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Cancer Epidemiology, Biomarkers & Prevention

Short Communication

Programmed Cell Death 1 (PD-1) and Its Ligand (PD-L1) in Common Cancers and Their Correlation with Molecular Cancer Type

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Abstract

Cancer cells expressing PD-1 ligands (PD-L1/PD-L2) inhibit immune-modulatory T-cell activation facilitating disease progression. Preliminary clinical trials exploring interruption of PD-1/PD-L1 signaling showed benefit in several cancer types. We analyzed the distribution of PD-1–positive tumor-infiltrating lymphocytes (TIL) and cancer cells' expression of PD-L1 in a molecularly profiled cohort of 437 malignancies (380 carcinomas, 33 sarcomas, and 24 melanomas). We showed that the presence of PD-1$^+$ TILs significantly varied among cancer types (from 0% in extraskeletal myxoid chondrosarcomas to 93% in ovarian cancer), and was generally associated with the increased number of mutations in tumor cells ($P = 0.029$). Cancer cell expression of PD-L1 varied from absent (in Merkel cell carcinomas) to 100% (in chondro- and liposarcomas), but showed the inverse association with the number of detected mutations ($P = 0.004$). Both PD-1 and PD-L1 expression were significantly higher in triple-negative breast cancers (TNBC) than in non-TNBC ($P < 0.001$ and 0.017, respectively). Similarly, MSI-H colon cancers had higher PD-1 and PD-L1 expression than the microsatellite stable tumors ($P = 0.002$ and 0.02, respectively). *TP53*-mutated breast cancers had significantly higher PD-1 positivity than those harboring other driver mutations (e.g., *PIK3CA*; $P = 0.002$). In non–small cell lung cancer, PD-1/PD-L1 coexpression was identified in 8 cases (19%), which lacked any other targetable alterations (e.g., *EGFR*, *ALK*, or *ROS1*). Our study demonstrated the utility of exploring the expression of two potentially targetable immune checkpoint proteins (PD-1/PD-L1) in a substantial proportion of solid tumors, including some aggressive subtypes that lack other targeted treatment modalities. *Cancer Epidemiol Biomarkers Prev; 1–6.* ©2014 AACR.

Introduction

Programmed death-1 (PD-1, CD279) is an immune-suppressive molecule that is upregulated on activated T cells and other immune cells. It is activated by binding to its ligand PD-L1 (B7-H1, CD274), which results in intracellular responses that reduce T-cell activation. Aberrant PD-L1 expression had been observed on cancer cells, leading to the development of PD-1/PD-L1–directed cancer therapies, which have shown promising results in late-phase clinical trials. Blockade of the PD-1 and PD-L1 interaction led to good clinical responses in several, but not all cancer types, and the heterogeneous cellular expression of PD-1/PD-L1 may underlie these selective responses (1–6).

PD-1/PD-L1 expression has been studied by various methods in different cancer subtypes (7). Most of the published articles focused on prognostic relevance of PD-1/PD-L1, whereas little is known about their predictive value as well as their relationship with molecular genetic alterations in solid tumors (1). In the present study, we analyzed the distribution of PD-1$^+$ tumor-infiltrating lymphocytes (TIL) and PD-L1 expression in the most common solid cancers and further correlated these biomarkers with genotypic and phenotypic characteristics of tumors.

Materials and Methods

Tumor samples

The study cohort consisted of 437 tumor samples (both primary and metastatic) representing both major and some rare solid cancer types: 380 carcinomas [breast, colon, lung, pancreas, prostate, Merkel cell, ovary, liver,

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endometrial, bladder, kidney, and cancers of unknown primary (CUP)], 33 soft tissue sarcomas (liposarcomas, chondrosarcomas, extraskeletal myxoid chondrosarcomas, and uterine sarcomas) and 24 malignant cutaneous melanomas.

Molecular methods

Tumor samples were evaluated using a commercial multiplatform approach consisting of protein analysis (immunohistochemistry), gene copy-number analysis (in situ hybridization) and gene sequencing (Next-Generation Sequencing; Caris Molecular Intelligence, Caris Life Sciences) as previously described (8).

The presence of PD-1$^+$ lymphocytes was evaluated with monoclonal antibody NAT105 (Cell Marque), whereas the expression of PD-L1 was analyzed with B7-H1 antibody (R&D Systems), using automated immunohistochemical methods.

Because of the biopsy size–related dependence on the detection of PD-1 TILs (9, 10), we evaluated their density using a hotspot approach, analogous to the previously described method for measuring neoangiogenesis (11). The whole tumor sample was reviewed at a low power (4× objective) and the area of highest density of TILs in direct contact with malignant cells of the tumor at 400× visual field (40× objective × 10× ocular) was enumerated (number of PD-1$^+$ TIL/HPF). The intensity of the cancer cells' expression of PD-L1 was recorded on a semiquantitative scale (0–3+): 0 for no staining, 1+ for weak cytoplasmic staining, 2+ moderate membranous and cytoplasmic staining, and 3+ strong membranous and cytoplasmic staining. Percentage of tumor cells expressing PD-L1 at the highest intensity was recorded.

Statistical methods

The two-tailed Fisher exact test and χ^2 test were applied for the correlation between the variables ($P \leq 0.05$).

Results

PD-1 and PD-L1 expression in solid tumors

PD-1 and PD-L1 expression in various solid tumors and their subtypes are summarized in Tables 1–4.

PD-1$^+$ lymphocytes were consistently identified in reactive, peritumoral lymphoid follicles, which served as an internal positive control. PD-1$^+$ TILs in direct contact with cancer cells were distinctly uncommon in some cancer types (e.g., 0% in extraskeletal myxoid chondrosarcoma), whereas triple-negative breast cancer (TNBC), bladder cancer, microsatellite instability high (MSI-H) colon cancer, non–small cell lung cancer (NSCLC), endometrial, and ovarian cancer were frequently (70%–100%) infiltrated with PD-1$^+$ TILs. When present, PD-1$^+$ TILs' density varied from 1 to >20/hpf (Table 1).

PD-L1 was consistently expressed in the tumor microenvironment, including endothelial cells, macrophages, and dendritic cells, at strong (2+/3+) intensity and was used as internal positive control. In contrast, the cancer cells expressed PD-L1 at widely varying levels and proportions. Consistent, strong membranous staining was a feature of only a few, specific cancer types, including endometrial carcinomas (Fig. 1) and malignant melanomas (88% and 92%, respectively), metaplastic breast carcinomas, chondrosarcomas and liposarcomas (both 100%; Tables 1 and 4).

Simultaneous expression of PD-L1 in tumor cells and presence of PD-1$^+$ TILs was frequently observed in kidney cancer (33%), ovarian cancer (36%), NSCLC (43%), TNBC

Table 1. Overview of PD-1 and PD-L1 expression in various types of solid tumors

Tumor types (n = 437 total)	PD-1 expression (% and range)	PD-L1 (tumor cells; %)	Concurrent PD-1 and PD-L1 expression (%)
Carcinomas (n = 380 total)			
Breast (n = 116)	51% (1–20)	45%	29%
Colon (n = 87)	50% (1–>20)	21%	12%
NSCLC (n = 44)	75% (1–20)	50%	43%
Pancreas (n = 23)	43% (1–16)	23%	9%
Prostate (n = 20)	35% (1–6)	25%	5%
Merkel cell carcinoma (n = 19)	17% (1–4)	0%	0%
Endometrium (n = 16)	86% (1–13)	88%	79%
Ovary (n = 14)	93% (1–16)	43%	36%
Liver (n = 13)	38% (1–5)	8%	0%
Bladder (n = 11)	73% (1–10)	55%	55%
Kidney (n = 11)	36% (1–3)	67%	33%
CUP (n = 6)	50% (1–4)	33%	33%
Sarcomas (n = 33 total)	30% (1–>10)	97%	30%
Melanoma (n = 24 total)	58% (1–15)	92%	58%

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Table 2. PD-1 and PD-L1 expression in breast cancers, according to the molecular subtype

Breast cancer subtypes ($n = 116$)	PD-1 expression/hpf (TILs; % and range)	PD-L1 (tumor cells; %)	Concurrent PD-1 and PD-L1 expression (%)
Luminal tumors ($n = 58$)			
Luminal A ($n = 33$)	25% (1–>10)	33%	13%
Luminal B ($n = 25$)	44% (1–20)	33%	17%
HER2 positive ($n = 5$)	60% (1–9)	20%	20%
Triple-negative ($n = 53$)	70% (1–20)[a]	59%[a]	45%[a]

Abbreviation: hpf, high-power fields.
[a]Significantly higher than in luminal tumors.

(45%), dedifferentiated liposarcomas (50%), bladder cancer (55%), malignant melanomas (58%), endometrial cancer (79%), but was infrequent in other cancer types [e.g., 0% in liver cancer and Merkel cell carcinoma, 4% microsatellite-stable (MSS) colon cancer, 5% prostate cancer, 8% liver cancer, 9% pancreatic cancer, and 13% in luminal A breast cancer (Table 1)].

Association of PD-1 and PD-L1 expression with genotypic and phenotypic characteristics of the tumors

In the entire study set, expression of PD-1$^+$ TILs was associated with an increasing number of mutations in tumor cells ($P = 0.029$, Fisher exact test), whereas PD-L1 status showed the opposite association ($P = 0.004$, Fisher exact test). Consequently, copresence of PD-1$^+$ TILs and cancer cells expressing PD-L1 showed no association with overall mutational status ($P = 0.67$, Fisher exact test).

In breast cancer PD-1$^+$ TILs were significantly more common in TNBC than in luminal-type tumors (70% vs. 25%–44%, $P < 0.001$, χ^2 test; Table 2). Similarly, PD-L1 expression was the highest in TNBC as compared with other subtypes (59% vs. 33% in luminal tumors, $P = 0.017$). Among TNBC, 9 cases were metaplastic breast carcinomas and all were positive for PD-L1. Consequently, coexpression of PD-1$^+$TIL/cancer cells PD-L1$^+$ was the highest in the TNBC subgroup (45% vs. 13%–17% non-TNBC, $P = 0.001$, χ^2 test). Similarly, *TP53*-mutated breast cancers exhibited significantly higher PD-1 TIL positivity compared with breast cancers that harbored other mutations (e.g., *PIK3CA* mutations) or breast tumors without mutations (42% vs. 10%, $P = 0.002$, χ^2 test). In contrast, PD-L1$^+$ did not correlate with any of the detected mutations in breast cancer.

In the colon cancer cohort, MSI-H tumors exhibited a significantly higher rate of positivity for PD-1$^+$ TILs than MSS colon cancers (77% vs. 39%, $P = 0.002$, Fisher exact test; Table 3). Also, the proportion of PD-L1$^+$ cancers was significantly higher in MSI-H than in the MSS colon cancers (38% vs. 13%, $P = 0.02$, Fisher exact test). Of note, MSI-H cases were predominantly stage I and II (75%), whereas the majority of the MSS cases were at advanced stage (III and IV, 93%; $P < 0.001$). Both PD-1 and PD-L1 positivity significantly decreased with the tumor stage in colorectal cancer ($P = 0.021$ and 0.031, respectively).

In NSCLC, PD-1$^+$ TILs and PD-L1–expressing tumor cells were seen in 18 of 42 cases (43%) of which 8 cases lacked other biologic targets (such as activating *EGFR* mutations, *HER2*, *cMET*, *ALK*, or *ROS1* rearrangements).

Discussion

Recent clinical trials have demonstrated that blocking of the PD-1/PD-L1 pathway induces an objective and durable remission in patients with advanced solid tumors (2–6). The efficacy of these agents has been primarily linked to the expression of PD-L1 in the tumor cells and PD-1 on activated T lymphocytes (12–14). Expression of both markers has already been explored in several human malignancies, particularly in renal cell carcinomas, malignant melanoma, and NSCLC (13–15). Our PD-L1 results for these three cancer types are comparable with the data provided by Taube and colleagues (13). Consistent with a

Table 3. PD-1 and PD-L1 expression in colorectal carcinomas in relationship to the microsatellite instability status

Colon cancer subtypes ($n = 87$)	PD-1 expression/hpf (TILs; % and range)	PD-L1 (tumor cells; %)	Concurrent PD-1/ PD-L1 expression (%)
MSS colon cancers ($n = 60$)	39% (1–11)	13%	4%
MSI-H colon cancers ($n = 27$)	77% (1–>20)[a]	38%[a]	32%[a]

Abbreviation: hpf, high-power fields.
[a]Significantly higher.

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Table 4. Overview of PD-1 and PD-L1 expression in sarcoma subtypes

Sarcoma subtypes ($n = 33$)	PD-1 expression/hpf (TILs; % and range)	PD-L1 (tumor cells; %)	Concurrent PD-1 and PD-L1 expression (%)
Liposarcoma ($n = 20$)	45% (1–>10)	100%	45%
Chondrosarcoma ($n = 8$)	12% (0–1)	100%	12%
Extraskeletal myxoid chondrosarcoma ($n = 3$)	0%	67%	0%
Uterine sarcoma ($n = 2$)	0%	100%	0%

previous report by Vanderstraeten and colleagues (16), endometrial cancer appears to be abundantly enriched with both PD-1 and PD-L1.

The broad array of tumors screened for this study also allowed the assessment of PD-1/PD-L1 expression in several less common cancer types. Our study revealed a low expression of both PD-1 and PD-L1 in several highly aggressive tumors, including Merkel cell carcinoma, hepatocellular, and pancreatic carcinoma. In contrast, PD-L1 expression was particularly high in dedifferentiated liposarcomas, which is in line with a recent report by Kim and colleagues (17). We also report for the first time the PD-L1 positivity in chondrosarcomas and extraskeletal myxoid chondrosarcomas. Furthermore, PD-1 and PD-L1 positivity was observed in cancers of unknown primary, a group of cancers with particularly difficult treatment decisions.

Marked variations in PD-1/PD-L1 positivity have also been observed within general histologic types, but subtype analysis revealed significant correlations. For example, PD-1/PD-L1 were differently expressed in molecular subtypes of breast (TNBC vs. non-TNBC)

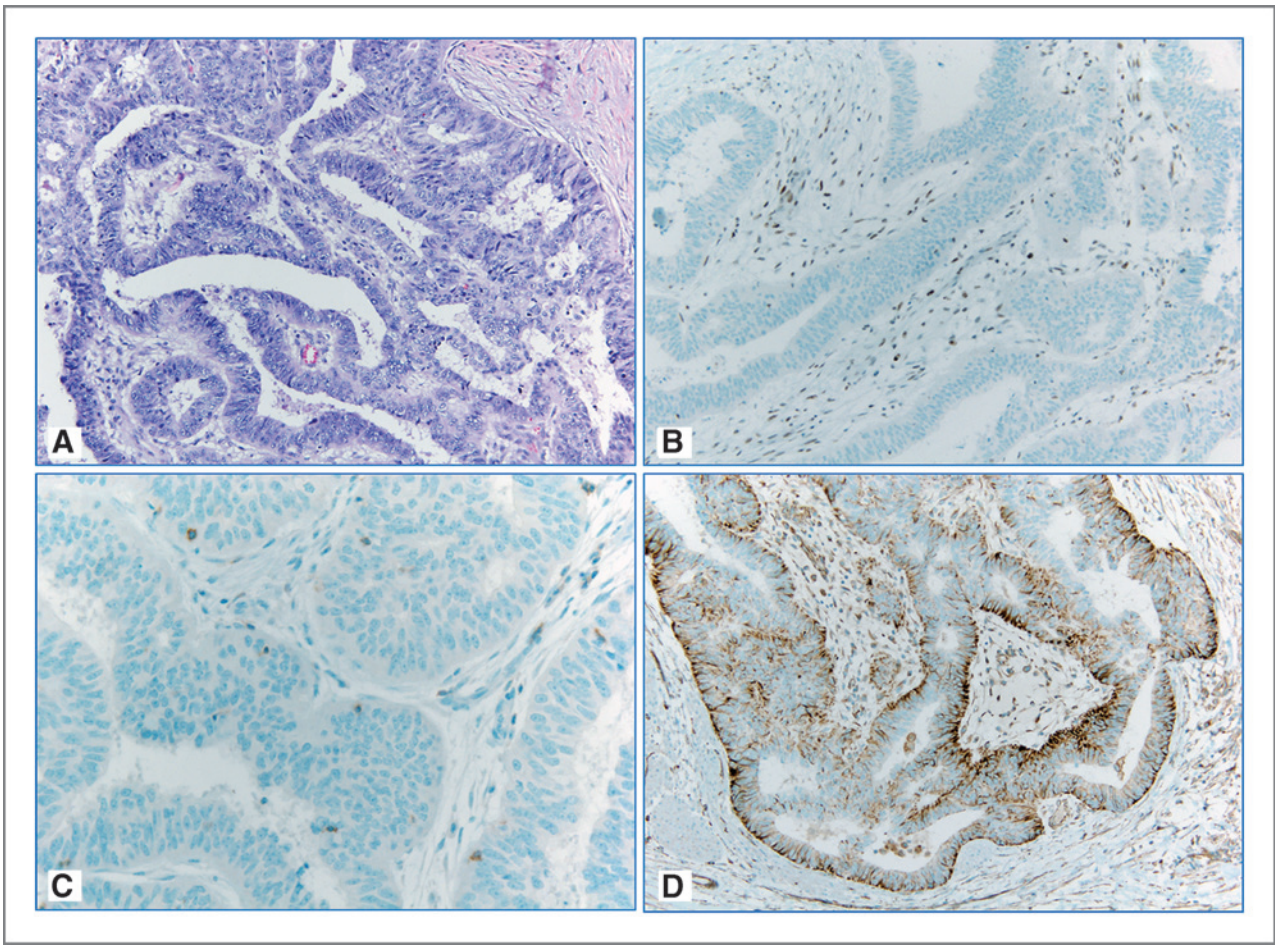

Figure 1. A case of endometrial adenocarcinoma (A, hematoxylin and eosin stained section) exhibiting microsatellite instability caused by the loss of MLH-1 protein (note retained MLH-1 protein expression in the nuclei of the tumor-infiltrating lymphocytes); B, immunohistochemical stain; PD-1$^+$ TILs (C, immunohistochemical stain); and aberrant expression of PD-L1 in the tumor cells' basolateral membranes (D, immunohistochemical stain).

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and colon cancer (MSI-H vs. MSS cases) providing an indication for potential benefit of targeted immunotherapy in aggressive subtypes of breast and colon cancers for which no targeted therapy is currently available. We found PD-L1 expression to be the highest in TNBC (59%) in contrast with a recent study that reported the highest frequency (34%) in HER2-positive breast cancers (18). However, our cohort was enriched (8%) for rare metaplastic TNBC, which were all PD-L1 positive, whereas we analyzed only 5 HER2-positive breast cases. Of note, *TP53*-mutated breast carcinomas exhibited significantly higher PD-1 expression in comparison with breast carcinomas harboring other types of mutations. High PD-1$^+$ TILs had been recently associated with a more aggressive phenotype and poorer outcome in operable breast cancers (19).

Some immunogenic tumors (e.g., MSI-H CRC) attract TILs, which produce IFNγ and could upregulate PD-L1 on tumor epithelial cells. Modulation of the IFNγ receptor (IFNγRα) expression on the tumor epithelial cells may play a critical role in tumor immunoediting (20), including acquisition of stem cell–like phenotype (21) and resistance to granule-mediated cytotoxic T-lymphocyte killing (22).

Our data for colon cancer also appear to differ from those reported by Droeser and colleagues who reported more frequent expression of PD-L1 in the MSS than in MSI-H colon cancers (23). The discrepancy may be caused by the fact that tested MSI-H and MSS cases differed significantly in regard to the tumor stage as the majority of MSI-H was at stage I and II, whereas MSS tumors were predominantly stage III and IV. Overall, the expression of both PD-1 and PD-L1 in colon cancer inversely correlated with the tumor stage.

Another relevant finding in our study is that a substantial proportion of NSCLCs with PD-1/PD-L1 positivity were devoid of the most common and targetable alterations (e.g., *EGFR*, *HER2*, *cMET*, *ALK*, *ROS1*). In contrast with previous studies, we did not find any association between PD-1/PD-L1 expression and *EGFR* alterations in lung cancer (24, 25).

In summary, our survey demonstrated expression of two potentially targetable immune checkpoint proteins (PD-1/PD-L1) in a substantial proportion of solid tumors including some aggressive subtypes that lack targeted treatment modalities.

Disclosure of Potential Conflicts of Interest

T. Maney has ownership interest (including patents) in the stocks of Caris Life Sciences. S. Vranic is a consultant/advisory board member for Caris Life Sciences. D.D. Von Hoff has ownership interest (including patents) in and is a consultant/advisory board member for Caris Life Sciences. O. Hamid is a consultant/advisory board member for Caris Life Sciences. Z. Gatalica, A. Ghazalpour, D. Holterman, N. Xiao, T. Maney, I. Rose, P. Overberg, and G. Basu are employees of Caris Life Sciences.

Authors' Contributions

Conception and design: Z. Gatalica, C. Snyder, D.A. Holterman, D.D. Von Hoff

Development of methodology: Z. Gatalica, C. Snyder, D.A. Holterman, O. Hamid

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Z. Gatalica, C. Snyder, I. Rose, H.T. Lynch, O. Hamid

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Z. Gatalica, A. Ghazalpour, D.A. Holterman, N. Xiao, S. Vranic, O. Hamid

Writing, review, and/or revision of the manuscript: Z. Gatalica, C. Snyder, T. Maney, A. Ghazalpour, G.D. Basu, S. Vranic, H.T. Lynch, D.D. Von Hoff, O. Hamid

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): P. Overberg, I. Rose, S. Vranic

Study supervision: Z. Gatalica, T. Maney, O. Hamid

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