GLUT1 Messenger RNA and Protein Induction Relates to the Malignant Transformation of Cervical Cancer

Christian Rudlowski, MD,1 Albert J. Becker, MD,2 Willibald Schroder, MD,3 Werner Rath, MD,1 Reinhard Büttner, MD,4 and Markus Moser, PhD5

Key Words: GLUT1; HPV; Human papillomavirus; Cervical neoplasm; Glucose metabolism

DOI: 10.1309/4KYNOM5862JW2GD7

Abstract

We studied whether induction of glucose transporters (GLUTs) 1 to 4 correlates with human papillomavirus (HPV)-dependent malignant transformation of cervical epithelium. Tissue samples of cervical intraepithelial neoplasia (CIN; grades 1 to 3), invasive carcinomas, and lymph node metastases were examined. HPV typing was performed. Tissue sections were immunostained with GLUT1 to GLUT4 antibodies. Messenger RNA (mRNA) in situ hybridization confirmed GLUT1 protein expression.

Weak expression of GLUT1 was found in nondysplastic HPV-positive and HPV-negative epithelium; significant expression was observed in preneoplastic lesions, correlating with the degree of dysplasia. In CIN 3 high-risk HPV lesions, cervical cancer, and metastasis, GLUT1 was expressed at highest levels with a strong correlation of GLUT1 mRNA and protein expression. Immunostains for GLUT2 to GLUT4 were negative.

Cervical tumor cells respond to enhanced glucose utilization by up-regulation of GLUT1. The strong induction of GLUT1 mRNA and protein in HPV-positive CIN 3 lesions suggests GLUT1 overexpression as an early event in cervical neoplasia. GLUT1 is potentially relevant as a diagnostic tool and glucose metabolism as a therapeutic target in cervical cancer.

It has been known for several decades that tumor cells show enhanced glucose metabolism compared with benign tissues.1 A continuous supply of glucose is the predominant source of adenosine triphosphate generation and substrate storage in mammalian cells. Molecular cloning of the glucose transporter protein 1 (GLUT1) that catalyzes the uptake of glucose in erythrocytes2 and the subsequent identification of homologous genes (GLUT2, GLUT3, GLUT4, and GLUT5) revealed a family of genes to facilitate diffusion of hexoses into mammalian cells.3 On the basis of sequence similarities and functional characteristics, GLUTs can be divided into 3 subfamilies, referred to as class I (GLUTs 1-4), class II (GLUTs 5, 7, 9, and 11), and class III (GLUTs 6, 8, 10, and 12 and the myo-inositol transporter HMIT1).4

Altered expression of glucose transporter proteins has been described in different tissues under various conditions such as transformation by oncogenes, hypoxia, and exposure to insulin.5 In vivo, the storage of glycogen has been related to the differentiation status of squamous cell epithelia.6,7 In glucose-deprived 3T3-L1 adipocytes, GLUT1 activation by glucosylation relates to increased storage of glycogen.8 Cell culture experiments showed that the expression of GLUT1 transporter protein is induced by certain oncogenes such as ras and src,9,10 and regulated by the growth factors such as platelet-derived growth factor and epidermal growth factor.11,12

Furthermore, members of the class I family of glucose transporter proteins were expressed strongly in various solid tumors such as breast cancer,13,14 renal cell carcinomas,15,16 brain tumors,17 and gastrointestinal malignomas.18 So far, class II and III GLUT members have not been observed to be relevant for tumorigenesis or tumor progression.19
Little is known about the expression pattern of GLUTs in cervical neoplasms. Increased glucose uptake demonstrated by positron emission tomography (PET) suggests a potential pathophysiologic role of glucose metabolism in cervical cancer. The malignant progression of cervical carcinomas from preinvasive lesions may serve as a paradigm for tumorigenesis along well-defined pathologic stages and pathogenesis. The development of cervical neoplasia is associated with the human papillomavirus (HPV). Viral integration guarantees perpetual expression of HPV-related viral oncogenes. These molecular changes are produced most consistently by the prototypic high-risk HPV types (eg, 16, 18, 31, and 33), but many others (low-risk types, eg, 6, 11, and 40) may be associated with invasive cancer.

We studied the relationship of HPV-related cervical tumor transformation, cellular glycogen storage and expression, and distribution of GLUT1, GLUT2, GLUT3, and GLUT4.

**Materials and Methods**

Tissue sections were prepared from formalin-fixed, paraffin-embedded archival specimens of cervical neoplasms obtained by surgery. Of 90 available tissue samples from cone biopsies performed for preneoplastic cervical lesions, 18 were mild cervical intraepithelial neoplasia (CIN 1), 24 were moderate (CIN 2), and 48 were severe dysplastic lesions (CIN 3). The cervical carcinoma specimens and the cervical lymph node metastasis specimens were obtained from 94 patients who underwent radical surgical resections at the Department of Gynecology and Obstetrics, University Hospital, Aachen, Germany, between August 1995 and September 1997. Tissue specimens from 22 pelvic lymph node metastases were studied. The histologic diagnosis and grade of dysplasia were confirmed by 2 pathologists (R.B. and M.M.) according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO classification) and the World Health Organization. The tissue specimens were 22 pelvic lymph node metastases were studied. The histologic diagnosis and grade of dysplasia were confirmed by 2 pathologists (R.B. and M.M.) according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO classification) and the World Health Organization. The tissue specimens were 22 pelvic lymph node metastases were studied. The histologic diagnosis and grade of dysplasia were confirmed by 2 pathologists (R.B. and M.M.) according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO classification) and the World Health Organization. The tissue specimens were 22 pelvic lymph node metastases were studied. The histologic diagnosis and grade of dysplasia were confirmed by 2 pathologists (R.B. and M.M.) according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO classification) and the World Health Organization. The tissue specimens were 22 pelvic lymph node metastases were studied. The histologic diagnosis and grade of dysplasia were confirmed by 2 pathologists (R.B. and M.M.) according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO classification) and the World Health Organization. The tissue specimens were 22 pelvic lymph node metastases were studied. The histologic diagnosis and grade of dysplasia were confirmed by 2 pathologists (R.B. and M.M.) according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO classification) and the World Health Organization. The tissue specimens were 22 pelvic lymph node metastases were studied. The histologic diagnosis and grade of dysplasia were confirmed by 2 pathologists (R.B. and M.M.) according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO classification) and the World Health Organization. The tissue specimens were 22 pelvic lymph node metastases were studied. The histologic diagnosis and grade of dysplasia were confirmed by 2 pathologists (R.B. and M.M.) according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO classification) and the World Health Organization. The tissue specimens were 22 pelvic lymph node metastases were studied. The histologic diagnosis and grade of dysplasia were confirmed by 2 pathologists (R.B. and M.M.) according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO classification) and the World Health Organization. The tissue specimens were 22 pelvic lymph node metastases were studied. The histologic diagnosis and grade of dysplasia were confirmed by 2 pathologists (R.B. and M.M.) according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO classification) and the World Health Organization. The tissue specimens were 22 pelvic lymph node metastases were studied. The histologic diagnosis and grade of dysplasia were confirmed by 2 pathologists (R.B. and M.M.) according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO classification) and the World Health Organization. The tissue specimens were 22 pelvic lymph node metastases were studied. The histologic diagnosis and grade of dysplasia were confirmed by 2 pathologists (R.B. and M.M.) according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO classification) and the World Health Organization. The tissue specimens were 22 pelvic lymph node metastases were studied. The histologic diagnosis and grade of dysplasia were confirmed by 2 pathologists (R.B. and M.M.) according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO classification) and the World Health Organization. The tissue specimens were 22 pelvic lymph node metastases were studied. The histologic diagnosis and grade of dysplasia were confirmed by 2 pathologists (R.B. and M.M.) according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO classification) and the World Health Organization. The tissue specimens were 22 pelvic lymph node metastases were studied. The histologic diagnosis and grade of dysplasia were confirmed by 2 pathologists (R.B. and M.M.) according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO classification) and the World Health Organization.

For immunohistochemical analysis, 3-µm sections were deparaffinized and rehydrated. After rinsing with phosphate-buffered saline, endogenous peroxidase activity was inhibited by incubation in 3% hydrogen peroxide solution for 30 minutes, and the slides were incubated in a 1:10 solution of equine normal serum to block nonspecific staining.

After antigen retrieval by microwave treatment (600 W) for 5 minutes (3 times) in a 10-mmol/L concentration of sodium citrate, slides were incubated for 60 minutes with polyclonal rabbit antihuman GLUT1 (DAKO, Hamburg, Germany) and polyclonal rabbit GLUT2, GLUT3, and GLUT4 antibodies (Biogenesis, New Field, England). The antibodies were diluted with bovine serum albumin according to the manufacturer’s instructions. As a negative control, slides were reacted with equal amounts of nonspecific IgG instead of the specific primary antibody. After rinsing in phosphate-buffered saline, slides were incubated with a 1:50 dilution of biotinylated secondary antibody (DAKO) for 30 minutes and developed using the ABC technique (Vectastain ABC Systems, Vector Laboratories, Peterborough, England) according to the manufacturer’s instructions. Immunocomplexes were visualized with the chromogen diaminobenzidine. Staining for glycogen was performed by the periodic acid–Schiff (PAS) reaction and counterstaining with toluidine blue.

The specificity of GLUT1 staining was confirmed routinely in all cases by staining of parallel tissue sections with GLUT1 antiserum that had been preincubated with the immunizing peptide (25µg/mL for 1 hour at 25°C). GLUT1 immunostaining was blocked by this peptide competition in all cases. The sections were evaluated semiquantitatively for immunoreactivity and PAS staining, based on a scoring system that was defined by the product of the intensity of the staining and the percentage of the stained cells. The specimens were subdivided into strong (50% or more marked cells), moderate (25%-49%), weak (10%-24%), and not marked for GLUT1 and glycogen (<10%). Grading was performed by consensus of 2 observers (R.B. and M.M.) in a blinded manner without previous knowledge of the histopathologic and clinical data for each case.

In situ hybridization was performed on paraffin-embedded tissue samples from different cervical biopsies as described previously, using phosphorus 33 (33P)-labeled sense and antisense complementary RNA riboprobes for rat GLUT1. Briefly, Proteinase K–pretreated slides (10µg/mL) were acetylated in acetic anhydride diluted 1:400 in a 0.1-mol/L concentration of triethanolamine (pH 8.0) and hybridized overnight in 50% formamide, 10% dextran sulfate, a 10-mmol/L concentration of tris(hydroxymethyl)aminomethane (pH 8.0), a 10-mmol/L concentration of sodium phosphate (pH 7.0), 2x standard saline citrate, a 5-mmol/L concentration of EDTA (pH 8.0), 150-µg/mL concentration of transfer RNA, a 10-mmol/L concentration of dithiothreitol, and a 10-mmol/L concentration of β-mercaptoethanol supplemented with 5 x 10⁴ cpm/µL of 33P-labeled sense or antisense riboprobes at 50°C. Finally, slides were washed twice in 50% formamide–2x standard saline citrate–20-mmol/L concentration of β-mercaptoethanol, digested with RNase A (20µg/mL) for 30 minutes at 37°C, and washed again 3 times with the same washing buffer for 30 minutes each at 50°C. After dehydrating, slides were...
coated with Kodak NTB2 emulsion (Kodak, Rochester, NY) and exposed for 8 to 10 days. The intensity of the silver staining was examined by darkfield microscopy, and digitalized images were examined using ImageJ 1.27z software (National Institutes of Health, Bethesda, MD). The Student t test was used for statistical analysis.

For detection and typing of HPV, tissue sections were digested by Proteinase K, and DNA was extracted using the DNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer’s instructions. To detect HPV DNA, a 2-tiered polymerase chain reaction (PCR)–direct sequencing method was performed according to Feoli-Fonseca et al with slight modifications. We used the general consensus primers GP5+/GP6+ and the MY09/MY11 primers for amplification of HPV DNA. Forty cycles of amplification were run with an initial denaturation at 95°C for 5 minutes and for 30 seconds in each cycle. Temperatures of 37°C and 58°C were set for 30 seconds for annealing of the primer pairs GP5+/GP6+ and MY09/MY11, respectively. An extension step was done at 72°C for 5 minutes. The integrity of human genomic DNA was verified by PCR amplification of the β-globin gene. This reaction served as a positive control. The amplification products of the 2 consensus primer pairs and the β-globin PCR were run on a 2% agarose gel and stained with ethidium bromide.

PCR products were purified using the High Pure PCR product purification kit (Roche Diagnostics, Mannheim, Germany) according to the manufacturer’s instructions. The sequence of 1 strand of the purified PCR fragments was determined with the Big-Dye Terminator sequencing kit (Applied Biosystems, Foster City, CA) using 3 to 5 pmol of GP5+ or MY09 as the sequencing primers. The results of the sequencing reactions were analyzed on an ABI Prism 310 automated sequencer (Applied Biosystems). The obtained sequences were compared with documented virus sequences available in the GenBank databank using the Blast program (Blast, Pittsboro, NC). The high-risk group comprised HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68, and the low-risk group included HPV types 6, 11, 40, 42, 43, and 44. The Student t test was used for statistical analysis.

**Results**

GLUT1-expressing epithelial cells were observed in squamous epithelial cells of normal and dysplastic cervical tissue probes. However, GLUT1 expression in normal epithelial cells was limited to the basal cell layers [Image 1A]. Staining intensity was weak and varied in the basal compartment from a focal to homogeneous pattern distribution. All 34 specimens obtained from benign cervical tissue were classified as weak or not marked. Compared with GLUT1 expression in the proliferative cell compartment in the basal cell layer, changes such as inflammatory atypia, metaplasia, and hyperplasia showed similar GLUT1 expression patterns and also were classified as weakly marked.

The intensity of GLUT1 expression was unaltered from the HPV status. Of 14 HPV-positive specimens, 6 showed high-risk positivity and 8 showed low-risk positivity [Table II].

Erythrocytes and vascular endothelium served as internal positive controls and demonstrated strong GLUT1 positivity. Simultaneous PAS staining of the epithelium revealed the glycogen content to be correlated inversely to the expression of GLUT1 [Figure 1]. The glycogen staining was limited predominantly to the upper cell compartments, which contain the functional epithelium. In good agreement with these immunostaining results, in situ hybridization showed GLUT1 messenger RNA (mRNA) expression to be present specifically in the basal epithelium [Image 1B].

In mildly dysplastic epithelium (n = 18), weak GLUT1 expression was limited to the basal cell layers [Image 1C] and [Image 1D], and in moderate dysplasia (n = 24), enhanced expression was extended to the basal and parabasal compartments. The GLUT1 expression pattern was independent of HPV status. In CIN 1 lesions, 4 cases were in the high-risk HPV group, 6 were in the low-risk HPV group, and 8 were HPV-negative cases. Compared with benign cervical changes, significantly increased GLUT1 expression was observed in CIN 1 lesions [Image 2].

Strong GLUT1 mRNA and protein expression was observed in all 48 CIN 3 lesions of the cervix uteri [Image 1E] and [Image 1F]. GLUT1 expression was continuously strong throughout the entire dysplastic epithelium, including the basal, suprabasal, and apical parts of the cervical epithelium. Of 48 CIN 3 lesions, 46 were HPV positive; 34 cases belong to the high-risk group and 12 to the low-risk group. No differences between the HPV type or status and GLUT1 expression were observed. Only weak glycogen storage was observed in CIN 3 lesional tissue samples.

Tumors with moderate dysplasia showed a high percentage of HPV positivity (high-risk HPV, 16 cases; low-risk HPV, 3 cases; HPV type not assignable, 2 cases; HPV-negative, 3 cases). The intensity of GLUT1 protein expression depended on the extent of dysplasia and was accompanied by inversely correlated glycogen content in the nondysplastic areas of the epithelium (Figure 1).

GLUT1 overexpression was demonstrated in all 94 cases of invasive cervical carcinoma and all 22 cervical metastases [Image 1G] and [Image 1H]. The intensity of GLUT1 protein expression did not vary significantly between different tumor stages, the degree of tumor differentiation, or HPV status. A high-risk HPV type was detectable in 84 cases and a low-risk type in 8 cases. In 2 specimens, no HPV was detectable.

GLUT1 expression was observed predominantly at the tumor periphery compared with the center of well-differentiated...
tumor areas. By PAS staining, we found an accumulation of glycogen in well-differentiated tumor areas, which was correlated inversely with GLUT1 expression. A similar distribution pattern was found in the lymph node metastases.

**Figure 2** illustrates the results of GLUT1 mRNA in situ hybridization. The intensity of the specific silver staining correlated significantly with the extent of cervical dysplasia and showed similar levels in CIN 3 lesions and cervical carcinoma. Overexpression of mRNA was limited to dysplastic cells and matched the patterns of GLUT1 protein distribution revealed by immunohistochemical analysis.

Immunostains for GLUT2, GLUT3, and GLUT4 were negative in epithelial cells of both benign and dysplastic lesions. Only inflammatory cells reacted with the antibodies and served as an internal positive control. In the advanced and poorly differentiated tumors, there was a pattern of expression similar to that in the dysplastic precursor lesions.

**Discussion**

Based on numerous molecular and epidemiologic studies, it has been demonstrated that specific types of HPV (high-risk HPVs, but also to a lower extent low-risk HPVs) can be detected in a transcriptionally active form in about 95% of cervical cancer biopsy specimens. Although the high-risk HPV-encoded oncogenes E6 and E7 induce
Table 1
HPV Status, GLUT1 Expression, and PAS Staining in the Study Group*

<table>
<thead>
<tr>
<th></th>
<th>Benign Cervical Tissue (n = 34)</th>
<th>CIN 1 (n = 18)</th>
<th>CIN 2 (n = 24)</th>
<th>CIN 3 (n = 48)</th>
<th>Cervical Cancer (n = 94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV positive</td>
<td>14 (41)</td>
<td>10 (56)</td>
<td>21 (88)†</td>
<td>46 (96)</td>
<td>92 (98)</td>
</tr>
<tr>
<td>High risk</td>
<td>6 (18)</td>
<td>4 (22)</td>
<td>16 (67)</td>
<td>34 (71)</td>
<td>84 (89)</td>
</tr>
<tr>
<td>Low risk</td>
<td>8 (24)</td>
<td>6 (33)</td>
<td>3 (13)</td>
<td>12 (25)</td>
<td>8 (9)</td>
</tr>
<tr>
<td>GLUT1 expression</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>PAS staining</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>

CIN, cervical intraepithelial neoplasia; GLUT, glucose transporter; HPV, human papillomavirus; PAS, periodic acid–Schiff; –, negative; +, weak; ++, moderate; ++++, strong.

† Data for HPV are given as number (percentage). High-risk HPV infection was related closely to the degree of dysplasia and coincided with increasing GLUT1 expression.

In 2 cases (8%), the HPV type was not assignable.
cellular immortalization, their expression alone is not sufficient to cause malignant transformation. Additional events must accumulate to convert a cell toward malignancy and to induce cervical cancer. It has been shown that the course of malignant disease not only is the result of failing intracellular and immunologic surveillance mechanisms but also is determined by efficient blood vessel formation to support the outgrowing tumor with nutrients, hormones, and oxygen. Many tumorigenic cells are characterized not only by increased mitotic rates but also by high catabolic utilization of glucose and an increased number of specific glucose transporters. A sufficient intracellular glucose supply mediated by glucose transporters seems to be a prerequisite for enhanced HPV transcription and the expression of the E6 and E7 oncoproteins. In cell culture experiments using cervical cancer cells, specific suppression of the HPV 18 transcription was found by adding the glycolytic pathway inhibitor 2-deoxyglucose.

Our results demonstrate that human cervical carcinomas and their metastases selectively overexpress GLUT1. In benign cervical epithelium, moderate GLUT1 expression was restricted to the proliferating basal cell layers of the mucosa and changes such as inflammatory or squamous atypia, immature metaplasia, or basal cell hyperplasia. These findings are in line with the differentiation-related expression pattern of GLUT1 in normal human epidermis, in which GLUT1 is expressed in the basal layer and, to a lesser extent, in the immediate suprabasal layer of the epidermis. GLUT1 mRNA expression precisely coincided with protein overexpression in normal epithelium, cervical dysplasia, and invasive cancers. These findings strongly suggest that the increased GLUT1 expression in cervical neoplasms is mediated by transcriptional mechanisms.

In vitro studies on fibroblasts transfected with ras and src oncogenes revealed elevated levels of GLUT1 expression and an increase of transmembranous glucose transport. These
results support our present findings indicating that GLUT1 overexpression parallels malignant transformation of cervical epithelial cells. However, the regulatory mechanisms of GLUT1 induction are, so far, poorly understood. Tumor hypoxia might be a key step for up-regulation of GLUT1 transcripts.32

However, we have observed overexpression in preneoplastic lesions. This might suggest direct oncogene-triggered mechanisms as potential factors for GLUT1 up-regulation. GLUT1 expression was not correlated with the HPV status or type in either benign or dysplastic cervical epithelium. High-risk HPV types were detectable predominantly in CIN 2 and 3 lesions and invasive cervical cancer and had good correlation with the dysplastic stage. All high-risk HPV-infected CIN 2 and 3 lesions and carcinoma showed enhanced GLUT1 expression. There is certain evidence that these cases are associated with virus transcription and the expression of E6 and E7 oncogenes.24 An enhanced cellular glucose supply mediated by an increasing number of GLUT1 transporters could be a requirement for successful HPV-dependent malignant transformation.

Our results indicate that the clinical observation of an increased glucose uptake of cervical cancer cells was related to an exclusive transmembranous overexpression of GLUT1. These data strongly suggest that the observed relationship between increased GLUT1 expression and the intracellular accumulation of 2-fluoro-deoxy-D-glucose (FDG) in tumor cells represents the biologic basis for diagnosis using fluorine 18-labeled FDG PET.20,33 Enhanced expression of GLUT1 was detected already in moderate cervical dysplasia and much more in carcinoma in situ. In these preneoplastic lesions, the staining pattern of GLUT1 expression was stronger than in normal or mildly dysplastic mucosa and extended into the superficial cell layers depending on the degree of dysplasia. The observation that the preneoplastic lesions with increased GLUT1 expression were not detected by PET analysis may be explained by the small dimension of the epithelial dysplasia and the limited resolution of PET.

We also analyzed the cellular glycogen content to determine whether alterations in glucose uptake are linked to tumor-associated changes in the storage of this polysaccharide. The glycogen content was of special interest because the presence of glycogen is known to be related to cellular maturation of squamous epithelium and disappears with loss of differentiation during neoplastic transformation.6 In the present study, glycogen was found only in nondividing cells of the superficial layers of the benign cervical epithelium, whereas the basal layers did not contain glycogen (Image 1A). The glycogen content in normal and preneoplastic lesions generally correlated inversely with GLUT1 expression, exhibiting intense glycogen storage in normal and reduced or absent storage in dysplastic epithelium. Thus, reduction of glycogen content was related closely to the degree of dysplasia and was associated strongly with increased GLUT1 expression.

The observed storage pattern of glycogen was correlated inversely with the extension of the proliferation compartment and is in line with previous observations showing an association between glycogen content and tumor cell development, as well as differentiation in squamous cell carcinoma tumorogenesis.34 This cellular feature reflects the growing and metastasizing potency of cervical carcinomas, as increased utilization of glucose is a necessary condition of growing tumors and may be the pathophysiologic basis for induction of glucose transporter protein expression in the cell membrane. The lack of expression in benign cervical tissue and in the well-differentiated center of some cervical tumors gives rise to the assumption that GLUT1 expression might be regarded as a characteristic feature of tumor cell clones with an increased energy requirement.

In contrast with data from colon35 and non–small cell pulmonary carcinoma,36 no correlation between GLUT1 expression and prognostic clinicopathologic features was found in the present study. This difference can be explained easily, since significant overexpression of GLUT1 is observed in premalignant cervical lesions and well-differentiated carcinomas. We, therefore, believe that GLUT1 overexpression is an early event in the development of cervical carcinomas. Our findings also may have substantial implications for the potential therapeutic application of cytotoxic agents conjugated to glucose in the treatment of premalignant or malignant cervical lesions. Further studies are required to explore whether this strategy will lead to more specific drug delivery to the neoplastic cell compartment.
From the 1Department of Gynecology and Obstetrics, University Hospital Heidelberg, Heidelberg; 2Department of Neuropathology and 3Institute of Pathology, University of Bonn Medical Center, Bonn; 4Central Hospital, Bremen, University of Bonn Medical Center; and 5Department for Molecular Medicine, Max-Planck-Institut for Biochemistry, Martinsried, Germany.

Address reprint requests to Dr Rudlowski: Dept of Gynecology and Obstetrics, University Hospital Heidelberg, Vossstr7-9, D-69115 Heidelberg, Germany.

References