CLINICAL SCIENCE

GLUT1 expression in malignant tumors and its use as an immunodiagnostic marker

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OBJECTIVE: To analyze glucose transporter 1 expression patterns in malignant tumors of various cell types and evaluate their diagnostic value by immunohistochemistry.

INTRODUCTION: Glucose is the major source of energy for cells, and glucose transporter 1 is the most common glucose transporter in humans. Glucose transporter 1 is aberrantly expressed in several tumor types. Studies have implicated glucose transporter 1 expression as a prognostic and diagnostic marker in tumors, primarily in conjunction with positron emission tomography scan data.

METHODS: Immunohistochemistry for glucose transporter 1 was performed in tissue microarray slides, comprising 1955 samples of malignant neoplasm from different cell types.

RESULTS: Sarcomas, lymphomas, melanomas and hepatoblastomas did not express glucose transporter 1. Forty-seven per cent of prostate adenocarcinomas were positive, as were 29% of thyroid, 10% of gastric and 5% of breast adenocarcinomas. Thirty-six per cent of squamous cell carcinomas of the head and neck were positive, as were 42% of uterine cervix squamous cell carcinomas. Glioblastomas and retinoblastomas showed membranous glucose transporter 1 staining in 18.6% and 9.4% of all cases, respectively. Squamous cell carcinomas displayed membranous expression, whereas adenocarcinomas showed cytoplasmic glucose transporter 1 expression.

CONCLUSION: Glucose transporter 1 showed variable expression in various tumor types. Its absence in sarcomas, melanomas, hepatoblastomas and lymphomas suggests that other glucose transporters mediate the glycolytic pathway in these tumors. The data suggest that glucose transporter 1 is a valuable immunohistochemical marker that can be used to identify patients for evaluation by positron emission tomography scan. The function of cytoplasmic glucose transporter 1 in adenocarcinomas must be further examined.

KEYWORDS: Glucose transporter 1; Immunohistochemistry; Protein expression; PET-scan; Malignant tumors.

Carvalho KC, Cunha IW, Rocha RM, Ayala FR, Cajaíba MM, Begnami MD, et al. GLUT1 expression in malignant tumors and its use as an immunodiagnostic marker. Clinics. 2011;66(6):965-972.

Received for publication on February 8, 2011; **First review completed on** February 28, 2011; **Accepted for publication on** February 28, 2011

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INTRODUCTION

Glucose metabolism governs many functions, because the oxidation of glucose generates a major source of metabolic energy in eukaryotic cells.[1] Thus, glucose regulates transcription, enzymatic activity, hormone secretion and the activity of glucoregulatory neurons. These functions typically are secondary to glucose uptake, which is controlled primarily by the glucose transporter family (GLUT 1–14).[2]

Facilitative glucose transporters in the plasma membrane mediate the flux of glucose between the extra- and intracellular enviroments;[3] their expression and kinetic and regulatory activities can be influenced by oncogenes and growth factors.[4]

The transport of glucose and other sugars is effected by a gradient between the external and internal faces of the plasma membrane.[5] Glucose uptake in nearly all cells is mediated by GLUTs.[2,3]

After glucose enters normal cells, it is converted into pyruvate through glycolysis. Subsequently, pyruvate is transformed into acetyl-CoA, which is used as substrate in mitochondria to generate ATP.[6] In contrast, aerobic glycolysis occurs in tumor cells—known as the Warburg effect—[7] also involving glucose transporter expression.[8] Hypoxia is a hallmark of cancer, upregulating GLUT expression.[9]

The GLUT family is expressed in the membrane of nearly all cell types;[10] GLUT isoforms have tissue-specific expression patterns. There are 14 GLUT members,[11] of which GLUT1, the first member of the GLUT family to be identified, has been the most extensively studied.

GLUT1 was reported originally as a marker of infantile skin hemangioma;[12] other vascular tumors and malformations do not express GLUT1 as robustly or ubiquitously.[13] Some groups have proposed the use of GLUT1 as a diagnostic marker for hemangiomas in various locations.[12-15]

GLUT1 is overexpressed in many tumors, including hepatic, pancreatic, breast, esophageal, brain, renal, lung, cutaneous, colorectal, endometrial, ovarian and cervical cancers.[16-25] Conversely, immunohistochemistry shows that GLUT1 expression is absent from certain human cancers. Further, GLUT1 positivity in malignant cells revealed by immunohistochemistry indicates increased proliferative activity, energy requirements and aggressive behavior.[26,27]

Increases in glucose consumption help supply the energy that is necessary for tumor cell proliferation and reflect adaptation to the adverse conditions of the tumoral environment. Thus, metabolic changes have prognostic and diagnostic value.[28] Although the metabolic consequences of increased glucose transport are not understood, GLUT1 expression apparently has significant clinical function in several tumors.

Currently, positron emission tomography (PET) scans are performed to evaluate glucose uptake by cancer cells. ^{18}F-fluorodeoxyglucose is a glucose analog that is used in PET to determine the anatomical and metabolic properties of tumors.[29,30] Thus, enhanced glycolysis of tumor cells can be detected, which is valuable in the diagnosis, staging, assessments of recurrence and response to therapy of many malignancies.[30,31] Tumors that express low levels of GLUT1, however, pose a challenge for evaluations by PET scan.

This study was performed to measure GLUT1 immunoexpression in 1955 samples of malignant tumors of various origins and locations and to evaluate its diagnostic value by immunohistochemistry.

MATERIALS AND METHODS

Patients

We obtained 1955 cases of malignant tumor from the archives of the Department of Anatomic Pathology, Hospital A.C. Camargo, Sao Paulo, Brazil. The primary sites, histological types and the number of samples evaluated are shown in Table 1.

This experimental research was approved by the ethics committee of our institution.

Table 1 - Samples evaluated by immunohistochemistry. Primary site, histological type and number (percentage) of positive and negative samples are indicated.

Tumor	GLUT1-stained samples			
	Positive n (%)		Negative n (%)	Total number of cases
Prostate	92 (47)		103 (53)	195
Thyroid	25 (29)	Papillary (35%) Follicular (19%)	60 (71)	85
Gastric	38 (10)	Intestine (17%) Diffuse (4%)	339 (90)	377
Breast	13 (5)		254 (95)	267
Head and neck	62 (36)		110 (64)	172
Cervix uterine	69 (42)		95 (58)	164
Glioblastomas	16 (18.6)		70 (81.4)	86
Retinoblastomas	12 (9.4)		116 (90.6)	128
Lymphomas	0		297 (100)	297
Sarcomas	0		97 (100)	97
Melanomas	0		67 (100)	67
Hepatoblastomas	0		20 (100)	20
Total number	327		1628	1955

Tissue Microarray

The cases were reviewed and selected based on the evaluations of 2 pathologists. Representative areas were obtained in 2 cores (2 mm each) for each tumor. The original blocks were retrieved from the hospital archives and used to construct the tissue microarrays (TMAs). The TMA blocks were sectioned onto coated slides (Starfrost, Lowestoft, UK®) at a thickness of 4 μm using adhesive tape for subsequent UV crosslinking (Instrumedics Inc®, Hackensack, NJ, USA), dipped in a layer of paraffin to prevent oxidation and stored at −20℃. One section was stained with hematoxylin and eosin to evaluate the morphology of each spot and the remaining slides were used in the immunohistochemistry study.

Immunohistochemistry

The sections were immunostained for GLUT1 using a polyclonal antibody and the Advance polymeric visualization system (DAKO, CA, USA). Two slides from the same TMA block, separated by 40 sections, were stained.

The sections were dewaxed, rehydrated and antigens retrieved into citrate buffer, pH 6.0, for 15 minutes in a pressure cooker (Pascal, Dako). After being cooled at room temperature and washed in water for 5 minutes, the sections were quenched in H_20_2 to block endogenous peroxidase activity, followed by protein block for 20 minutes.

The primary antibody was applied for 2 hours at room temperature and the stains were visualized with 3,3′-diaminobenzidine tetrachloride for 5 minutes. The slides were counterstained lightly with hematoxylin, dehydrated in ethanol and xylene and mounted with cover slips using permanent mounting medium. In negative control slides, the primary antibody was nonimmune IgG, with erythrocytes, which were present in every section, serving as internal controls. All immunohistochemical reactions were performed in duplicate.

Semiquantitative analysis was performed, as previously described,[30,32,33] wherein tumors with up to 10% of cells stained were considered to be negative and those with more than 10% were positive.

RESULTS

GLUT1 expression patterns varied between malignant tumor samples (Figure 1 and Table 1). Sarcomas, lymphomas, melanomas and hepatoblastomas did not express GLUT1 (Figure 2 and Table 1). However, in adenocarcinoma, cytoplasmic and diffuse patterns of staining were observed concomitantly with membranous staining (Figure 3).

In 195 prostate tumors, the proportion of GLUT1-positive:GLUT1-negative tumors was 92 : 103 (47% positive), 25 : 60 in 85 cases of thyroid tumor (29% positive cases, 35% of which were papillary and 19% follicular tumors), 38 : 339 in 377 gastric tumor samples (10% positive, 17% of which were intestinal and 14% diffuse tumors) and 13 : 254 in 267 breast tumor cases (5% positive) (Figure 3). Tables 1 and 2 summarise the immunohistochemistry results.

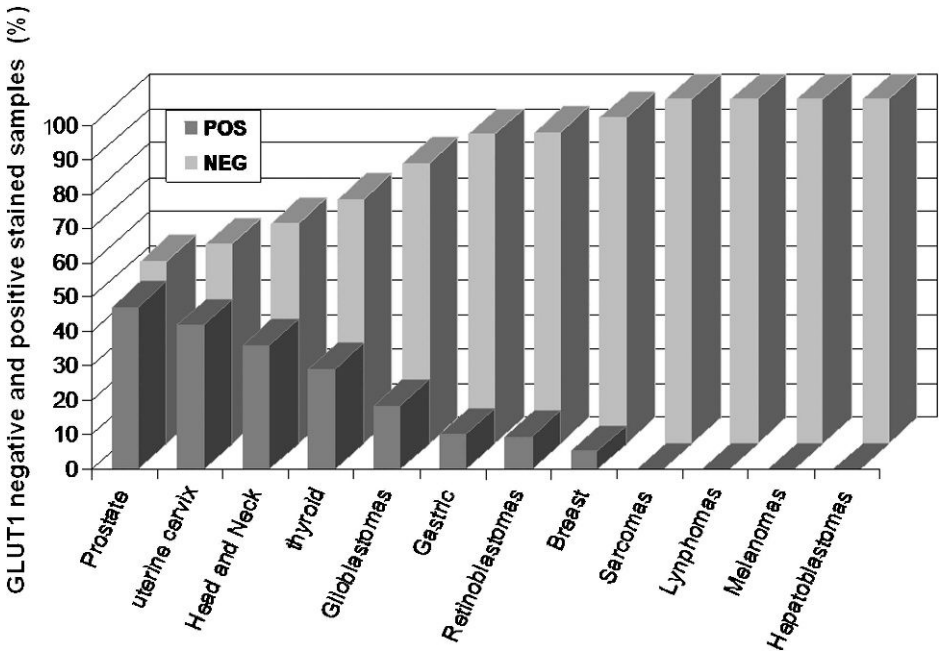

Figure 1 - Profile of GLUT1 expression by histological tumor type. The graph shows the percentage of GLUT1-positive (POS) and -negative (NEG) samples determined by immunohistochemistry.

Conversely, squamous cell carcinomas expressed GLUT1 exclusively in the membrane. In 172 cases of head and neck tumors, the proportion of GLUT1-positive:GLUT1-negative cases was 62 : 110 (36% positive) compared with 69 : 95 in 164 cervix uterine samples (42% positive) (Figure 3).

Glioblastoma and retinoblastoma samples showed membranous GLUT1 expression in 16 of 86 cases and 12 of 128 (18.6% and 9.4% positive cases), respectively.

DISCUSSION

Glucose transporters, such as GLUT1, mediate basal glucose transport in cancer cells, regulating the maintenance of energy metabolism in the cells located in limited supply tissue regions.[34] Hypoxia (low tissue oxygen pressure) is a hallmark of various cancers and is often associated with disease progression. That process occurs when tumors outgrow the existing vasculature. Thus, tumors respond to hypoxic conditions by activating genes that regulate glycolysis and glucose transport.[35]

Malignant cells require high energy levels via glycolytic generation of ATP to proliferate and survive. In cancer-induced starvation, GLUT1 overexpression governs mechanisms that favor tumor growth at the expense of host tissues.[36,37] Thus, we examined GLUT1 expression, because higher levels of GLUT1 in cancer indicate a poor prognosis.[38,39]

This study performed a novel examination of GLUT1 expression in several tumor types. GLUT1 expression and its function have not been previously reported in most of the tumors that we examined. We analyzed several primary sites and histological types of tumors (1955 tumors of 12 histological types; see Table 1 for reference) and observed that GLUT1 expression varied between tumor types. GLUT1 was evaluated by immunohistochemistry using a standardized scale, which considers tumors in which more than 10% of cells per field are stained to be positive.[30-33]

The patterns of GLUT1 expression in adenocarcinomas and squamous cell carcinomas differed in location and frequency in tumor cell compartments. Prostate, breast, gastric and thyroid adenocarcinomas showed cytoplasmic expression with varying intensities. The highest frequency of GLUT1 expression was observed in prostate (47%) and thyroid tumors (29%).

Some groups evaluated GLUT expression in human prostate cancer, noting GLUT1 and GLUT12 mRNA and protein expression.[40] Also, they observed membranous and cytosolic GLUT1 and GLUT12 expression in prostate carcinoma cell lines, demonstrating GLUT1 colocalization with the Golgi.

Recently, Jans et al.[41] suggested that cytoplasmic GLUT1 expression is an important prognostic factor. They showed that patients with elevated levels of GLUT1 have significantly shorter times before biochemical recurrence after radical prostectomy. Nevertheless, it is unknown whether elevated GLUT1 expression accurately reflects the hypoxic state of the tumor (the hypoxic state influences disease progression) or whether elevated GLUT1 levels are an indication of the altered metabolic state of tumor cells. Regardless, cytoplasmic GLUT1 expression can be used as a prognostic marker in prostate cancer.[40,42]

Our prostate adenocarcinoma samples showed robust cytoplasmic GLUT1 expression, consistent with other reports. But, the significance of cytoplasmic GLUT1 expression in several tumors is unknown, because it is active as a transporter only in the cell membrane. Recently, Taganaka and Frommer[43] examined whether glucose transporters that are destined for the plasma membrane are active during endoplasmic reticulum transit, concluding that GLUTs mediate endoplasmic reticulum glucose transport en route to the plasma membrane.

We grouped thyroid adenocarcinoma cases into 2 subtypes—papillary (35% positivity) and follicular (19% positivity)—both of which showed GLUT1 cytoplasmic

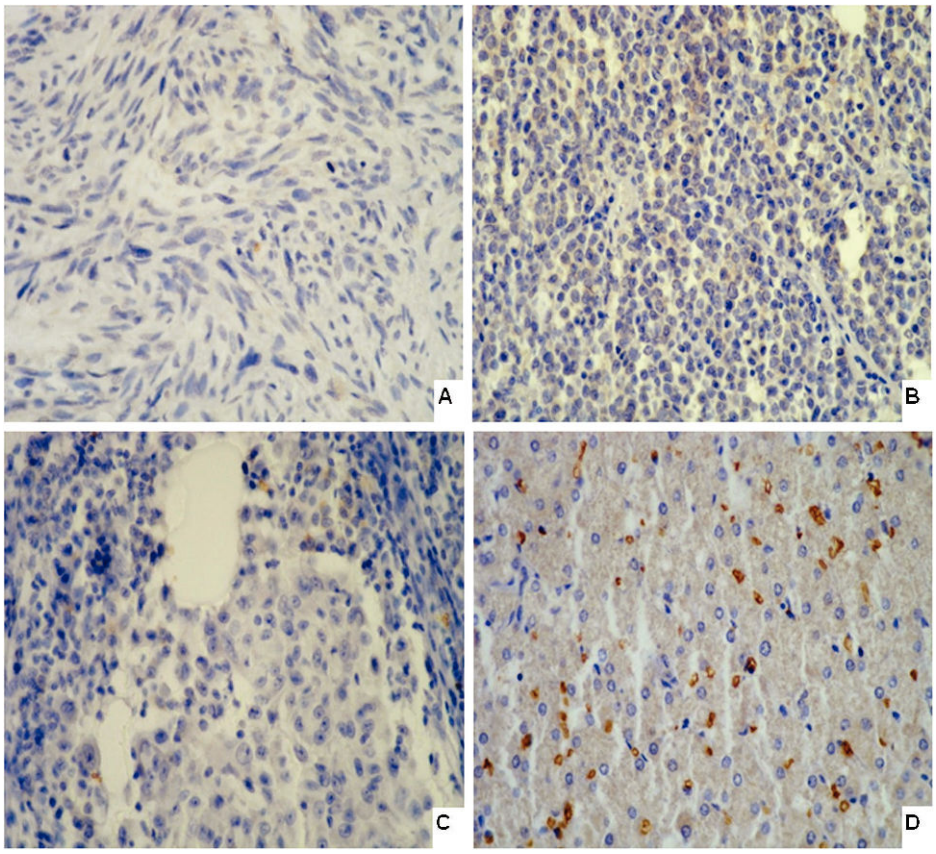

Figure 2 - Absence of GLUT1 expression. A, sarcoma sample; B, lymphoma; C, melanoma; D, hepatoblastoma.

expression. Similarly, a study[44] analyzed 268 cases of thyroid carcinoma by immunohistochemistry and observed that papillary carcinoma cells had membranous staining patterns (19%) and some cytoplasmic staining (52%). Moreover, they noted GLUT1 expression in 5% of follicular carcinomas but that all follicular adenomas and adenomatous goiters were negative. Their results suggest that GLUT1 can be used to distinguish papillary and follicular carcinomas and benign diseases. Also, GLUT1 might aid the determination of papillary carcinoma and lymph node metastasis; its membranous expression appears to have greater clinical value than its cytoplasmic expression.[44]

Another study[45] analyzed the expression of several GLUT isoforms in tumor cell lines from anaplastic, papillary, follicular and medullary human thyroid carcinomas. GLUT1 mRNA was expressed in malignant tissues and was the most prevalent isoform in less-differentiated cells.[45]

Ten per cent of gastric tumors (including intestinal and diffuse tumors) are positive for GLUT1, generating cytoplasmic patterns. In 2001, Kawamura et al.[46] evaluated 667 gastric tumors (including 50 tubular gastric adenomas and 617 gastric carcinomas) by immunohistochemistry and showed that 182 gastric carcinomas, but none of the tubular gastric adenomas, expressed GLUT1. Moreover, in an analysis of clinicopathological characteristics, GLUT1 was expressed late in carcinogenesis, increasing with disease progression. The authors considered only membrane-specific reactions to be positive.[46]

Subsequently, Wei et al.[47] examined GLUT1 expression in gastric carcinomas and observed a stronger correlation between expression and clinical parameters, suggesting that GLUT1 is a prognostic factor. In our study, we evaluated many samples and noted robust cytoplasmic staining and, additionally, some gastric tumors showed membranous staining. Both membrane and cytoplasmic staining patterns were considered to be positive in our analysis.

GLUT expression[48-54] has been correlated to tumor grade in breast cancer.[54,55] Hao et al.[56] linked GLUT1 overexpression and progression of breast carcinoma. However, GLUT1 is absent in fibroadenoma and hyperplastic lesions, suggesting it as a target for treatment. Groves et al.[57] examined the correlation between ^{18}F-FDG uptake and GLUT1 or CD105 expression in 20 patients with early breast cancer, observing a poor association. A stronger correlation was noted between CD105, a marker of angiogenesis, and PET results in patients with early breast cancer. No significance was observed in GLUT1 analysis. In our experiments, only 5% of breast tumors (13/254 samples) expressed GLUT1.

Because we did not assess the clinical characteristics of our patients, we could not determine whether the smaller number of GLUT1-expressing samples was due to variations in disease status and development. Also, several compounds have been reported to regulate glucose transporter expression in breast cancer, such as hypoxia, estradiol and epidermal growth factor.[7]

Polymorphisms in *GLUT1* have also been considered as a regulator of expression. Grabellus et al.[58] analyzed 3 *GLUT1* polymorphisms and observed increased glucose uptake in samples that harbored the *XbaI* G>T single nucleotide

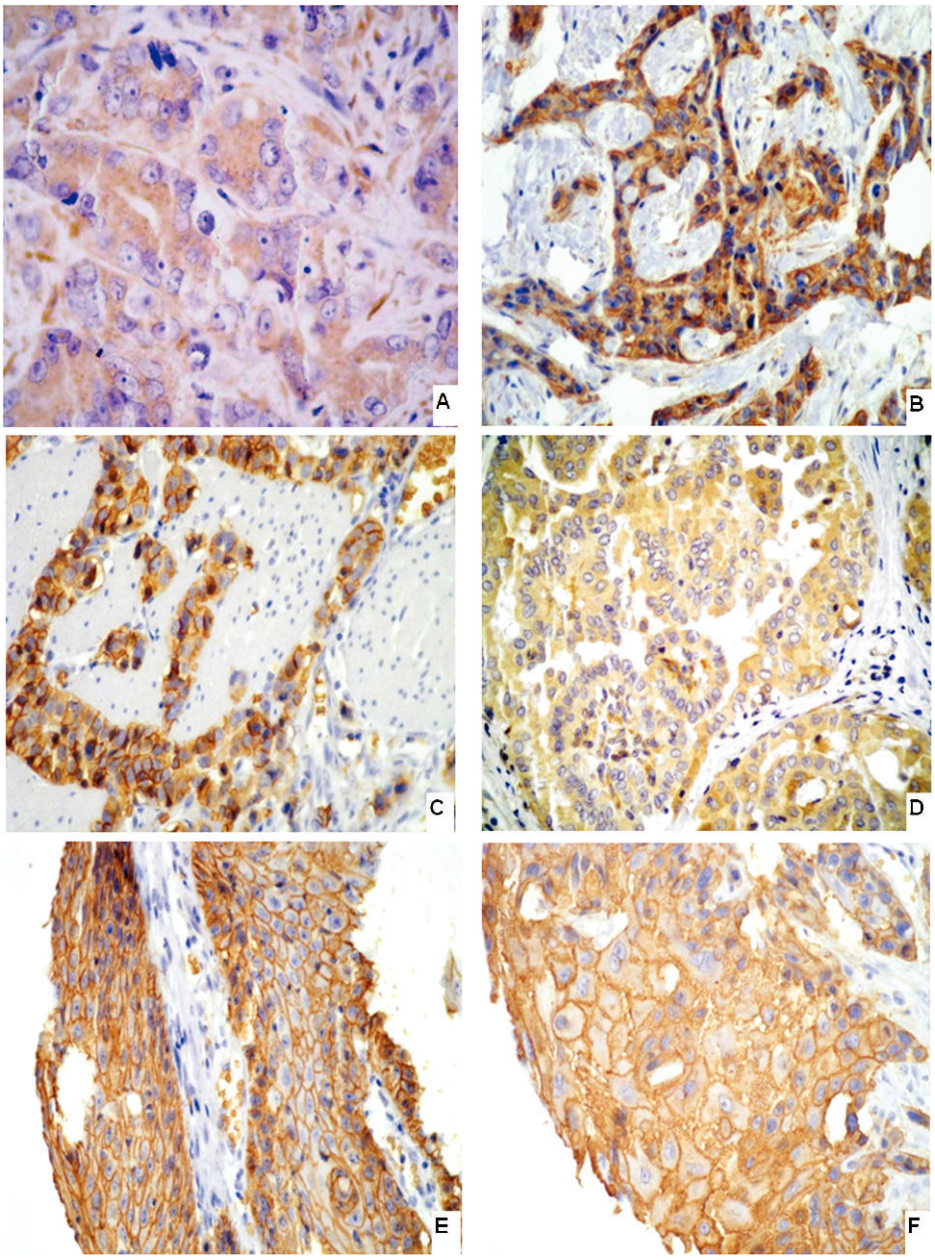

Figure 3 - Cytoplasmic GLUT1 expression in adenocarcinomas and membrane expression in squamous cell carcinomas. A, prostate tumor; B, papillary thyroid tumor; C, gastric tumor; D, breast tumor; E, squamous cell carcinoma of uterine cervix; F, squamous cell carcinoma of the head and neck.

polymorphism by PET. They did not assess GLUT1 levels but noted that *GLUT1* polymorphisms interfered with glucose uptake in tumors. However, the variability in GLUT1 expression in breast tumor must be further examined.

In general, we observed adenocarcinomas with cytoplasmic GLUT1 expression (with or without continuous staining of the membrane). This expression profile has not previously been described in tumors, necessitating further investigation of its effects on tumor behavior and biology.

Head and neck (36%) and cervix uterine squamous cell carcinomas (42%) showed significant membranous staining in our samples. GLUT1 function in squamous cell carcinoma biology and behavior is being examined by our group. Invariably, GLUT1 is overexpressed in head and neck tumors. Similarly, Baer et al.[59] noted consistent overexpression of GLUT1 (100%) in 48 biopsy specimens from patients with laryngeal invasive carcinoma; this expression does not influence survival rates.

GLUT1 is highly expressed in squamous cell carcinomas of the head and neck (HNSCCs).[60] That GLUT1 expression increases in dysplastic lesions and sustains its expression in squamous cell carcinoma indicates that changes in GLUT1 levels represent early events during the development of HNSCCs. The study authors concluded that GLUT1 is a reliable marker in the diagnosis of premalignant lesions of the oropharyngeal mucosa. Recently, we demonstrated that higher GLUT1 expression in oral squamous cell carcinoma is associated with poor prognosis.[61]

Table 2 - Profile of GLUT1 immunoexpression in tumors according to location.

Tumor type	GLUT1 staining	
	Cytoplasm (%)	Membrane (%)
Adenocarcinomas		
Prostate	47	-
Thyroid	29	-
Gastric	10	-
Breast	5	-
Squamous cell carcinomas		
Head and neck	-	36
Cervix uterine	-	42
Glioblastomas	-	18.6
Retinoblastomas	-	9.4

Few studies have examined GLUT expression in melanomas, lymphomas, sarcomas and hepatoblastomas, and some of these concluded that GLUT1 levels in melanoma samples by immunoblotting contribute to variability in the responses of these tumors to treatment.[62]

GLUT1 is also expressed in sarcomas, detected in 50% of intrauterine leiomyosarcomas and 25% of extrauterine sarcomas by immunohistochemistry. GLUT1 positivity correlates closely with aggressive biological behavior, reflected by distant metastatic spread.[63] Our samples comprised a wide and heterogeneous group of sarcomas, but we failed to detect GLUT1 in any of these cases.

There was no detectable expression of GLUT1 in our sarcoma, melanoma, hepatoblastoma or lymphoma samples, which suggests that another glucose transporter maintains glycolytic metabolism in these tumors or that GLUT1 is expressed at specific stages of carcinogenesis. Lymphomas might be such an example. These tumors rarely express GLUT1 but frequently express GLUT3. Recent studies with PET have shown that primarily T-cell lymphomas and indolent malignant lymphomas have lower metabolic activity.[64,65] Our group examined GLUT3 expression in non-Hodgkin lymphoma samples, observing higher levels in tumor cells (data not shown). Also, some studies have shown that prostate adenocarcinomas preferentially express GLUT12, in association with lower levels of GLUT1.[66]

We cannot reject the hypothesis that inhibitory elements block GLUT1 protein, such as post-transcriptional regulatory factors, GLUT1 polymorphisms and epigenetic events. Nevertheless, GLUT1 can be a useful marker for the differential diagnosis of negative tumors and others.

To this end, PET scans are useful in determining the prognosis of several tumors, as described for breast, lymphomas, thyroid, oral squamous cell carcinomas and other cancers,[33,41,56,58,67] providing anatomical and metabolic data on tumors. PET scans have provided indirect evidence about the function of GLUT1 in carcinogenesis, and several studies have correlated glucose analog (^{18}F-FDG) uptake and tumor aggressiveness.[68-70] Thus, this technique demonstrates the value of ^{18}F-FDG as a prognostic factor for hepatocarcinomas, breast and colorectal cancers, thymic epithelial tumors and other cancers.

Tumors that express little or no GLUT1 may pose a challenge for PET scan analysis—for example, when tumors express another glucose transporter that cannot be recognized or does not have affinity for ^{18}F-FDG. Our results suggest that immunohistochemical staining of GLUT1 can identify patients for evaluation by PET.

Similarly to other reports, our results demonstrate variable GLUT1 expression in different tumor types. Yet, we believe that its absence in sarcomas, melanomas, hepatoblastomas and lymphomas suggests that other glucose transporters regulate the glycolytic pathway in these tumors. The true function of cytoplasmic GLUT1 in adenocarcinomas must be examined further.

ACKNOWLEDGMENTS

Financial support was provided by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Fundação de Amparo à Pesquisa no Estado de São Paulo (FAPESP). The authors thank the Fundação Antônio Prudente, Hospital A. C. Camargo. We also are thankful for José I. Neves, Carlos F. Nascimento and Severino S. Ferreira for their expert technical assistance.

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