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Review

Programmed Death Ligand 1: Unveiling its Impact on Endometrial Carcinogenesis

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Abstract. *Endometrial cancer is a commonly diagnosed gynecological malignancy presenting an increasing incidence worldwide. The immune response plays a crucial role in the mechanisms underlying carcinogenesis and the progression of tumors. In recent times, there has been a discernible surge in the acknowledgment of the importance of programmed death ligand 1 (PDL1) in evading the immunological response of the host and promoting the growth of malignancies. The primary aim of this review is to consolidate the existing corpus of evidence pertaining to the role of PDL1 in the etiology and progression of endometrial cancer and investigate the molecular mechanisms involved in the expression of PDL1 in cells impacted by endometrial cancer. Finally, the association between PDL1 expression and clinical outcomes, as well as the potential therapeutic uses of targeting the PDL1 pathway are being analyzed.*

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Endometrial cancer (EC) is the most often diagnosed gynecological malignancy worldwide (1). The global incidence of the disease has been progressively increasing, possibly because of the rising prevalence of obesity, a well-recognized predisposing factor for the ailment (2). The significance of EC is emphasized not only by its widespread prevalence but also by its ability to demonstrate aggressiveness and invasiveness, particularly in later stages (3). The selection of treatment for EC depends on the particular stage and grade of the tumor. Surgical intervention, often including a hysterectomy and bilateral salpingo-oophorectomy, is the main method used in the management of early-stage disease. In later stages of the condition, treatment strategy may include surgical procedures, radiation therapy, chemotherapy, and hormone therapy (4). Hence, there is clearly a need to identify new prognostic markers and therapeutic targets for EC that will facilitate disease management.

The immune system plays a critical role in protecting the host organism against illnesses and also aids in the surveillance of malignancies. Immune checkpoints, such as the programmed cell death protein 1 (PD-1) and its ligand, programmed death-ligand 1 (PDL1), are intricate regulatory

mechanisms that modulate immune responses to prevent the development of autoimmunity. Nevertheless, it is plausible that tumors might use these pathways as a mean to evade immune destruction (5). The PD-1 receptor is present on activated T-cells and functions as an inhibitory receptor. In the context of the tumor microenvironment (TME), tumor cells and immune cells produce PDL1, which functions as the ligand for PD-1. The interaction between PDL1 and PD-1 results in the transmission of an inhibitory signal, which impedes the activation and proliferation of T-cells. As a result, this creates a conducive environment for tumor growth by suppressing the immune system (6).

However, the role of PDL1 in endometrial carcinogenesis has not been sufficiently examined. This review aims to provide an informative synthesis of the current state of knowledge on the role of PDL1 in EC and highlight its potential as a prognostic and therapeutic target for EC.

Methodology

A literature review of the Medline (PubMed), Scopus, and Web of Science databases was conducted using the following terms: *PDL1* expression, EC, tumor, PD1.

The Etiology of Altered PDL1 Expression in Endometrial Cancer

The etiology of altered PDL1 expression in EC is complex and multifactorial. Up-regulation of PDL1 may be ascribed to genetic and epigenetic modifications, such as DNA methylation and histone modifications (7). Research has also indicated that inflammatory signals within the tumor microenvironment (TME), particularly those facilitated by cytokines, such as interferon-gamma, can increase the expression of PDL1 (8). Furthermore, specific molecular subtypes of EC exhibit a positive correlation with PDL1 expression, which may indicate a genetic predisposition to particular malignancies (9).

Genetic and epigenetic changes in PDL1 expression and cancer. The expression of *PDL1* in cancer may be influenced by genetic and epigenetic changes. Genomic variations, such as mutations or copy number variations, may result in the over-expression of *PDL1* (10). In a large study investigating the potential of using *PDL1* gene copy number (CN) changes as a biomarker for immune checkpoint inhibitor (ICPI) treatment, it was found that *PDL1* CN gains were significantly associated with PDL1 positivity and with microsatellite instability (MSI) status in clinically relevant tumor types, including uterine endometrial adenocarcinoma (OR=3.2), which showed low frequencies of *PDL1* CN deprivation (16.6%) (n=1,971). Additionally, *PDL1* CN gain was significantly correlated with tumor mutational burden (TMB) in only four tumor types including uterine endometrial adenocarcinoma (OR=2.3, $p<0.001$). In the tumor types in which MSI is most clinically relevant including uterine endometrial adenocarcinoma, a significant correlation was observed between *PDL1* CN gains and MSI-High (OR=3.2, $p=2.1\times10^{-6}$). These results demonstrated that the association of *PDL1* CN gains with PD-L1 positivity and MSI status, as well as with TMB in uterine endometrial adenocarcinoma can be used as a biomarker for ICPI treatment. Huang *et al*. analyzed data on *PDL1* copy number changes across a large dataset encompassing 244,584 patient samples. As an example, certain signaling pathways associated with the development of cancer, such as the PI3K/AKT/mTOR pathway were shown to be correlated with increased expression of PDL1 (11). The regulation of *PDL1* gene is significantly influenced by epigenetic processes whereby DNA methylation patterns and histone modifications are important elements in this regulatory process. Prior studies have shown a positive association between hypomethylation of the promoter region of the *PDL1* gene and increased expression in some forms of cancers (12). Furthermore, post-transcriptional regulation, mediated by microRNAs, contributes an extra layer of to the regulation of the expression of *PDL1*, as shown in chemoresistant ovarian cancer (13).

The influence of the tumor microenvironment. The TME is of utmost importance in the modulation of *PDL1* expression in endometrial malignancies. The TME is subject to several influences, one of which is the presence of inflammatory cytokines, particularly interferon-gamma. The aforementioned stimuli induce the expression of PDL1 on both neoplastic cells and immune cells that have invaded the TME (14). Moreover, previous studies have shown that the hypoxic conditions inside the TME might lead to increased *PDL1* expression, hence facilitating immune evasion and suppression by the tumor (15). In addition, cancer-associated fibroblasts and tumor cells inside the TME are also involved in the modulation of the PD-1/PDL1 axis (16).

PDL1 Expression as a Potential Prognostic Marker in Endometrial Cancer

The multifaceted role of PDL1 in the progression of EC and its complex interplay with the immune system have garnered growing interest regarding its potential as a prognostic marker. Studies have reported on the association between the expression of *PDL1* and the grade of tumors in EC. Increased levels of gene expression are often observed in malignancies characterized by a high degree of cellular differentiation, suggesting a plausible correlation with augmented tumor aggressiveness (17). In addition to tumor grade, associations between *PDL1* expression and other prognostic markers, such as lymphovascular invasion and greater depth of myometrial invasion, have been observed

(18). Noteworthy, the expression of PDL1 might potentially demonstrate a relationship with certain molecular subtypes of EC, therefore providing significant insights into the intrinsic heterogeneity of this disease (19).

Research has also shown a significant association between increased *PDL1* expression levels and reduced rates of both overall survival and disease-free survival (20). Therefore, *PDL1* is now becoming recognized as both a potentially effective therapeutic target and a marker for patient classification, enabling the implementation of personalized treatment approaches. The prognostic significance of *PDL1* expression, however, may vary depending on the specific context and requires interpretation in conjunction with other clinical and molecular indicators (21-24).

PDL1 Expression and Other Clinicopathological Features

PDL1 expression in EC is not seen in isolation. A significant association exists between the expression of *PDL1* and several clinicopathological characteristics. For example, it has been shown that cancers characterized by high microsatellite instability (MSI-H), which is indicative of a failure in mismatch repair, often have increased *PDL1* expression levels (25). Furthermore, the complex link between PDL1 and other immunological checkpoints, including cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), suggests that PDL1 is involved in the immune evasion mechanisms of the tumor (26). Increased expression of *PDL1* has been shown to be related with lymphovascular invasion, deeper myometrial invasion, and higher histological grades, hence introducing additional levels of intricacy in the interpretation of prognosis (27).

In a recent review of the association of *PDL1* expression and its association with clinicopathological features in 3023 EC cases, it was found that the overall pooled prevalence of *PDL1* expression was 34.26% in tumor cells and 51.39% in immune cells among women with EC. *PDL1* expression was found to be significantly associated with Stage III/IV disease (in both tumor and immune cells) and correlated with the presence of lympho-vascular invasion in immune cells. Noteworthy, *PDL1* expression in tumor cells was not associated with age, histology types, myometrial invasion, and lympho-vascular invasion, whereas in immune cells, *PDL1* expression was not associated with age, histology type, and myometrial invasion. Finally, the meta-analysis revealed a significant correlation with poorer overall survival in patients with high PDL1 expression in immune cells, but not in tumor cells (28, 29).

A similar but earlier meta-analysis of 1,615 patients with EC, also showed that high expression of *PDL1* was not significantly correlated with overall survival (HR=1.20, 95%CI=0.41-3.52, p=0.737) or progression-free survival (HR=1.12, 95%CI=0.50-2.54, p=0.778), whereas *PDL1* expression was significantly associated with poor differentiation (OR=2.82, 95%CI=1.96-4.06, p<0.001) and advanced stage (OR=1.71, 95%CI=1.12-2.60, p=0.013) (30).

The PDL1 Pathway as a Therapeutic Target in Endometrial Cancer

The PD-1/PDL1 pathway is of utmost importance for facilitating the immune system's capacity to differentiate between self and non-self, hence aiding in the prevention of autoimmunity. In several types of malignancies, such as EC, this biological pathway may be exploited, enabling neoplastic cells to evade immune detection. Given the growing evidence of the involvement of PDL1 in the advancement of EC and the favorable outcomes seen with ICPIs in many malignancies, there is substantial enthusiasm around the potential of targeting the PD-1/PDL1 axis for therapeutic interventions (31, 32).

Monoclonal antibodies known as PD-1/PDL1 inhibitors have been specifically developed to impede the interaction between PD-1 and PDL1. There are two main categories: a) PD-1 inhibitors that specifically bind to the PD-1 receptor found on T cells. Prominent examples of PD-1 inhibitors include pembrolizumab (commercially known as Keytruda) and nivolumab (marketed as Opdivo). b) PDL1 inhibitors designed to selectively target PDL1 expressed on tumor cells, as well as other cells present within the TME. Examples of PDL1 inhibitors are atezolizumab (Tecentriq), durvalumab (Imfinzi), and avelumab (Bavencio) (33).

Pembrolizumab, an anti-PD-1 antibody, has shown encouraging outcomes in clinical studies conducted on individuals with EC who had high levels of MSI or mismatch repair deficiency (29). Several studies are currently conducted to evaluate the effectiveness of PD-1/PDL1 inhibitors as standalone treatments and/or in conjunction with other treatments, such as chemotherapy or targeted therapies (31). Furthermore, there is ongoing research to investigate strategies aimed at improving the effectiveness of these inhibitors, including the potential benefits of combining them with radiation therapy or other immunomodulatory drugs (29). As our understanding of the immunological milieu in EC expands, enhanced prospects for efficacious treatment strategies will arise correspondingly.

Numerous clinical studies have been conducted to assess the efficacy of PD-1/PDL1 inhibitors in the context of EC. The clinical study KEYNOTE-028, which included the usage of pembrolizumab, demonstrated positive outcomes in a specific subgroup of individuals with EC. Notably, these good responses were seen in patients with elevated levels of MSI or *PDL1* expression (34). A subsequent clinical study using avelumab showed instances of partial responses in individuals with recurrent or persistent EC (35). The studies' results highlight the potential efficacy of immunotherapy as a treatment for EC, emphasizing the need for patient classification. The findings of different immune checkpoint

blockade therapies in gynecological cancers, including EC, have been recently reviewed (36).

Although PD-1/PDL1 inhibitors have shown potential, they are not devoid of obstacles. To begin with, it should be noted that not all patients respond to medication. Additionally, although predictive biomarkers might provide valuable insights, they are not entirely conclusive (37), and there is a noteworthy thought about immune-related adverse effects, which can occur in several organ systems (38). In anticipation of future developments, the use of combination medicines holds significant promise. The augmentation of response rates might potentially be achieved by integrating PD-1/PDL1 inhibitors with other treatment modalities, including chemotherapy, targeted treatments, or other immunotherapies (39). Furthermore, there exists considerable promise in the investigation of alternative immune checkpoints or the development of medicines that directly target the TME.

Recap the Importance of PDL1 in Endometrial Cancer Progression

PDL1 has emerged as a significant factor in the context of EC. The role of PDL1 in facilitating immune evasion by tumor cells contributes to the establishment of a microenvironment that supports the growth of cancer. The association between its expression and advanced-stage disease, recurrence, and lower overall survival has been demonstrated (22, 23). The use of the PD-1/PDL1 axis as a mechanism for immune evasion highlights the potential advantages of targeting therapeutic interventions to this pathway. The association between PDL1 and other clinical-pathological characteristics, such as MSI and higher histological grades, underscores its pivotal involvement in the progression of EC (25, 27).

Currently, precision medicine aims to customize medical therapies based on specific patient characteristics, with the goal of maximizing therapeutic efficacy and decreasing the occurrence of side effects. Biomarkers, such as the expression of *PDL1* or the status of MSI, have the potential to inform therapy choices, therefore identifying individuals who are most likely to get significant benefits from PD-1/PDL1 inhibitors (34). The process of patient stratification has the potential to provide improved results, particularly when used in conjunction with other molecular and genetic indicators. With the advancement of multi-omics technologies, there is an expectation of adopting a comprehensive and patient-centered strategy that integrates genomics, transcriptomics, and immune profiling to develop optimal treatment methods (40).

Conclusion

Significant progress has been achieved in comprehending the involvement of PDL1 in EC; yet, there exist various domains that need further investigation. One of the primary obstacles is the understanding of the processes of resistance. Despite the potential efficacy of PD-1/PDL1 inhibitors, the development of resistance, whether it is inherent or acquired, continues to pose a substantial challenge. Understanding the processes behind this resistance is essential for optimizing treatment approaches (41). Combination of medicines provide a potentially fruitful approach. As previously shown, there exists promise in the integration of PD-1/PDL1 inhibitors with complementary therapeutic approaches. The identification of the most effective combinations, sequences, and dosage regimens will be a crucial undertaking in the future (35). Moreover, in addition to the realm of PDL1, there is a need to delve into the wider TME and its many immunological complexities. Gaining a more profound comprehension in this context will provide valuable insights into other treatment targets (42). In conclusion, the current use of *PDL1* expression and MSI status as biomarkers represents a continuous effort to identify more accurate and comprehensive predictors of response to immunotherapy (43).

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

A.K., Z.F., and V.M. contributed to conception and design. E.N.K. was responsible for overall supervision. P.P., A.S.; Drafted the manuscript, which was revised by N.G. and V.T.. All Authors read and approved the final manuscript.

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