoma, epithelioid sarcoma, and angiosarcoma	-	Yes	-	[59]
Brain	Glioma	BCH	Yes	-	[60]
Bladder	Bladder cancer	JPH203	Yes	-	[61]
Head and neck	Oral cancer	BCH, JPH203	-		[62]

clinical application. The efficacies of the SLC7A5 inhibitors, BCH and JPH203, in cancer cells are listed (Table 1). Inhibition of SLC7A5 by BCH or JPH203 suppresses the growth of breast and other cancer cell types (Table 1). Interestingly, high SLC7A5 expression levels are associated with therapeutic resistance in breast, prostate, pancreas, ovary, and uterine cancer cells, suggesting that SLC7A5 inhibitors may be valuable as therapeutic agents for cancer even against some drug-resistant tumors (Table 1).

7 | SLC7A11 IN BREAST CANCER CELLS

SLC7A11 is a bidirectional amino acid transporter. SLC7A11 localizes to the plasma membrane and mediates cystine uptake with a simultaneous efflux of glutamate (Figure 3). In addition, cystathionine was identified as a novel substrate of SLC7A11.[21] Glutamine auxotroph analysis in breast cancer cells revealed that inhibition of SLC7A11 suppressed cell proliferation, while cystine depletion in culture medium attenuated cell proliferation in ER− breast cancer cells. Furthermore, the expression levels of SLC7A11 mRNA and the cystine consumption were higher in ER− breast cancer cells compared with in ER+ breast cancer cells,[22] suggesting that cystine is specifically required for the proliferation of ER− breast cancer cells.

Structural analyses have indicated that SLC7A11 contains 12 transmembrane domains and binds to SLC3A2 by disulfide bonding and hydrophobic interactions at the protein surface (Figure 3).[23] Although the membrane trafficking mechanism underlying SLC7A11 function remains unresolved, membrane localization of SLC7A11 is reportedly stabilized by association with the CD44 variant, CD44v, and mucin 1 (MUC1) in ER− breast cancer cells.[24]

With regard to the cystine/glutamate antiporter, SLC7A11, intracellular glutamate is needed for cystine uptake. Glutamine catabolism supports glutamate supplementation of continuous cystine transport in ER− breast cancer cells. ER− breast cancer cells express high levels of the glutamine transporter, SLC1A5, and glutaminase, leading to upregulated glutamine metabolism.[22,25,26] ER− breast cancer cells uptake glutamine via SLC1A5. Intracellular glutamine is catabolized to glutamate by glutaminase. Then, increased intracellular glutamate accelerates cystine uptake into cells, leading to aberrant proliferation of ER− breast cancer cells (Figure 3).

Intriguingly, SLC7A11 expression in ER− breast cancer cells is regulated by oxidative stress.[27,28] Oxidative stress induces the dissociation of NRF2, an antioxidant transcription factor, from KEAP1, an E3 ubiquitin ligase adaptor that triggers the protein degradation of NRF2. The accumulated NRF2 translocates to the nucleus and binds to the ARE in the promoter of its target *SLC7A11*.

8 | SLC7A11 IN CANCER TISSUES

Overexpression of SLC7A11 has been reported in many cancer tissues, while high expression levels of SLC7A11 mRNA have been found to be associated with poor clinical prognoses in various forms of cancer (Table 2). Interestingly, SLC7A11 overexpression is associated with the acquisition of chemoresistance in small-cell lung cancer and prostate cancer cells (Table 2).

Sulfasalazine (SASP) and erastin inhibit the transport activity of SLC7A11. The tumor-suppressive effect of SASP and erastin in various types of cancer cells is summarized (Table 2). Overall, inhibition of SLC7A11 induces a non-apoptotic form of cell death termed ferroptosis in cancer cells, suggesting that SLC7A11 may be an attractive target in some cancer tissues.

9 | CONCLUSION

We presented a summarized view of the effect exerted by the overexpression of amino acid transporters, SLC7A5 and SLC7A11, on

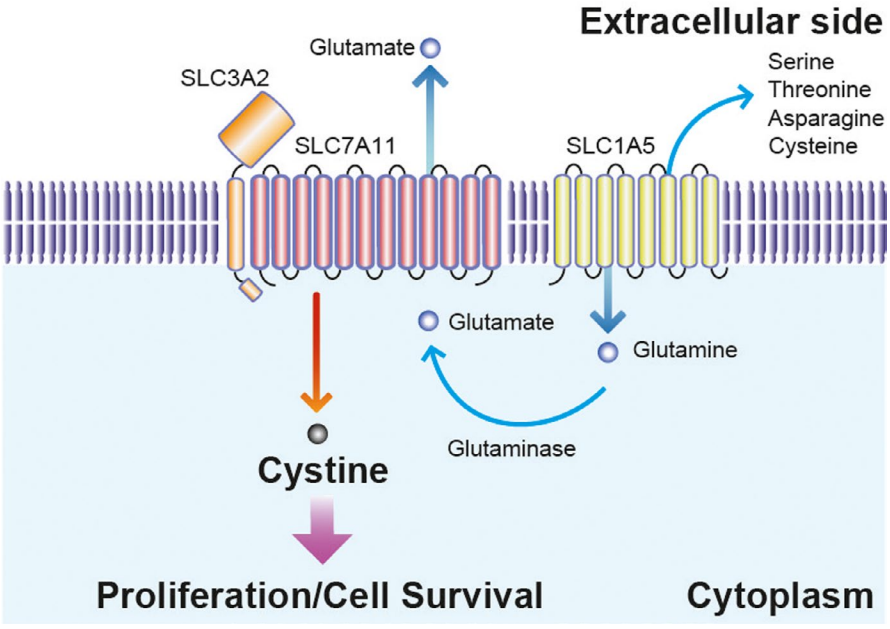

FIGURE 3 Schematic of amino acid flux by SLC7A11/SLC3A2 in ER− breast cancer cells. The bidirectional amino acid transporter, SLC7A11, interacts with SLC3A2 on the plasma membrane. In ER− breast cancer cells, cystine uptake by SLC7A11 is required for cell proliferation. Highly activated cystine uptake requires glutamate consumption to activate SLC7A11. Glutamine taken in by SLC1A5 is catabolized to glutamate by glutaminase, resulting in the activation of SLC7A11 in ER− breast cancer cells

TABLE 2 Summary of SLC7A11 involvement in cancer tissues

Tissue	Type of cells	SLC7A11 inhibitors used	Patient data (IHC or K-M plot)	Relationship to therapeutic resistance	References
Breast	Basal type of breast cancer	SASP	Yes	-	[22]
Esophagus	Squamous cell carcinoma	SASP	-	-	[63]
Colon	Colorectal cancer	SASP	Yes	-	[64]
Lung	Non–small-cell lung cancer (NSCLC)	SASP	Yes	-	[65]
	KRAS-mutant lung adenocarcinoma	SASP	Yes	-	[66]
	Small-cell lung cancer	SASP	Yes	Yes	[67]
Prostate	Advanced prostate cancer	Erastine	Yes	Yes	[68]
Pancreas	Pancreatic ductal adenocarcinoma	Erastine	-	-	[69]
Liver	Hepatocellular carcinoma	SASP	Yes	-	[70]
	Hepatocellular carcinoma	-	Yes	-	[71]
Head and Neck	Squamous cell carcinoma	SASP	Yes	-	[72]
	Oral cavity squamous cell carcinoma	-	Yes	-	[73]
Brain	Glioblastoma	-	-		[74]
	Glucose-depleted glioma cells	SASP	-	-	[75]
Blood	Multiple myeloma	-	Yes	-	[76]
	Lymphoma	SASP	-	-	[77]
Thyroid	Papillary thyroid carcinoma	-	Yes	-	[53]

many cancer tissues. These 2 contributed significantly to the proliferation of breast cancer cells, depending on ER status. However, overexpression of both SLC7A5 and SLC7A11 has also been reported in non–small-cell lung cancer, pancreatic cancer, hepatocellular carcinoma, and esophageal cancer. Therefore, further investigations may be needed to better comprehend the pathological significance of amino acid transporters and amino acid usage in these tumors.

ER– breast cancer cells overexpress both SLC7A5 and SLC7A11. The cell surface levels of SLC7A5 are lower in ER– breast cancer cells, thereby minimizing the effect of SLC7A5 on the growth of ER– breast cancer cells. Therefore, the molecular basis of complex formation between SLC7A5 and SLC3A2 or between SLC7A11 and SLC3A2 may help to better understand the preferential role played by SLC7A11 in ER– breast cancer cells.

Finally, an understanding of the mechanism underlying the trafficking of SLC7A5/SLC3A2 and SLC7A11/SLC3A2 to the plasma membrane may enhance the knowledge needed to develop transporter-targeting therapies in breast cancers.

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DISCLOSURE

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