

# Physiological and Pathophysiological Roles of Ion Transporter-Mediated Metabolism in the Thyroid Gland and in Thyroid Cancer

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**Abstract:** Thyroid cancer is the most common type of endocrine tumor and has shown an increasing annual incidence, especially among women. Patients with thyroid cancer have a good prognosis, with a high five-year survival rate; however, the recurrence rate and disease status of thyroid cancer remain a burden for patients, which compels us to further elucidate the pathogenesis of this disease. Recently, ion transporters have gradually become a hot topic in the field of thyroid gland biology and cancer research. Additionally, alterations in the metabolic state of tumor cells and protein molecules have gradually become the focus of scientific research. This review focuses on the progress in understanding the physiological and pathophysiological roles of ion transporter-mediated metabolism in both the thyroid gland and thyroid cancer. We also hope to shed light on new targets for the treatment and prognosis of thyroid cancer.

**Keywords:** thyroid cancer, metabolism, ion transporters, physiology and pathophysiology, regulation factors

## Introduction

Globally, the incidence of thyroid cancer (TC) is increasing annually according to the latest global statistics on the epidemiology of this malignancy published by the International Agency for Research on Cancer. TC ranks ninth among malignancies, killing more than 40,000 people annually, most of whom are women.<sup>1</sup> Therefore, clarification of its etiology and pathogenesis is important for identifying effective therapeutic targets for early diagnosis and prevention.

It is well known an adequate energy supply is required for the growth and survival of cells, including tumor cells, which provides a good entry point for tumor research. The metabolic status of tumor cells has been studied for nearly a hundred years, and as research has progressed, researchers have found that metabolic reprogramming is ubiquitous among tumor cells.<sup>2-4</sup> Healthy cells use carbohydrates, fats, amino acids, and other substances to produce energy in the form of adenosine triphosphate (ATP) as well as biomacromolecules to maintain normal cell function. This complex process involves glycolysis, oxidative phosphorylation (OXPHOS), gluconeogenesis, and the tricarboxylic acid (TCA) cycle and requires a stable internal environment and an adequate oxygen supply within the cell. For tumor cells, with their high metabolic needs and proliferative activities, the above processes are adjusted accordingly, which means they need rapid ATP production to

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maintain their energy consumption and increased biosynthesis of macromolecules. Thus, the carbohydrate, lipid, protein, and nucleic acid requirements necessary for cell maintenance are increased. Decades ago, Professor Otto Warburg described a metabolic phenotype observed in cancer cells in which the cells relied on glycolysis rather than the OXPHOS pathway to produce ATP, even when oxygen concentrations were sufficient.<sup>2</sup> This phenomenon, later known as the “Warburg effect”, greatly aided subsequent studies of tumor metabolism and led to the accepted theory of aerobic glycolysis. Glycolysis pathways are less efficient at producing ATP than is OXPHOS, so as the demand for glucose in tumor cells increases, the glycolytic production of pyruvates and lactates also increases. Furthermore, increased glucose consumption by tumors has been confirmed to correlate with poor tumor prognosis.<sup>5</sup> Glutamine is an amino acid that is essential for cell survival and is used as a precursor for the biosynthesis of proteins, nucleotides, and amino sugars; furthermore, its carbon skeleton structure can be used in the production process of the mitochondrial TCA cycle.<sup>6</sup> Studies have confirmed that in fast-growing tumors, cells are more likely to use glutamine for energy production.<sup>7–10</sup> Lactate produced by glycolysis in tumor cells also plays a very important role in tumor development. The levels of lactate from glycolysis in tumor cells and surrounding cells have been associated with tumor invasion and progression.<sup>11–14</sup> In addition to the three molecules mentioned above, there are changes in the tumor microenvironment, metabolism-related organelle functions and ions in the metabolic process of tumor cells. TC, as a rapidly growing solid tumor, unavoidably undergoes the above metabolic changes, and alterations such as these have an impact on the growth, proliferation, metastasis and treatment resistance of TC.<sup>15</sup>

Ion transport proteins, which are widely distributed in cells, dominate the transport of cellular metabolites. Studies have reported that different ion transporters in various tumors play an essential role in tumor cell proliferation, metastasis, invasion, and apoptosis.<sup>16–20</sup> The sodium-iodide symporter and thyroid hormone (TH) transporter in the thyroid gland, which are responsible for iodine uptake and TH secretion, respectively, are critical proteins that are thought to play an important role in TC.<sup>21–23</sup> The expression and activity of ion transporters associated with tumor metabolism, such as glucose metabolism-related glucose transporters, lactate metabolism-related monocarboxylate transporters, amino

acid metabolism-related amino acid transporters, and L-type amino acid transporters, are also changed.<sup>24–28</sup> Several studies have confirmed that these ion transporters control the prognosis of patients with TC.

TC undergoes extensive metabolic changes related to the growth, proliferation, metastasis, and invasion of tumor cells, and ion transporters mediate the transmission of substances required for metabolism; therefore, the regulation of metabolism by ion transporters is vital for tumor cell survival. The main purpose of this review is to illuminate how some ion transporters in TC regulate metabolism and thus affect the development and progression of TC.

## **Sodium-Iodide Symporter (NIS) and Iodide Metabolism in TC**

### **Physiological Role of NIS in the Thyroid Gland**

NIS is an integral plasma membrane glycoprotein that is encoded by the *SLC5A5* gene and is widely expressed in different organs in the human body.<sup>22</sup> In the thyroid gland, NIS is expressed on the basolateral membrane of follicular cells and can absorb  $I^-$  into the cells for the synthesis of THs and the maintenance of iodine homeostasis in humans.<sup>21</sup> This  $I^-$  uptake process is passive; after a  $Na^+$  concentration gradient is produced by the  $Na^+/K^+$  ATPase,  $I^-$  enters the cell together with two  $Na^+$  ions.<sup>29</sup> Based on the iodine uptake function of the thyroid gland mediated by NIS, the application of radioiodide in the diagnosis and treatment of primary TC and its metastatic lesions has become an important clinical approach.<sup>30</sup> In the healthy thyroid gland, the expression of NIS is mainly controlled by thyroid-stimulating hormone (TSH), which can regulate the expression and distribution of NIS in thyroid follicular cells via cyclic adenosine 3',5'-monophosphate (cAMP).<sup>21,31,32</sup> Additionally, studies have demonstrated that adenosine monophosphate-activated protein kinase (AMPK) can regulate the expression of NIS in thyroid cells.<sup>33,34</sup> Organisms can control NIS expression via these methods to maintain metabolic iodine homeostasis in the human body. Based on these descriptions, we know that NIS is involved in the maintenance of iodine homeostasis in vivo and plays a certain role in the treatment of thyroid diseases. It is also regulated by various factors, which impact thyroid function.

## **Aberrant NIS Expression Regulates $I^-$ Metabolism at the Onset of TC**

Radioactive iodine (RAI) has been used for decades to treat TC, especially micrometastases after thyroidectomy.<sup>35,36</sup> The

basis for this treatment is that NIS is expressed on the membrane of the thyroid follicles and can transport  $^{131}\text{I}$  into the nidus. However, several studies have demonstrated that NIS in TC has abnormalities relative to that in normal thyroid cells, such as altered expression, different intracellular localization, and loss of function.<sup>21,22,36–41</sup> More than 20 years ago, Professor Sebastiano Filetti demonstrated abnormalities in the function and expression of NIS in various TC samples and indicated that abnormal changes in NIS function would reduce iodine uptake.<sup>42</sup> These changes in NIS interfere with the treatment of some TCs, which can lead to poor prognosis and relapse; moreover, abnormal iodine metabolism in TC also affects the process of tumor proliferation.<sup>43</sup> Researchers have conducted relevant studies to identify the underlying mechanism and pointed out that these changes in NIS expression and function may be directly or indirectly related to mutations in tumor suppressor genes or oncogenes, activation of signaling pathways, modifications in the metabolic status, changes in the intracellular environment and other factors.<sup>33,34,44–49</sup> It is obvious that the change in NIS iodine uptake is not caused by a single factor but by several interlaced factors, which finally leads to the alteration of the NIS functional state. Studies have elucidated that the *BRAF-V600E* mutation and mutant *RAS* genes, which are the most commonly mutated genes in TC, cause the activation of signaling pathways such as the mitogen-activated protein kinases (MAPK), phosphatidylinositol 3 kinase (PI3K)/protein kinase B (AKT), AMPK and mammalian target of rapamycin (mTOR) pathways. These alterations affect the expression of NIS and change I metabolism.<sup>34,46,49,50</sup> Previous studies have shown that the *BRAF-V600E* mutation can cause downregulation of NIS expression and is associated with the MAPK pathway.<sup>50</sup> PI3K and its downstream molecule mTOR also exert an impact on the function of NIS and reduce  $\text{I}^-$  absorption.<sup>33,51</sup> Andrade's group demonstrated that AMPK affects the uptake of iodine and glucose in rat thyroid cells, which ultimately display decreased iodine uptake, and further confirmed that AMPK is upregulated in TC.<sup>34,52–54</sup> Moreover, studies have shown that AMPK can downregulate NIS expression in TC.<sup>54,55</sup> Therefore, we can see that the upregulation and activation of AMPK in TC can downregulate the expression of NIS and thus reduce the uptake of  $\text{I}^-$ . Additionally, NIS expression is regulated by microRNAs. Studies have shown that microRNA-339-5p can regulate NIS expression at the RNA level in TC, thereby affecting iodine uptake.<sup>56</sup> Last year, one study identified two key factors that interact with NIS, and blocking these factors

allowed NIS to resume normal function in TC cells, thus improving the prognosis of patients.<sup>57</sup> Furthermore, El Mokh's group demonstrated that by inhibiting NIS-related regulators (BRAF-V600E, MAPK, PI3K), iodine uptake levels in TC could be effectively promoted.<sup>58</sup> To date, pre-clinical and clinical studies on NIS as a therapeutic target have been conducted, some of which have been selected and are presented in Table 1. It can be concluded that NIS plays a significant role in TC; its aberrant expression in TC is caused by many factors and leads to abnormal iodine metabolism, meaning that radioactive iodide ions cannot be effectively taken up, thus affecting the prognosis of TC. Interestingly, abnormal iodide metabolism is associated with the proliferation of TC.

## Glucose Transporters (GLUTs) and Energy Metabolism in TC

### Physiological Role of GLUTs in the Thyroid Gland

The GLUT family comprises transmembrane proteins encoded by *SLC2* genes, which are widely expressed on the plasma membrane of various eukaryotic cells, and the main function of these proteins is to mediate the transport of carbohydrates into cells.<sup>59</sup> In the human body, 14 members of the GLUT family are distributed on different cells.<sup>60</sup> The main function of GLUTs in human cells is to absorb glucose from the extracellular environment and blood circulation into cells for energy metabolism.<sup>18</sup> Studies have confirmed that GLUTs regulate glucose uptake and energy metabolism in thyroid cells.<sup>61–65</sup> GLUT1, GLUT3, GLUT4, and GLUT10 are expressed in rat thyroid cells, with GLUT1 being the main metabolism-related subtype.<sup>61,62,65</sup> Matsuzu's team summarized previous studies and verified the expression of GLUTs in the thyroid gland; they also found that GLUT1 was of great significance to thyroid gland function.<sup>61</sup> GLUT1 is encoded by the *SLC2A1* gene and is expressed on the plasma membrane.<sup>59</sup> However, due to technical limitations, the only certainty is that GLUT1 is expressed on the plasma membrane, and any specific localization is unclear.<sup>61</sup> The primary substrate for GLUT1 is glucose, but it is also involved in the transport of mannose, glucosamine, galactose, and reduced ascorbate.<sup>66</sup> GLUT1 can transport glucose into thyroid cells, which is then converted into ATP via biosynthesis processes such as glycolysis and OXPHOS to provide energy for cell survival. GLUT1 expression in the thyroid gland is regulated by

**Table 1** Expression, Influence, Related MicroRNA, Clinical/Preclinical Trials of Ion Transporters in Thyroid Cancer

Named	Transporter	Gene Symbol	Influence in Thyroid Cancer	Related Micro-RNA	Clinical/Preclinical Trials Inhibitor
NIS	NIS	<i>SLC5A5</i>	Prognosis relapse proliferation	miRNA-339-5p	ES-1 <sup>57</sup> NMS-873 <sup>57</sup> P-325901 <sup>58</sup>
GLUTs	GLUT1	<i>SLC2A1</i>	Invasion Prognosis Proliferation growth	miRNA-125b	Metformin <sup>84,85</sup>
	MCT1	<i>SLC16A1</i>	Invasion proliferation	miRNA-342-3p	AZD3965 <sup>111</sup>
MCTs	MCT4	<i>SLC16A3</i>	Invasion proliferation	miRNA-145	AZ93 <sup>112</sup> Bindarit <sup>113</sup>
	MCT8	<i>SLC16A2</i>	Differentiation	miRNA-375	TKI <sup>114</sup>
ASCTs	ASCT2	<i>SLC1A5</i>	Proliferation Metastasis invasive	miRNA-137	BenSer <sup>27</sup>
LATs	LAT1	<i>SLC7A5</i>	Growth, proliferation prognosis	miRNA-126	JPH203 <sup>146,153</sup>

**Abbreviations:** ES-1, Eeyarestatin-1; TKI, tyrosine kinase inhibitor.

TSH and AMPK.<sup>52,61</sup> From the above observations, we can conclude that as a member of the GLUT family GLUT1 is necessary for the energy metabolism of the thyroid gland.

## GLUT1 Regulates Metabolism at the Onset of TC

GLUT1 has been extensively studied. Researchers have found that GLUT1 expression is upregulated in many different types of tumor cells and is closely linked to tumor progression.<sup>67–69</sup> Based on the “Warburg effect”, we know that tumor cells are significantly more dependent on ATP than are normal cells and that this dependence depends on activation of aerobic glycolysis.<sup>2–4,70,71</sup> As a transporter directly related to the intracellular energy source, GLUT1 is bound to be closely related to cellular metabolism. Studies have reported a substantial increase in GLUT1 expression in TC cells.<sup>18,25,26</sup> By analyzing the immunohistochemical data of more than 500 patients with TC, Nahm et al<sup>25</sup> found that GLUT1 expression was increased in TC and that its activity was enhanced in cells with increased glycolysis. They also noted that increased GLUT1 expression is associated with invasion and poor prognosis of TC.<sup>25</sup> TC, as a tumor with high proliferative and metabolic activity, has a high energy demand and rapidly consumes ATP, which mainly depends on the glucose transport function of GLUT1. Therefore, only increased expression and enhanced function of GLUT1 can meet the energy needs of TC. The study also confirmed that glucose uptake was

significantly increased with upregulated GLUT1 expression in TC cells.<sup>72</sup> At this point, we can conclude that when GLUT1 expression is upregulated, the amount of glucose entering the cells and the subsequent levels of substrates involved in aerobic glycolysis, OXPHOS and gluconeogenesis increase, which provides hospitable conditions for the growth and proliferation of tumor cells. The expression of GLUT1 in TC is regulated by many factors. Studies have demonstrated that the PI3K pathway can upregulate the expression of GLUT1 in *RAS*-mutated TC cells.<sup>73</sup> The transcription factor hypoxia-inducible factor 1  $\alpha$  (HIF-1 $\alpha$ ), whose expression is induced in hypoxic tumor environments, has also been linked to GLUT1 expression in TC. Józwiak’s group demonstrated that in the TC cell lines FTC-133 and 8305c, HIF-1 $\alpha$  can upregulate the expression of GLUT1 and promote glucose uptake of cancer cells.<sup>74</sup> In addition, after applying siRNA to knockdown GLUT1 expression in TC cells, they found that the cells’ ability to uptake glucose was reduced and that their ability to proliferate was also diminished.<sup>74</sup> HIF-1 $\alpha$  is an important factor in the metabolic changes in tumor cells and can activate the glycolytic pathway and inhibit OXPHOS in mitochondria.<sup>75,76</sup> Studies have shown that HIF-1 $\alpha$  can activate many transporters associated with cellular aerobic glycolysis, including GLUT1, and enhance their expression in TC.<sup>24–26,77</sup> There have been many well-executed experiments on the regulation of GLUT1 expression in TC and other cancers. In addition to the two factors mentioned above, oncogenes and tumor suppressor factors such as



Raf, Myc, Src, p53 and PTEN have also been proven to regulate GLUT1 expression in TC and promote glucose uptake.<sup>78–82</sup> Moreover, there exists a regulatory microRNA that targets GLUT1. Zhang et al confirmed that microRNA-125b can reduce glucose uptake in TC cells by downregulating GLUT1 expression, thus affecting the development and progression of cancer.<sup>83</sup> Due to these changes in TC, GLUT1 expression increases to compensate for the metabolic reprogramming so that enough glucose can be taken up to fulfill the needs of TC cells with high metabolism and elevated proliferative activities, and such changes in TC are associated with its growth, proliferation and progression. In summary, we can conclude that after the occurrence of TC, many factors in TC can promote GLUT1 expression, which further regulates the uptake of glucose through its own changes in expression and then affects the energy metabolism of cells to confront the needs of TC cells to maintain their growth, proliferation and progression. GLUT1 has been used as an effective target for tumor therapy in many studies. In TC, a preclinical study by Shen et al confirmed that metformin could effectively reduce GLUT1 expression and thus inhibit the progression of TC.<sup>84</sup> Other studies have identified GLUT1 as an important therapeutic target in treating tumors, and these studies have been well summarized in an excellent review by Zambrano.<sup>85</sup>

## Monocarboxylate Transporters (MCTs) and Metabolism in TC

### Physiological Role of MCTs in the Thyroid Gland

The MCT family, encoded by the *SLC16* gene, is a proton-linked membrane transport protein located in the cell membrane.<sup>86</sup> It consists of 14 members; however, only MCT (1–4) are involved in monocarboxylate transport in human cells.<sup>86</sup> Their main function is to transport intracellular monocarboxylic acid substances, such as lactate, pyruvate and ketone bodies.<sup>86</sup> These substances are necessary for the energy metabolism and material synthesis of organelles. When the oxygen supply fails to meet the metabolic needs of the cell, the cell relies on glycolysis to produce energy, which increases the production of lactate and pyruvate and consequently leading to the accumulation of these products in the cell. MCTs can transport these redundant substances out of the cell or into other cells for further metabolism, thus maintaining cellular homeostasis. In healthy thyroid tissues, MCT (1–4) have

not been precisely defined, but under pathological conditions, MCT1 and MCT4 are clearly expressed in the thyroid and are closely related to the energy metabolism of cells.<sup>25,87</sup> MCT1, which is encoded by the *SLC16A1* gene, is a bidirectional transporter located on the plasma membrane whose main function is to transport lactate into the cell.<sup>16,88</sup> The lactate that enters the cell can be reversibly converted to pyruvate by lactate dehydrogenase (LDH) or to other energy materials by gluconeogenesis.<sup>16</sup> The factors that regulate MCT1 expression in normal tissues have not been clearly elucidated, but studies have found that it is associated with metabolism and AMPK.<sup>88</sup> MCT4, encoded by *SLC16A3*, is also distributed across the plasma membrane.<sup>16</sup> Compared with MCT1, MCT4 is mainly involved in glycolysis metabolism in cells and has a different functional structure.<sup>16,88</sup> It has a low affinity for lactate, and its primary function is to transport intracellular lactate out of the cell.<sup>89</sup> Studies have reported that MCT4 expression is mainly regulated by cell metabolism and the hypoxic environment.<sup>90</sup> In addition to these two transporters, MCT8, a member of the MCT family, is related to TH transport and is also distributed in the thyroid gland.<sup>91</sup> MCT8 is encoded by the *SLC16A2* gene and is widely distributed in the basolateral membrane of thyroid follicular epithelial cells.<sup>91</sup> Its main function is to transport THs, especially 3,3',5-triiodothyronine (T3).<sup>91</sup> TH is synthesized in thyroid follicular epithelial cells and then transported by MCT8 to cells throughout the body to act on the corresponding cell receptors, thereby causing a series of biological reactions.<sup>92</sup> In healthy thyroid cells, MCT8 expression is mainly regulated by cAMP and TSH.<sup>23</sup> In summary, MCT1, MCT4 and MCT8 play a significant role in the energy metabolism of and transport of materials between cells.

## MCTs Regulate Metabolism in the Onset of TC

MCT1 and MCT4 are essential in the metabolic process of TC cells. As noted above, most tumor cells rely on anaerobic glycolysis to provide energy for their growth and survival; this process eventually produce a large amount of lactate, which plays an important role in cancer metabolism.<sup>93,94</sup> During aerobic glycolysis in tumor cells, a large amount of pyruvate is produced when excessive glucose is consumed to produce ATP; then, pyruvate is converted to lactate via LDH. This process is reversible, which means that lactate can also be transformed into

pyruvate.<sup>3,95,96</sup> In addition, there is another source of lactate in TC cells: the surrounding fibroblasts, immune cells, epithelial cells and so on constitute the tumor micro-environment. Studies have shown that cancer-associated fibroblasts (CAFs), also called stromal fibroblasts, play an important role in tumor metabolism and clarified that these cells are definitely present in TC.<sup>97,98</sup> CAFs can produce lactate via aerobic glycolysis and release lactate into the surrounding environment; then, tumor cells absorb this lactate and convert it into pyruvate to produce energy in mitochondria.<sup>13</sup> This process, known as the “Reverse Warburg Effect”, allows CAFs to provide some lactate that is absorbed by highly metabolic tumor cells to further participate in the TCA cycle to produce energy. The transportation of lactate is dependent on MCT1 and MCT4. Studies have confirmed that the expression levels of MCT1 and MCT4 are increased to varying degrees in different types of TC.<sup>89,99,100</sup> Pioneering researchers conducted an immunohistochemical analysis of orthotopic xenograft tumors and clinicopathological specimens and found that MCT1 was highly expressed relative to MCT4 in anaplastic TC (ATC).<sup>87</sup> Nahm et al conducted a similar experiment with the clinicopathological specimens of 566 patients with TC and immunohistochemically analyzed the expression of proteins related to tumor glycolysis.<sup>25</sup> They finally concluded that MCT4 expression increased, mainly in ATCs.<sup>25</sup> Other researchers have found that MCT4 is associated with the invasion and proliferation of different tumors.<sup>99,101</sup> Therefore, as a highly invasive and metastatic tumor, the incidence of ATC may be associated with MCT4. Studies also stated that cellular hypoxia can induce upregulated MCT4 expression through the action of HIF-1 $\alpha$  interacting with the promoter of MCT4 to adapt tumor cells to hypoxia, maintain intracellular acid-base balance and prevent intracellular lactic acid accumulation.<sup>90,102</sup> Currently, studies on the regulation of microRNA-mediated MCT1/4 expression in TC are lacking, but there relevant reports in other tumors. Studies have confirmed that microRNA-342-3p can target MCT1 in breast cancer and then change the metabolic state of tumor cells.<sup>103</sup> Regarding MCT4, studies have confirmed that microRNA-145 can act on MCT4 in hepatocellular carcinoma, thereby changing the homeostasis of tumor cells.<sup>104</sup> The above two microRNAs can serve as potential therapeutic targets for further study in TC, a tumor with high levels of proliferation and metabolic characteristics. The expression of MCT1 and MCT4 in TC is increased through various factors and accelerates the transport of

lactate and other energy substances to satisfy the energy requirements of the cells. In summary, MCT1 and MCT4 play an essential role in the metabolism of TC because they regulate the uptake and release of metabolic compounds to adjust to the changing metabolic needs of TC via changes in their expression levels, thus promoting the growth, proliferation and invasion of TC. MCT8 is a member of the MCT family, and its functional role in TC is quite different from that of MCT1 and MCT4. Bidziong et al demonstrated that MCT8 expression in TC tissues was significantly lower than that in healthy thyroid tissues; therefore, MCT8 could be regarded as a biomarker of TC differentiation.<sup>23</sup> It is worth mentioning that, as a TH transporter, MCT8 (namely, downregulation of its expression) is of great significance in TC. Studies have confirmed that TH can promote the proliferation, metastasis and development of TC through the MAPK and PI3K signaling pathways.<sup>105</sup> Therefore, downregulation of MCT8 expression in TC can effectively reduce TH secretion and thus lead to the accumulation of TH in TC tissue, which ultimately promotes the progression of TC. Currently, there are few studies on MCT8 in TC. Smith et al proved that pituitary tumor transforming gene-binding factor (PBF) could regulate the expression and function of MCT8 in TC.<sup>106</sup> At the microRNA level, MCT8 has been shown to be a target of microRNA-375 in TC.<sup>107</sup> In summary, we have highlighted the role of MCTs in the development of TC and their regulatory factors in TC. Currently, there are many preclinical trials regarding them as tumor therapeutic targets; however, there have been few preclinical trials investigating MCTs as a druggable target in TC.<sup>108–110</sup> Polanski et al demonstrated that the inhibitor AZD3965 can block MCT1 function in small cell lung cancer, thereby stunting tumor development.<sup>111</sup> This inhibitor is currently in clinical trials, and we believe that its effects on TC will be reported in the near future. For MCT4, AstraZeneca has developed AZ93, a specific inhibitor of MCT4, but it has not yet entered preclinical trials.<sup>112</sup> Futagi et al confirmed that bindarit effectively inhibits MCT4 in human cells and could be used in antitumor research.<sup>113</sup> MCT8 is regulated by TSH, but no direct inhibitor has been reported in TC. Krajewska summarized the study of MCT8 as a therapeutic target and found that tyrosine kinase inhibitors can affect the transport function of MCT8.<sup>114</sup> In summary, MCTs play an important role in TC and may be a potential therapeutic target, but further research is needed.

## Neutral Amino Acid Transporters (ASCTs) and Energy Metabolism in TC

### Physiological Role of ASCTs in the Thyroid Gland

ASCTs, encoded by the *SLC1* gene, belong to the amino acid transporter family.<sup>115</sup> In humans, the amino acid transport family consists of seven members, five of which mostly transport glutamate and the other two mainly transport neutral amino acids.<sup>115</sup> ASCTs, including ASCT1 and ASCT2, facilitate the transport of neutral amino acids; these proteins are encoded by *SLC1A4* and *SLC1A5*, respectively.<sup>115</sup> In the thyroid, we focused on the functional role of ASCT2. ASCT2 is located in the cell plasma membrane and is widely expressed in various tissues of the human body.<sup>115,116</sup> The name ASCT2 comes from its ability to transport alanine, serine, cysteine, and threonine.<sup>117,118</sup> In fact, ASCT2 can transport glutamine as well as these neutral amino acids with high affinity.<sup>119</sup> Glutamine is used as a precursor for the biosynthesis of many proteins, nucleotides, and amino sugars, and its carbon skeleton structure can be used in the production process of the mitochondrial TCA cycle.<sup>6</sup> When cells are in a proliferative state, all biosynthetic and metabolic requirements increase, and the requirements of glutamine also rise; these changes rely on the function of transporters, ASCT2 among them.<sup>120,121</sup> Glutamine is transported into cells by ASCT2 and then into mitochondria, where it is converted to glutamate by phosphate-dependent glutaminase. Furthermore, glutamate is converted into  $\alpha$ -ketoglutarate ( $\alpha$ -KG) for use in the TCA cycle of mitochondria and participates in energy metabolism.<sup>122</sup> At present, studies on factors influencing the regulation of ASCT2 expression in normal tissues are not clear. Most of the studies are in tumors, which will be elaborated in the next section. In conclusion, ASCT2 plays an important role in the energy supply and material transfer of cells.

### ASCT2 Regulates Metabolism in the Onset of TC

As previously mentioned, to meet the needs of growth and proliferation, tumor cells change their metabolic state, mainly producing energy by replacing OXPHOS with aerobic glycolysis, and some studies suggest that mitochondrial function in tumor cells is impaired.<sup>123</sup> However, after much research and debate, researchers found that these claims are

not rigorous. Researchers have found that in tumor cells, mitochondria still function normally.<sup>122,124,125</sup> In addition to using glucose for energy, cancer cells also uptake fats, proteins, and amino acids to survive and proliferate, and mitochondria play an important role in the metabolism of these molecules. In a study on the metabolism of tumor cells, researchers discovered another important substance – glutamine.<sup>6</sup> Studies have confirmed that in fast-growing tumors, tumor cells are more likely to use glutamine for energy production.<sup>9,10</sup> Aerobic glycolysis cooperates with glutamine metabolism to maintain cell proliferation, while glutamine can also maintain mitochondrial function and participate in the synthesis of nonessential amino acids and nucleotides (purines and pyrimidines) in mitochondria.<sup>9,10</sup> Some researchers have realized that these changes in energy metabolism in tumor cells cause the cells to produce an energy stress response, which is associated with tumor proliferation and metastasis.<sup>126</sup> Above, we stated the importance of glutamine in the energy metabolism of tumor cells. After glutamine enters the cell, it is first catalyzed by glutaminase to produce glutamate, which is transported into the mitochondria and then converted into  $\alpha$ -KG, alanine, aspartate and other substances by metabolism-related enzymes to participate in intracellular metabolic functions.<sup>127</sup> Therefore, ASCT2, as a transporter of glutamine, occupies a significant position in the regulation of cancer metabolism. Kim's group used immunohistochemistry to stain for glutamine metabolism-related proteins in a TMA comprising 557 TC samples and found that ASCT2 was expressed in all TC tissues; however, the expression level was dissimilar in different types of TC samples.<sup>27</sup> They analyzed the statistical correlations between these staining results and eventually discovered that the expression of glutamine metabolism-related proteins was highest in ATC and *BRAF-V600E*-mutated papillary TC (PTC) and that ASCT2 expression was higher in medullary TC (MTC) than in other types of TC.<sup>27</sup> Several studies have reported that proteins involved in glutamine metabolism, such as ASCT2, are associated with tumor aggressiveness.<sup>128,129</sup> Among the subtypes of TC, PTC with the *BRAF-V600E* mutation and MTC are both highly invasive and prone to metastatic behavior.<sup>36,44,130,131</sup> Therefore, ASCT2 may be associated with the invasive characteristics and poor prognosis of TC. ASCT2 expression in TC is affected by a variety of factors, among which include gene mutations that cause changes in signaling pathways involved in ASCT2 expression. In TC, in addition to the common *BRAF* and *RAS* gene mutations, *MYC* gene

mutations also exist, which mainly occur in MTC.<sup>132,133</sup> MYC can stimulate ASCT2 expression and promote the utilization of glutamine.<sup>134</sup> In addition, ASCT2 is regulated by microRNA-137.<sup>135</sup> In summary, we can conclude that TC, as a tumor with high metabolic needs, has increased energy demands, so utilizing glutamine as a source of energy is necessary, and that ASCT2, as a transporter of glutamine into cells, cannot be neglected. Abnormal expression of ASCT2 regulates glutamine metabolism to meet the energy metabolism needs of TC and is related to tumor growth, proliferation, metastasis, invasion, and poor prognosis. Researchers have demonstrated that ASCT2 can be a therapeutic target for tumors and that blocking ASCT2 can prevent tumor growth and progression.<sup>136</sup> Wang et al demonstrated that BenSer, an inhibitor of ASCT2, can significantly attenuate tumor proliferation in malignant melanoma.<sup>27</sup> However, this needs to be further verified in TC.

## L-Type Amino Acid Transporters (LATs) and Energy Metabolism in TC

### Physiological Role of LATs in the Thyroid Gland

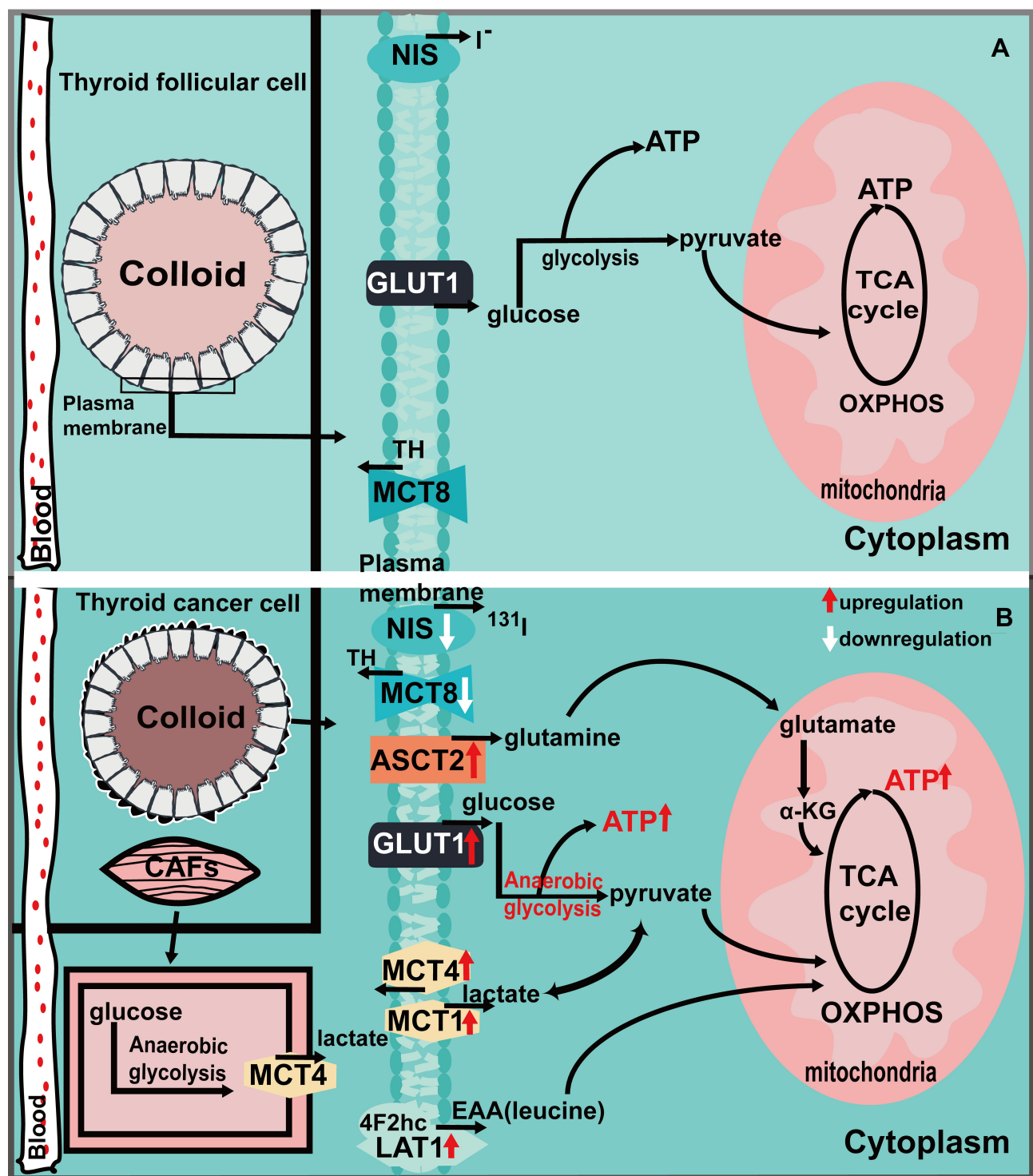
The SLC7 solute carrier family consists of two subfamilies: LATs and cationic amino acid transporters (CATs).<sup>137</sup> The LAT subfamily comprises four members, LAT1-4, which are widely distributed on the plasma membrane of various specific cells in the human body, and their key function is to participate in the transport of essential amino acids (EAAs) throughout the human body.<sup>138</sup> Furthermore, due to differences in their function and structure, the four members of the LATs are divided into two groups. LAT1 and LAT2, which have a high affinity for EAAs, must combine with the 4F2 antigen heavy chain (4F2hc) to constitute a heterodimer.<sup>139,140</sup> However, LAT3 and LAT4 do not need to form a heterodimer; they can directly participate in EAA transport, but with low affinity.<sup>141,142</sup> Amino acids provide a nitrogen source for the synthesis of nucleotides, amino sugars and proteins in cells; meanwhile, the carbon skeleton of amino acids can be used for OXPHOS to produce ATP, which is also involved in lipid synthesis in cells.<sup>143</sup> Therefore, as carriers of human amino acids, LATs play a very important role in human metabolism. Of the four members of the LAT family, LAT1, which is encoded by the *SLC7A5* gene, has been the most extensively studied, so it has existing research

value in thyroid physiology and pathology. In polarized epithelial cells, LAT1 is mainly localized to the basolateral membrane.<sup>137,144</sup> On the cell membrane, LAT1 and 4F2hc constitute a heterodimer that transports EAAs, such as leucine and phenylalanine, and at the same time participate in the exchange of EAAs and glutamine in a Na<sup>+</sup>-independent manner.<sup>139,145</sup> Through this transport function of LAT1, cells can meet their growth and proliferation needs. Unfortunately, however, the expression of LAT1 protein was not detected in healthy thyroid tissue, but it was clearly expressed in pathological tissue.<sup>146</sup> The regulatory factors of LAT1 expression in healthy tissues have not been elaborated in detail, as most are regulatory studies in pathological conditions, which will be elaborated in the next part. In summary, LAT1 plays a specific role in human metabolism, and abnormalities in its expression can cause changes in human cell metabolism, which can be used in tumor research.

### LAT1 Regulates Metabolism in the Onset of TC

Tumor cells are characterized by high proliferation and metabolism, which depend on the consumption of nutrients such as glucose, glutamine and EAAs. By consuming these nutrients, cells can synthesize proteins and produce ATP.<sup>11,147,148</sup> More than 60 years ago, after conducting experiments with HeLa cells, Harry Eagle discovered that EAAs are needed for cell proliferation.<sup>149</sup> Studies have reported a higher uptake of EAAs in a variety of tumors than that in healthy tissue, suggesting that EAAs are necessary for cell proliferation.<sup>143,150,151</sup> Of the eight EAAs needed by the human body, leucine is worth mentioning because it is an effective activator of mechanistic target of rapamycin kinase complex 1 (mTORC1), and this signaling pathway can promote the growth, proliferation and apoptosis resistance of tumor cells.<sup>152</sup> In addition, leucine is an allosteric agent of glutamate dehydrogenase, which can regulate the activity of glutamate dehydrogenase in mitochondria and thus affect glutamate metabolism.<sup>147</sup> Therefore, as a transporter of EAAs (including leucine), LAT1 plays an important role in the metabolic regulation of amino acids in tumor cells. Professor Enomoto proved through experiments that LAT1 and 4F2hc are overexpressed in ATC tissues and were expressed in ATC cell lines (8505C, OCUT-2, and OCUT-6); moreover, these two proteins are closely related to the growth and proliferation of tumor cells.<sup>146</sup> Furthermore, the experiment verified that the uptake of EAAs decreased and that the mTOR signaling





**Figure 1** Ion transporters and the metabolic situation in normal thyroid cells (A) and cancer cells (B). Figure (A) shows that normal thyroid cells rely on GLUT1 transport of glucose to provide energy through glycolysis and oxidative phosphorylation, NIS is involved in intracellular iodide metabolism, and MCT8 is involved in the transporation of TH. The expression of MCT1/4, ASCT2, and LAT1 has not been elucidated. Figure (B) shows the upregulation of GLUT1, ASCT2, LAT1 and MCT1/4 in thyroid cancer, which regulates the metabolism of tumor cells to meet their growth and proliferation needs through the transport of corresponding metabolic substrates. The downregulated expression of NIS leads to the decreased function of iodine intake, affects the treatment of radioactive iodine, and promotes the poor prognosis of the tumor. The downregulation of MCT8 expression affects the transport of TH, thus affecting the progression of thyroid cancer.

pathway was stalled after inhibition with LAT1.<sup>146</sup> Other researchers conducted similar experiments in ATC, PTC and their cell lines (8505c, LNCaP, SW1736, Hth104, KTC1 and

TPC-1) and observed that LAT1 was overexpressed in both of these tumor tissues. These studies concluded that this growth was related to the growth, proliferation and prognosis of tumor

cells.<sup>153</sup> At the same time, they also confirmed that inhibition of LAT1 would affect the mTORC1 pathway.<sup>153</sup> From these studies, we can see that LAT1 plays a role in the amino acid metabolism of TC. The regulatory factors of LAT1 expression have not been thoroughly studied in TC, but some other tumor studies have shown that the expression of LAT1 is affected by many factors. Studies have shown that LAT1 expression is regulated by vascular endothelial growth factor and that this process is related to the hypoxic environment of tumor cells.<sup>154–156</sup> Studies have also shown that the overexpression of LAT1 is related to the amplification of the *MYC* gene.<sup>157</sup> In addition, one study confirmed that LAT1 expression was related to the Ras-MEK-ERK signaling pathway in a mouse thyroid tumor model.<sup>153</sup> Furthermore, studies have confirmed that LAT1 is the target of microRNA-126.<sup>158,159</sup> In summary, we can conclude that LAT1 plays an important role in the amino acid metabolism of TC. Various factors in TC caused alterations in LAT1 expression, and LAT1 transported more leucine through these changes to meet the metabolic needs of TC, thus promoting the development of TC. The existence of LAT1 is also associated with the prognosis of TC. At present, there are relevant studies on LAT1 as a therapeutic target in TC. Hafliger et al demonstrated that JPH203, an inhibitor of LAT1, could effectively block LAT1 function and thus inhibit TC proliferation in a mouse model.<sup>153</sup> Furthermore, Enomoto et al demonstrated that JPH203 could inhibit the progression of TC via LAT1.<sup>146</sup>

## Conclusions and Perspectives

The prevalence of TC is increasing every year. Although the prognosis may be acceptable, it (along with the recurrence rate) of TC with a high degree of malignancy still cannot be ignored. Alterations in intracellular metabolic status and associated ion transporters are markers of tumorigenesis. However, the relationship among TC, cell metabolism, and ion transporters has not been thoroughly elucidated. We attempted to clarify the physiological and pathophysiological connections (Figure 1). In this paper, the status of NIS in TC related to the treatment of TC and its relationship with metabolism are described, providing both a reference for the treatment of patients resistant to radiotherapy and profound ideas for TC researchers. We also discussed GLUT1, MCT1/4/8, ASCT2, and LAT1 plasma membrane transporters and their association with energy metabolism in TC while also confirming their association with TC and metabolism in previous studies. In TC, these ion transporters can regulate the metabolism of corresponding substances through both their own function and expression changes to meet the

needs of TC cells. Although many studies have investigated the abovementioned ion transporters, few effective drugs have been applied in clinical practice, and the incidence of TC and prognosis of patients have not been significantly improved. This paper summarizes the metabolism-related ion transporters, their regulatory factors, and relevant preclinical and clinical trials in TC (Table 1) with the goal of providing hope for TC patients and researchers with in-depth research directions.

## Abbreviations

$\alpha$ -KG,  $\alpha$ -ketoglutarate; AMPK, adenosine monophosphate-activated protein kinase; ATP, adenosine triphosphate; ASCTs, amino acid transporters; ATC, anaplastic thyroid cancer; CAFs, cancer-associated fibroblasts; cAMP, cyclic adenosine 3',5'-monophosphate; HIF-1 $\alpha$ , hypoxia-inducible factor 1 alpha; EAA, essential amino acids; GLUTs, glucose transporters; LATs, L-neutral amino acid transporters; LDH, lactate dehydrogenase; MAPK, mitogen-activated protein kinases; MCTs, monocarboxylate transporters; MTC, medullary thyroid cancer; mTOR, mammalian target-of-rapamycin; mTORC1, mechanistic target of rapamycin kinase complex 1; NIS, sodium-iodide symporter; OXPHOS, oxidative phosphorylation; PTC, papillary thyroid cancer; PI3K/AKT, phosphatidylinositol 3 kinase/protein kinase B; RAI, radioactive iodine; TC, thyroid cancer; TCA, tricarboxylic acid; TH, thyroid hormone; TSH, thyroid-stimulating hormone; 4F2hc, 4F2 antigen heavy chain; T3, 3, 3', 5-triiodothyronine.

## Data Sharing Statement

Not applicable.

## Ethics Approval and Consent to Participate

Not applicable.

## Consent for Publication

Not applicable.

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## Disclosure

The authors declare that they have no conflicts of interest for this work.

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