Journal of Cancer Research and Clinical Oncology (2019) 145:2519–2527
https://doi.org/10.1007/s00432-019-03017-8

ORIGINAL ARTICLE – CANCER RESEARCH

EP3 receptor is a prognostic factor in TA-MUC1-negative ovarian cancer

Bastian Czogalla[1] · Christina Kuhn[1] · Sabine Heublein[1,2] · Elisa Schmöckel[3] · Doris Mayr[3] · Thomas Kolben[1] · Fabian Trillsch[1] · Alexander Burges[1] · Sven Mahner[1] · Udo Jeschke[1] · Anna Hester[1]

Received: 10 August 2019 / Accepted: 30 August 2019 / Published online: 4 September 2019

Abstract

Purpose Prostaglandin-mediated inflammatory reactions play a major role in different cancers. Recently, it has been observed that prostaglandin E2-receptor 3 (EP3) might be an independent prognostic factor for overall survival in cervical and endometrial cancer. The role of EP3 expression in ovarian cancer is currently unknown.

Methods EP3 expression was analyzed by immunohistochemistry in 156 patient samples using the IR-scoring system. Expression levels were correlated with clinical and pathological parameters and with overall survival (OS) to assess for prognostic relevance. Data analysis was performed using Spearman's correlations, Kruskal–Wallis test and Kaplan–Meier estimates.

Results EP3 expression was significantly higher in clear-cell carcinoma ($p < 0.001$) compared to the other histological subtypes. No further correlations with clinical parameters could be found. EP3 expression correlated significantly with FSH-receptor expression ($p < 0.001$), galectin-1 expression in the tumor ($p = 0.012$) and with cytoplasmatic TA-MUC1 expression ($p = 0.001$). None of these parameters showed significant correlation with OS. In the TA-MUC1 negative subgroup, EP3 negative patients showed significantly longer OS (median OS: 102 months vs. 34 months in EP3 positive patients, $p = 0.035$), while EP3 did not appear to have prognostic relevance in the TA-MUC1-positive subgroup.

Conclusion The potential prognostic relevance of EP3 expression for OS in TA-MUC1 negative patients might reflect an interplay between the COX and the MUC1 pathway, as it has been shown that MUC1 could induce COX2 expression. Our findings support the importance of the prostanoid signaling in TA-MUC1 negative ovarian cancer; however, future studies are necessary to characterize specific pathways and possible interactions.

Keywords EP3 · Ovarian cancer · TA-MUC1 · Gatipotuzumab · Prognostic factor

Introduction

Ovarian cancer is one of the five most frequent cancer deaths among women and the most lethal gynecological malignancy (Siegel et al. 2019). Relative five-year survival is less than 45% for patients with ovarian cancer (EOC) (Baldwin et al. 2012). Main reasons for impaired prognosis are insufficient screening methods, detection in advanced tumor stage, and ultimately resistance to chemotherapy over the clinical course. Recommended therapy consists of cytoreductive surgery and platinum-based chemotherapy combined with antiangiogenics or PARP inhibitors. Residual disease after initial debulking surgery is the most reliable prognostic factor, while further clinical and pathological prognostic factors include the international federation of gynecology and obstetrics (FIGO) stage, ascites volume, patient age, and histological subtype (du Bois et al. 2009; Aletti et al. 2006; Vergote et al. 2001; Dembo et al. 1990). However, widely accepted prognostic markers are missing. EOC are classified as serous, mucinous, endometrioid, and clear-cell histology, being distinguished in terms of phenotype, molecular background, and etiology (Kossai et al. 2018).

Numerous factors are currently investigated due to the urgent need of developing a useful prognostic factor in ovarian cancer. Studied factors include

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00432-019-03017-8) contains supplementary material, which is available to authorized users.

✉ Udo Jeschke
udo.jeschke@med.uni-muenchen.de

Extended author information available on the last page of the article

carbohydrate-binding proteins such as the subgroup of galectins (Chetry et al. 2018; Schulz et al. 2018; Schulz et al. 2017) or mucins (Hou et al. 2017; Heublein et al. 2019), and the expression of specific subtypes of these proteins has been linked to an impact on prognosis in ovarian cancer.

In various cancer subtypes, the role of prostaglandins and its receptors has come into focus of research during the last years. The EP3 receptor is one of the four identified receptors that mediate the effects of prostaglandin E2 (PGE2) (Sugimoto and Narumiya 2007). PGE2 is known as a key mediator in inflammatory and anaphylactic processes, but has also a pivotal role in tumor development and progression (Williams et al. 1999). Consequently, the prostaglandin-signaling cascade including the role of prostaglandin receptors are increasingly investigated in the context of different malignancies. The prostaglandin synthesis from arachidonic acid is driven by cyclooxygenase (COX) enzymes. Two different isoforms of the COX enzyme exist: whereas COX-1 is expressed constitutively, the COX-2 expression is inducible by various stimuli (Reader et al. 2011), among others by inflammation. However, a COX-2 overexpression and consecutive elevation of PGE2 levels has also been shown in various tumors such as colon, prostate, or lung cancer (Tsujii et al. 1997; Wang and Dubois 2010), but also in gynecological malignancies such as endometrial (Zhu et al. 2018) and cervical (Heidegger et al. 2017) cancer. Trials using COX-2 inhibitors such as celecoxib for the prevention and treatment of cancers have shown promising results, supporting the evidence of the importance of the COX-PGE2 axis in carcinogenesis (Bertagnolli et al. 2006; Harris 2009). However, the clinical use of coxibes is limited due to their rare, but serious cardiovascular side effects (Bertagnolli et al. 2006; Howe 2007). The role of the specific PGE2 receptors EP1-4 might be tumor and cell-type specific. The EP3 receptor exists in various isoforms, generated by alternative mRNA splicing, which might be partly causal for the divergent effects described in the previous studies (Reader et al. 2011). Recently, it has been shown that the EP3 receptor is an independent negative prognostic factor in gynecological malignancies (Zhu et al. 2018; Heidegger et al. 2017), EP3 expression levels correlated with tumor stages as well as clinical outcome. Similarly, EP3 antagonism reduced the proliferation and migration of endometrial carcinoma cells (Zhu et al. 2018).

This study now aimed to elucidate the role of EP3 receptor expression in ovarian cancer. It evaluates the EP3 expression in ovarian cancer, its association to clinical and pathological parameters and to overall survival, aiming to find a prognostic and potentially targetable marker in ovarian cancer.

Methods

Patients and specimens

Tissue samples of 156 consecutive patients who underwent surgery for EOC at the Department of Obstetrics and Gynecology, Ludwig-Maximillian's-University Munich from 1990 to 2002, were analyzed in this study. Various pathological parameters were already determined in this collective in the previous studies (Heublein et al. 2019), which allowed correlation analysis of newly established markers. Clinical data were obtained from the patient's charts and follow-up data from the Munich Cancer Registry. All samples had been formalin-fixated and paraffin-embedded (FFPE). Patients with benign or borderline tumors were excluded and no patient had neoadjuvant chemotherapy. Specialized pathologists for EOC examined and classified the samples for histological subtypes: serous ($n=110$), endometrioid ($n=21$), clear cell ($n=12$), and mucinous ($n=13$). The serous ovarian cancer samples were divided into low and high grading. Endometrioid ovarian cancer was graded according to G1–G3. For the mucinous carcinoma, there is no WHO classification; however, the subtype is often classified into G1–G3. The clear-cell cancer was always categorized as G3. Staging was performed using FIGO (WHO) classification: I ($n=35$), II ($n=10$,) III ($n=103$), and IV ($n=3$). Data on lymph node involvement in 95 cases N0 ($n=43$), N1 ($n=52$). Data on distant metastasis was available in nine cases M0 ($n=3$), M1 ($n=6$).

Ethical approval

This study was approved by the Ethics Committee of the Ludwig-Maximilians-University, Munich, Germany (approval number 227-09 and 18-392). All tissue samples used for this study were obtained from material from the archives of the Department of Obstetrics and Gynecology, University Hospital, LMU Munich, Munich, Germany, initially used for pathological diagnostics. The diagnostic procedures were completed before the current study was performed. During the analysis, the observers were fully blinded for patients' data.

Immunohistochemistry

Immunohistochemistry was performed as previously described (Zhu et al. 2018; Heidegger et al. 2017; Semmlinger et al. 2018). Placental tissue (Ye et al. 2018) was used for positive and negative controls. Tissue microarrays of ovarian cancer samples of paraffin-embedded and formalin-fixed tissues after epitope retrieval were stained with primary

anti-EP3-antibodies (polyclonal rabbit IgG, Abcam, Cambridge, UK). Detection was performed via polymer method (ZytoChem Plus HRP Polymer System mouse/rabbit, Zytomed Systems Berlin, Germany) and the chromogen diaminobenzidine (Dako, Hamburg, Germany). A well-established immunereactivity scoring system (IR score, IRS or Remmele score) was employed to quantify immunostaining in a semi-quantitative manner using a Leitz (Wetzlar, Germany) microscope. The IRS multiplies the intensity of the staining (0 = no, 1 = weak, 2 = moderate, 3 = strong staining) with the percentage of positive cells (0 = no staining, 1 = < 10% positive cells, 2 = 11–50% positive cells, 3 ≥ 50% positive cells).

Staining evaluation

Cut-off points for the IR scores for the EP3 staining, the Galectin-1 staining in the tumor, the cytoplasmatic Gatipotuzumab staining, and the FSH-receptor expression were selected considering the distribution pattern of IR scores in the collective. Therefore, the RUC curve was drawn which is considered as one of the most reliable methods for cut-off point selection. In this context, the ROC curve is a plot representing sensitivity on the *y*-axis and (1-specificity) on *x*-axis. Dian et al. (2013) Consecutively Youden index, defined as the maximum (sensitivity + specificity-1) Ledermann et al. (2017), was used to find the optimal cut-off maximizing the sum of sensitivity and specificity. The EP3 expression was regarded as negative with an IR score 0–1 and as positive with an IRS > 1. The cytoplasmatic Gatipotuzumab expression was regarded as negative with an IRS 0 and as positive with IRS > 0. The FSH-receptor expression was regarded as low with an IRS 0–1 and as high with IRS > 1. The Galectin-1 staining in the tumor was regarded as low with IRS 0–4 and as high with IRS > 4.

Statistics

IBM SPSS Statistics 25 was used for statistical analyses (PASW Statistic, SPSS Inc., IBM, IL, USA). Correlations between findings of immunohistochemically staining were calculated using Spearman's analysis. Survival times were analyzed by Kaplan–Meier (log-rank) estimates. *p* values ≤ 0.05 were considered as statistically significant. Figures were designed with SPSS 25 and Microsoft Power Point 2016.

Results

EP3 expression correlates with clinical and pathological data

Clinicopathologic characteristics of the analyzed ovarian cancer patients are listed in Table 1. EP3 staining was observed in 148 cases (95%). Median (range) immunoreactivity scores (IRS) for EP3 were 2 (0,12). An IRS ≥ 2 was determined as cutoff for positive EP3 expression via ROC-curve analysis (methods).

When comparing EP3 expression between the different histological subtypes (Fig. 1a–d), the highest IR scores were detected for clear-cell histology (median IRS = 11 with a range from 6 to 12; $p < 0.001$).

Furthermore, correlation between EP3 and clinicopathological data such as grading (low vs. high grade in serous carcinoma), G1–G3 in the other histology, affected lymph nodes (pN), distant metastasis (pM), and FIGO classification

Table 1 Clinicopathologic characteristics of the ovarian cancer patients

Clinicopathologic parameters	*N*	Percentage (%)
Histology		
Serous	110	70.5
Clear cell	12	7.7
Endometrioid	21	13.5
Mucinous	13	8.3
Lymph node		
pNX	61	39.1
pN0	43	27.6
pN1	52	33.3
Distant Metastasis		
pM0/X	150	96.2
pM1	6	3.8
Grading Serous		
Low	24	23.0
High	80	77.0
Endometrioid		
G1	6	31.6
G2	5	26.3
G3	8	42.1
Mucinous		
G1	6	50.0
G2	6	50.0
G3	0	0
Clear cell		
G3	9	100
FIGO		
I	35	23.1
II	10	6.6
III	103	68.2
IV	3	2.0
Age		
≤ 60 years	83	53.2
> 60 years	73	46.8

were analyzed. No significant differences for these parameters and EP3 expression were noted (Table 2).

EP3 expression was also compared to other pathological parameters that are currently investigated concerning their prognostic relevance in ovarian cancer. Significant correlations were found to the cytoplasmatic expression of tumor-associated mucin-1 (TA-MUC1), which is reflected by cytoplasmatic Gatipotuzumab staining, to the FSH-receptor expression and to the galectin-1 expression in the tumor.

Cytoplasmatic TA-MUC1 staining could be performed in 143 cases (92%, in the other cases TA-MUC1 staining was not successful for technical reasons); however, 74 patients were TA-MUC1 negative. For survival analysis, patients were grouped in TA-MUC1 positive and negative cases. In the TA-MUC1 positive patients ($n = 60$), the median IRS was 1. A strong correlation of cytoplasmatic TA-MUC1 expression and EP3 expression was detected (cc = 0.276, $p = 0.001$).

FSH-receptor staining could be performed in 149 cases (95%) with a median IRS of 3. For survival analyses, an IRS ≥ 2 was considered as high expression due to cut-off determination via ROC-curve analysis. The FSH-receptor staining correlated strongly with the EP3 receptor expression (cc = 0.418, $p < 0.001$).

Galectin-1 staining in the tumor could be performed in 151 cases (97%) with a median IRS of 4. For survival analysis, an IRS ≥ 5 was considered as high expression due to

Table 2 Correlation between EP3 expression and clinical data

Variables	*p*	Correlation coefficient
Histological subtypes	0.577	− 0.046
Grading serous	0.092	− 0.170
Grading mucinous, clear cell, endometrioid	0.06	0.300
FIGO	0.288	0.089
pN	0.102	0.172
pM	0,901	− 0,049

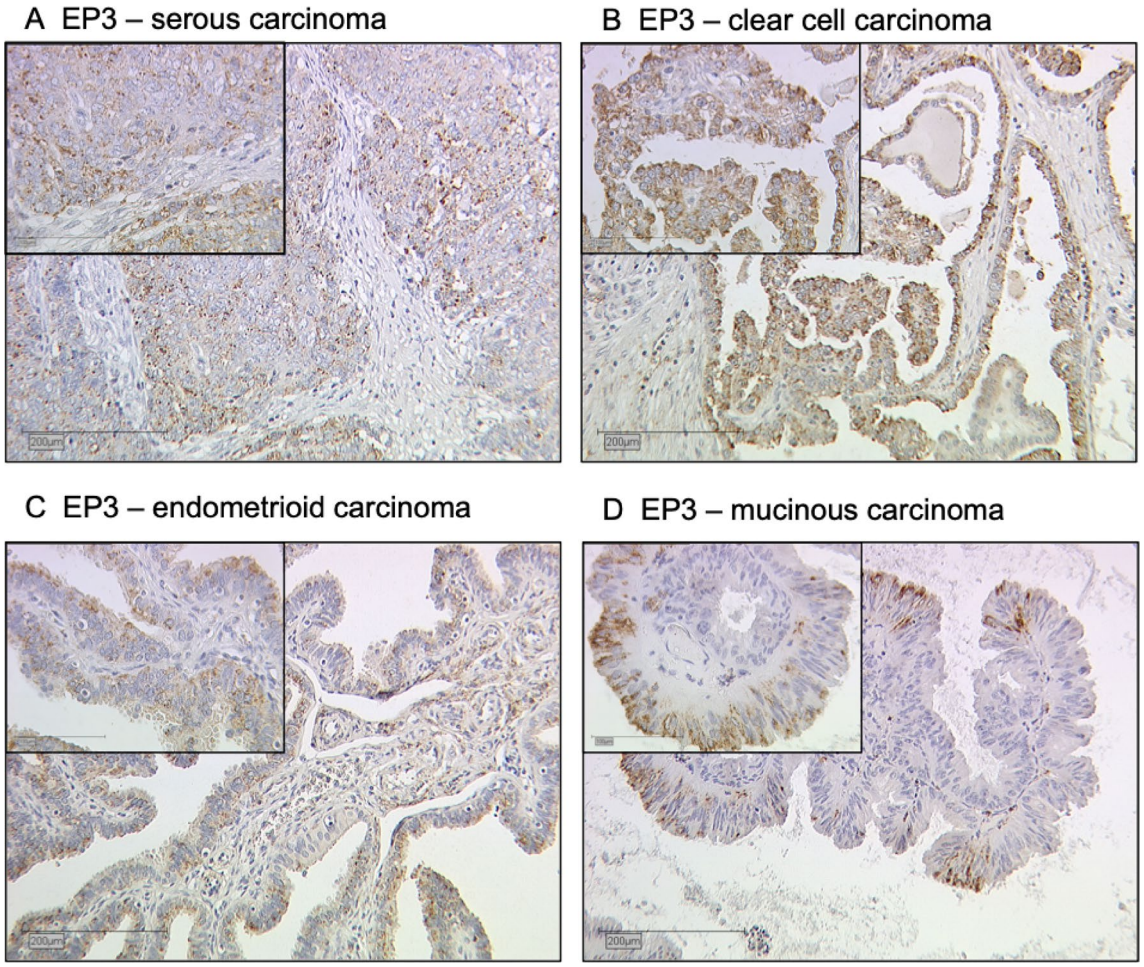

Fig. 1 EP3 expression in different ovarian cancer subtypes

cut-off determination via ROC-curve analysis. The galectin-1 staining in the tumor also correlated with the EP3 receptor expression (cc = −0.209, $p = 0.012$) (Table 3)

Negative EP3 expression in the subgroup without cytoplasmatic TA-MUC1 expression is associated with improved overall survival

In the overall cohort, patients with a positive EP3 expression showed an impaired OS (median OS 37 months vs. 60 months in EP3 negative patients, Fig. 2a), although this difference was not statistically significant ($p = 0.134$). The presence of cytoplasmatic TA-MUC1 expression alone also did not significantly influence OS (median OS 35 months vs. 45 months in patients without cytoplasmatic TA-MUC1 expression, $p = 0.87$, Fig. 2b). Similarly, high FSH-receptor expression (median OS 35 months vs. 52 months in FSH-receptor low-expressing patients, $p = 0.495$, Fig. 2c) or high galectin-1 expression in the tumor (median OS 45 months vs. 38 months in patients with low galectin-1 expression in the tumor, $p = 0.961$, Fig. 2d) did not significantly influence OS.

Due to the correlation between the EP3 expression with the cytoplasmatic TA-MUC1 expression (reflected by cytoplasmatic Gatipotuzumab staining), with the FSH-receptor expression and the galectin-1 expression in the tumor, the prognostic relevance of the EP3 expression dependent on the expression of the other proteins was analyzed.

In the TA-MUC1 (Gatipotuzumab) negative subgroup ($n = 74$), EP3-negative patients showed a significantly improved OS (median OS 102 months vs. 34 months in EP3 positive patients, $p = 0.035$). In the TA-MUC1 positive subgroup ($n = 60$), negative EP3-expression did not have a prognostic effect on OS (median OS 35 months vs. 37 months in EP3 positive patients, $p = 0.99$, Fig. 3).

The absence of EP3 receptor expression did not show prognostic relevance for OS neither in the FSH-receptor high expressing subgroup ($n = 115$, median OS 44 months vs. 35 months in EP3 positive patients, $p = 0.36$), nor in the FSH-receptor low-expressing subgroup ($n = 27$, median OS 83 months vs. 52 months in EP3 positive patients, $p = 0.44$, supplementary Fig. 1).

Similarly, the EP3 receptor did not show significant prognostic relevance for OS dependent on the galectin-1 expression in the tumor: in the subgroup with high galectin-1 expression in the tumor, EP3 negative patients showed prolonged OS ($n = 48$, median OS 63 months vs. 33 months in EP3 positive patients, $p = 0.115$, supplementary Fig. 2); however, this prolongation was not significant. In the galectin-1 low-expressing subgroup, EP3 negative patients did not show improved OS ($n = 94$, median OS 38 months vs. 41 months in EP3 positive patients, $p = 0.435$, supplementary Fig. 2).

Table 3 Correlation analysis

Staining	EP3 receptor	TA-MUC 1 cytoplasm	FSH receptor	Galectin-1 tumor
EP3 receptor				
cc	1.000	0.276	0.418	−0.209
p	.	0.001	<0.001	0.012
n	148	135	143	143
TA-MUC 1 cytoplasm				
cc	0.276	1.000	−0.059	0.206
p	0.001	.	0.497	0.015
n	135	143	136	138
FSH receptor				
cc	0.418	−0.059	1.000	−0.120
p	<0.001	0.497	.	0.148
n	143	136	149	147
Galectin-1 tumor				
cc	−0.209	0.206	−0.120	1.000
p	0.012	0.015	0.148	
n	143	138	147	151

Discussion

In the present study, we examined the expression of EP3 in different histological types of ovarian cancer (serous, clear cell, endometrioid, and mucinous) and its association with clinicopathological data and overall survival. Immunohistochemical evaluation of EP3 correlated with ovarian cancer histology with the highest expression in clear-cell carcinoma. Furthermore, we could detect a correlation between EP3 and FSH-receptor as well as with galectin-1 without a significant correlation with overall survival. The gonadotropin receptors LH and FSH play a well-known important role in ovarian cancer carcinogenesis (Zhuandi et al. 2018; Perales-Puchalt et al. 2017; Emons et al. 1990). The functional interplay between EP3 and these factors is not understood so far. The previous analyses showed that FSH via its receptor stimulates PGE2 and hereby potentially influences EP3 expression in human ovary (Niringiyumukiza et al. 2018). The putative functional association between EP3 and FSH receptors as well as galectin-1 has to be elucidated in future investigations.

Our study shows that positive EP3 expression was a negative prognostic factor in ovarian cancer that lacks cytoplasmatic expression of tumor-associated epithelial mucin 1 (MUC1). TA-MUC1 expression was detected by Gatipotuzumab staining; Gatipotuzumab is an antibody that detects a tumor-specific epitope of MUC1 (TA-MUC1). MUC1 is expressed in most carcinomas, including ovarian cancer (Dian et al. 2013), with a changed cellular distribution

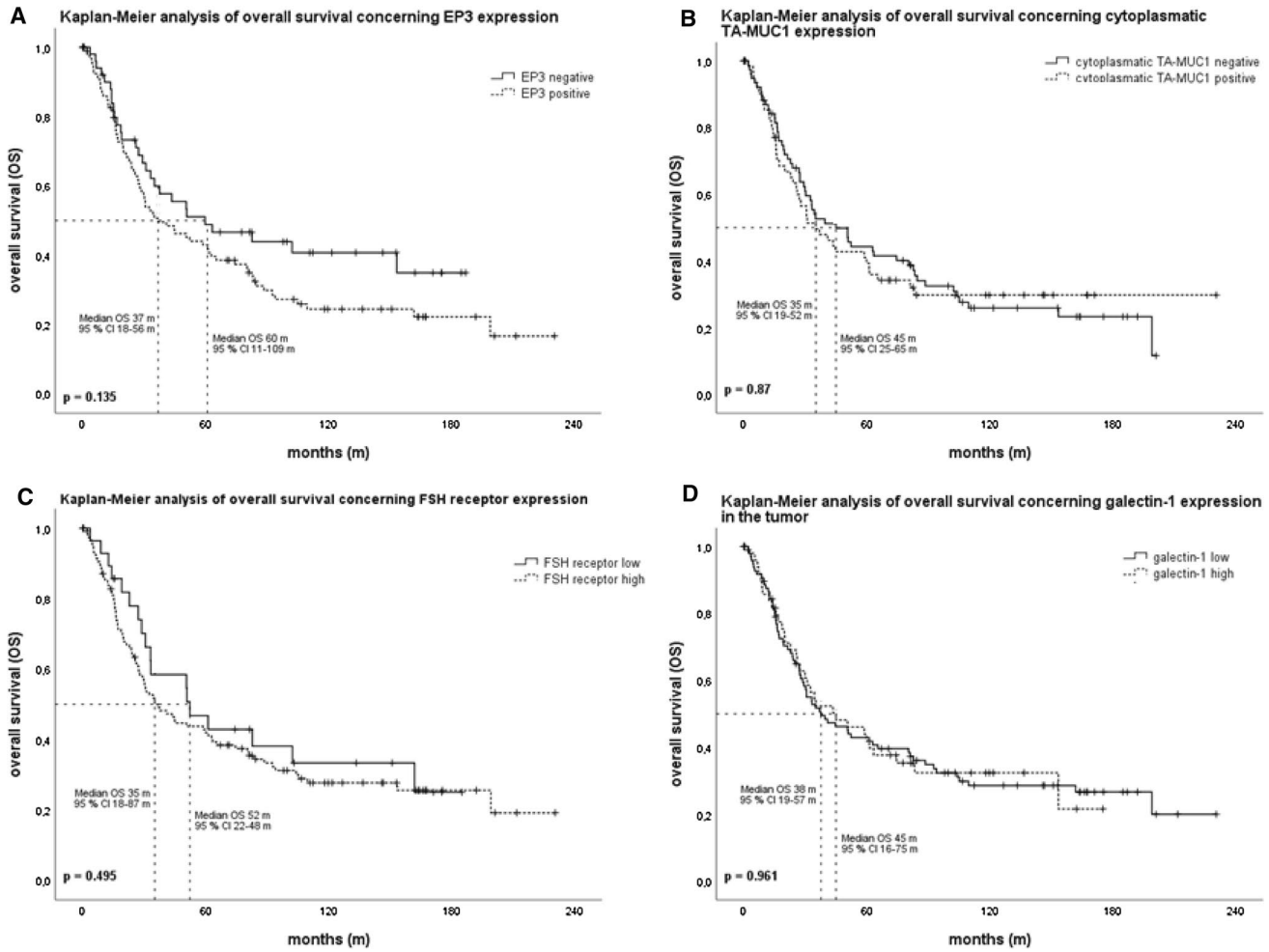

Fig. 2 Overall survival concerning EP3, cytoplasmatic TA-MUC1, FSH receptor, and galectin-1 expression

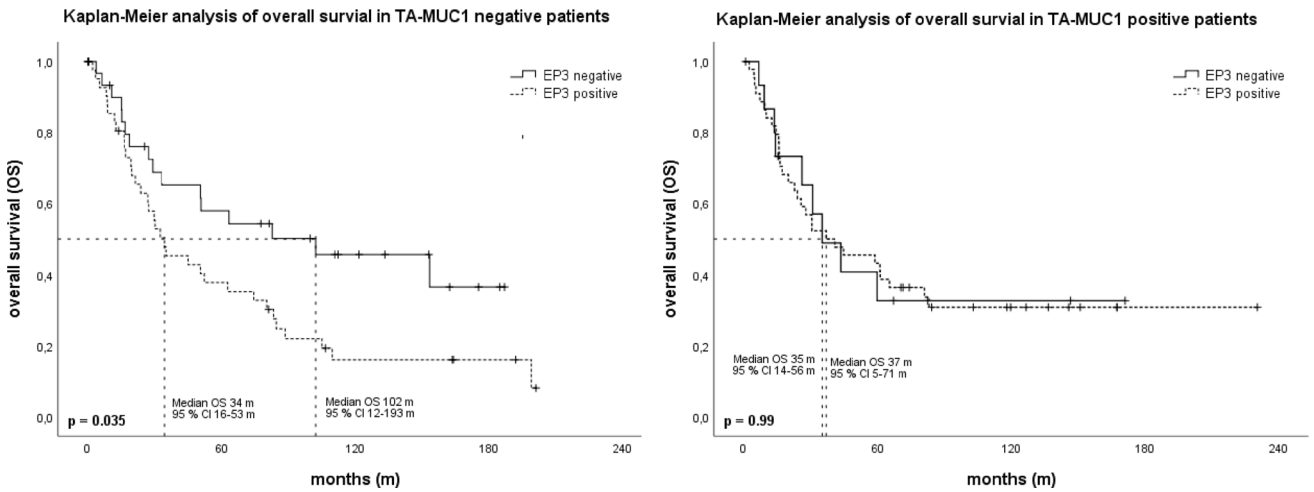

Fig. 3 Overall survival concerning EP3 expression in cytoplasmatic TA-MUC1 negative and positive patients

during malignant transformation. TA-MUC1 can be detected in the cytoplasm and on the cell surface due to receptor shuttling. There have been different aims to target MUC1 in targeted therapies for ovarian cancers. Gatipotuzumab is one of the antibodies evaluated for targeted therapies, although the effect as monotherapy for maintenance treatment did not significantly impact the clinical course (Ledermann et al. 2017; Dian et al. 2013).

Increased cytoplasmatic expression of MUC1 has been associated with impaired prognosis in cancer patients (Matsumura et al. 2002) and elevated cytoplasmatic Gatipotuzumab-staining levels were detected in high-grade ovarian carcinomas (Dian et al. 2013). Tumors with high MUC1 expression do also show high levels of COX-2 and PGE2 (Tinder et al. 2008; Nath et al. 2015). Furthermore, a mouse model of pancreatic ductal adenocarcinoma overexpressing MUC1 was attributed with celecoxib resistance, a specific COX-2 inhibitor (Mukherjee et al. 2009). This suggests a correlation of MUC1 expression with the COX-PGE2-axis, a pathway with a known important role in cancer development and progression. In pancreatic cancer, MUC1 was identified to induce COX-2 expression via colocalization with NFκB, translocation to the nucleus and binding to the COX-2 promotor region (Nath et al. 2015). Therefore, MUC1-positive tumors seem to be able to induce COX-2 and cause high PGE2 levels. In our study, the TA-MUC1 positive subgroup was the subgroup, where we could not show a negative prognostic effect of EP3-receptor expression. We speculate that the EP3-driven pathway might be less important in MUC1-positive tumors with high endogenous production of PGE2 via COX-2 induction. In MUC1 negative tumors with less endogenous PGE2 production, the EP3-driven pathway might be more relevant.

The role of the COX overexpression in ovarian cancer has been addressed in various studies; however, results were not consistent so far. Ovarian carcinomas show increased COX-2 expression with a correlation of the COX-2 increase to the tumor stage (Rask et al. 2006). In high-grade advanced serous ovarian carcinoma, elevated COX-2 expression correlated with tumor proliferation and angiogenesis (Ali-Fehmi et al. 2005). Ovarian cancer patients with COX-2 overexpression showed significantly impaired survival in the univariate, but not in the multivariate analysis (Ali-Fehmi et al. 2005). Treatment of ovarian cancer cells lines with NSAIDs and COXibs resulted in increased apoptosis (Rodriguez-Burford et al. 2002). PGE2 induced by COX-2 overexpression could stimulate myeloid-derived suppressor cells to migrate to ovarian cancer ascites. Myeloid-derived suppressor cells can inhibit T cells, and this might allow ovarian cancer cells to escape immune surveillance (Obermajer et al. 2011).

However, a clear mechanism and a pathway how COX-2 overexpression and elevated PGE2 affect ovarian cancer are not revealed yet. We suggest that an EP3-related pathway might be predominantly relevant in MUC1 negative tumors without endogenous driven COX-2 induction. Further studies targeting COX-2 or directly the EP3 receptor with antagonists in MUC1 negative tumors will have to clarify these correlations.

Funding This study was funded by laboratory resources.

Data availability The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest A.H. has received research grants from the "Walter Schulz Stiftung" and honoraria from Roche and Pfizer. S.M. received research support, advisory board, honoraria and travel expenses from AstraZeneca, Clovis, Medac, MSD, PharmaMar, Roche, Sensor Kinesis, Tesaro and Teva. F.T. declares research support, advisory board, honoraria and travel expenses from AstraZeneca, Medac, PharmaMar, Roche, and Tesaro. S.H. reports grants from Baden-Württemberg Ministry of Science, Research and the Arts, from StuRa Ruprecht-Karls-University of Heidelberg, FöFoLe LMU Munich Medical Faculty, grants from FERRING, personal fees from Roche, other from Astra Zeneca, grants from Novartis Oncology, grants and non-financial support from Apceth GmbH, non-financial support from Addex and grants from Heuer Stiftung. She further reports grants from Deutsche Forschungsgemeinschaft within the funding program Open Access Publishing, by the Baden-Württemberg Ministry of Science, Research and the Arts and by Ruprecht-Karls-University Heidelberg, outside the submitted work. All other authors declare no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The current study was approved by the Ethics Committee of the Ludwig-Maximilians-University, Munich, Germany (approval number 227-09 and 18-392).

Informed consent This study used tumor tissue that had initially been collected for histo-pathological diagnostics. At the time, the tissue was examined for the current study, all diagnostic procedures had already been fully completed, and the tissue used was thus classified as left-over material. All patient data were fully anonymized, the Ethics Committee of the Ludwig-Maximilians-University (Munich, Germany) approved the study (227-09 and 18-392), and the study was performed according to the standards set in the Declaration of Helsinki 1975. As per declaration of our ethics committee, no written informed consent of the participants or permission to publish is needed given the circumstances described above. Researchers were blinded from patient data during experimental and statistical analyses.

References

Aletti GD, Gostout BS, Podratz KC, Cliby WA (2006) Ovarian cancer surgical resectability: relative impact of disease, patient status, and surgeon. Gynecol Oncol 100(1):33–37

Ali-Fehmi R, Morris RT, Bandyopadhyay S, Che M, Schimp V, Malone JM Jr et al (2005) Expression of cyclooxygenase-2 in advanced

stage ovarian serous carcinoma: correlation with tumor cell proliferation, apoptosis, angiogenesis, and survival. Am J Obstet Gynecol 192(3):819–825

Baldwin LA, Huang B, Miller RW, Tucker T, Goodrich ST, Podzielinski I et al (2012) Ten-year relative survival for epithelial ovarian cancer. Obstet Gynecol 120(3):612–618

Bertagnolli MM, Eagle CJ, Zauber AG, Redston M, Solomon SD, Kim K et al (2006) Celecoxib for the prevention of sporadic colorectal adenomas. N Engl J Med 355(9):873–884

Chetry M, Thapa S, Hu X, Song Y, Zhang J, Zhu H et al (2018) The Role of galectins in tumor progression, treatment and prognosis of gynecological cancers. J Cancer 9(24):4742–4755

Dembo AJ, Davy M, Stenwig AE, Berle EJ, Bush RS, Kjorstad K (1990) Prognostic factors in patients with stage I epithelial ovarian cancer. Obstet Gynecol 75(2):263–273

Dian D, Lenhard M, Mayr D, Heublein S, Karsten U, Goletz S et al (2013) Staining of MUC1 in ovarian cancer tissues with PankoMab-GEX detecting the tumour-associated epitope, TA-MUC1, as compared to antibodies HMFG-1 and 115D8. Histol Histopathol 28(2):239–244

du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J (2009) Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). Cancer 115(6):1234–1244

Emons G, Pahwa GS, Ortmann O, Knuppen R, Oberheuser F, Schulz KD (1990) LHRH-receptors and LHRH-agonist treatment in ovarian cancer: an overview. J Steroid Biochem Mol Biol 37(6):1003–1006

Harris RE (2009) Cyclooxygenase-2 (cox-2) blockade in the chemoprevention of cancers of the colon, breast, prostate, and lung. Inflammopharmacology 17(2):55–67

Heidegger H, Dietlmeier S, Ye Y, Kuhn C, Vattai A, Aberl C et al (2017) The prostaglandin EP3 receptor is an independent negative prognostic factor for cervical cancer patients. Int J Mol Sci 18(7):1571. https://doi.org/10.3390/ijms18071571

Heublein S, Page S, Mayr D, Schmoeckel E, Trillsch F, Marme F et al (2019) Potential interplay of the gatipotuzumab epitope TA-MUC1 and estrogen receptors in ovarian cancer. Int J Mol Sci 20(2):295. https://doi.org/10.3390/ijms20020295

Hou R, Jiang L, Liu D, Lin B, Hu Z, Gao J et al (2017) Lewis(y) antigen promotes the progression of epithelial ovarian cancer by stimulating MUC1 expression. Int J Mol Med 40(2):293–302

Howe LR (2007) Inflammation and breast cancer. Cyclooxygenase/prostaglandin signaling and breast cancer. Breast Cancer Res 9(4):210

Kossai M, Leary A, Scoazec JY, Genestie C (2018) Ovarian cancer: a heterogeneous disease. Pathobiology 85(1–2):41–49

Ledermann J, Sehouli J, Zurawski B, Raspagliesi F, De Giorgi U, Banerjee S et al (2017) LBA41A double-blind, placebo-controlled, randomized, phase 2 study to evaluate the efficacy and safety of switch maintenance therapy with the anti-TA-MUC1 antibody PankoMab-GEX after chemotherapy in patients with recurrent epithelial ovarian carcinoma. Ann Oncol 28(suppl_8):viii46–viii50

Matsumura N, Yamamoto M, Aruga A, Takasaki K, Nakano M (2002) Correlation between expression of MUC1 core protein and outcome after surgery in mass-forming intrahepatic cholangiocarcinoma. Cancer 94(6):1770–1776

Mukherjee P, Basu GD, Tinder TL, Subramani DB, Bradley JM, Arefayene M et al (2009) Progression of pancreatic adenocarcinoma is significantly impeded with a combination of vaccine and COX-2 inhibition. J Immunol 182(1):216–224

Nath S, Roy LD, Grover P, Rao S, Mukherjee P (2015) Mucin 1 regulates Cox-2 gene in pancreatic cancer. Pancreas 44(6):909–917

Niringiyumukiza JD, Cai H, Xiang W (2018) Prostaglandin E2 involvement in mammalian female fertility: ovulation, fertilization, embryo development and early implantation. Reprod Biol Endocrinol 16(1):43

Obermajer N, Muthuswamy R, Odunsi K, Edwards RP, Kalinski P (2011) PGE(2)-induced CXCL12 production and CXCR38 expression controls the accumulation of human MDSCs in ovarian cancer environment. Can Res 71(24):7463–7470

Perales-Puchalt A, Svoronos N, Rutkowski MR, Allegrezza MJ, Tesone AJ, Payne KK et al (2017) Follicle-stimulating hormone receptor is expressed by most ovarian cancer subtypes and is a safe and effective immunotherapeutic target. Clin Cancer Res 23(2):441–453

Rask K, Zhu Y, Wang W, Hedin L, Sundfeldt K (2006) Ovarian epithelial cancer: a role for PGE2-synthesis and signalling in malignant transformation and progression. Mol Cancer 5:62

Reader J, Holt D, Fulton A (2011) Prostaglandin E2 EP receptors as therapeutic targets in breast cancer. Cancer Metastasis Rev 30(3–4):449–463

Rodriguez-Burford C, Barnes MN, Oelschlager DK, Myers RB, Talley LI, Partridge EE et al (2002) Effects of nonsteroidal anti-inflammatory agents (NSAIDs) on ovarian carcinoma cell lines: preclinical evaluation of NSAIDs as chemopreventive agents. Clin Cancer Res 8(1):202–209

Schulz H, Schmoeckel E, Kuhn C, Hofmann S, Mayr D, Mahner S et al (2017) Galectins-1, -3, and -7 are prognostic markers for survival of ovarian cancer patients. Int J Mol Sci 18(6):1230. https://doi.org/10.3390/ijms18061230

Schulz H, Kuhn C, Hofmann S, Mayr D, Mahner S, Jeschke U et al (2018) Overall survival of ovarian cancer patients is determined by expression of galectins-8 and -9. Int J Mol Sci 19(1):323. https://doi.org/10.3390/ijms19010323

Semmlinger A, von Schoenfeldt V, Wolf V, Meuter A, Kolben TM, Kolben T et al (2018) EP3 (prostaglandin E2 receptor 3) expression is a prognostic factor for progression-free and overall survival in sporadic breast cancer. BMC Cancer 18(1):431

Siegel RL, Miller KD, Jemal A (2019) Cancer statistics. CA Cancer J Clin 69(1):7–34

Sugimoto Y, Narumiya S (2007) Prostaglandin E receptors. J Biol Chem 282(16):11613–11617

Tinder TL, Subramani DB, Basu GD, Bradley JM, Schettini J, Million A et al (2008) MUC1 enhances tumor progression and contributes toward immunosuppression in a mouse model of spontaneous pancreatic adenocarcinoma. J Immunol 181(5):3116–3125

Tsujii M, Kawano S, DuBois RN (1997) Cyclooxygenase-2 expression in human colon cancer cells increases metastatic potential. Proc Natl Acad Sci USA 94(7):3336–3340

Vergote I, De Brabanter J, Fyles A, Bertelsen K, Einhorn N, Sevelda P et al (2001) Prognostic importance of degree of differentiation and cyst rupture in stage I invasive epithelial ovarian carcinoma. Lancet 357(9251):176–182

Wang D, Dubois RN (2010) Eicosanoids and cancer. Nat Rev Cancer 10(3):181–193

Williams CS, Mann M, DuBois RN (1999) The role of cyclooxygenases in inflammation, cancer, and development. Oncogene 18(55):7908–7916

Ye Y, Vattai A, Ditsch N, Kuhn C, Rahmeh M, Mahner S et al (2018) Prostaglandin E2 receptor 3 signaling is induced in placentas with unexplained recurrent pregnancy losses. Endocr Connect 7(5):749–761

Zhu J, Trillsch F, Mayr D, Kuhn C, Rahmeh M, Hofmann S et al (2018) Prostaglandin receptor EP3 regulates cell proliferation and migration with impact on survival of endometrial cancer patients. Oncotarget 9(1):982–994

Zhuandi G, Tuanjie C, Luju L, Abdiryim A, Yingying D, Haoqin L et al (2018) FSH receptor binding inhibitor restrains follicular development and possibly attenuates carcinogenesis of ovarian cancer through down-regulating expression levels of FSHR and ERbeta in normal ovarian tissues. Gene 668:174–181

Affiliations

Bastian Czogalla[1] · Christina Kuhn[1] · Sabine Heublein[1,2] · Elisa Schmöckel[3] · Doris Mayr[3] · Thomas Kolben[1] · Fabian Trillsch[1] · Alexander Burges[1] · Sven Mahner[1] · Udo Jeschke[1] · Anna Hester[1]

Bastian Czogalla
Bastian.czogalla@med.uni-muenchen.de

Christina Kuhn
christina.kuhn@med.uni-muenchen.de

Sabine Heublein
sabine.heublein@med.uni-heidelberg.de

Elisa Schmöckel
elisa.schmoeckel@med.uni-muenchen.de

Doris Mayr
doris.mayr@med.uni-muenchen.de

Thomas Kolben
Thomas.kolben@med.uni-muenchen.de

Fabian Trillsch
fabian.trillsch@med.uni-muenchen.de

Alexander Burges
alexander.burges@med.uni-muenchen.de

Sven Mahner
sven.mahner@med.uni-muenchen.de

Anna Hester
anna.hester@med.uni-muenchen.de

[1] Department of Obstetrics and Gynecology, University Hospital, LMU Munich, Marchioninistr. 15, 81377 Munich, Germany

[2] Department of Gynecology and Obstetrics, University of Heidelberg, 69120 Heidelberg, Germany

[3] Department of Pathology, Ludwig-Maximilians University of Munich, 81337 Munich, Germany