Up-Regulation of HDAC6 Results in Poor Prognosis and Chemoresistance in Patients with Advanced Ovarian High-Grade Serous Carcinoma

Mitsutake Yano
Saitama Medical University International Medical Center
Mariko Miyazawa
Tokai University School of Medicine
Naoki Ogane
Ashigarakami Hospital
Aiko Ogasawara
Saitama Medical University International Medical Center
Kosei Hasegawa
Saitama Medical University International Medical Center
Hisashi Narahara
Oita University Faculty of Medicine
Masanori Yasuda (m_yasuda@saitama-med.ac.jp)
Saitama Medical University International Medical Center https://orcid.org/0000-0002-0769-360X

Research

Keywords: histone deacetylase 6, ovarian cancer: high-grade serous carcinoma, programmed cell death ligand-1, hypoxia inducible factor-1α, prognosis

Posted Date: July 7th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-40241/v1

Version of Record: A version of this preprint was published at Anticancer Research on March 1st, 2021. See the published version at https://doi.org/10.21873/anticanres.14927.

Abstract

Background: Ovarian high-grade serous carcinoma (HGSC) gradually acquires chemoresistance after recurrence. In our previous study on ovarian clear cell carcinoma, histone deacetylase 6 (HDAC6) led to chemoresistance. This study aimed to evaluate HDAC6 as a predictor of chemoresistance and therapeutic target for ovarian HGSC.

Methods: We evaluated the clinical significance of HDAC6 as a predictor of prognosis and chemoresistance in HGSC. Immunohistochemical expressions of HDAC6, programmed cell death ligand-1 (PD-L1), and hypoxia inducible factor-1α (HIF-1α) were analyzed using clinical samples from 88 patients with ovarian HGSC. The clinicopathological characteristics were reviewed.

Results: Twenty-three patients had high HDAC6 expression; 10, positive PD-L1 expression; and 33, high HIF-1α expression. HDAC6 up-regulation was correlated with not undergoing interval debulking surgery ($p < 0.001$), incomplete surgical resection ($p = 0.002$), and frequent occurrence of stable disease/progressive disease according to the RECIST ($p = 0.005$) criteria. On Kaplan-Meier analysis, high HDAC6 expression was significantly associated with decreased progression-free survival ($p = 0.001$) and overall survival ($p = 0.008$). On multivariate analysis, high HDAC6 expression (hazard ratio = 1.65; 95% confidence interval 1.03–2.66, $p = 0.039$) and surgery status were independent prognostic factors of progression-free survival. PD-L1 and HIF-1α expressions positively correlated with HDAC6.

Conclusion: HDAC6 is a potential therapeutic target since HDAC6 up-regulation might cause poor prognosis in patients with ovarian HGSC.

Background

Ovarian cancer is the leading cause of death owing to cancers of the female genital tract, with high-grade serous carcinoma (HGSC) being the most frequent histological type [1]. The most important prognostic factor for patients with HGSC is the tumor stage; approximately 75–80% of patients have advanced stage disease when they start showing symptoms, and only < 25% of patients with stage III/IV HGSC are curable using current therapies [2]. Typically, HGSC shows a good response to a combination of platinum and taxane agents, which is a standard chemotherapy regimen for epithelial ovarian cancers. However, HGSCs recur frequently and gradually acquire resistance to these standard chemotherapy regimens [2]. The most common molecular changes in HGSCs are *TP53* alterations and inactivation (germline or somatic mutation or promoter methylation) of *BRCA1* and *BRCA2* in approximately 50% of HGSCs [3]. *TP53* activation could sensitize cells to platinum-based chemotherapy, leading to cell cycle arrest and apoptosis [4]. Recently, new strategies have been devised for patients with ovarian cancer with *BRCA* mutations [5] or platinum-sensitive recurrence [6]. However, treatments for patients with *TP53* mutations or those with platinum-resistant recurrence have yet to be developed.

Histone deacetylases (HDACs), which comprise 18 subtypes identified in humans, regulate tissue differentiation, apoptosis, migration, mitosis, and angiogenesis by chromatin-modification via the deacetylation of histone or non-histone proteins [7]. The inhibitors that target multiple HDACs exhibit cytotoxic effects in various cancers, including ovarian cancer [8], but they are limited in their application for cancer treatment because of various toxicities [9]. Therefore, more selective and effective HDAC inhibitors are required. Our previous study showed that high HDAC6 expression was an independent poor prognostic factor in epithelial ovarian cancer [10]. HDAC6 increases deacetylated α-tubulin levels, which up-regulate cancer cell growth by enhancing microtubule dynamics [11, 12]. HDAC6 down-regulation stabilizes p53 by increasing total p53 levels and p53 phosphorylation [13]. In contrast, HDAC6 up-regulation leads to platinum-resistance, and HDAC6 down-regulation enhances platinum agent-induced DNA damage and apoptosis [13]. Moreover, HDAC6 up-regulates several factors that cause chemoresistance, including hypoxia inducible factor-1α (HIF-1α) [14] and programmed death ligand-1 (PD-L1) [15]. HDAC6-selective inhibitors were shown to be safe in clinical trials for multiple myeloma [16, 17]. HDAC6-selective inhibitors also suppress the proliferation of *ARID1A*-mutated ovarian clear cell carcinoma and improved the survival of the tumor-bearing mice [18].

In the current study, using clinical samples of HGSC, we immunohistochemically analyzed the association between HDAC6 expression and HGSC prognosis, and aimed to evaluate HDAC6 as a predictor of chemoresistance and therapeutic target for ovarian HGSC.

Methods

Patients and samples

All the methods, including the review of the electronic medical charts and pathological analysis, were performed in accordance with the 1975 Declaration of Helsinki after obtaining the approval of the institutional review board (IRB number, 16-257) and informed consent (or with a formal waiver of consent). Altogether, 88 patients with ovarian HGSC that was surgically resected and pathologically confirmed at the Saitama Medical University International Medical Centre between 2007 and 2017 were recruited. The clinicopathological characteristics of these patients were reviewed, including age, recurrence, progression-free survival (PFS), overall survival (OS), FIGO stage, treatment methods, surgical status (complete or incomplete resection), response evaluation criteria in solid tumors (RECIST) status [19], and chemotherapy response score (CRS) [20, 21]. The RECIST was used to stratify patients according to the following responses: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) by using computed tomography before and after chemotherapy [19]. Based on omental examination results, CRS was used to classify patients as follows: patients with CRS of 3 had a complete/near complete response; those with CRS of 2 had a partial response; and those with CRS of 1 had no or minimal response [20, 21].

Immunohistochemical staining

Immunohistochemical expression of HDAC6 (polyclonal rabbit anti-HDAC6, 1:500, ab1440, Abcam, Cambridge, UK), PD-L1 (monoclonal rabbit anti-PD-L1, 1:100, 28-8 pharmDx, Dako North America, CA, USA), and HIF-1α (polyclonal rabbit anti-HIF-1α, 1:100, NB100-479, Novus Biologicals, CO, USA) was analyzed by using 4-μm serial sections of formalin-fixed paraffin-embedded blocks. Dako Autostainer Link 48 (Agilent technologies, CA, USA) was used per the manufacturer's protocol. The Target Retrieval Solution was applied for antigen retrieval at 98°C for 20 minutes. Sections were incubated with the primary antibodies at 25°C for 60 minutes, followed by incubation with the secondary antibodies (EnVision FLEX/HRP, Agilent technologies, CA, USA) at 25°C for 30 minutes. The chromogen reaction was performed with diaminobenzidine plus H_2O_2.

Interpretation of immunohistochemical results

One gynecologic oncologist (Mitsutake Yano) and one gynecologic pathologist (Masanori Yasuda), both of who were blinded to the clinicopathological characteristics, evaluated the degree of immunohistochemical staining (Figure 1). The following scoring system was used: 0% stained cells indicated negative staining; 1%–50% stained cells, mild staining; and 51%–100% stained cells, marked staining. To optimize the differences in PFS and OS, the raw data were binarized for statistical analysis. For HDAC6 and HIF-1α, marked expression was considered to indicate high expression, while completely negative and mild expression was considered low expression. For PD-L1, mild and marked expression was defined as positive, while completely negative expression was considered negative.

Statistical analysis

Fisher's exact test or Pearson's chi-squared test was used to analyze the correlation between immunohistochemical expressions and the clinicopathological characteristics. Univariate survival analysis was performed by generating Kaplan-Meier curves, and differences between the groups were assessed using the log-rank statistic. The Cox proportional hazards model was used to perform univariate and multivariate survival analyses. All analyses were performed using SPSS v24.0 (SPSS Inc., IL, USA). *P*-values < 0.05 were considered statistically significant.

Results

Patient characteristics and immunohistochemical expression

Table 1 shows the characteristics of the 88 patients with HGSC. All the patients included in the study were Japanese. All patients underwent platinum-based systemic chemotherapy as neoadjuvant treatment; however, interval debulking surgery was not performed in 26 patients (30%) because of unresectable lesions. Among the 88 patients, 23 patients (26.1%) showed high HDAC6 expression, 10 patients (11.4%) showed positive PD-L1 expression, and 33 patients (37.5%) showed high HIF-1α expression. Table 2 shows the correlations between patient characteristics and immunohistochemical expression of HDAC6, HIF-1α, and PD-L1. High

HDAC6 expression was significantly correlated with not undergoing interval debulking surgery ($p < 0.001$), incomplete surgical resection ($p = 0.002$), and frequently showing SD/PD according to the RECIST criteria ($p = 0.005$), but there was no significant correlation with CRS. A high expression of HIF-1α was correlated with the recurrence ($p = 0.029$). There was no significant correlation between PD-L1 expression and the clinicopathological characteristics. HDAC6 expression showed significantly positive correlations with PD-L1 ($p = 0.002$) and HIF-1α ($p = 0.008$) expression.

Table 1
Clinicopathological characteristics of patients

Characteristic	**N = 88**
Age (years)	
Median (range)	61.1 (41–82)
≤60	38
>60	50
Cancer antigen 125 (U/mL)	
Median (range)	2658 (37–24,200)
≤500	19 (22%)
>500	69 (78%)
Treatment	
NAC + IDS	62 (70%)
NAC only	26 (30%)
FIGO stage	
III	64 (73%)
IV	24 (27%)
Surgery	
Complete resection	44 (50%)
Incomplete resection	**44 (50%)**
RECIST status	
CR	14 (16%)
PR	62 (71%)
SD	5 (6%)
PD	6 (7%)
CRS (n = 61)	
1	9 (14%)
2	16 (26%)
3	36 (60%)
Recurrence	
Present	73 (83%)
Absent	15 (17%)
Survival status	
Dead	46 (52%)
Alive	42 (48%)

NAC, neoadjuvant chemotherapy; IDS, interval debulking surgery; FIGO, International Federation of Obstetrics and Gynecology; RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CRS, chemotherapy response score

Table 2
Clinicopathological characteristics and immunohistochemistry expressions in patients with high-grade serous carcinoma (N = 88)

	HDAC6 expression			HIF-1α expression			PD-L1 expression		
Characteristic	Low	High	p-value	Low	High	p-value	Negative	Positive	p-value
Age (years)									
≤60	28	10	0.582	26	12	0.219	33	5	0.446
>60	37	13		29	21		45	5	
Cancer antigen 125 (U/mL)									
≤500	13	6	0.368	11	8	0.416	17	2	0.631
>500	52	17		44	25		61	8	
FIGO stage									
III	48	16	0.443	43	21	0.109	55	9	0.180
IV	17	7		12	12		23	1	
IDS									
Performed	53	9	**< 0.001**	13	13	0.093	21	5	0.129
Not performed	12	14		42	20		57	5	
Surgical status									
Complete	39	5	**0.002**	31	13	0.093	40	4	0.369
Incomplete	26	18		24	20		38	6	
RECIST									
CR/PR	61	15	**0.005**	50	26	0.063	69	7	0.110
SD/PD	4	7		4	7		8	3	
CRS (n = 61)									
1 = resistant	7	2	0.482	7	2	0.425	8	1	0.833
2 = intermediate	15	1		9	7		15	1	
3 = sensitive	32	4		26	10		34	2	
Recurrence									
Present	53	20	0.406	42	31	**0.029**	64	9	0.460
Absent	12	3		13	2		14	1	
Survival status									
Dead	31	8	0.114	25	21	0.076	41	5	0.571
Alive	34	8		30	12		37	5	

HDAC6, histone deacetylase 6; HIF-1α, hypoxia inducible factor-1α; PD-L1, programmed death-1 ligand; FIGO, International Federation of Obstetrics and Gynecology; IDS, interval debulking surgery; RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CRS, chemotherapy response score. *P*-values < 0.05 are shown in bold.

Correlation between HDAC6, PD-L1, and HIF-1α expressions and survival

On Kaplan-Meier survival curves, high HDAC6 expression was significantly associated with a decrease in the PFS ($p = 0.001$, Fig. 1A) and OS ($p = 0.008$, Fig. 1B). High HIF-1α expression was significantly associated with a decrease in the PFS ($p = 0.006$, Fig. 1C) and

OS (p = 0.033, Fig. 1D). Positive PD-L1 expression was significantly associated with a decrease in the PFS (p = 0.029, Fig. 1E) and OS (p < 0.05, Fig. 1F). On univariate analysis using the Cox proportional hazards model, high HDAC6 expression, RECIST status, CRS, and surgery status were prognostic factors for the PFS and OS (Table 3). On multivariate analysis, high HDAC6 expression (hazard ratio (HR) = 1.65; 95% confidence interval (CI) 1.03–2.66, p = 0.039) and surgery status (HR = 2.18; 95% CI 1.35–3.52, p = 0.002) were independent prognostic factors for the PFS. The surgery status (HR = 2.45; 95% CI 1.33–4.51, p = 0.004) was the only independent prognostic factor for the OS on multivariate analysis (Table 3).

Table 3
Univariate and multivariate analyses using the Cox proportional hazards model for patients with high-grade serous carcinoma

	Univariate analysis (PFS)			**Multivariate analysis (PFS)**			**Univariate analysis (OS)**			**Multivariate analysis (OS)**		
Variable	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age (≤ 60 vs. >60 years)	0.97	0.61–1.54	0.893				1.03	0.57–1.87	0.917			
FIGO stage (III vs. IV)	1.48	0.90–2.43	0.120				1.49	0.81–2.74	0.199			
Surgery (complete vs. incomplete resection)	**2.39**	**1.49–3.84**	**< 0.001**	**2.43**	**1.31–4.52**	**0.005**	**2.50**	**1.37–4.59**	**0.003**	**2.45**	**1.33–4.51**	**0.004**
RECIST status (CR/PR vs. SD/PD)	**2.69**	**1.41–5.13**	**0.003**				**2.39**	**1.06–5.43**	**0.037**			
CRS (1/2 vs. 3)	**1.43**	**1.07–1.90**	**0.017**				**1.47**	**1.01–2.15**	**0.042**			
HDAC6 expression (low vs. high)	**1.53**	**1.17–1.99**	**0.002**	**1.65**	**1.03–2.66**	**0.039**	**1.51**	**1.10–2.08**	**0.011**			

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; FIGO, International Federation of Obstetrics and Gynecology; RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CRS, chemotherapy response score; HDAC6, histone deacetylase 6. P-values < 0.05 are shown in bold.

Discussion

The current study showed that high HDAC6 expression was an independent poor prognostic factor in patients with advanced ovarian HGSC. HDAC6 up-regulation was significantly positively correlated with indicators of chemoresistance, such as surgical residual tumors and frequent SD/PD according to the RECIST criteria. Consistent with the results of our study, Wang et al. [13] had shown that HDAC6 up-regulation leads to resistance to platinum agents, and HDAC6 down-regulation enhances platinum agent-induced DNA damage and apoptosis. *TP53* activation, the most common mutation in HGSC, could sensitize cells to platinum agents, leading to cell cycle arrest and apoptosis [4]. HDAC6 down-regulation stabilized p53 by increasing the total p53 levels and p53 phosphorylation [13]. Moreover, the deacetylation of alpha-tubulin, induced by HDAC6, decreases the effect of taxane agents as a microtubule-stabilizing agent (Fig. 2) [22]. When HDAC6 is blocked, the resistance to taxane agents is reversed in epithelial ovarian cancer [22, 23]. These results suggest that HDAC6 up-regulation is among the refractory factors of standard platinum-based chemotherapy for HGSC.

Optional treatment agents for ovarian cancer include bevacizumab (anti-vascular endothelial growth factor [VEGF] therapy) and olaparib (Poly[ADP-ribose] polymerase [PARP] inhibitors) for *BRCA* mutant or platinum-sensitive recurrent tumors [4, 5] as well as pembrolizumab (PD-1/PD-L1 blockage) for microsatellite instability-high tumors [24]. The current study showed there was a positive correlation between HDAC6 and PD-L1 expression. HDAC6 inhibition enhanced the response to immunotherapy via PD-1/PD-L1 [25].

The anti-cancer effect of HDAC6 inhibitors was triggered by the G2/M cell cycle arrest, apoptosis, and loss of mitochondrial membrane potential via the decreased VEGF and PARP [26]. In the present study, the expression of HDAC6 and HIF-1α, an upstream factor of VEGF, showed a significantly positive correlation (Fig. 2). Therefore, HDAC6 could be a potential therapeutic target for HGSC that is resistant to standard and/or optional chemotherapy.

HDAC6-selective inhibitors exhibit an anti-tumor effect in several cancer cell lines [16, 26–28], and they are well tolerated with minimal toxicity observed in clinical trials [16]. The incidence of kidney failure [29] and peripheral neuropathy [30], which are common adverse effects caused by platinum and taxane agents, respectively, were reduced after using HDAC6-selective inhibitors. Therefore, we suggest that HDAC6 is a potentially important and safe therapeutic target for HGSC. Our study had several limitations. Although the sample size used in this study was small, the current study was the first to verify the correlation between HDAC6 and the indicators of chemoresistance by using clinical samples. Before drawing a conclusion based on the results of this study, further confirmation is warranted via a multi-ethnic population study and on a larger scale. Secondly, the present study consisted solely of qualitative IHC analysis and lacked both quantitative protein analysis and molecular correlations. Therefore, further studies are required to quantitatively analyze HDAC6 protein and mRNA expression.

Conclusions

In summary, HDAC6 up-regulation resulted in poor prognosis for patients with advanced ovarian HGSC because of chemoresistance. Therefore, HDAC6-selective inhibitors might be promising therapeutic agents for ovarian HGSC that is resistant to the current standard and/or optional chemotherapy regimens.

List Of Abbreviations

CI Confidence interval

HGSC High-grade serous carcinoma

HR Hazard ratio

IRB Institutional review board

OS Overall survival

PFS Progression-free survival

VEGF Vascular endothelial growth factor

CR Complete response

CRS Chemotherapy response score

PD Progressive disease

PR Partial response

RECIST Response evaluation criteria in solid tumors

SD Stable disease

Declarations

Acknowledgements

We thank Tomomi Katoh, Kouichi Kamada, Yusuke Hosonuma, Satoshi Kanno, Nobuyuki Suzuki, and Yasuo Kamakura, Department of Pathology, Saitama Medical University International Medical Center, for their great technical support. In addition, we would like to thank Editage (www.editage.com) for English language editing.

Author contributions

MiY contributed to the conception, design, acquisition, analysis, interpretation of the data, and drafting of the manuscript. MaY contributed to the conception, design, and critical revision of the manuscript for the inclusion of important intellectual content and supervised the writing. KH contributed to the acquisition of data and supervision. AO contributed to the acquisition of data. HN contributed to the critical revision of the manuscript to ensure that important intellectual content was present. MarM and NO contributed to the conception and design of the manuscript to ensure that important intellectual content was present.

Funding

This study was funded by Hidaka Research Projects in the Saitama Medical University (Grant numbers: 30-D-1-3) and Grants-in-Aid from the Ministry of Education, Science, Sports and Culture of Japan (Research Project Numbers: 18K06997).

Competing interests

The authors declare no competing interests.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

All the methods, including the review of the electronic medical charts and pathological analysis, were performed in accordance with the 1975 Declaration of Helsinki after obtaining the approval of the institutional review board (IRB number, 16-257) and informed consent (or with a formal waiver of consent).

Consent for publication

Consent for publication was obtained.

References

1. Heintz AP, Odicino F, Maisonneuve P, Quinn MA, Benedet JL, Creasman WT, et al. Carcinoma of the ovary. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2006;95 Suppl 1:S161-92.
2. Bookman MA. First-line chemotherapy in epithelial ovarian cancer. Clin Obstet Gynecol. 2012;55:96–113.
3. Integrated genomic. analyses of ovarian carcinoma. Nature. 2011;474:609–15.
4. Kigawa J, Sato S, Shimada M, Kanamori Y, Itamochi H, Terakawa N. Effect of p53 gene transfer and cisplatin in a peritonitis carcinomatosa model with p53-deficient ovarian cancer cells. Gynecol Oncol. 2002;84:210–5.
5. Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2018;379:2495–505.
6. Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. The Lancet Oncology. 2017;18:1274–84.
7. Falkenberg KJ, Johnstone RW. Histone deacetylases and their inhibitors in cancer, neurological diseases and immune disorders. Nature reviews Drug discovery. 2014;13:673–91.
8. Sonnemann J, Gange J, Pilz S, Stotzer C, Ohlinger R, Belau A, et al. Comparative evaluation of the treatment efficacy of suberoylanilide hydroxamic acid (SAHA) and paclitaxel in ovarian cancer cell lines and primary ovarian cancer cells from patients. BMC Cancer. 2006;6:183.
9. Modesitt SC, Sill M, Hoffman JS, Bender DP. A phase II study of vorinostat in the treatment of persistent or recurrent epithelial ovarian or primary peritoneal carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2008;109:182–6.

10. Yano M, Yasuda M, Sakaki M, Nagata K, Fujino T, Arai E, et al. Association of histone deacetylase expression with histology and prognosis of ovarian cancer. Oncology letters. 2018;15:3524–31.
11. Miyake Y, Keusch JJ, Wang L, Saito M, Hess D, Wang X, et al. Structural insights into HDAC6 tubulin deacetylation and its selective inhibition. Nature chemical biology. 2016;12:748–54.
12. Hubbert C, Guardiola A, Shao R, Kawaguchi Y, Ito A, Nixon A, et al. HDAC6 is a microtubule-associated deacetylase. Nature. 2002;417:455–8.
13. Wang L, Xiang S, Williams KA, Dong H, Bai W, Nicosia SV, et al. Depletion of HDAC6 enhances cisplatin-induced DNA damage and apoptosis in non-small cell lung cancer cells. PloS one. 2012;7:e44265.
14. Yano M, Katoh T, Miyazawa M, Miyazawa M, Ogane N, Miwa M, et al. Clinicopathological correlation of ARID1A status with HDAC6 and its related factors in ovarian clear cell carcinoma. Scientific reports. 2019;9:2397.
15. P ML. PV, T K, M P, E S, J P, et al. Essential role of HDAC6 in the regulation of PD-L1 in melanoma. Molecular oncology. 2016;10:735–50.
16. Yee AJ, Bensinger WI, Supko JG, Voorhees PM, Berdeja JG, Richardson PG, et al. Ricolinostat plus lenalidomide, and dexamethasone in relapsed or refractory multiple myeloma: a multicentre phase 1b trial. The Lancet Oncology. 2016;17:1569–78.
17. Santo L, Hideshima T, Kung AL, Tseng JC, Tamang D, Yang M, et al. Preclinical activity, pharmacodynamic, and pharmacokinetic properties of a selective HDAC6 inhibitor, ACY-1215, in combination with bortezomib in multiple myeloma. Blood. 2012;119:2579–89.
18. Bitler BG, Wu S, Park PH, Hai Y, Aird KM, Wang Y, et al. ARID1A-mutated ovarian cancers depend on HDAC6 activity. Nat Cell Biol. 2017;19:962–73.
19. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer (Oxford, England: 1990). 2009;45:228 – 47.
20. Bohm S, Faruqi A, Said I, Lockley M, Brockbank E, Jeyarajah A, et al. Chemotherapy Response Score: Development and Validation of a System to Quantify Histopathologic Response to Neoadjuvant Chemotherapy in Tubo-Ovarian High-Grade Serous Carcinoma. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2015;33:2457–63.
21. Cohen PA, Powell A, Bohm S, Gilks CB, Stewart CJR, Meniawy TM, et al. Pathological chemotherapy response score is prognostic in tubo-ovarian high-grade serous carcinoma: A systematic review and meta-analysis of individual patient data. Gynecologic oncology. 2019.
22. Angelucci A, Mari M, Millimaggi D, Giusti I, Carta G, Bologna M, et al. Suberoylanilide hydroxamic acid partly reverses resistance to paclitaxel in human ovarian cancer cell lines. Gynecol Oncol. 2010;119:557–63.
23. Marcus AI, O'Brate AM, Buey RM, Zhou J, Thomas S, Khuri FR, et al. Farnesyltransferase inhibitors reverse taxane resistance. Cancer research. 2006;66:8838–46.
24. Marcus L, Lemery SJ, Keegan P, Pazdur R. FDA Approval Summary: Pembrolizumab for the Treatment of Microsatellite Instability-High Solid Tumors. Clinical cancer research: an official journal of the American Association for Cancer Research. 2019;25:3753–8.
25. Bae J, Hideshima T, Tai YT, Song Y, Richardson P, Raje N, et al. Histone deacetylase (HDAC) inhibitor ACY241 enhances anti-tumor activities of antigen-specific central memory cytotoxic T lymphocytes against multiple myeloma and solid tumors. Leukemia. 2018;32:1932–47.
26. Dong J, Zheng N, Wang X, Tang C, Yan P, Zhou HB, et al. A novel HDAC6 inhibitor exerts an anti-cancer effect by triggering cell cycle arrest and apoptosis in gastric cancer. Eur J Pharmacol. 2018;828:67–79.
27. Azuma K, Urano T, Horie-Inoue K, Hayashi S, Sakai R, Ouchi Y, et al. Association of estrogen receptor alpha and histone deacetylase 6 causes rapid deacetylation of tubulin in breast cancer cells. Cancer research. 2009;69:2935–40.
28. Amengual JE, Johannet P, Lombardo M, Zullo K, Hoehn D, Bhagat G, et al. Dual Targeting of Protein Degradation Pathways with the Selective HDAC6 Inhibitor ACY-1215 and Bortezomib Is Synergistic in Lymphoma. Clinical cancer research: an official journal of the American Association for Cancer Research. 2015;21:4663–75.

29. Tang J, Shi Y, Liu N, Xu L, Zang X, Li P, et al. Blockade of histone deacetylase 6 protects against cisplatin-induced acute kidney injury. Clinical science (London, England: 1979). 2018;132:339 – 59.
30. Krukowski K, Ma J, Golonzhka O, Laumet GO, Gutti T, van Duzer JH, et al. HDAC6 inhibition effectively reverses chemotherapy-induced peripheral neuropathy. Pain. 2017;158:1126–37.

Figures

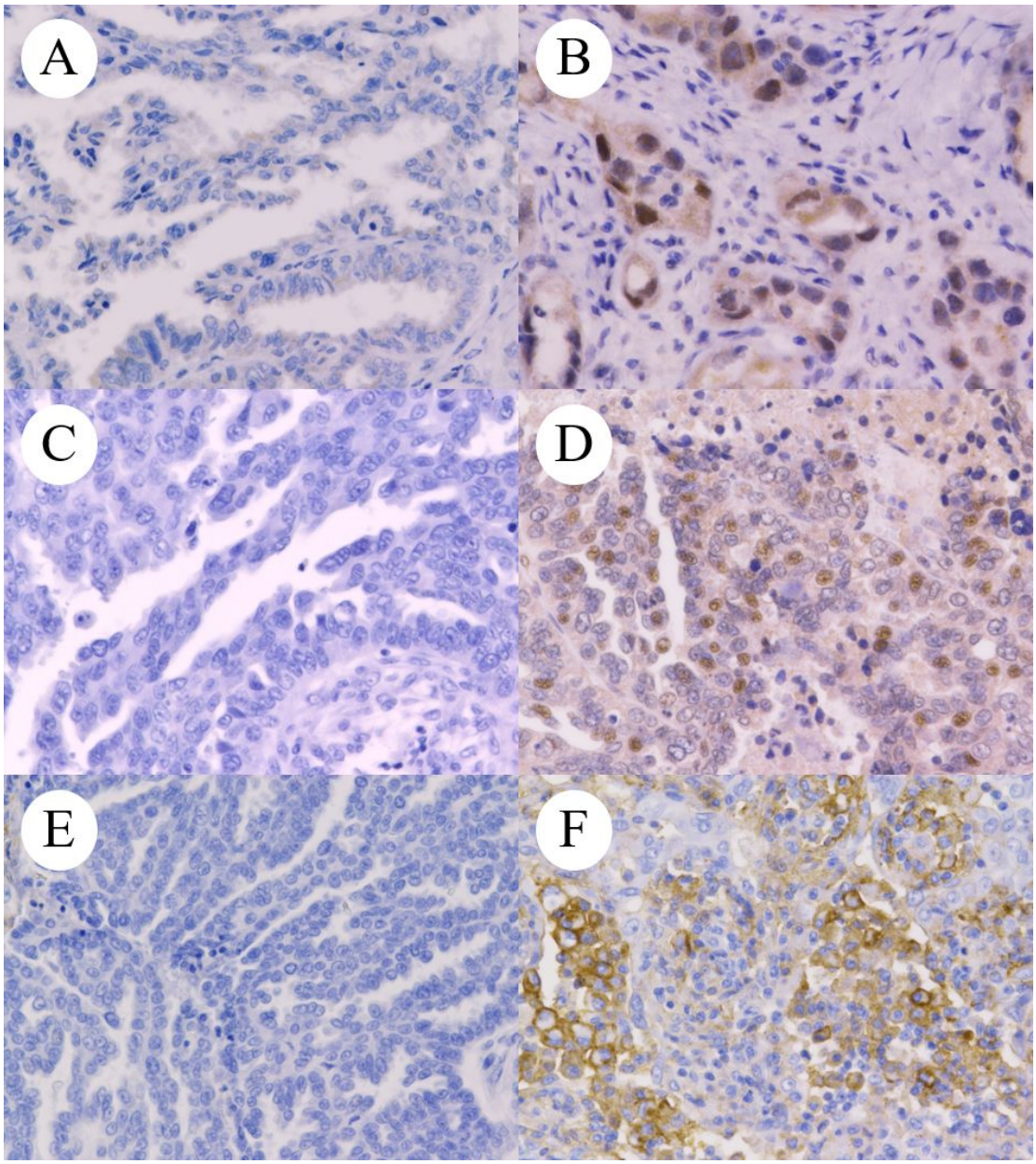

Figure 1

Kaplan-Meier survival analysis: HDAC6 (a, PFS; b, OS), HIF-1α (c, PFS; d, OS), and PD-L1 (e, PFS; f, OS). P-values were obtained using the log rank test.

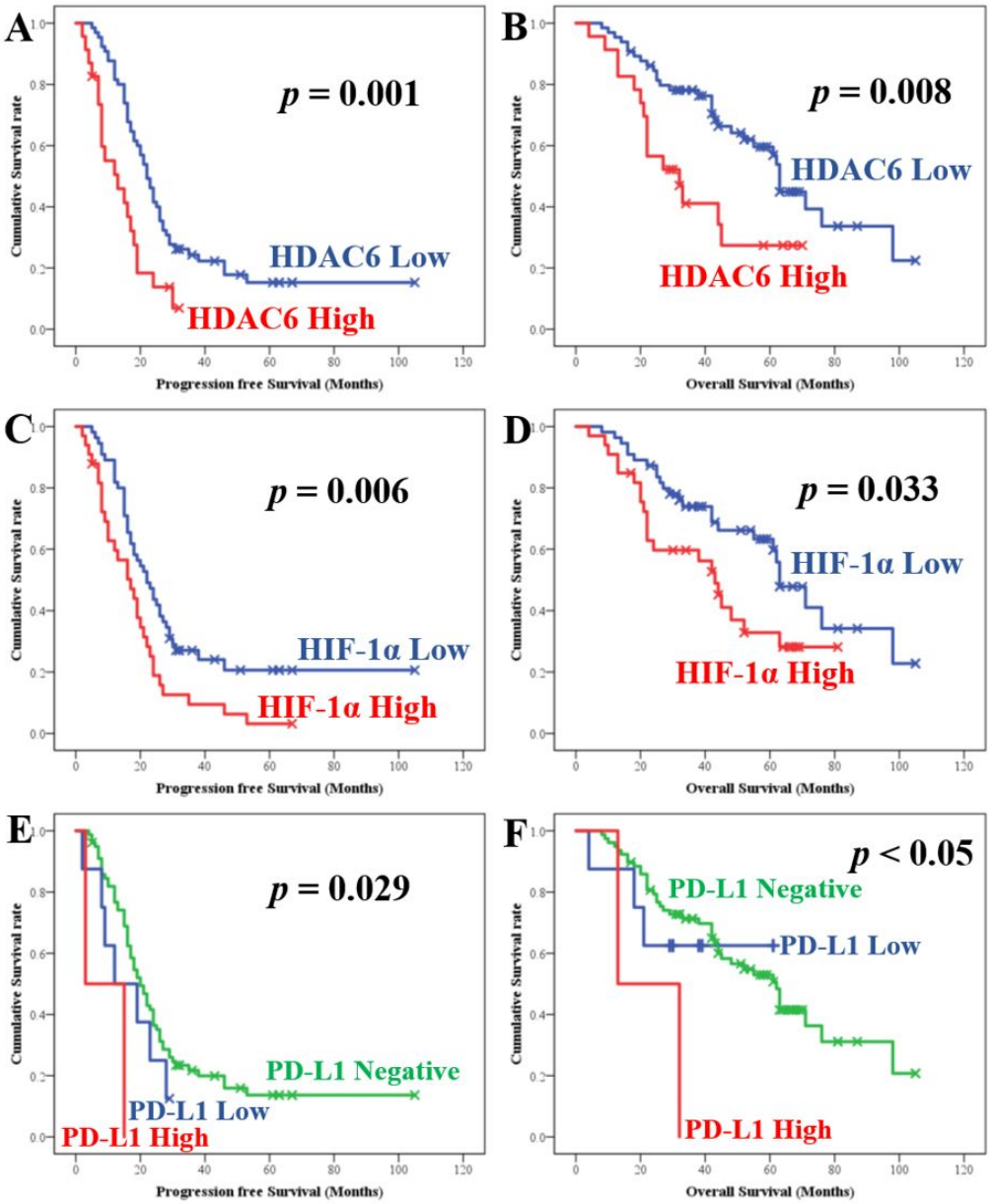

Figure 2

Scheme of HDAC6 functions: HDAC6 destabilizes TP53 by deacetylation and suppresses apoptosis. These effects of HDAC6 are responsible for platinum agent resistance. HDAC6 also leads to microtubule dynamics, tolerance to hypoxia and immunotherapy, and DNA repair dysfunction via tubulin, HIF-1α, PD-L1, and PARP. HDAC6 results in tolerance to taxane agents, cytotoxic T cells, immune-checkpoint inhibitors, bevacizumab, and olaparib.

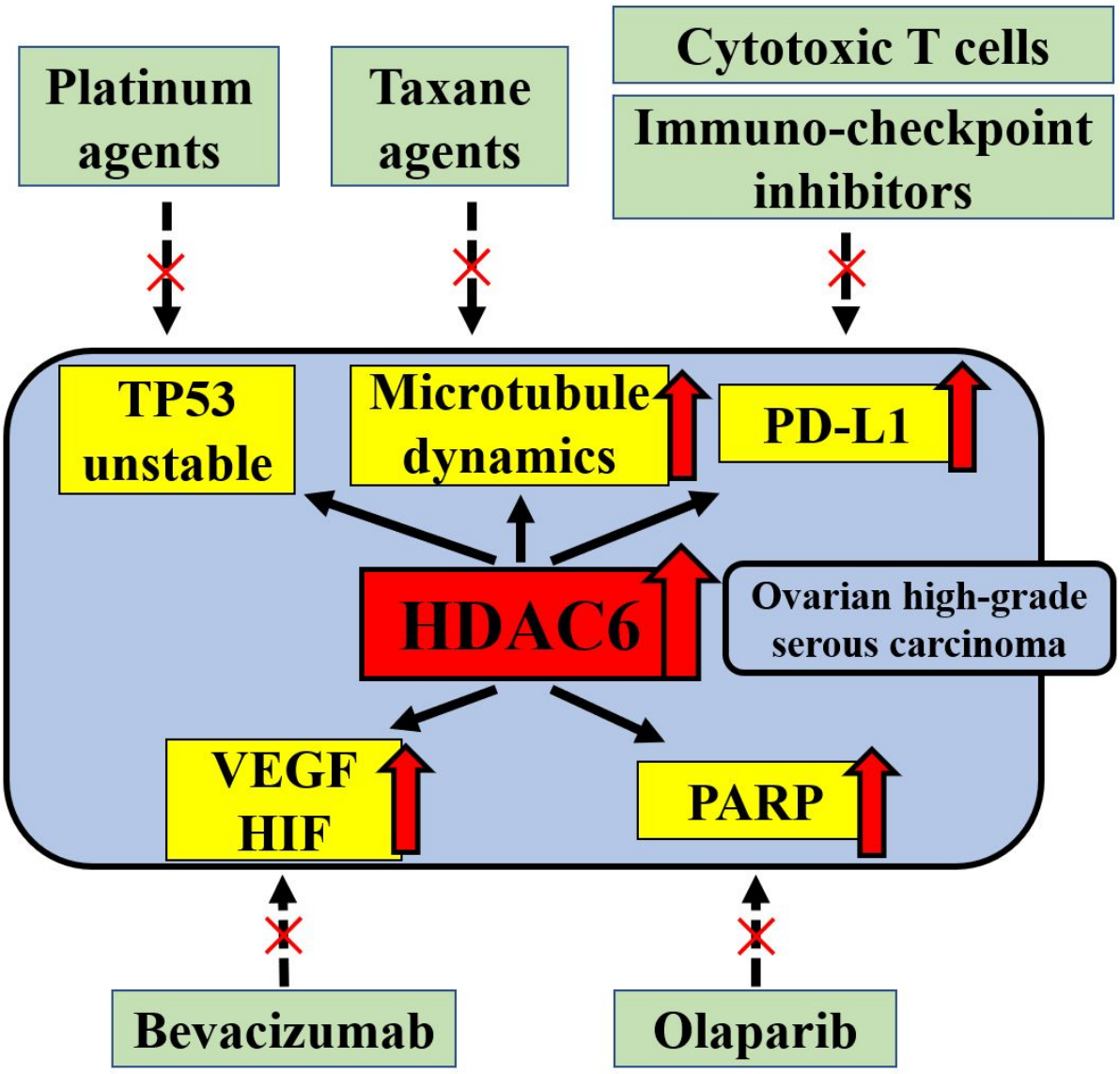

Figure 3

Immunohistochemical expression of HDAC6 (a, low; b, high), HIF-1α (c, low; d, high), and PD-L1 (e, negative; f, positive).