Observational Study

INTERNATIONAL JOURNAL OF SURGERY ONCOLOGY

OPEN

UDP-glucose 6-dehydrogenase expression as a predictor of survival in patients with pulmonary adenocarcinoma

Shekhar Saha, MD[a], Sha Yao, MD[b], Omar Elakad, MS[b], Anna-Maria Lois, MD[b], Hannah Henric-Petri, MD[b], Judith Buentzel, MD[c], Marc Hinterthaner, MD[a], Bernhard C. Danner, MD[a], Philipp Ströbel, MD[b], Alexander Emmert, MD[a], Hanibal Bohnenberger, MD[b,*]

Background: UDP-glucose-6-dehydrogenase (UGDH) plays an important role in the production of hyaluronic acid, an extracellular matrix component that is responsible for the promotion of normal cellular growth and migration. Increased levels of UGDH have been linked to the progression of epithelial cancers, such as those of the breast, colon and prostate. Therefore we aimed to analyze if the expression level of UGDH does also influence patients survival of lung cancer patients.

Methods: UGDH expression levels were analyzed by immunohistochemistry in 96 samples of pulmonary adenocarcinoma (AC), 84 cases of squamous cell lung carcinoma (SQCLC) and 33 samples of small cell lung cancer (SCLC) and correlated with clinicopathologic characteristics and patient outcome.

Results: UGDH was expressed in 62.5% cases of AC, 70.2% cases of SQCLC, and 48.5% cases of SCLC. In AC, expression of UGDH was significantly associated with lymph node metastasis and worse overall survival of the affected patients. However, UGDH expression had no significant correlation to prognosis in SQCLC or SCLC patients.

Conclusions: In our study, expression of UGDH was associated with worse prognosis of patients with pulmonary adenocarcinoma so that expression of UGDH might help to guide treatment decisions. Furthermore, UGDH might present a potential novel drug target in AC as it displays inhibitable catalytic activity.

Keywords: UDP-glucose 6-dehydrogenase, Adenocarcinoma, Lung cancer, Prognostic marker

Lung cancer results in about 1.6 million deaths worldwide each year[1]. About 85% of the patients suffer from a histologic sub-type of lung cancer collectively known as non–small cell lung carcinoma (NSCLC). Among these patients, pulmonary adenocarcinoma (AC) and squamous cell lung cancer (SQCLC) are the most common sub-types. Fifteen percent of all lung cancer patients are diagnosed with small cell lung cancer (SCLC)[1]. Patients with NSCLC in UICC (Union for international cancer control) stages I, II, and IIIA are treated by radical surgery if the tumor is resectable and if the patients are functionally operable[2] potentially followed by adjuvant chemotherapy. Currently, adjuvant treatment is mainly guided by TNM classification. However, additional prognostic estimation by molecular characterization may support critical treatment decisions to determine the best adjuvant therapeutic procedure.

Approximately 40% of patients are diagnosed with lung cancer in UICC stage IV and are mainly excluded from surgical treatment options[2]. In addition to the histologic differentiation, molecular studies have discovered numerous genetic subgroups of lung cancer. Adenocarcinomas are characterized by a high number of genomic alterations. With 32% of the cases, mutations in the K-Ras gene represent the largest genetic subgroup, followed by mutations in the EGFR gene (11%)[3]. Fusion of ALK, Ros, and Ret genes occurs in 1%–3% of cases[4]. In about 25% of cases, no genetic driver mutation have yet been identified[5,6]. The discovery of activating genetic mutations in the EGFR and ALK kinases, together accounting for ~15% of AC cases, has significantly improved the prognosis of these specific subgroups of patients through the use of targeted kinase inhibitors[7,8]. Unfortunately, similar therapeutic successes from molecular therapies have not yet been achieved in 85% of patients with a K-Ras mutation or without driver mutation, so that the majority of patients continue to receive conventional chemotherapy.

UDP-glucose 6-dehydrogenase (UGDH) catalyzes a 2-fold oxidation reaction resulting in the formation of UDP-α-D-glucuronic acid (UDP-GlcA) from UDP-α-D-glucose (UDP-Glc) using NAD^+ (Nicotinamide adenine dinucleotide) as the oxidant[9,10]. UDP-GlcA in turn plays an important role in the formation of hyaluronic acid (HA),

[a]Department of Thoracic and Cardiovascular Surgery, University Medical Center, [b]Institute of Pathology, University Medical Center and [c]Department of Hematology and Medical Oncology, University Medical Center, Göttingen, Germany

S.S. and S.Y. have contributed equally to the manuscript.

This manuscript has been peer reviewed.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: Institute of Pathology, University Medical Center, Robert-Koch-Street 40, Goettingen 37075, Germany. Tel.: +495513965051; fax: +49 551 39 8627. E-mail address: hanibal.bohnenberger@med.uni-goettingen.de (H. Bohnenberger).

International Journal of Surgery Oncology (2020) 5:e85

Received 5 December 2019; Accepted 25 January 2020

Published online 20 March 2020

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.IJSOncology.com.

http://dx.doi.org/10.1097/IJ9.0000000000000085

which promotes the cellular growth and migration of physiological cells[11,12]. Elevated levels of matrix glycosaminoglycan HA have been shown to be associated with the progression of epithelial cancers such as those of the breast, colon and prostate[9,13–16]. Downregulation of UGDH in colorectal carcinoma cell lines delayed cell aggregation and impaired cell motility. This effect was reversed by the addition of exogenous HA which implies that UGDH may be important for the regulation of cancer cell motility and metastasis[16]. Furthermore, HA interacts with CD44 which leads to the formation of large RTK-containing signaling complexes, which in turn leads to malignant transformation of intestinal epithelial cells[17]. In addition, UGDH has been identified as a potential diagnostic biomarker for prostate cancer that may complement the use of biopsy specimens in the diagnosis of prostate cancer[15]. Other studies have also demonstrated that downregulation of UGDH could arrest the proliferation of glioblastoma by preventing the production of components of the extracellular matrix[18,19]. A recent study by Haguida et al[20] has reported UGDH to be an early sero-diagnostic marker in addition to being a poor prognostic indicator in patients suffering from pulmonary AC. UGDH has also been reported to play a role in the development of chemoresistance in patients with NSCLC[21].

In this study, we therefore investigated the protein expression levels of UGDH in tissue samples and its influence on clinicopathologic characteristics and overall survival in patients suffering from lung cancer.

Material and methods

Tissue samples

Approval for using the samples in this study was obtained from the Ethics Committee of the University Medical Center Göttingen (#1-2-08). Informed consent was obtained from all patients. All procedures were conducted in accordance with the Declaration of Helsinki (Version of October 2013) and institutional, state and federal guidelines. Tissue samples were obtained from surgical resections at the Department of Thoracic and Cardiovascular Surgery of the University Medical Center, Göttingen. Exclusion criteria for patients' selection were neoadjuvant treatment, unresectable tumor, histology other than AC, SQCLC or SCLC, and age below 18 years.

Immunohistochemical staining

Tissue samples were assembled in tissue microarray. Immunohistochemical staining was performed as described previously[22]. Briefly, tissue sections were incubated in EnVision Flex Target Retrieval Solution, pH low (Dako) followed by incubation of primary antibodies against UGDH (Sigma, 1:500) for 20 minutes at room temperature. HRPO peroxidase coupled to polymeric secondary antibodies (EnVision Flex+, Dako) and DAB (Dako) were applied for visualization. Tissue samples were analyzed by light microscopy considering staining intensity (0 = negative; 1 = weakly positive; 2 = strongly positive).

Statistical analysis

The correlation between the patients' pathologic features and UGDH protein expression was analyzed by contingency tables and χ^2 tests. Kaplan-Meier analysis was used to compare patients' survival to UGDH protein expression. *P*-values were calculated according to Mantel-Cox log-rank test. Statistical significance of *P*-values was suggested at $P < 0.05$. GraphPad Prism (Version 7.00 for Windows, GraphPad Software, La Jolla, CA) was used for statistical analyses and extraction of the graphs.

Table 1

Patient characteristics.

Features	Cases	AC	SQCLC	SCLC
Total	213	96	84	33
Age median (range) (y)	67 (34–85)	67.5 (34–85)	67 (49–83)	65 (34–81)
Sex, n (%)				
Male	142 (66.7)	53 (37.3)	66 (46.5)	23 (16.2)
Female	71 (33.3)	43 (60.6)	18 (25.4)	10 (14.1)
Age, n (%)				
< 60	69 (32.4)	29 (42.0)	27 (39.1)	13 (18.8)
> 60	144 (67.6)	67 (46.5)	57 (39.6)	20 (13.9)
Degree of differentiation, n (%)				
I + II	136 (63.8)	69 (50.7)	67 (49.3)	0 (0.0)
III	77 (36.2)	27 (35.1)	17 (22.1)	33 (42.9)
Lymph node metastasis, n (%)				
No	120 (58.8)	58 (48.3)	45 (37.5)	17 (14.2)
Yes	84 (41.2)	36 (42.9)	39 (46.4)	9 (10.7)
Clinical stage, n (%)				
I + II	152 (74.5)	72 (47.4)	57 (37.5)	23 (15.1)
III + IV	52 (25.5)	23 (44.2)	26 (50.0)	3 (5.8)
Resection status, n (%)				
R0	187 (91.7)	87 (46.5)	75 (40.1)	25 (13.4)
RI + 2	17 (8.3)	5 (29.4)	8 (47.1)	4 (23.5)

AC indicates adenocarcinoma; SCLC, small cell lung cancer; SQCLC, squamous cell lung cancer.

Results

Patient characteristics

For this study, 213 patients (142 male, 71 female) with lung cancer were included. The median age of this cohort was 67 years (range, 34–85 y) and 144 patients (67.6%) were older than 60 years. A total of 180 patients (84.5%) were diagnosed with NSCLC of whom 96 patients (45.1%) were diagnosed with AC, 84 patients (39.4%) with SQCLC, and 33 patients (15.5%) with SCLC. All patients were treated with surgical tumor resection. According to UICC (seventh edition) stage, 152 patients (74.5%) were classified as stage I or II and 52 patients (25.5%) as stage III or IV. Nodal status was positive in 84 (41.2%) patients and for 187 patients (91.7%) R0 resection of the tumor was achieved. The patient characteristics are summarized in **Table 1** and all patient characteristics can be found in Supplementary Table 1 (Supplemental Digital Content 1, http://links.lww.com/IJSO/A4).

Expression of UGDH in lung cancer patients and correlation with clinicopathologic characteristics

Expression levels of UGDH in lung cancer tissue samples were analyzed by immunohistochemistry. According to staining intensity, expression of UGDH was described as negative (staining score 0) or positive (staining score 1 or 2) and analyzed for each tumor entity (**Figs. 1A–C**). UGDH was expressed in 62.5% of AC, 70.2% in SQCLC and 48.5% in SCLC (**Fig. 1 D**). In cases of adenocarcinoma, expression of UGDH was significantly correlated with the occurrence of lymph node metastasis ($P = 0.018$) meanwhile sex, age, degree of differentiation or UICC stage showed no association with UGDH expression. By contrast, the clinicopathologic characteristics

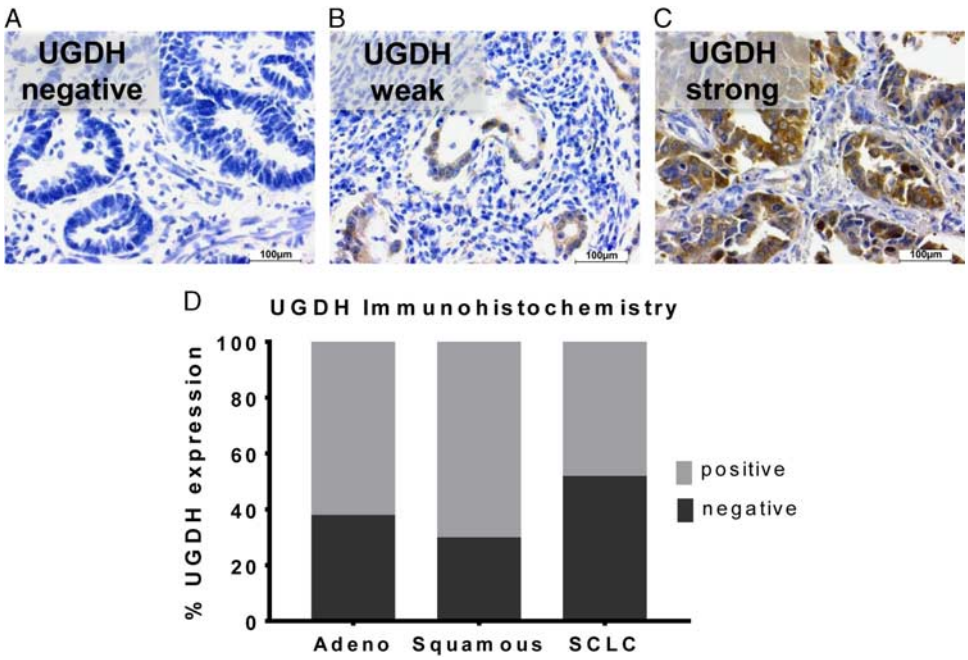

Figure 1. Representative immunohistochemical stainings with no (score 0) (A), weak (score 1) (B) and strong (score 2) (C) staining of UGDH in pulmonary adenocarcinoma. Scale bar: 100 μm. Staining intensity of UGDH sorted by entity (D). SCLC indicates small cell lung cancer; UGDH, UDP-glucose-6-dehydrogenase.

of patients with SQCLC and SCLC showed no significant correlation with UGDH (**Tables 2–4**).

Impact of UGDH expression on patient's prognosis

We next analyzed the influence of UGDH expression on overall survival for each cancer entity separately. The median follow-up time was 23.5 months (range, 1–125). Patients with an adenocarcinoma and expression of UGDH showed a significantly worse overall survival in Kaplan-Meyer-Estimation (Median survival 34 vs. 40 mo, hazard ratio = 0.4995, $P = 0.0454$, **Fig. 2A**). Overall survival of patients with SQCLC and SCLC showed no correlation with UGDH expression (**Figs. 2B, C**).

Table 2

UGDH expression in adenocarcinoma samples sorted by clinical features.

		UGDH		
Features	**Cases**	**–**	**+**	***P***
Sex, n (%)				
Male	53	22 (41.5)	31 (58.5)	0.368
Female	43	14 (32.6)	29 (67.4)	NS
Age, n (%)				
< 60	29	9 (31.0)	20 (69.0)	0.389
> 60	67	27 (40.3)	40 (59.7)	NS
Degree of differentiation, n (%)				
I + II	69	27 (39.1)	42 (60.9)	0.598
III	27	9 (33.3)	18 (66.7)	NS
Lymph node metastasis, n (%)				
No	58	27 (46.6)	31 (53.4)	0.018
Yes	36	8 (22.2)	28 (77.8)	*
Clinical stage, n (%)				
I + II	72	29 (40.3)	43 (59.7)	0.397
III + IV	23	7 (30.4)	16 (69.6)	NS
Resection status, n (%)				
R0	87	35 (40.2)	52 (59.8)	0.367
RI + 2	5	1 (20.0)	4 (80.0)	NS

*Significant.

P values are calculated according to χ^2 test.

NS indicates nonsignificant; UGDH, UDP-glucose-6-dehydrogenase.

Table 3

UGDH expression in squamous cell lung cancer samples sorted by clinical features.

		UGDH		
Feature	**Cases**	**–**	**+**	***P***
Sex, n (%)				
Male	66	22 (33.3)	44 (66.7)	0.170
Female	18	3 (16.7)	15 (83.3)	NS
Age, n (%)				
< 60	27	9 (33.3)	18 (66.7)	0.622
> 60	57	16 (28.1)	41 (71.9)	NS
Degree of differentiation, n (%)				
I + II	67	19 (28.4)	48 (71.6)	0.576
III	17	6 (35.3)	11 (64.7)	NS
Lymph node metastasis, n (%)				
No	45	17 (37.8)	28 (62.2)	0.084
Yes	39	8 (20.5)	31 (79.5)	NS
Clinical stage, n (%)				
I + II	57	18 (31.6)	39 (68.4)	0.668
III + IV	26	7 (26.9)	19 (73.1)	NS
Resection status, n (%)				
R0	75	23 (30.7)	52 (69.3)	0.281
R1 + 2	8	1 (12.5)	7 (87.5)	NS

P values are calculated according to χ^2 test.

NS indicates nonsignificant; UGDH, UDP-glucose-6-dehydrogenase.

Table 4

UGDH expression in small cell lung cancer samples sorted by clinical features.

Feature	Cases	UGDH		
		–	+	*P*
Sex, n (%)				
Male	23	12 (52.2)	11 (47.8)	0.909
Female	10	5 (50.0)	5 (50.0)	NS
Age, n (%)				
< 60	13	8 (61.5)	5 (38.5)	0.353
> 60	20	9 (45.0)	11 (55.0)	NS
Degree of differentiation, n (%)				
I + II	0	0 (0.0)	0 (0.0)	—
III	33	17 (51.5)	16 (48.5)	
Lymph node metastasis, n (%)				
No	17	9 (52.9)	8 (47.1)	0.899
Yes	9	5 (55.6)	4 (44.4)	NS
Clinical stage, n (%)				
I + II	23	12 (52.2)	11 (47.8)	0.636
III + IV	3	2 (66.7)	1 (33.3)	NS
Resection status, n (%)				
R0	25	11 (44.0)	14 (56.0)	0.823
RI + 2	4	2 (50.0)	2 (50.0)	NS

P values are calculated according to χ^2 test.
NS indicates nonsignificant; UGDH, UDP-glucose-6-dehydrogenase.

Discussion

Treatment decisions for patients suffering from lung cancer are mainly based on UICC cancer stage. In early stage lung cancer, 5-year survival rate ranges approximately from 80% in stage I to 33% in stage IIIA[23–25]. The main treatment option in early stages is surgical resection of the tumor followed by adjuvant chemotherapy. Meta-analysis demonstrated a 4%–5.4% decreased risk of death after 5 years using cisplatin-based adjuvant regimens compared with no chemotherapy[26,27]. Prognostic biomarkers could support treatment decisions for the selection of those patients who benefit the most from the adjuvant therapy.

In this study we investigated the protein expression levels of UGDH in human lung cancer tissue samples and found that UGDH was expressed in 63.4% of the patients. In patients with pulmonary AC a strong protein expression of UGDH was significantly associated with lymph node metastasis and poor overall survival. That supports the theory that UGDH expression plays a role in the migration and metastatic of tumor cells[12,16,28]. Accordingly, a recent report by Hagiuda et al[20] presented UGDH expression as an indicator for poor prognosis in patients suffering from AC.

HA and other components of the extracellular matrix play important roles in tumor growth and metastasis[12,17,29]. UGDH is the rate limiting step in production of several components of the extracellular matrix such as HA, chondroitin sulfate proteoglycan, and heparan sulfate proteoglycans[19]. Downregulation of UGDH reduces tumor cell migration and proliferation in glioblastomas[18]. UGDH expression promotes androgen independent tumor growth in human prostate cancer[28]. Therefore, UGDH could be evaluated as a biomarker for progression and metastasis of pulmonary adenocarcinomas. This in turn may play an important role in the decision-making process for the application of adjuvant chemotherapy for the treatment of those patients. However, repetitive screening of UGDH expression in different and larger patient cohorts with different characteristics will be essential to build a stable tumor biomarker that can be used in routine diagnostic. Especially, precise and accurate validation and standardization will be crucial for the clinical application of UGDH as a biomarker for lung cancer.

Patients diagnosed with late stage lung cancer (UICC IIIB–IV) are mainly treated with systemic therapy regimens. While the prognosis of patients especially with an AC harboring a drugable molecular alteration like an EGFR or ALK mutation has greatly improved in the last years, 85% of patients with adenocarcinoma and, for example, a K-Ras mutation or without an identified driver mutation are still treated with conventional chemotherapy leading to a 5-year survival rate of <20%[30].

The blockade of UDP-GlcA in tumor cells by antagonizing UGDH is an upcoming therapeutic option to treat cancer[9]. Hwang et al[31] found that polyphenols such as gallic acid and quercetin were effective inhibitors of UGDH which demonstrated a strong antiproliferative effect on MCF7 human breast cancer cells. There has also been an interest in the development of UGDH inhibitors, these include UDP-α-D-xylose which is a strong feedback inhibitor of UGDH and UDP-chloroacetol which acts against the active-site cysteine residue. However, the production of such novel therapeutic agents is still in its infancy[9].

However, further functional and in vivo experiments will be needed to scrutinize the possibilities of UGDH inhibitors in clinical management of lung cancer patients.

In summary, expression of UGDH in patients with AC may be considered as a prognostic biomarker for patient stratification and therapeutic decisions. In addition, UGDH should be further

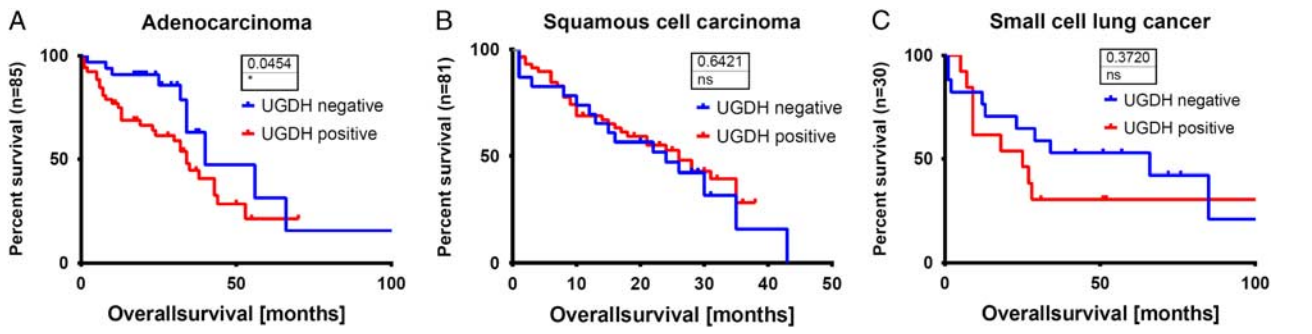

Figure 2. Kaplan-Meier analysis of overall survival in which all patients with adenocarcinoma (A), squamous cell lung carcinoma (B) and small cell lung cancer (C) were grouped according to staining intensity of UGDH. The *P*-value is from a log-rank test. *Significant. UGDH indicates UDP-glucose-6-dehydrogenase.

investigated as a novel drug target in AC as it displays inhibitable catalytic activity.

Ethical approval

None.

Sources of funding

The authors are supported by the German Research Foundation and the Open Access Publication Funds of the Göttingen University. H.B. and O.E. are supported by the Deutsche Krebshilfe Foundation (grant: 70112551). H.B. is supported by the University medical center Göttingen and the Else-Kröner-Fresenius-Foundation. J.B. is supported by the "Göttinger Kolleg für Translationale Medizin" (funded by the Ministery for Science and Culture of Lower Saxony). S.Y. is supported by the Chinese Scholarship Counsil.

Author contributions

H.B. conceived and supervised the project. S.S., O.E., and J.B., performed statistical analyses. H.H.-P., S.Y., and A.-M.L. performed experiments. A.E., B.C.D., M.H., and P.S. contributed clinical samples and/or patient characteristics. H.B., J.B., and S.S. wrote the manuscript with final approval of all authors.

Conflict of interest disclosures

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Research registration unique identifying number (UIN)

None.

Guarantor

None.

Acknowledgment

The authors thank Jennifer Appelhans for her technical support.

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