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Evaluation of Golgi Phosphoprotein 3 (GOLPH3) in Endometrial Carcinomas: A Molecular and Immunohistochemical Study

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Abstract

Introduction: Recent studies on Endometrial Carcinoma (EC) have focused on determining the clinicopathological factors that can be effectively considered in the prognosis, mortality risk, and targeted treatment of this disease. For this purpose, we investigated prognostic value of Golgi Phosphoprotein 3 (GOLPH3), which is associated with many different solid tumors, in EC. Although GOLPH3 has been shown to be a tumor-associated marker, the correlation between GOLPH3 expression, clinicopathological parameters, and clinical outcomes in EC has not been analyzed previously.

Materials and Methods: GOLPH3 expression was examined in 90 cases of EC and 11 cases of benign endometrial tissue. We investigated the association between GOLPH3 expression and clinicopathological features, chemotherapy, radiotherapy response, and prognosis using Polymerase Chain Reaction (PCR) and Immunohistochemistry (IHC).

Results and Discussion: GOLPH3 PCR protein levels were highly correlated with IHC expression in EC ($p = 0.000$). The GOLPH3 PCR value was also associated with distant metastasis and response to the treatment ($p = 0.022$ and $p = 0.014$, respectively). Neither IHC study nor PCR analysis showed statistically significant results for other clinicopathological parameters or survival. Moreover, no statistically significant difference was observed in histological grading and/or the malignant/benign distinction.

Conclusion: GOLPH3 overexpression in EC may be useful as a prognostic factor for predicting response to treatment and metastasis potential. However, the results must be evaluated in large patient groups to obtain detailed information.

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Introduction

Endometrial Carcinoma (EC) is the most common gynecological cancer in developed countries and the fifth most common cancer in women globally [1]. More than 60,000 new EC cases and 10,000 deaths from the disease are reported annually in the United States and other developed countries [2]. Worldwide, there are approximately 280,000 new cases each year [3]. The number of newly diagnosed cases has made EC a prominent issue in the gynecological field. Golgi phosphoprotein 3 (GOLPH3), also referred to as GPP34/GMx33/MIDAS, is an exciting new class of oncoproteins. Localized in the trans-Golgi network, the oncogene GOLPH3 has been described as a "first-in-class Golgi oncoprotein" [4-6]. Studies suggest that GOLPH3-dependent oncogenesis is associated with cell lineage in mammalian Targets of Rapamycin (mTOR) signaling and sensitivity to mTOR inhibitors. Although activation of mTOR signaling remains unclear, several lines of evidence suggest that GOLPH3 is associated with oncogenicity, which plays a role in vesicular trafficking and glycosylation from the Golgi to the plasma membrane [7]. Recent studies have shown that GOLPH3 can promote cellular transformation and tumor growth [4]. GOLPH3 protein is encoded by a gene on chromosome 5p13 that is frequently amplified in multiple solid tumors [4]. Many research

Table 1: Relationship between immunohistochemical GOLPH3 expression and histopathological features in endometrial carcinomas.

		GOLPH3				
		Low	High	Total	X^2	p
Histopathologic features	Endometrioid	42 (55.3%)	34 (44.7%)	76	5.498	0.064
	Serous	8 (57.1%)	6 (42.9%)	14		
	Control group	2 (18.2%)	9 (81.8%)	11		
Grade groups	Grade 1	19 (55.9%)	15 (44.1%)	34	0.100	0.951
	Grade 2	19 (55.9%)	15(44.1%)	34		
	Grade 3	4 (50.0%)	4 (50.0%)	8		

Table 2: Correlation between immunohistochemical GOLPH3 expression and clinicopathological variables in patients with endometrial carcinoma.

		GOLPH3				
Clinicopathological variables		Low	High	Total	X^2	p
Age (years)	≤60	24 (54.5%)	20 (45.5%)	44	0.036	0.850
	>60	26 (56.5%)	20 (43.5%)	46		
Tumor size	≤4 cm	25(58.1%)	18 (41.9%)	43	0.067	0.795
	>4 cm	25 (53.2%)	22 (46.8%)	47		
Myometrial invasion	<50%	32 (60.4%)	21 (39.6%)	53	0.785	0.375
	>50%	18 (48.6%)	19 (51.4%)	37		
Cervical invasion	negative	37 (53.6%)	32 (46.4%)	69	0.175	0.676
	positive(stromal)	13 (61.9%)	8 (38.1%)	21		
Lymphovascular invasion	negative	41 (60.3%)	27 (39.7%)	68	1.806	0.179
	positive	9 (40.9%)	13 (59.1%)	22		
Lymph node involvement	negative	41(55.4%)	33(44.6%)	74	0.000	0.588
	positive	9 (56.3%)	7 (43.8%)	16		
Stage	low	38 (56.7%)	29 (43.3%)	67	0.018	0.893
	high	12 (52.2%)	11 (47.8%)	23		
Risk group	low	16 (53.3%)	14 (46.7%)	30	0.177	0.915
	intermediate	17 (54.8%)	14 (45.2%)	31		
	high	41 (57.7%)	30 (42.3%)	71		
Distant metastasis	negative	41 (57.7%)	30 (42.3%)	71	0.301	0.583
	positive	9 (47.4%)	10 (52.6%)	19		

studies have considered the role of the new oncogene GOLPH3 in lung, breast, prostate, oral tongue, colorectal, and gastric cancers; esophageal squamous cell carcinoma; hepatocellular carcinoma; rhabdomyosarcoma; epithelial ovarian carcinoma; pancreatic ductal adenocarcinoma; and glioma [7-27]. In this study, we investigated the Immunohistochemical (IHC) GOLPH3 expression and Polymerase Chain Reaction (PCR) protein levels, as well as the correlation with clinicopathological features and prognosis, in EC cases.

Materials and Methods

This retrospective study was performed by analyzing total abdominal hysterectomy–bilateral salpingo-oophorectomy and regional lymphadenectomy materials, which were sent to Selçuk University Faculty of Medicine, Department of Pathology between 2009 and 2015. A total of 101 cases were examined, including 90 EC and 11 nontumoral endometrial tissues. All Hematoxylin and Eosin (H&E)-stained preparations in our hospital's archives were reevaluated using light microscopy. Assessment of histopathological features and staging were performed according to the International Federation of Gynecology and Obstetrics (FIGO) 2009 scheme [28]. Histological type and grade were established according to the 2014 World Health Organization (WHO) criteria. Two staging groups were identified; the low-stage group comprised stages I and II, while the high-stage group included stages III and IV. Stage IA grades 1 and 2 were included in the low-risk group; stage IA grade 3, stage IB, and stage II in the medium-risk group; and stages III, IV and serous types in the high-risk group [29].

The blocks of preparations best representing the tumor were identified, and sections (4 μm) were cut by microtome. The sections, taken on positively charged, poly-L-lysine-coated slides, were deparaffinized in the oven for 60 minutes at 60°C. The sections were then preprocessed with citrate for 8 minutes and incubated with anti-GOLPH3 antibody (1/50; rabbit polyclonal) for 24 minutes according to standard protocols.

Immunostaining for GOLPH3 was detected in the cytoplasm using prostate adenocarcinoma as a control. Endometrial tissue sections stained using IHC were analyzed and scored by two pathologists (PK, BSY) who were blinded to the clinical parameters. Cytoplasmic dark brown staining was used to identify positive results.

Table 3: Correlation between GOLPH3 PCR levels with clinicopathological features.

		N(%)	Rank average	Mann Whitney-U test	p
Tumor size	≤4 cm	43(47.8%)	43,03	904.500	0.392
	>4 cm	47(52.2%)	47,76		
Myometrial invasion	<%50	53(58.9%)	42.02	796.000	0.130
	>%50	37(41.1%)	50.49		
Cervical invasion	negative	69(76.7%)	45.47	722.500	0.985
	positive (stromal)	21(23.3%)	45.60		
Lymphovascular invasion	negative	68(75.6%)	43.78	631	0.272
	positive	22(24.4%)	50.82		
Lymph node involvement	negative	74(82.2%)	44.89	546.500	0.631
	positive	16(17.8%)	48.34		
Stage	low	67(74.4%)	44.16	681.000	0.408
	high	23(25.6%)	49.39		
Distant metastasis	negative	71(78.9%)	42.23	442.500	**0.022**
	positive	19(21.1%)	57.71		
Age (years)	≤60	44(48.9%)	43.47	922.500	0.470
	>60	46(51.1%)	47.45		
GOLPH3 expression (immunohistochemistry)	low	50(55.6%)	36.22	536.000	**0.000**
	high	40(44.4%)	57.10		
Lymph node involvement region	pelvic	7(43.7%)	6.29	16.000	0.114
	paraaortic	9(56.3%)	10.22		
Response to therapy	response	46(69.7%)	29.65	6.099	**0.014**
	no response	20(30.3%)	42.35		

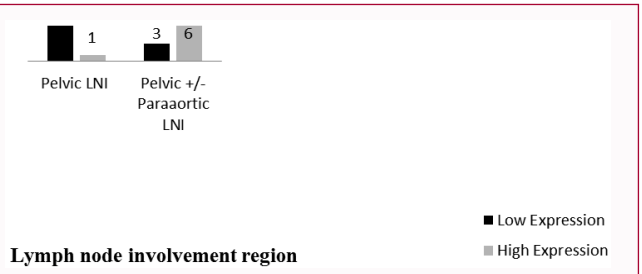

Figure 1: Correlation between GOLPH3 expression and lymph node involvement region.

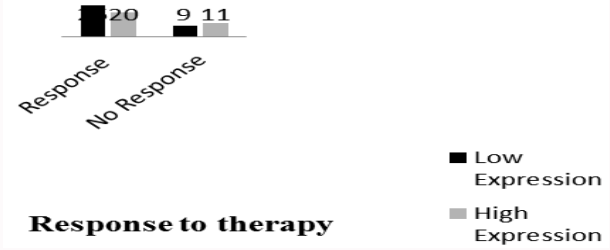

Figure 2: Correlation between GOLPH3 expression and response to therapy and no response to therapy.

Accordingly, staining intensity was scored as follows: 0, no staining; 1, weak staining (yellow); 2, moderate staining (yellow-brown); and 3, strong staining (brown) [18] (Figures 3-5). The percentage of positively stained tumor cells was scored as follows: 0 for 0–5%, 1 for 6–25%, 2 for 26–50%, and 3 for >50%. The intensity score and percentage of positively stained cells were added, and the sum was graded as 0, 1, 2, 3, 4, 5, or 6 [25] for the statistical analyses. Cases with an overall score of <4 were defined as low expression; those with scores of ≥4 were defined as high expression (Figures 3-5).

Overall Survival (OS) was determined for dead patients from the date of first diagnosis to the date of death; for living patients, OS was calculated from the date of first diagnosis until the last follow-up visit. Progression-Free Survival (PFS) was determined from the date of first diagnosis until the recurrence/metastasis date, or for those with no recurrence or metastasis, until the last follow-up visit or date of death.

The 66 patients who died from the disease or had metastasis recurrence after radiotherapy and/or chemotherapy were evaluated as "not responsive to the treatment." Those who were stable and surviving were defined as "responsive to the treatment."

For real-time PCR (RT-PCR), total RNA was isolated using a High Pure FFPET-RNA Isolation Kit. A Transcriptor First Strand cDNA Synthesis Kit was used on a Thermal Cycler in accordance with the manufacturer's instructions. Quantitation of GOLPH3 mRNA was performed by RT-PCR using a Light Cycler 480 SYBR Green I Master (Roche, Indianapolis, USA). Cycling conditions were as follows: 95°C for 10 minutes, 45 cycles of 95°C for 10 seconds and 60°C for 1 minute, an decrease in temperature to 72°C over 1 minute, and cooling by 4°C for 1 minute. Primers for GOLPH3 and β-actin were used, and gene expression levels were analyzed using the $2^{\Delta\Delta ct}$ method.

Our project was approved by the Non-Interventional Clinical Research Ethics Committee of Selçuk University, Faculty of Medicine. Statistical analysis was performed using SPSS 18.0 software. Associations between GOLPH3 expression and clinicopathological

variables were analyzed using the chi-squared test. The Pearson, Yates, and Fisher's exact chi-squared tests were used according to the expected value of the tables, 2*2 chi-squared. The Mann–Whitney U test statistic and Kruskal–Wallis H-test were used when the continuous variables had two or more groups. P-values <0.05 were considered statistically significant.

Results

The average patient age was 58.6 years (range, 33–82). Fifteen patients died. The mean tumor size was 4.5 cm (range, 1 cm-1 cm). In terms of histopathological subtypes, 75% of patients (n=76) were endometrioid, 14% (n=14) were serous, and 11 (n=11) were admitted as controls (nontumoral endometrium; Table 1). Of the 76 patients whose histopathological subtypes were endometrioid, 45% (n=34) were grade 1, 45% (n=34) were grade 2, and 10% (n=8) were grade 3 (Table 1).

59% of 90 EC cases (n=53) had <50% MI, and 41% cases (n=37) had >50% MI. 23% (n=21) had cervical stromal invasion, while %77 (n=69) had no cervical stromal invasion. 24% (n=22) had positive LVI, while %76 cases (n=68) were not found to have LVI.

All cases were exposed to pelvic and para-aortic lymph node dissection; 18% of cases (n=16) had metastasis. Of these, %44 (n=7) were determined to have pelvic lymph node metastasis alone, while 56% (n=9) were found to have pelvic ± para-aortic lymph node metastasis (Figure 1). 21% (n=19) had distant metastasis.

Using the FIGO staging system, 42% (n=38) of patients were categorized as stage IA, 18% (n=16) as stage IB, 14% (n=13) as stage II, 1% (n=1) as stage IIIA, 9% (n=8) as stage IIIC1, 8% (n=7) as stage IIIC2, and 8% (n=7) as stage IV. Arranged in risk groups, 29 cases were classified as low, 30 as intermediate, and 31 as high risk. Of the 66 treated patients, 46 (70%) were responsive, while 20 (30%) were not.

IHC GOLPH3 expression levels were significantly higher in nontumoral tissue, and GOLPH3 expression was found in about 82% (n=9). High GOLPH3 expression was detected in 34 of the 76 endometrioid-type carcinomas and 6 of the 14 serous carcinomas. In all cases, low GOLPH3 expression was found in 2% (n=2) of the controls, 42% (n=42) of the endometrioid-type carcinomas, and 8% (n=8) of the serous carcinomas (Table 1). Regarding the grade of endometroid-type tumors, 44% (n=15) of grade 1, 44% (n=15) of grade 2, and 12% (n=4) of grade 3 tumors showed high GOLPH3 expression (Table 2). Thus, there was no correlation between GOLPH3 expression and histopathological grading or malignant/benign endometrial lesions (p=0.0951 and p =0.064, respectively) (Table 2) summarizes GOLPH3 expression's association with various clinicopathological features of ECs. Statistical analysis showed no correlation between GOLPH3 expressions, as determined using both IHC staining and the clinicopathological features. In addition, no statistical correlation was found between GOLPH3 expression and either pelvic lymph node involvement or para-aortic ± pelvic lymph node involvement (p=0.055). There was no statistically significant correlation between GOLPH3 expression and treatment response (p=0.553).

Statistical analysis showed a significantly strong relationship between GOLPH3 PCR levels and GOLPH3 IHC expression (p=0.000). GOLPH3 PCR levels were also correlated with distant metastasis (p=0.022). High GOLPH3 PCR levels identified patients with distant metastasis. A significant correlation was found between GOLPH3 PCR levels and response to treatment (p=0.014). There were no statistically significant differences in the GOLPH3 PCR levels related to other clinicopathological features (Table 3).

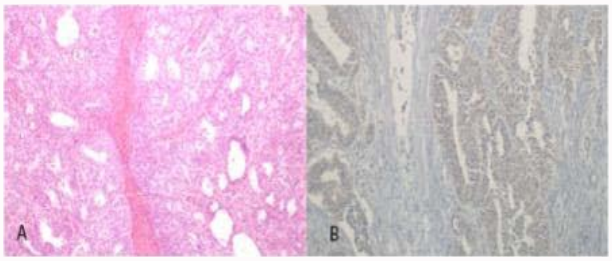

Figure 3: A- Grade 1 Endometrioid Adenocarcinoma (H&E, X100). **B**- Grade 1 Endometrioid Adenocarcinoma +1 staining pattern (GOLPH3 IHC, X200).

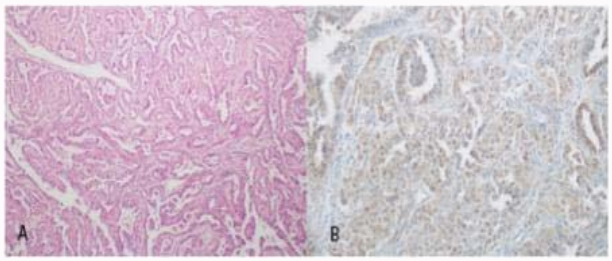

Figure 4: A- Serous Adenocarcinoma (H&E, X100). **B-** Serous Adenocarcinoma +1 staining pattern (GOLPH3 IHC, X200).

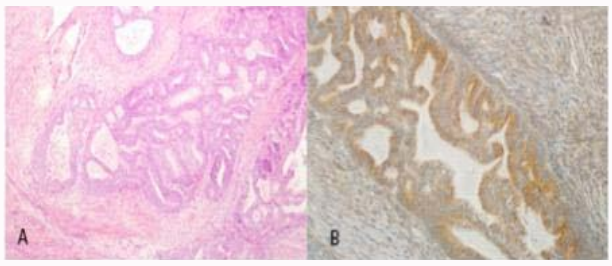

Figure 5: A- Grade 1 Endometrioid Adenocarcinoma (H&E, X100). **B**- Grade 1 Endometrioid Adenocarcinoma +3 staining pattern (GOLPH3 IHC, X200).

The median OS was 42 months (range, 11–73 months); the PFS was 37 months (range, 6–75 months). Fifteen patients died during the study period. The OS was longer in patients whose GOLPH3 PCR levels were low. There were no statistically significant differences in GOLPH3 PCR levels or IHC expression for either OS/PFS.

Discussion

Recently, the increasing number of new EC cases has gained importance due to the high likelihood of mortality. Studies have sought to determine effective clinicopathological factors for determining its prognosis, mortality risk, and targeted treatment. We investigated the presence and prognostic value of a new oncoprotein, GOLPH3, in EC, which has been associated with poor prognosis in other organ cancers [7-9,13-16,22-24].

The potential role of GOLPH3 in the pathogenesis of EC or other cancers remains unclear. The Human Protein Atlas internet site provides information about GOLPH3 expression in EC, indicating medium expression in endometrial glandular cells and no expression in stromal cells. The site's analysis of 22 EC cases showed medium

expression in 6, low expression in 8, and no expression in 8 cases [30].

Regarding GOLPH3 expression in benign and malignant tissues in the literature, GOLPH3 expression and protein levels were significantly higher in ovarian carcinoma [25], gastric carcinoma [20], pancreatic carcinoma [27], non–small cell lung carcinoma [31], and colorectal carcinoma [32] than in normal tissues. In this study, in contrast to previous research, 9 of 11 cases in the nontumoral group showed high GOLPH3 expression by IHC. Nevertheless, PCR protein levels were correlated with IHC findings. In addition, there was no difference in GOLPH3 expression between any histopathological grades and the control group.

Ma et al. found positive correlations between high expressions of GOLPH3 and histopathological grade, and lymph node metastasis in epithelial ovarian carcinomas [25]. These findings suggest that a high expression of GOLPH3 correlates with a poor prognosis. Similar findings were reported for other malignancies [8,11,14,16-19]. The present study's IHC and PCR assessments showed no statistical differences in EC patients between clinicopathological parameters and the presence of GOLPH3 ($p>0.05$). Guo et al. [32] evaluated 62 colorectal cancer patients and found positive correlations between a high expression of GOLPH3 and lymph node involvement. Cases without lymph node involvement mostly showed low expression of GOLPH3 ($p=0.02$). In the present study, 6 of 7 cases with pelvic lymph node involvement showed low GOLPH3 expression; conversely, most cases with para-aortic ± pelvic lymph node involvement, a worse prognosis, showed high GOLPH3 expression. These results are meaningful in terms of prognostics, but they are not statistically significant ($p=0.055$ and $p=0.179$, respectively). This is thought to be due to the low number of high-grade tumors in our study (Figure 1).

When evaluating prognoses in the literature, Wang et al. [33], found that high GOLPH3 expression in non–small cell carcinoma correlated with distant metastasis and worse prognosis. We mostly observed high GOLPH3 expression in cases with distant metastasis (9/19) and low expression in cases without distant metastasis (41/71; Table 2). Although the IHC expression was not statistically significant, in agreement with the literature, there was a significant correlation between the PCR protein levels of GOLPH3 and distant metastasis. GOLPH3 PCR protein levels were higher with and lower without distant metastasis, as described for other solid tumors in the literature ($p=0.022$; Table 3).

Zhou et al. reported that in glioblastoma, patients with low GOLPH3 expression who receive postoperative chemoradiotherapy have a better prognosis, and GOLPH3 expression can be used as a criterion for predicting the effect of chemo radiotherapy [11].

Consistent with the literature, our study found higher GOLPH3 PCR protein levels in cases with no response to treatment ($p=0.014$). Thus, higher GOLPH3 protein levels may be associated with poor EC prognosis, as indicated for other solid tumors. High expression of GOLPH3 was detected on IHC evaluation in most (9/11) patients with no response to treatment; low expression of GOLPH3 was detected in most patients who responded to treatment (20/26, Figure 2). Although these findings were important prognostically, they were not statistically significant ($p=0.553$), probably because of the limited number of cases involving high-grade tumors.

A study evaluating GOLPH3 expression in glioblastomas revealed that GOLPH3 expression was correlated with OS/PFS. Lower GOLPH3 expression was associated with longer OS/PFS; thus, high GOLPH3 expression indicates a poor prognosis [11]. In other studies, high GOLPH3 expression was proportional to short survival [18,28,32]. In our study, IHC and GOLPH3 PCR protein levels alone were not associated with OS/PFS ($p=0.460$ and $p=0.610$, respectively). Although the result was not statistically significant, it is notable that GOLPH3 PCR values increased as OS/PFS decreased. This finding may have been due to the low number of patients in our study with high grade and poor prognosis.

In recent studies, GOLPH3 expression has been predominantly evaluated using both IHC and PCR. We found a significant correlation between the GOLPH3 expressions of IHC and PCR protein levels ($p=0.000$). This indicates that the IHC is as reliable as PCR for GOLPH3 expression in EC. However, since PCR was quantitatively calculated with more sensitive numerical values, clinical prognostic factors, such as distant metastasis and response to treatment, were significant when assessed by PCR ($p=0.022$ and $p=0.014$, respectively), but not IHC ($p=0.0583$ and $p=0.553$, respectively). Consequently, high GOLPH3 values are thought to be related to a poor EC prognosis, as found for some solid tumors mentioned in the literature. Strength of our study is that, to the best of our knowledge, no previously published research has investigated the presence of GOLPH3 in EC by IHC or PCR. As a limitation, although our cases' distribution rates (34% grade 1, 34% grade 2, 22% grade 3 and serous) were proportional according to grades, the number of cases, especially for grade 3 and serous, was lower. In conclusion, we think that the expression and protein levels of GOLPH3 can be useful in determining the treatment protocol, predicted response to therapy, and metastatic potential. However, additional studies with a larger cohort are needed to determine the value of this indicator in routine practice. GOLPH3 may also be expressed in benign endometrial tissues, and it should only be considered as a clinical prognostic factor in EC.

Acknowledgments

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Conflict of Interest

The authors declare no conflicts of interest.

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