World Journal of Obstetrics and Gynecology

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DOI: 10.5317/wjog.v5.i1.118

World J Obstet Gynecol 2016 February 10; 5(1): 118-126
ISSN 2218-6220 (online)

ORIGINAL ARTICLE

Basic Study

Alpha1B adrenoceptor expression is a marker of reduced survival and increased tumor recurrence in patients with endometrioid ovarian cancer

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Supported by Financial support from the Fritz Bender Foundation (Munich; to Dascha Deutsch, Frank Entschladen and Kurt S Zänker); from the Nottingham University Hospital Trustees (contributed to the reagent costs).

Institutional review board statement: This study was approved by the Derbyshire ethics committee (reference 07/H0401/156) and Department of Research and Innovation, Queens Medical Centre, Nottingham University Hospitals Trust, Nottingham NG7 2UH, United Kingdom.

Institutional animal care and use committee statement: No animals were used in this study.

Conflict-of-interest statement: The authors have declared no conflict of interest.

Data sharing statement: No additional data are available.

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Received: April 24, 2015
Peer-review started: April 29, 2015
First decision: June 9, 2015
Revised: October 14, 2015
Accepted: November 10, 2015
Article in press: November 11, 2015
Published online: February 10, 2016

Abstract

AIM: To investigate the expression patterns of different adrenoceptor isoforms in ovarian cancer and their association with survival and tumor recurrence.

METHODS: The protein expression levels of α1B, α2C and β2 adrenoceptor were assessed in unselected ovarian cancer using immunohistochemistry on micro-arrayed archival tissue samples. A database containing clinical and pathology parameters and follow-up was used

to investigate the association between adrenoceptor isoform expression with ovarian specific survival and tumor recurrence, using univariate and multivariate statistical analysis.

RESULTS: Expression of α1B showed an association with reduced ovarian specific survival (P = 0.05; CI: 1.00-1.49) and increased tumor recurrence (P = 0.021, CI: 1.04-1.69) in the whole patient group. On sub-analysis the expression of α1B in endometrioid cancers (χ^2 = 5.867, P = 0.015) was found to predict reduced ovarian specific survival and increased tumor recurrence independently of tumor grade, clinical stage and chemotherapy. An association with clinical outcome was not seen for α2C or β2 AR.

CONCLUSION: Alpha1B adrenoceptor protein was found to predict increased risk of tumor recurrence and reduced mortality in patients with endometrioid type ovarian cancer and should be investigated as a biomarker for identifying patients at increased risk of disease progression. Furthermore, α adrenergic receptor antagonists with α1B selectivity should be investigated as a possible adjuvant therapy for treating patients with endometrioid cancer. Proof of principle could be tested in a retrospective population study.

Key words: Alpha adrenoceptor; Beta adrenoceptor; β-blockers; α-blockers; Ovarian cancer; Prognosis; Cancer therapy

Core tip: Epidemiological studies suggest that β-blockers might have a role in reducing metastatic spread and tumor recurrence and thereby prolong patient survival in some cancer types. In this novel study we found α1B adrenoceptor is a biomarker of tumor recurrence in endometrioid ovarian cancer. Further studies are needed to test if selective α1 adrenergic receptor antagonists inhibit tumor recurrence and prolong survival in patients with this type of cancer.

Deutsch D, Deen S, Entschladen F, Coveney C, Rees R, Zänker KS, Powe DG. Alpha1B adrenoceptor expression is a marker of reduced survival and increased tumor recurrence in patients with endometrioid ovarian cancer. *World J Obstet Gynecol* 2016; 5(1): 118-126 Available from: URL: http://www.wjgnet.com/2218-6220/full/v5/i1/118.htm DOI: http://dx.doi.org/10.5317/wjog.v5.i1.118

INTRODUCTION

Ovarian cancer is the fifth leading cause of cancer related death amongst women in the United Kingdom and the second most common gynaecological malignancy. The lifetime risk of developing ovarian cancer is estimated at 1 in 68 for women in the United States[1]. It arises with non-specific symptoms, thus about 70% of patients are diagnosed with late stage disease with a 5-year survival rate of less than 30%. In contrast, patients diagnosed with early-stage disease have a > 90% 5-year survival rate[2]. Endometrioid type tumors account for 10%-20% ovarian cancers and compared to other forms have a relatively better 5-year survival rate. Patients would benefit from earlier cancer detection improved therapies for preventing metastasis and disease recurrence.

Increased levels of catecholamine hormones are linked with poor prognosis in ovarian cancer[3-5] possibly explained by their ability at promoting cell invasion and proliferation *via* activation of adrenergic receptors (adrenoceptors, AR)[5,6]. Recent laboratory studies suggest that beta adrenergic receptor antagonists (β-blockers) abrogate cancer cell migration[7-9], an essential element of metastasis, and disrupt the stress/inflammatory/cancer pathway interactions[10]. Sloan *et al*[10] showed that epinephrine-induced beta2 (β2) adrenoceptor activated cancer cells produce mediators that recruit tumor associated macrophages, and the process is inhibited by the β-blocker propranolol[11].

There are 9 adrenoceptor subtypes classified in two major classes, α and β, belonging to the G-protein coupled receptor family[12]. Promiscuous AR coupling results in the activation of multiple cancer cell signalling pathways[13]. Included among these, β2 activation induces phosphokinase A (PKA) and ERK[14] cell signalling in response to upregulation of cyclic AMP (cAMP)[15], leading to migration in some cancer cell types. ERK1/2 phosphorylation may occur following α1B adrenoceptor activation in ovarian cancer cells[15-17] but opposing this, α2C adrenoceptor can preferentially inhibit *cAMP* and *PKA* gene transcription[17]. For this reason it can be hypothesised that activation of α2C adrenoceptors may have an anti-cancer regulatory role compared to α1B and β2 receptors.

A small number of conflicting population studies have investigated the impact of β-blocker usage on survival in ovarian cancer patients. These have either shown potential benefits[7,18] or no effectiveness[19,20]. Such differences could possibly be explained by AR expression heterogeneity and so the current study is designed to assess the distribution and pattern of α1B, α2C and β2 AR proteins expressed in ovarian tumors and association with clinical outcome. Knowledge of this information will improve the study design when assessing the feasibility of using adrenergic receptor antagonists for targeted adjuvant cancer therapeutics. It was found that α1B rather than β2 adrenoceptor expression correlated with poor survival and tumor recurrence in epithelioid tumors.

MATERIALS AND METHODS

The protein expression of α1B, α2C and β2 was chara-

cterised in formalin-fixed paraffin-embedded tissue microarrays of ovarian cancer from unselected patients attending Nottingham University Hospitals Trust. Damaged tissue cores and those that did not contain invasive carcinoma were censored. The study was approved by the Derbyshire ethics committee (07/H0401/156).

Patient selection

Following a diagnosis of ovarian cancer, patients were selected for chemotherapy treatment according to the East Midlands Cancer Network ovarian cancer treatment algorithm (http://www.eastmidlandscancernetwork.nhs.uk/Library/OvarianTreatmentAlgorithm.pdf). Tissue microarrays were produced by incorporating cores of archival formalin fixed ovarian tumor tissue from Nottingham patients presenting in 1991-2006. The presence of cancer was confirmed by a pathologist. Clinicopathological data was available for patients up to 240 mo post-diagnosis and was categorised as poor (< 60 mo) or better (> 60 mo) prognosis.

Immunohistochemistry

Four micron thick TMA sections had immunohistochemistry performed using a linked streptavidin peroxidase/biotinylated AB technique in accordance to the supplier's recommendations (DAKO, Cambs, United Kingdom). Microwave antigen retrieval was performed in 0.01 mol/mL citrate buffer (pH6). The primary antibodies were previously optimized in full face breast cancer tissues as previously described[21] and in ovarian TMA sections with negative controls. Primary rabbit polyclonal_antibodies against α1B (ab13297, Abcam, Cambs, United Kingdom), α2C (ab46536, Abcam), and β2 (ab13163, Abcam) AR were used diluted at 1:50, 1:750 and 1:450, respectively.

Statistical analysis

Statistical analysis was performed using statistical software, SPSS 20.0 (SPSS Inc., Chicago, IL, United States). Levels of adrenoceptor protein expression were microscopically assessed for staining intensity in malignant epithelium only and patients categorised into negative (negative or weak intensity) verse positive (moderate to strong intensity). Patients with missing clinical data were censored. Association between AR expression and different clinicopathology factors was evaluated using the non-parametric χ^2 test. Survival and tumor recurrence analysis was modelled using the Kaplan-Meier method with a univariate log rank test to assess significance. Patients that died due to causes other than ovarian cancer were censored during survival analysis. Multivariate Cox proportional hazard regression (95%CI) was used to evaluate the independence of adrenoceptors for predicting survival and tumor recurrence compared to other clinical variables. A *P* value of < 0.05 was considered to indicate statistical significance.

Table 1 Distribution of adrenoceptor protein expression according to age, tumor type and tumor grade in patients with ovarian cancer

		Adrenergic receptor	Absent	Present	χ^2	*P*
Age at diagnosis	< 49	α-1B	25 (66)	13 (34)	1.076	0.584
	50-69		55 (59)	38 (41)		
	> 70		24 (54)	20 (46)		
	< 49	α-2C	11 (29)	27 (71)	2.600	0.273
	50-69		38 (42)	52 (58)		
	> 70		19 (45)	23 (55)		
	< 49	β2	9 (31)	20 (69)	1.956	0.376
	50-69		36 (43)	47 (57)		
	> 70		13 (33)	26 (67)		
Tumour type	High grade serous	α-1B	49 (55)	40 (45)	14.648	0.005
	Low grade serous		4 (67)	2 (33)		
	Endometrioid		25 (60)	17 (40)		
	Clear cell		16 (94)	1 (6)		
	Mucinous		4 (29)	10 (71)		
	High grade serous	α-2C	44 (48)	47 (52)	11.038	0.026
	Low grade serous		4 (67)	2 (33)		
	Endometrioid		8 (21)	31 (79)		
	Clear cell		6 (35)	11 (65)		
	Mucinous		5 (33)	10 (67)		
	High grade serous	β2	25 (32)	54 (68)	13.559	0.009
	Low grade serous		1 (17)	5 (83)		
	Endometrioid		20 (54)	17 (46)		
	Clear cell		8 (61)	5 (39)		
	Mucinous		1 (9)	10 (91)		
Tumour grade	1	α-1B	11 (42)	15 (58)	3.472	0.176
	2		6 (55)	5 (45)		
	3		81 (62)	50 (38)		
	1	α-2C	9 (35)	17 (65)	0.456	0.796
	2		4 (36)	7 (64)		
	3		54 (41)	77 (59)		
	1	β2	4 (18)	18 (82)	4.236	0.12
	2		4 (44)	5 (56)		
	3		47 (41)	68 (59)		
Mortality (5 yr)	No	α-1B	55 (69)	25 (31)	4.821	0.028
	Yes		47 (52)	43 (48)		
	< 5 yr	α-2C	31 (39)	48 (61)	0.001	0.969
	> 5 yr		34 (39)	52 (61)		
	< 5 yr	β2	25 (36)	44 (64)	0.284	0.594
	> 5 yr		32 (41)	47 (59)		

Proportion of patients showing each adrenoceptor (percentage).

RESULTS

Patient characteristics and adrenoceptor expression

Tissue cores were available for assessment in 168 patients stained for α1B and α2C expression and 146 for β2 adrenoceptor protein. The reduced number of cores available for β2 assessment was due to detachment during immunohistochemistry processing. Adrenoceptor protein appeared localised in the cytoplasm of malignant ovarian tissue (Figure 1).

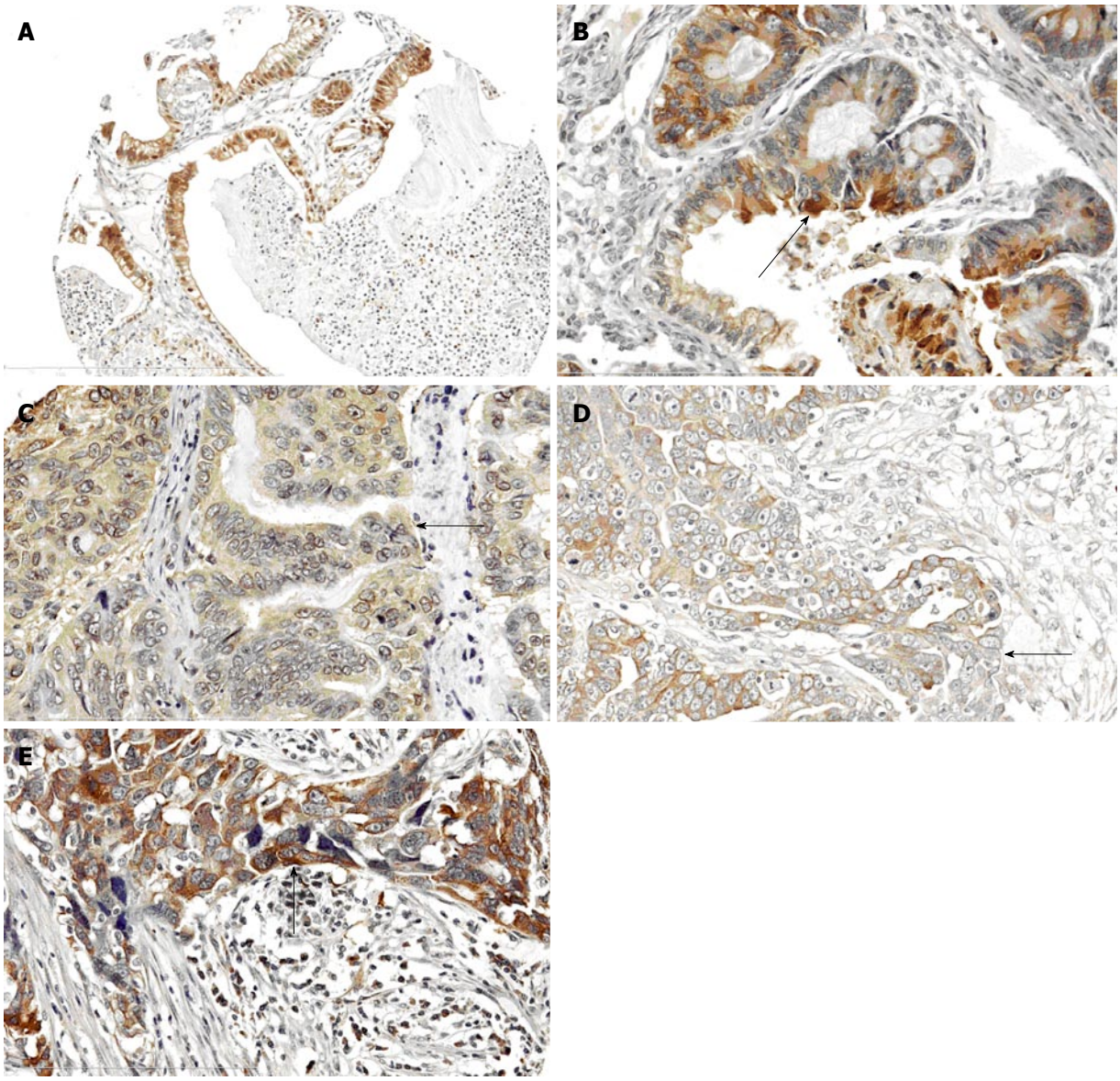

Figure 1 Following immunostaining, adrenergic receptor proteins were seen as brown staining in ovarian cancer tissue. A: Strong α1B staining in a mucinous tumor; B: Strong α1B - high grade serous tumor; C: Moderate α2C - endometrioid tumor; D: Weak β2-AR - high grade serous tumor; E: Strong β2-AR - high grade serous tumor. AR: Adrenergic receptor.

The median age at cancer diagnosis was 61 years (range 31-87) and the proportion of different cancer subtypes is shown in Table 1. Just over half (53%) of the patient cohort investigated in this study were categorised with poor survival (less than 5 years post-diagnosis) and the remainder survived 5-20 years.

The distribution of adrenoceptor expression differed by tumor type with 41%, 60%, 62% of the full cohort showing expression of α1B, α2C and β2 respectively (Table 1). Increased α1B expression was more frequently seen in mucinous cancers but in contrast was reduced in low grade serous and clear cell tumors. Levels of α2C were increased in endometrioid, clear cell and mucinous tumors. β2 expression was more frequently increased in high and low grade serous tumors and mucinous cancers (Table 1). No association was found between individual adrenoceptor types and tumor grade or clinical stage (Table 1). Patients with tumors expressing α2C adrenoceptor showed an association with low stage clinical disease (Table 2).

Clinical outcome

A Kaplan-Meier technique with a log rank test was used to model the independence of adrenoceptor protein expression in predicting ovarian cancer specific survival and tumor recurrence in the full patient cohort. High α1B protein expression was associated with reduced survival across the full patient cohort due to ovarian cancer specific mortality (P = 0.05; 95%CI: 1.00-1.49), resulting in a reduction in the median survival time from 63.5 to 44 mo (Figure 2 and Table 3). Similarly, α1B adrenoceptor protein expression was associated with increased tumor recurrence (P = 0.021, 95%CI: 1.04-1.69). A subanalysis of survival (χ^2 = 3.907, P =

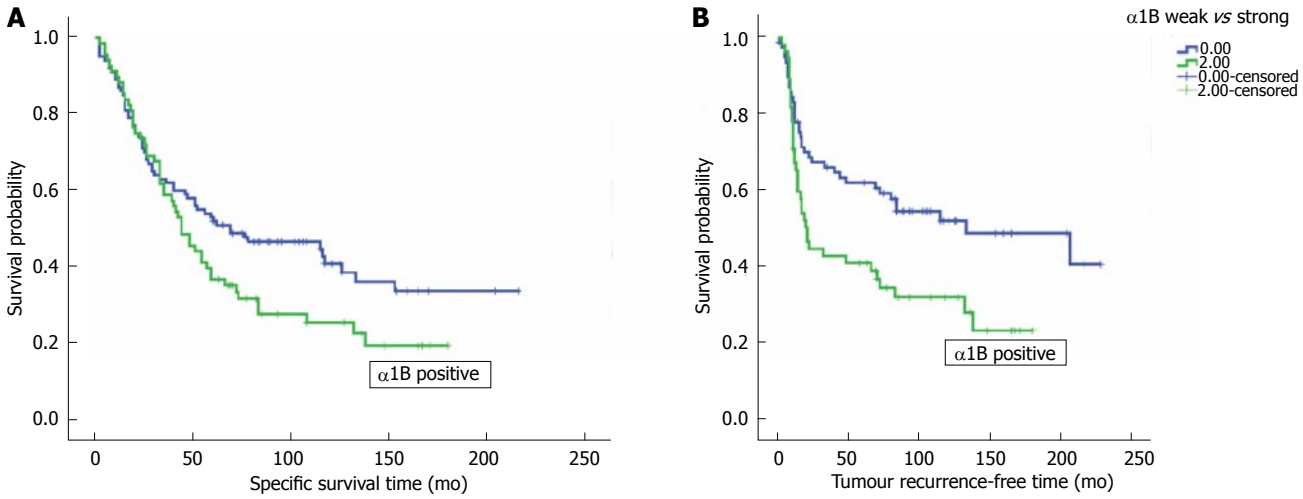

Figure 2 High alpha1B protein expression (green curve) showed an association with poor survival (*P* = 0.045) (A), and (B) tumor recurrence (*P* = 0.007) in the whole cohort of patients with ovarian cancer.

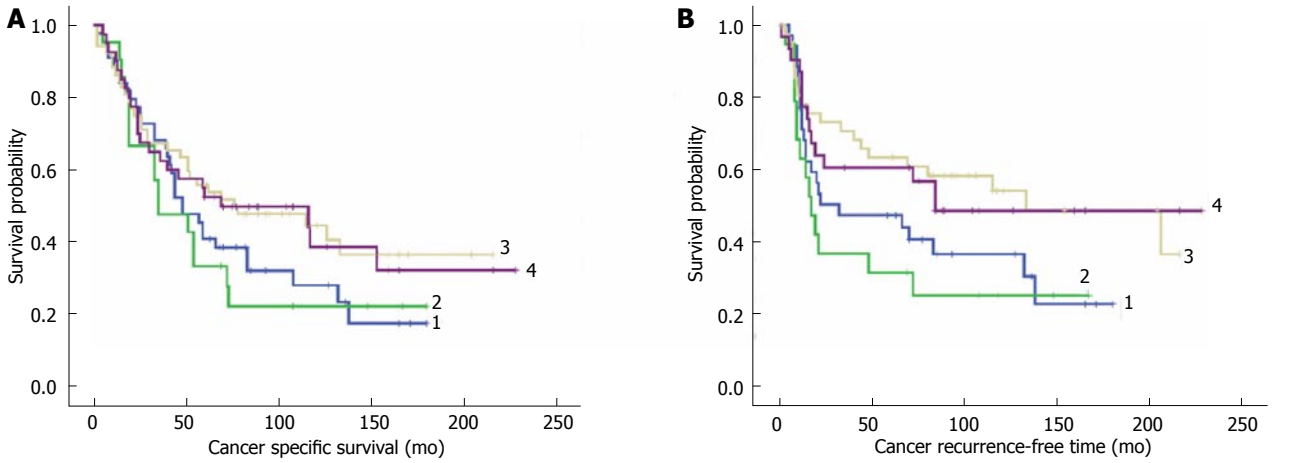

Figure 3 Four adrenoceptor groups were modelled for (A) ovarian cancer specific survival (*P* = 0.284) and (B) tumor recurrence (*P* = 0.061) according to the relative expression of α1B and α2C. Group 1: $\alpha1B^{positive}/\alpha\ \alpha2C^{positive}$; Group 2: $\alpha1B^{positive}/\alpha2C^{negative}$; Group 3: $\alpha1B^{negative}/\alpha2C^{positive}$; Group 4: $\alpha1B^{negative}/\alpha2C^{negative}$. Patients showing α1B expression (Groups 1 and 2) showed worse survival compared to patients that had α2C positive tumors without α1B expression.

0.048) and tumor recurrence (χ^2 = 5.867, *P* = 0.015) in the different cancer subclasses showed an association with endometrioid type cancer. No association was found for α2C or β2 AR with survival or tumor recurrence.

In the full patient cohort, tumor adrenoceptor protein expression showed no association with chemoresistance or responsiveness. A subanalysis of patients with endometrioid tumors showed similar results.

Relative expression of α1B and α2C adrenoceptor proteins: Association with survival

To test the hypothesis that patient clinical outcome might be influenced by the balance of G_s-adrenoceptor proteins (α1B and β2 are proposed biomarkers of disease progression) compared to those with G_i-protein affinity (α2C is proposed as a biomarker of good prognosis), patients were categorised into different groups according to their relative expression levels of tumor-stimulating α1B and tumor-inhibitory α2C. Four patient groups were defined comprising: Group 1: $\alpha1B^{positive}/\alpha\ \alpha2C^{positive}$; Group 2: $\alpha1B^{positive}/\alpha2C^{negative}$; Group 3: $\alpha1B^{negative}/\alpha2C^{positive}$; and Group 4: $\alpha1B^{negative}/\alpha2C^{negative}$.

No significant difference was identified between the four adrenoceptor groups with ovarian cancer specific survival (χ^2 = 4.211, *P* = 0.240) or tumor recurrence (χ^2 = 7.361, *P* = 0.061). For tumor recurrence, the best separation between plots was achieved between the singly positive Group 2 ($\alpha1B^{positive}/\alpha2C^{negative}$) and Group 3 ($\alpha1B^{negative}/\alpha2C^{positive}$) ($\chi^2$ = 5.136, *P* = 0.023). Groups showing co-expression of α1B/α2C showed intermediate risk of tumor recurrence suggesting the presence of α2C expression has a modifying effect on α_{1B} expression population studies (Figure 3).

Similarly, the relationship involving relative expression between β2 and α2C was tested by defining 4 patient subgroups: Group 1: $\beta2^{positive}/\alpha2C^{positive}$; Group 2: $\beta2^{positive}/\alpha2C^{negative}$; Group 3: $\beta2^{negative}/\alpha2C^{positive}$; and Group 4: $\beta2^{negative}/\alpha2C^{negative}$.

The effect of clinical outcome was assessed using

Table 2 Distribution of adrenoceptor protein expression in patients with ovarian cancer according to clinical stage, chemotherapy received and chemotherapy failure

		Adrenergic receptor	Absent	Present	χ^2	*P*
Clinical stage	1	α-1B	39 (65)	21 (35)	2.486	0.478
	2		12 (50)	12 (50)		
	3		47 (59)	33 (41)		
	4		4 (44)	5 (56)		
	1	α-2C	17 (29)	41 (71)	6.014	0.111
	2		10 (42)	14 (58)		
	3		38 (49)	40 (51)		
	4		2 (25)	6 (75)		
	1	β2	18 (37)	31 (63)	6.508	0.089
	2		4 (20)	16 (80)		
	3		31 (42)	43 (58)		
	4		5 (71)	2 (29)		
Stage 1 *vs* other stages	Stage 1	α-1B	37 (63)	22 (37)	0.894	0.344
	Other stages		59 (55)	48 (45)		
	Stage 1	α-2C	17 (29)	42 (71)	4.376	0.036
	Other stages		49 (45)	59 (55)		
	Stage 1	β2	18 (36)	32 (64)	0.090	0.764
	Other stages		37 (39)	59 (61)		
Chemotherapy regimen	Before surgery	α-1B	11 (58)	8 (42)	0.734	0.693
	After surgery		84 (57)	62 (43)		
	Before surgery	α-2C	8 (42)	11 (58)	0.702	0.704
	After surgery		58 (40)	87 (60)		
	Before surgery	β2	8 (47)	9 (53)	1.316	0.518
	After surgery		46 (36)	80 (64)		
Chemotherapy resistance	Refractory	α-1B	8 (80)	2 (20)	2.647	0.266
	Resistant within 6 mo		4 (44)	5 (56)		
	Responsive		72 (58)	52 (42)		
	Refractory	α-2C	2 (25)	6 (75)	2.342	0.310
	Resistant within 6 mo		6 (60)	4 (40)		
	Responsive		50 (41)	73 (59)		
	Refractory	β2	5 (56)	4 (44)	1.010	0.604
	Resistant within 6 mo		4 (40)	6 (60)		
	Responsive		40 (38)	64 (62)		

Proportion of patients showing each adrenoceptor (percentage).

Kaplan-Meier with a log rank test. No significant difference was seen between the patient subgroups when considering survival (χ^2 = 2.253, *P* = 0.689) or tumor recurrence-free time (χ^2 = 0.463, *P* = 0.927).

α1B is an independent prognostic biomarker

Multivariate Cox regression hazard analysis was used to test the independence of α1B as a prognostic biomarker for predicting ovarian cancer specific survival and tumor recurrence in patients with ovarian cancer. Tumor grade, clinical stage and systemic chemotherapy were included in the model. α1B adrenoceptor expression was found to contribute significant prediction ability concerning survival (HR = 1.221, *P* = 0.05, 95%CI: 1.000-1.493) and tumor recurrence (HR = 1.326, *P* = 0.021, 95%CI: 1.043-1.687) over and above the routinely used clinical parameters included in the model (Table 3).

Table 3 A Cox regression analysis was performed to test the independence of tumor alpha1B protein expression as a biomarker compared to tumor grade, clinical stage and chemotherapy treatment

	HR	95%CI		*P* value
Cancer specific survival				
Alpha1B expression	1.221	1.000	1.493	0.050
Tumor grade	1.353	0.992	1.844	0.056
Clinical stage	1.922	1.529	2.416	< 0.001
Chemotherapy	0.556	0.283	1.090	0.087
Tumor recurrence				
Alpha1B expression	1.326	1.043	1.687	0.021
Tumor grade	1.390	0.949	2.035	0.091
Clinical stage	2.469	1.825	3.340	< 0.001
Chemotherapy	0.614	0.257	1.467	0.272

Tumor α1B protein is an independent marker of reduced cancer-associated survival and increased tumor recurrence.

DISCUSSION

Ovarian cancer has a complex pathogenesis but recent studies have focused on the association between cancer progression and stress[4,22,23] involving the catecholamine hormones epinephrine and norepinephrine, and activation of β2 adrenoceptors. A recent paradigm proposed for a mouse model of breast cancer suggests cross-talk between cancer cells and macrophages triggering pro-metastasis cell signalling[10]. This paradigm might also extend to ovarian cancer because macrophages are implicated in ovarian metastasis, immunosuppression, angiogenesis and poor clinical outcome[24,25]. Consequently, it has been proposed that blockade of adrenoceptors using β-blockers could inhibit tumor progression in a number of cancer types including ovary[7], breast[26-28], prostate[29] and skin[30,31]. In addition, there is increasing evidence from patient[21] and *in vitro*[32] studies that alpha adrenoceptors are also implicated in breast cancer progression and for this reason we sought to identify the distribution and pattern of different adrenoceptor types in ovarian cancer patients.

The pattern of adrenoceptor expression was altered in different ovarian tumor types but overall, no association was found with tumor grade. Serous and endometrioid tumors generally differ in their prognostic outlook with the endometrioid type having better prognosis. A significant difference in pro-(β2) and anti-migratory (α2C) adrenoceptor expression patterns was identified. Compared to serous tumors, endometrioid cancers less frequently expressed β2 receptors (46% *vs* 68%) and were more likely to show α2 receptor

expression (79% *vs* 52%). But a subset of patients (40%) with endometrioid tumors expressed high levels of α1B protein and this correlated with poor prognosis due to a significantly shortened survival time and reduced tumor recurrence-free interval, independently of chemotherapy, tumor grade and clinical stage. The pathogenesis of endometrioid tumors is thought to be associated with endometriosis[33] and notable gene mutations in the phosphoinositide-3-kinase (PI3K) cell signalling pathway including PIK3CA and *PTEN* genes[34] in endometrial-derived cancer[35]. Activation of adrenoceptors provide a route to PI3K upregulation via the intermediary cAMP. Our findings suggest that α1B is a candidate biomarker and here it identified 17% of patients with endometrioid type cancer that require more intensive therapy and follow-up surveillance. Moreover, our findings suggest adrenoceptor antagonists and PI3K inhibitors provide potential for a targeted adjuvant therapy approach to complement existing therapies. In considering candidate anti-α adrenergic receptor drugs consideration has to be given to their selectivity and adverse effects. Alpha AR antagonists are used in the treatment of benign prostatic hyperplasia (*e.g.*, Prazosin, Doxazosin), urinary tract symptoms and hypertension. The non-selective drugs phenoxybenzamine and phentolamine would not be advocated, whereas some current tricyclic antidepressants could be considered but a recent study found amitriptyline, nortriptyline and imipramine are relatively weak α1B antagonists[36]. More promising is the recent development of a new family of 8-OMe benzodioxane analogues of the research drug WB4101 which has been shown to have high affinity for α1B AR[37]. The side effects of α1 antagonists including postural hypotension (Prazosin, Doxazosin), arrhythmia and CNS disturbances (tricyclic antidepressants) can be reduced by careful titration and active monitoring.

Cancer cell line studies have shown that norepinephrine activates α AR resulting in HIF1α dependent vascular endothelial growth factor transcription, required for angiogenesis[38]. Interestingly, Park *et al*[38] found that the α1 adrenoceptor inhibitor prazosin blocks the angiogenic pathway in the epithelial-to-mesenchymal type MDA-MB-231 breast cancer cell line, but not in liver (SK-Hep1) or prostate (PC3) cancer cells[38]. To translate this to ovarian cancer, we tested the proposal that α1B and 2C adrenoceptors might have an opposing promoting and inhibitory affect respectively on cancer progression and survival. To do this, patients were sub-classified according to α/β adrenoceptor phenotype, by comparing survival in patients with tumors expressing only one adrenoceptor (α1B, α2C or β2 positive) to those with co-expression of α2C. Although Kaplan-Meier models suggest α2C expression improves tumor recurrence-free times the finding was insignificant. Further studies are needed to better stratify patients for assessing possible therapeutic response to adrenoceptor antagonists.

No significant association between β2 protein expression levels and clinical outcome was found in this study. Recent laboratory studies show a significant pathologic role for neouroendocrine-induced progression in ovarian cancer (reviewed by Kang *et al*[39]), mediated by the β adrenoceptor activated cAMP - PKA cell signalling pathway. Increased cAMP activates Rap guanine-nucleotide-exchange-factor 3 (EPAC) leading to increased cell: Matrix adhesion needed for cancer cell implantation. Cancer growth is maintained due to enhanced cell survival resulting from γSrc-FAK signalling and STAT3 induced angiogenesis. These mechanisms explain the murine *in vivo* observation that the β2 antagonist propranolol inhibits ovarian cell growth[40]. However, other *in vitro* studies suggest that β-blockers would not be effective. In some instances, β2 agonists have been found to reduce cell proliferation[32,41,42] and migration[43]. In the latter case, it is proposed that β blockers could actually increase ovarian disease progression by promoting cell migration. Another explanation is that β blockers induce increased cell proliferation leaving unopposed α2C AR activity[42] in contrast to our findings suggesting that α1B is moderated by α2C in ovarian cancer. Recent proof-of-concept population studies of β-blocker users among ovarian cancer patients have produced conflicting findings. One study showed an association between increased progression-free survival (PFS) in users (n = 23) compared to non-users[7]. In contrast, a more recent study found no benefit in PFS or overall survival in platinum-sensitive patients prescribed β-blockers (n = 8)[5]. Clearly, larger studies are needed allowing for possible confounders and tumor receptor typing. Although previous studies have focused on the use of β-blockers to retard disease progression, the results presented here and in a recent breast cancer study[21] suggest that the possible therapeutic benefits of alpha adrenoceptor antagonists should be investigated.

ACKNOWLEDGMENTS

We thank Brett Blackbourn and Claire Boag for photographic assistance.

COMMENTS

Background

Many cancers are treatable by surgery, radio-/chemotherapy, or targeted drug treatments, or any combination of these. In some instances a cancer can spread (metastasise) to tissues distant from the original site. This process can place a patient at increased risk of disease progression and demise and in addition, it can present clinicians with more challenging medical management of a patient's disease. Knowledge about the biological process involved in cancer spread is increasing but there remains an unmet need to develop new treatment approaches to prevent it. Being able to identify patients that are at increased risk of metastasis can rationalise clinical management by focusing extensive treatment on those that will best benefit. Laboratory experiments have shown that some cancer cells are stimulated to migrate when adrenergic receptor proteins (stress receptors) are activated by stress hormones. Drugs are available that inhibit adrenergic receptor function and could be used to neutralise certain cancer cell functions.

Research frontiers

Identifying the expression pattern of adrenergic receptors (AR) in different cancer

types and their association with disease progression and survival could provide insight into using AR inhibitor drugs for targeted anti-cancer treatment.

Innovations and breakthroughs

The expression pattern of 3 AR proteins (αB1, α2C and β2) was investigated and its significance statistically related to survival and metastasis outcome in patients with different types of ovarian cancer. Only αB1 was found to predict shortened survival and increased risk of tumor recurrence, especially in patients with endometrioid type cancer, independently of tumour grade, clinical stage and chemotherapy treatment.

Applications

The results suggest that adrenergic receptor antagonists with anti-α1B selectivity could be used to limit disease progression in patients with endometrioid type tumors expressing α1B AR.

Terminology

Metastasis development is a major cause of mortality in patients with cancer and involves a multistep biological pathway resulting in tumor cells leaving the primary cancer and disseminating to distant body tissues. AR belong to a family of G protein-coupled receptors comprising 9 members.

Peer-review

This is a well written paper.

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