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Mini-review

Beyond the PD-L1 horizon: In search for a good biomarker to predict success of immunotherapy in gastric and esophageal adenocarcinoma

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ABSTRACT

Gastric adenocarcinoma and esophageal adenocarcinoma are aggressive cancers with a poor prognosis. Therefore, new therapeutic strategies are needed, especially for patients refractory to conventional treatment. Cancer immunotherapy (CIT), is a promising new treatment option and is effective in a proportion of patients with gastroesophageal malignancies. Biomarkers for selecting patients likely to benefit from CIT in gastro-esophageal malignancies remain unproven. Programmed cell death ligand-1 (PD-L1), which is a validated biomarker in non-small cell lung cancer (NSCLC), is often also used to select patients for CIT in the context of gastroesophageal cancer, although this marker has not been validated for this purpose. We question the use of PD-L1 as a biomarker in gastroesophageal cancers, as there are fundamental differences in PD-L1 expression between NSCLC and gastroesophageal cancers. This review discusses the value of PD-L1 in selecting patients for CIT in esophageal and gastric cancer. Potential alternatives, especially microsatellite instability and Epstein-Barr virus positivity, are discussed.

1. Introduction

Gastric adenocarcinoma (GA) and esophageal adenocarcinoma (EAC) are aggressive cancers with a variable response to neo-adjuvant therapy and poor overall prognosis. Despite significantly improved survival since the introduction of perioperative chemotherapy and neo-adjuvant chemoradiotherapy, the 5-year overall survival after treatment with curative intent is 35% for patients with stage > II GA, and 47% in esophageal cancer [1,2]. Therefore, there is a high clinical need for novel and more effective treatment options for these patient groups, especially for patients refractory to standard therapies.

Cancer immunotherapy (CIT) has emerged as a promising new treatment option for several cancer types. As cancer cells use pathways responsible for immune-tolerance to avoid elimination by the host immune system, so called “immune checkpoint pathways”, targeted therapies against these pathways have emerged as a new powerful tool in the treatment of cancer patients. Most currently used immune checkpoint inhibitors are directed against the programmed cell death-1/programmed cell death ligand-1 (PD-1/PD-L1) pathway and against cytotoxic T lymphocyte associated antigen 4 (CTLA4). Immune checkpoint inhibitors have become standard therapy for, amongst others, melanoma [3], and non-small cell lung cancer (NSCLC) [4–7]. For other malignancies, including GA and EAC, there are ongoing clinical trials investigating the effect of CIT. In 2017, the FDA approved pembrolizumab for patients with previously treated locally advanced or metastatic gastric or gastro-esophageal junction (GEJ) cancer whose tumors express PD-L1 [8]. At this moment our knowledge of patient selection criteria for CIT is very limited and enrichment strategies are urgently required to select those patients who are likely to benefit from immune checkpoint inhibitors. In many CIT clinical trials an effort was done to elucidate whether a biomarker can predict response to the therapy (summarized in Table 1). Often these analyses were done retrospectively and the results are debatable.

Recent advances in basic, translational and clinical research in the field of cancer immunotherapy have resulted in the definition of a concept called the “cancer immunogram” which aims to describe the interaction between cancer and the immune system. Typically, such immunograms distinguish seven parameters that are considered likely to affect the antitumor immune response [9]. These parameters include: tumor PD-L1 expression, tumor mutational burden, the general immune status of the patient, presence of T cell immune infiltrates, sensitivity of tumor cells to T-cell killing, a myeloid cell-mediated inflammation, and

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Table 1
Overview of immunotherapy studies and researched biomarkers.

Author	Tumor type	Therapy	Biomarker	Reference
Chen et al.	Melanoma	CTLA-4 blockade + PD-L1 blockade	TILs	[39]
Fehrenbacher et al.	NSCLC	Atezolizumab	PD-L1	[18]
Fuchs et al.	Gastric + GEJ cancer	Pembrolizumab	PD-L1	[8,22]
Garon et al.	NSCLC	Pembrolizumab	PD-L1	[27]
Hamid et al.	Melanoma	Ipilimumab	TILs	[38]
Herbst et al.	NSCLC	Pembrolizumab vs docetaxel	PD-L1	[28]
Kang et al.	GEJ cancer	Nivolumab	PD-L1	[24]
Kawazoe et al.	Gastric cancer	Pembrolizumab	MSI, EBV, PD-L1	[31]
Luksza et al.	Melanoma, lung cancer	CTLA-4 blockade or PD-L1 blockade	Neoantigens	[42]
Reck et al.	NSCLC	Pembrolizumab	PD-L1	[20]
Rizvi et al.	NSCLC	Pembrolizumab	Mutational load	[43]
Shitara et al.	Gastric + GEJ cancer	Pembrolizumab vs. paclitaxel	PD-L1	[25]
Snyder et al.	Melanoma	Ipilimumab and tremelimumab	Mutational load	[44]
Topalian et al.	Melanoma, prostate cancer, colon cancer, renal-cell cancer and NSCLC	Nivolumab	PD-L1	[17]
Tumeh et al.	Melanoma	Pembrolizumab	TILs	[37]
Rittmeyer et al.	NSCLC	Atezolizumab	PD-L1	[19]

NSCLC = non-small cell lung cancer; GEJ = gastro-esophageal junction; CTLA-4 = cytotoxic T lymphocyte associated antigen 4.
PD-L1 = programmed cell death-1; TILs = tumor infiltrating lymphocytes; MSI = microsatellite instability; EBV = Epstein-Barr virus.

high serum lactate dehydrogenase (LDH). Building on this 'cancer immunogram' concept, approaches for selecting the most promising biomarkers with respect to CIT can be explored and are thus being evaluated in various studies. The main directions in this respect are: PD-L1 expression, the amount of tumor infiltrating lymphocytes, mutational or neoantigen burden, peripheral blood markers (e.g. lymphocyte and neutrophil counts as well as the size of the different subcompatrments), immune gene expression signatures, or multiplex immunohistochemistry to characterize the tumor infiltrating immune compartment [10]. At this moment PD-L1 is the most widely used biomarker for patient selection for CIT in clinical practice.

2. The role of PD-L1 in inflammation and tumor immune evasion

2.1. The role of PD-L1 in regulation of inflammatory response

PD-L1 is a ligand expressed mainly by antigen-presenting macrophages and dendritic cells. PD-L1 binds to PD-1 expressed on activated T cells. This binding leads to downregulation and limitation of the T-cell response in inflammation. During the inflammatory response, naïve T-cells in the lymph nodes are exposed to antigens, expressed on MHC class I by antigen presenting cells (APC), especially the mature dendritic cells. If an antigen is immunogenic, antigen presentation leads to activation of the T-cell receptor (TCR) on T-cells. The resulting canonical TCR signal transduction provokes expression of TCR signaling-specific genes finally resulting in T-cell activation. In turn, T-cell activation provokes T cell proliferation, production of cytokines and differentiation towards cytotoxic T-cells or T helper cells. Activated T-cells leave lymph nodes and execute effector functions, for instance killing virus-infected cells. As such responses can result in exaggerated immunity and damage to healthy tissue, powerful mechanisms to regulate the extent of this immune response are involved. These control mechanisms are manifold and include immune-downregulation by the interaction between PD-L1 and PD-1. The latter provides a strong tolerogenic signal to the T cell and hence protects tissue from collateral damage during inflammation and diminishes the possibility of autoimmune reactions (Fig. 1). The tolerogenic function of PD-L1 and PD-1 interaction is well illustrated by the fact that anti-PD-L1 treatment can result in auto-immune-like side-effects such as colitis, type 1 diabetes and hepatitis [11].

2.2. Anti-cancer immune response

Cancer cells produce cancer-specific peptides, so called neo-antigens, which are presented on the cancer cell's surface by MHC class I molecules. Without cross presentation of cancer-specific neo-antigens by APCs, the immune system is unable to activate T-cells and produce a sufficient response to eliminate the tumor. In general tumor cells do not have sufficient co-stimulatory activity to activate a naïve T cell. Nevertheless, neo-antigens are released to the extracellular medium due to natural tumor cell death and then are taken up by dendritic cells or macrophages, which can subsequently present these neo-antigens to T-cells with sufficient co-stimulatory activity, to activate TCR signaling in naïve T cells [12]. The activated T-cells produce anti-tumor cytokines, proliferate and differentiate into $CD8^+$ positive cytotoxic T-cells, which participate in an effective immune response against the tumor. The resulting death of tumor cells and subsequent release of further neo-antigens provokes further activation of the immune system and, in an ideal situation complete tumor elimination [13](Fig. 2).

2.3. Mechanism of PD-1/PD-L1 induced tumor immune evasion

The PD-1/PD-L1 immune inhibitory axis is exploited by many tumors to evade T-cell-mediated anti-tumor immune response [14]. Tumor microenvironment plays an important role in this context where, for example upon stimulation by certain pro-inflammatory cytokines, PD-L1 becomes expressed on cancer cells as well as on tumor-infiltrating immune cells, especially myeloid cells, such as macrophages and dendritic cells [15]. This PD-L1 upregulation is, amongst others, a consequence of IFN-y production by activated T-helper cells, CD8 positive cytotoxic T-cells and NK-cells, whose presence is common to the cancer microenvironment, especially at the periphery of the tumor.

A correlation exists between PD-L1 expression, the amount of tumor infiltrating lymphocytes and IFN-y production in the tumor microenvironment [16,17]. The most well-known cytokine responsible for PD-L1 upregulation in the gastro-intestinal tract is the regulatory cytokine interleukin 10. Moreover, even independently of pro-inflammatory signals, cancer cells may show constitutive expression of PD-L1 due to genetic alterations and activation of oncogenic signaling pathways, such as the AKT or STAT3, but this requires further investigation in the context of tumors of proximal tract tumors [18]. The extracellular binding of PD-L1 to PD-1 results in intracellular inhibition of TCR signaling. Following PD-L1 binding, PD-1 displays oligomerization and this in turn allows the non-receptor tyrosine phosphatase SHP-2 to bind to the so-called PD-L1 immunoreceptor tyrosine inhibitory motif (ITIM) and immunoreceptor tyrosine switch motif (ITSM). This subsequently allows SHP-2 to exert its immune-inhibitory action on TCR signaling and also other Th1 immune signaling pathways [19,20]. This finally culminates in ineffective immune responses to tumor associated neo-antigens and finally to tumor immune evasion [21] (Fig. 3). By use of immune checkpoint inhibitors this mechanism of

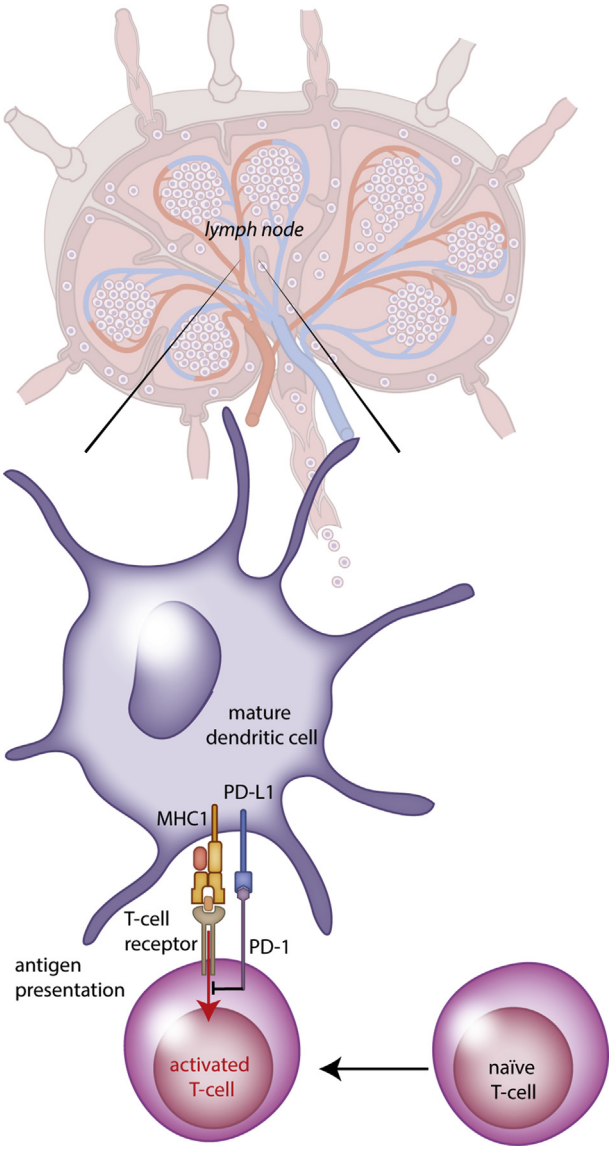

Fig. 1. Mechanism of T-cell activation by antigen presenting cells. In the lymph nodes dendritic cells present antigens to naïve T-cells on MHC1 class I molecules (MHC1). Upon binding MHC1-antigen complex with a compatible T-cell receptor naïve T-cells become activated and further induce T-cell response during inflammation. This process can be downregulated/blocked by PD-L1/PD-1 interaction.

tumor immune evasion can be combated. Therefore, assessing the expression of PD-L1 on tumor cells seems like a rational strategy for determining which patients are likely to benefit from therapy with immune checkpoint inhibitors.

3. Evidence for PD-L1 as a predictive biomarker for response to cancer immunotherapy

3.1. Clinical trials in melanoma and NSCLC

A correlation between PD-L1 immunohistochemical positivity and response to CIT has been shown in a limited number of clinical trials. These studies have been performed almost invariably in patients with either metastatic melanoma or NSCLC. In a study by Topalian [22], nivolumab was effective in 20–25% of patients with melanoma or NSCLC. Thirty-six percent of patients with PD-L1 positive tumors had an objective response, compared to none of the patients with PD-L1 negative tumors, suggesting a relationship between response and tumor cell PD-L1 expression. Also, in the POPLAR study, atezolizumab compared to docetaxel significantly improved survival in patients with previously treated NSCLC. The improvement was correlated to the levels of PD-L1 immunohistochemistry expression on tumor cells and tumor-infiltrating immune cells, suggesting that PD-L1 expression is predictive of atezolizumab benefit [23]. Also, in the OAK trial, the greatest survival benefit was seen in patients with tumors expressing high levels of PD-L1, although overall survival was also significantly improved in patients with less than 1% PD-L1 expression [24].

So far, the most convincing evidence for correlation between PD-L1 expression and response to CIT was shown in the KEYNOTE-024 study [25]. In this study, with patients with advanced NSCLC and PD-L1 expression on at least 50% of the tumor cells, pembrolizumab was associated with significantly longer progression-free and overall survival than with platinum-based chemotherapy. Based on these and similar results, PD-L1-based selection of patients for CIT has gained a role in clinical management of several cancer types. However, even in NSCLC and melanoma, several challenges arise with using PD-L1 as a biomarker, including the dynamics and differential expression of PD-L1 within a tumor and the lack of a standard definition for overexpression. Detailed description of these and other limitations can be found in a previously published review by Topalian et al.) [26].

3.2. Clinical trials in gastroesophageal malignancies

There is little data on CIT biomarkers in GA and EAC. It is tempting to draw parallels between lung and esophageal and gastric adenocarcinoma, since these are all epithelial malignancies with many similarities in etiology, morphology and mutational profile. Extrapolating the correlations observed to EAC and GA, it would appear that PD-L1-based selection for CIT in EAC and GA is rational. Therefore, many clinical trials are already using PD-L1 expression as a selection criterion for CIT, either alone or in combination with chemotherapy. But, in the absence of compelling data in gastrointestinal cancers, the question arises whether it is reasonable to draw parallels between NSCLC and EAC and GA. For example, in the KEYNOTE-059 study responses to CIT were seen in both PD-L1 positive and negative gastroesophageal cancers, with objective response rates of 15.5% and 6.4% respectively. These data support the inadequacy of PD-L1 as a predictive a biomarker [8,27]. Additionally, in a comprehensive review about immunotherapy in gastroesophageal cancers, response rates of single-agent checkpoint inhibitors in metastatic GA and EAC of approximately 22%–27% for PD-L1 + patients vs 10%–17% for unselected patients were described [28]. Moreover, in a recent issue of the Lancet, Kang et al. showed a survival benefit in patients with advanced gastroesophageal junction (GEJ) or GA who were treated with nivolumab [29]. Although this study was designed to investigate the effect of nivolumab in patients unselected for PD-L1 tumor expression, retrospective immunostaining for this biomarker showed that the effect of nivolumab was independent of PD-L1 positivity. In the KEYNOTE-061 study, pembrolizumab did not significantly improve overall survival compared with paclitaxel in advanced PD-L1 positive gastroesophageal cancers [30]. In all, the available data suggest that PD-L1 may not be the ideal biomarker to select patients with gastroesophageal cancer for immunotherapy.

3.3. Expression pattern of PD-L1 in gastroesophageal malignancies

Muro et al. reported PD-L1 expression in around 40% of GEJ and GA. It is important to note that this expression is mainly observed in immune cells and not in the epithelial cancer cells, which is fundamentally different from what is seen in NSCLC [31]. In this study the tumors were considered positive, if at least 1% of assessable cells were positive, while membranous PD-L1 expression of more than 50% of only epithelial tumor cells was needed to demonstrate benefit of

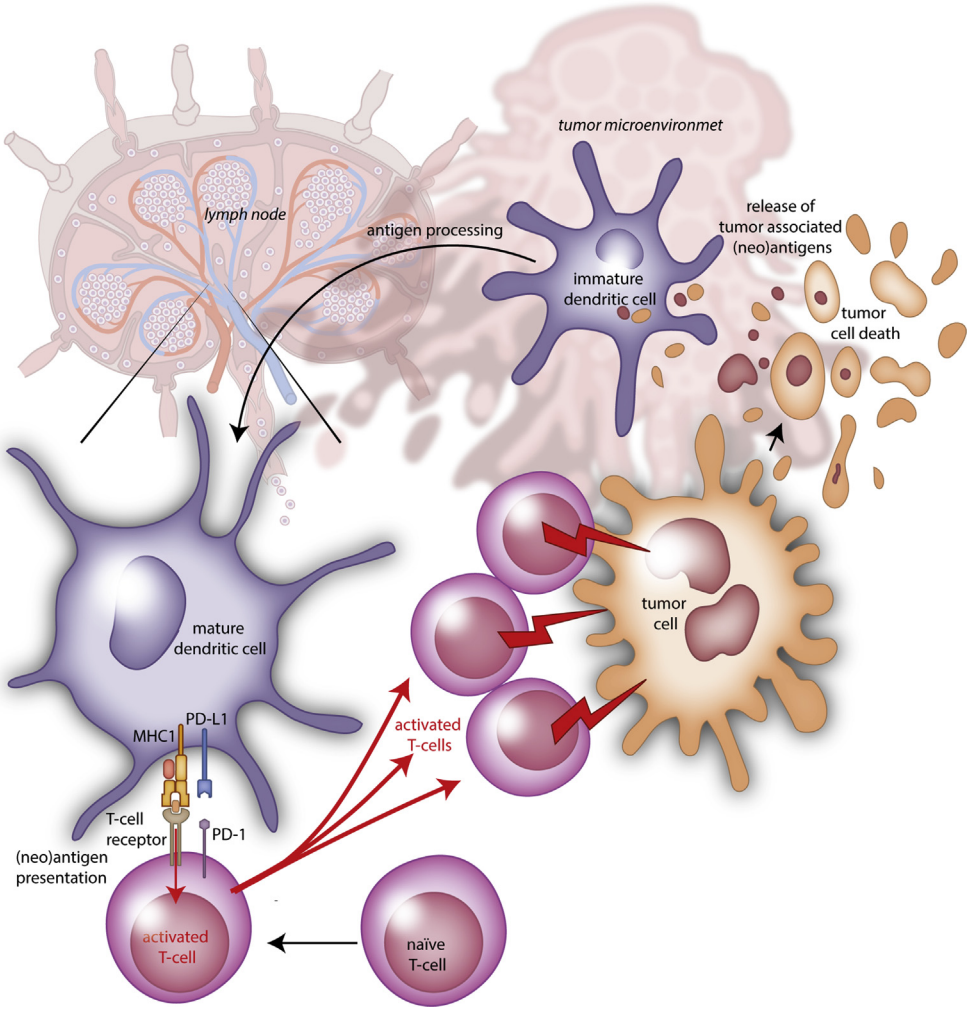

Fig. 2. Immune response against cancer. Neoplastic cells release tumor associated (neo)antigens, which are taken up by immature dendritic cells. These (neo)antigens are then processed and are presented by mature dendritic cells on MHC class I molecules (MHC1) to naïve T-cells, leading to activation of the T-cell receptor (TCR) on T-cells. This results in an activation of the canonical TCR signal transduction, expression of TCR-signaling specific genes and T-cell activation. The activated T-cells produce anti-tumor cytokines, proliferate and differentiate into cytotoxic T-cells. This results in an active attack of the tumor by the immune system and tumor cell death with a subsequent release of large amount of tumor associated (neo)antigens and further activation of the immune system.

immunotherapy over chemotherapy in NCSLC [32,33]. Similar results were published by Thompson, reporting PD-L1 positivity in only 12% of tumor cells and 44% of immune stroma [34]. In gastric adenocarcinoma only 14% of tumors were positive for PD-L1 in > 1% of epithelial tumor cells and 11% of tumors in > 1% of stroma cells [35]. In the study of Kawazoe A et al., most gastric adenocarcinomas (61,4%) showed positivity in tumor infiltrating immune cells and only 22,8% in the epithelial tumor cells [36]. These data suggest that PD-L1 expression in EAC and GA cancers cannot be evaluated in the same manner as in NSCLC. In our experience we also observe a different pattern of PD-L1 expression in lung adenocarcinomas and gastric adenocarcinomas, unpublished data (Fig. 4). In lung adenocarcinomas PD-L1 positive cells are observed in both compartments: the immune cells and in the epithelial cells. In contrast, most EAC and GA show PD-L1 expression (if positive) only in the immune cell compartment. To our opinion, future research should explore the association between PD-L1 expression in different tumor compartments in EAC and GA (epithelial cells versus immune stroma, with a particular focus on the immune stroma) and the associated response to CIT.

4. Other biomarkers for patient selection in cancer immunotherapy

4.1. Microsatellite instability and EBV status

If PD-L1 is not the best biomarker in gastroesophageal cancers, which other options do we have? In a large and comprehensive TCGA study including 295 primary GA, four subtypes of stomach cancer were identified: 9% of tumors showed positivity for Epstein-Barr virus (EBV subtype), 22% of tumors were classified as a microsatellite instability (MSI) subtype, 50% of tumors demonstrated high chromosomal instability (CIN subtype), and 20% were categorized as a genomically stable subtype [37]. Two of these subtypes, MSI and EBV tumors, are particularly interesting in regard to CIT. As such, a recent phase II trial described salvage treatment with pembrolizumab in metastatic gastric cancer patients. Patients with MSI-high (MSI-H) and EBV-positive tumors showed responses to pembrolizumab, with an overall response rate of 85,7% in MSI-high and 100% in EBV-positive gastric cancers [38]. These findings, which need to be validated prospectively, have the potential to substantially improve the treatment in a subset of gastric cancer patients and make MSI-H and EBV positivity reliable predictive biomarkers. Underlying mechanisms explaining the good response of these gastric cancer subtypes to CIT have not been elucidated yet, but such factors as high tumor mutational burden, increased immune cell infiltration in the tumor microenvironment (TME) and a high neo-antigen load can play a role.

4.2. The role of tumor infiltrating lymphocytes in MSI and EBV tumors

The amount of tumor infiltrating lymphocytes (TILs) may be related to the efficacy of anti-cancer immune responses, a feature also appreciated by the “cancer immunogram”. A recent meta-analysis showed that a high density of intratumoral $CD8^+$ and CD3 T-cells is significantly associated with improved overall survival in gastric cancer patients [39]. In colorectal cancer patients, tumor infiltrating lymphocytes and the immunoscore are considered to be useful prognostic

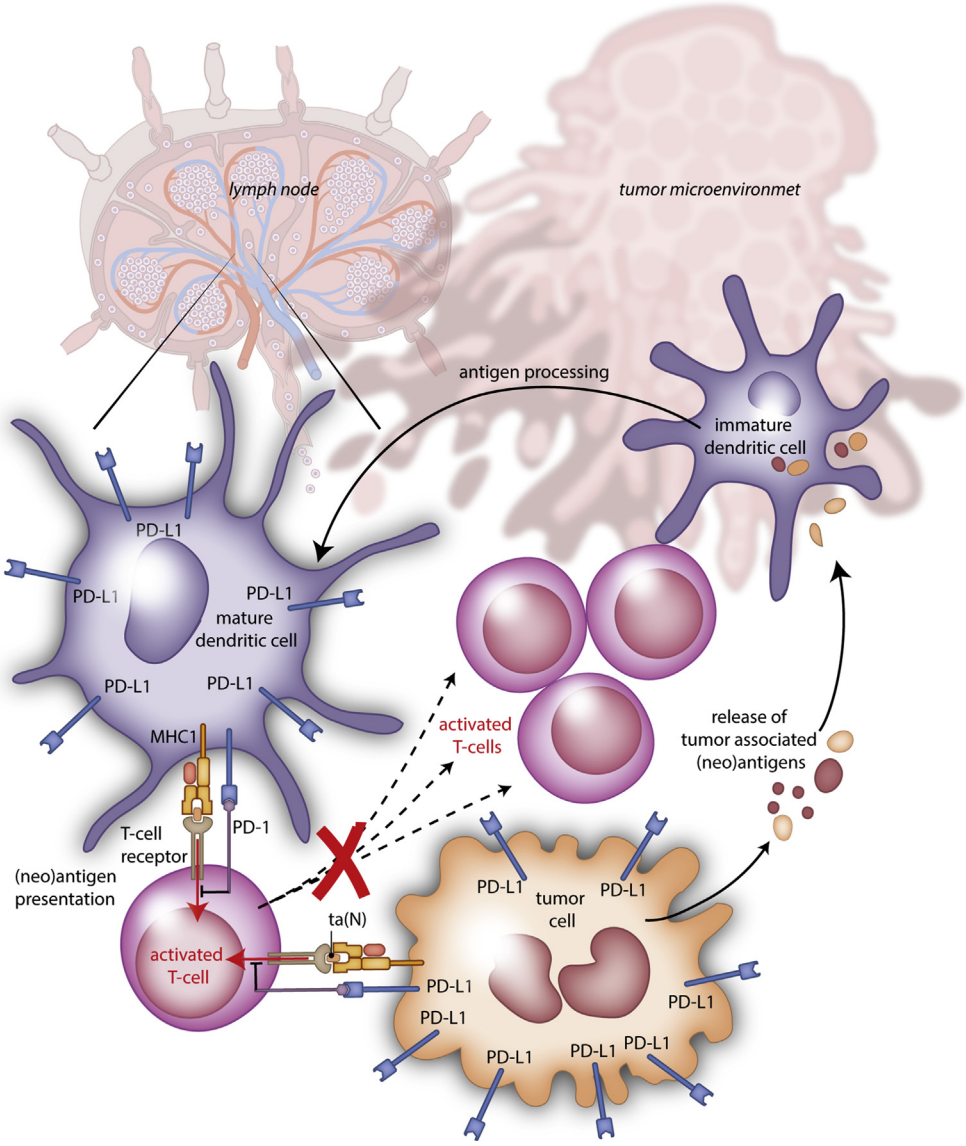

Fig. 3. PD-1/PD-L1 induced immune evasion in cancer. Under certain circumstances PD-L1 becomes expressed on cancer cells. Moreover, cancer cells produce cytokines that enhance expression of PD-L1 on antigen presenting cells (dendritic cells and macrophages). Binding of PD-L1 to PD-1 on T-cells results in inhibition of T-cell receptor signaling, unsuccessful response to tumor associated (neo) antigens (ta(N)) and downregulation of the anti-tumor immune response, thereby protecting the tumor from attack of the immune system.

markers of survival [40,41]. The immunohistochemistry based assessment of T-cells in melanoma patients reveals the association between CIT efficacy and increased numbers of TILs [42–44]. At this moment there are no published data regarding the role of TILs as a separate biomarker in gastroesophageal cancers. However, tumors of both the EBV and MSI subtype exhibit high levels of tumor infiltrating lymphocytes. It is probable that such subtypes interact very differently with the immune system than other GA subtypes. Therefore, it is possible that the high level of TILs in the EBV and MSI subtypes of GA may correspond to increased success of CIT, and studies addressing this notion are currently under progress in our institution as well as elsewhere. Yet, TILs as a single marker is unlikely to be a successful strategy for selection of patients, as different subpopulations of lymphocytes exhibit different functions and can either potentiate or reduce tumor growth. Moreover, the interaction between the host immune system and tumor cells is extremely complex and depends on multiple factors, not only on the amount of TILs. Most likely, the amount of cytotoxic CD8-positive T-cells, in combination with other markers such as mutational load, PD-L1 expression, markers of IFN-γ pathway etc, will be more successful as a multifactorial biomarker in CIT [26].

4.3. The role of high mutational load and neo-antigens in MSI tumors

MSI tumors are known to harbor high mutational loads, which in turn is associated with improved survival and response to immune checkpoint inhibitors [45]. This relationship could be explained by increases in tumor "foreignness" due to expression of deviant proteins/peptides as products of mutated genes (these represent the earlier-mentioned tumor-associated neo-antigens). It is probable that high numbers of TILs, characteristic of this GA subtype, is the result of this increased immunological "foreignness". This increased propensity to provoke an immunological response may indicate that immune-checkpoint targeted therapy will be relatively successful for such cancers. It is also encouraging in this respect that, in a recent issue of Nature, a neo-antigen-based stratification approach to predict tumor response to checkpoint blockade immunotherapy in pancreatic cancer was published [46,47]. The authors identified neo-antigens as a biomarker predicting immunogenic pancreatic tumors in patients prone to benefit

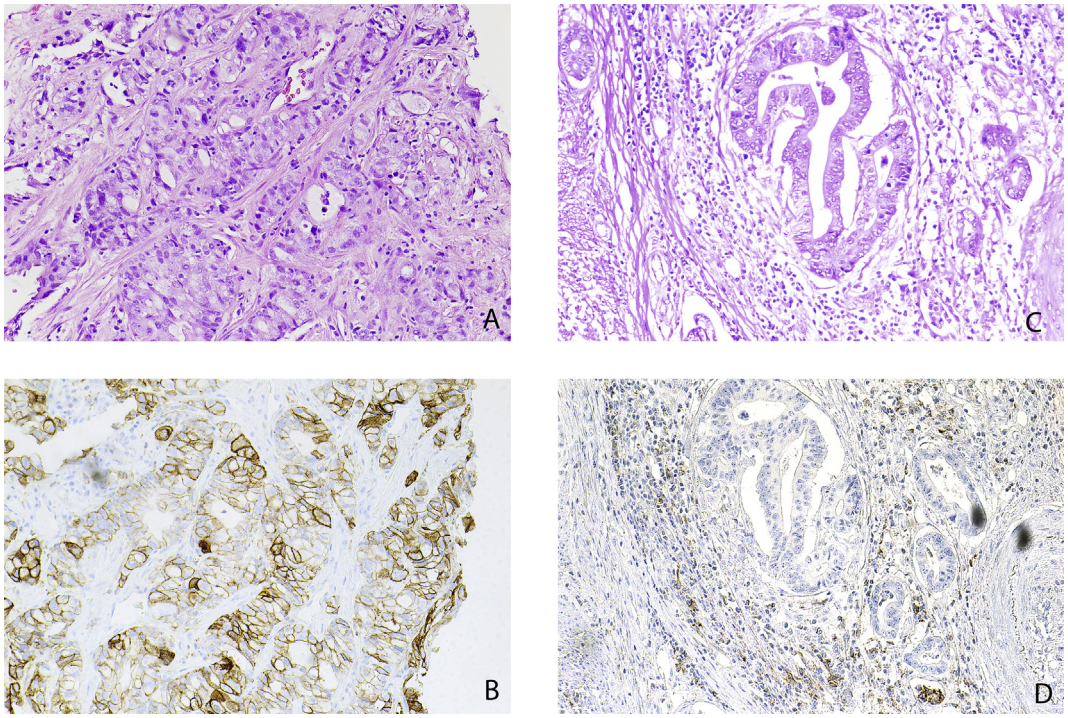

Fig. 4. Differences in expression of PDL1 in lung adenocarcinoma and gastric adenocarcinoma. A, B: Histology (A) and PD-L1 immunohistochemistry (B) in lung adenocarcinoma. The tumor epithelial cells show moderate to strong expression of PD-L1. C,D: Histology and corresponding PD-L1 immunohistochemistry in gastric adenocarcinoma. The tumor epithelial cells are completely negative, and immune cells in stroma are positive.

from immunotherapy. This adds to the idea that MSI subtypes of GA are likely to respond to CIT. Based on these data one may hypothesize that the proposed TCGA subtyping of GA performs better in correlation to immune checkpoint inhibitor efficacy than the tumor PD-L1 expression currently favored in most clinical practice. Supporting this are the results of a subgroup analysis (post-hoc analysis) of MSI high tumors in the KEYNOTE-061 study. Even though pembrolizumab as second-line therapy did not significantly improve overall survival compared with paclitaxel in patients with PD-L1 positive advanced GA or GEJ cancer, pembrolizumab was beneficial in the MSI-high subgroup [30].

However, mutational load is also not a perfect predictor of response. Patients with NSCLC with a higher mutational load benefitted more from pembrolizumab than patients with lower mutational load, but there were clear outliers making it imperfect [48]. The same has been reported for ipilimumab and tremelimumab in melanoma patients, where mutational load correlated significantly to response to CIT but on its own was not enough to be used as a biomarker [22,49].

4.4. Other possible biomarkers

The “cancer immunogram” suggests other biomarkers as general lymphocyte count, MHC expression and high serum LDH concentrations. Although some of them have been investigated in other cancer types, none of these additional biomarkers have been tested in EAC and GA, underlining the need for further research in this area. At this moment there are also no data available on specific mutations in tumor-suppressor genes or tumor-promoter genes in association with response to immunotherapy in EAC and GA. However, the recent systematic review and meta-analysis by Lee et al. reported that in advanced NSCLC, checkpoint inhibitors improved overall survival compared to docetaxel and had a significantly improved overall survival for EGFR wild-type over EGFR mutant tumors [50]. Immunotherapy prolonged overall survival in EGFR wild-type patients (HR, 0.67; 95% CI, 0.60–0.75; P < .001), but not in EGFR mutant patients (HR, 1.11; 95% CI, 0.80–1.53; P = .54). Also, CIT prolonged overall survival in the KRAS mutant subgroup (HR, 0.65; 95% CI, 0.44–0.97; P = .03) but not in the KRAS wild-type subgroup (HR, 0.86; 95% CI, 0.67–1.11; P = .24). Whether specific mutations in GA and EAC are associated with response to CIT remains to be elucidated.

There is also a possible role for PD-L2 expression in gastric cancer as a biomarker. Though current research has only focused on it as a prognostic factor for survival. Whether PD-L2 expression can be used as biomarker for PD-L1 blockade therapy in gastroesophageal carcinomas should be further explored [51–53].

5. Discussion

The currently available data imply that PD-L1 expression in cancer cells can be a good predictor of response to CIT in patients with NSCLC, but there is insufficient evidence to apply this approach for patients with gastroesophageal malignancies. The expression pattern of PD-L1 in gastroesophageal malignancies is different from the expression pattern in NSCLC. In gastroesophageal cancer, PD-L1 expression is mainly observed in immune stroma rather than in epithelial cells, in contrast to NSCLC. Therefore, an extrapolation of findings in NSCLC to gastroesophageal cancer does not seem reasonable. This topic needs to be addressed in future research.

As cancer-immune system interaction is complex and depends on many factors, it is likely that strategies to combine multiple markers may be more successful in comparison to a single marker with respect to prediction of clinical success of CIT. As such, it is plausible that tumors with a high expression of PD-L1 but with a low amount of tumor infiltrating lymphocytes respond less to CIT than tumors exhibiting both these features. Therefore, it seems to be important to study a combination of markers to get to an optimal prediction model for the response to CIT.

Presently, in gastroesophageal cancers, MSI and EBV status are the most promising predictive biomarkers for CIT. The exact biological mechanism of the striking effect of CIT in these tumors has not yet been fully elucidated, but a complex interplay between tumor cells and

immune microenvironment, including tumor mutational load, TILs and PD-L1 expression, plays an important role. For an accurate selection of patients most likely to respond to CIT, future studies need to aim for a combination of improved biomarker strategies in conjunction with MSI status, EBV status, precise characterization of the immune infiltrate and the neo-antigen burden in different types of gastroesophageal cancer separately.

Conflicts of interest

None.

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