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Review

Gyneco-oncological genomics and emerging biomarkers for cancer treatment with immune-checkpoint inhibitors

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ABSTRACT

In gynecological cancers tumor infiltrating lymphocytes and upregulation of immune-related gene signatures have been associated with a better prognosis. Knowledge of tumor immunogenicity and associated gene signatures suggests that the tumor immune landscape is a key determinant to define patient prognosis and potentially to predict response to immune-checkpoint inhibitors. The aim of this review is to give an overview of immune gene signatures across gynecology histological cancer types, defining their prognostic and potential predictive role. In the current review we will present data on these gene signatures, on immunohistochemical features and their potential importance to select patients potentially eligible to trials with immune-checkpoint inhibitors.

1. Introduction

Multiple studies have found clear associations between the density, localization and functional orientation of the tumor immune infiltrate and clinical outcome [1]. The effects of the immune infiltrate on tumor cells can be bidirectional, either in favor of tumor growth by inducing inflammation [2] or protective by controlling tumor growth according to the immunoediting theory [3]. Overall, intratumoral immune infiltration has been associated with favorable prognosis in most cancer types, including breast cancer [4,5]. Phase I of Cancer Genome Atlas Project (TCGA) tested the research infrastructure based on the characterization of selected tumours having poor prognosis: brain, lung, and ovarian cancers. Since then, phase II analyses have expanded to more than 30 different tumor types, including endometrial and cervical cancers [6]. In the field of gynecological malignancies, advances in innovative genome analysis technologies have resulted in an increasing understanding of molecular mechanisms with respect to the genomic features of ovarian, endometrial, and cervical cancer [7]. The technological advances in the research field in combination with the success of immunotherapy, have propelled widespread characterization of the tumor immune landscape on both cellular and molecular levels. Consequently, the number of proposed immune-based classifications for tumors in general, as well as breast cancer specifically, has increased tremendously over the last years.

Typically, an immune response defined by a polarized Th1 phenotype, characterized by expression of CXCR3/CCR5 chemokine-receptor ligands, activation of interferon stimulated genes and production of cytotoxic molecules by effector immune cells, has been associated with immune-mediated tumor rejection [8]. Tumors bearing this phenotype are also characterized by a simultaneous activation of immune suppressive mechanisms, including expression of IDO1, CTLA4, PDL1, PD1 and FOXP3 [9]. As the attributes of this inflammatory phenotype have consistently been encountered in other forms of immune-mediated tissue rejection, including autoimmunity, allograft rejection and graft-versus host disease, the concept of the immunologic constant of rejection (ICR) was introduced [9]. Over the last decade, evidence supporting this phenomenon has accumulated, provided by gene signatures reflecting anti-tumor immune responses [10]. In the context of breast cancer specifically, prognostic and predictive immune signatures repeatedly describe genes included in the ICR pathways [9].

In this review, we will focus on the development of tumor immune classifications that rely on transcriptomic data and discuss their prognostic and predictive performance in different clinicopathological and molecular contexts. In addition, efforts to obtain consensus between proposed immune-based classifications and the potential benefits of implementation of immune subtypes in clinical settings will be presented. Finally, more recent insights in the potentially underlying mechanisms shaping the immune landscape will be presented, mainly concentrating on tumor derived genetic determinants.

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2. Tumor infiltrating lymphocytes in gynecological cancers

2.1. Tumor infiltrating lymphocytes in ovarian cancer

The tumor immune infiltrate is composed of distinct cell type populations, of which various are consistently described for their anti-tumoral activity, like memory T-cells, CD8+ cytotoxic T-cells (CTLs), CD3+ T-cells and NK cells, while others are associated with poor prognosis in various cancer types, including type 2 macrophages (M2) and T-helper 17 cells [11]. In the context of ovarian cancer cancer specifically, it has been clearly demonstrated that the presence of tumor-infiltrating lymphocytes (TILs) is associated with improved clinical outcome in ovarian cancer patients [11,12]. Patients with increased frequencies of intraepithelial CD8 + TIL (55 versus 26 months, HR = 0.33, 95% CI 0.18–0.60, P = 0.0003) [11]. A meta-analysis of ten studies with 1815 ovarian cancer patients confirmed the observation that a lack of intraepithelial lymphocytes (TILs) is significantly associated with a worse survival among ovarian cancer patients [13]. Together, these studies support the notion that tumor infiltration by lymphocytes is a reflection of a tumor-related immune response. An international working group has set up recommendations to implement evaluation of tumor infiltrating lymphocytes (TILs) into clinical settings by determining TIL density in the stromal compartment of the tumor [4,5].

2.2. Immune gene signatures

Over the last years, transcriptomic analysis has led to the identification of numerous immune-based gene expression signatures. So far, most studies have used expression data from bulk tumors (including both tumor and stromal compartments) as a starting point for their analyses due to the high feasibility of this approach as well as the wide availability of public data repositories derived from bulk tumor samples. In a large-scale cross-platform study of six microarray data sets consisting of 1054 ovarian cancer patients, authors developed a gene expression signature for predicting overall survival by applying elastic net and 10-fold cross-validation to a Japanese data set A and evaluated the signature in five other data sets [14]. They also investigated differences in the biological characteristics between high- and low-risk ovarian cancer groups. In this study authors identified a 126-gene expression signature for predicting overall survival in patients with ovarian cancer. The gene signature has been validated for its predictive ability with five other data sets using multivariate analysis. Through gene ontology and pathway analyses, they identified a significant reduction in expression of immune-response-related genes, especially on the antigen presentation pathway, in high-risk ovarian cancer patients [14].

Other immune gene signatures have been published in the context of ovarian cancers. Although tumor-associated macrophages (TAMs) are essential for cancer progression, connections between different clinical outcomes and transcriptional networks have not been reported. In a study authors have addressed this issue by analyzing global expression patterns of TAMs isolated from the ascites of ovarian cancer patients [15]. TAMs isolated from different ovarian cancer patients can be stratified by coexpression or principal component analysis into subgroups with specific biological features and associated with distinct clinical outcomes. A hallmark of subgroup A was a high expression of clinically unfavorable markers, including (i) high CD163 expression, a surface receptor characteristic of an anti-inflammatory activation state, (ii) increased PCOLCE2 expression, indicative of enhanced extracellular matrix organization, and (iii) elevated ascites levels of IL-6 and IL-10, linked to the aggressiveness of ovarian cancer and immune suppression. In contrast, subgroup B TAMs are characterized by the upregulation of genes linked to immune defense mechanisms and interferon (IFN) signaling. Intriguingly, analysis of published data for 1763 ovarian cancer patients revealed a strong association of this transcriptional signature with a longer overall survival [16]. Consistent with these results, IFNγ was able to abrogate the suppressive effect of ovarian cancer ascites on the inducibility of IL12B expression and IL-12 secretion, a key determinant of a cytotoxic immune response. Also in this study was quite clear that the survival of ovarian cancer patients is linked to the presence of TAMs with a transcriptional signature that is characterized by a low expression of protumorigenic and immunosuppressive markers and an upregulation of genes linked to interferon signaling. Approximately 50% of high grade serous ovarian cancers (HGSOCs) harbor genetic and epigenetic alterations in gene members of the homologous recombination (HR) DNA repair pathway, most commonly in BRCA1 and BRCA2 genes [16,17]. BRCA1/2-mutation status is a favorable prognostic factor in this disease, which may be traditionally thought to be primarily due to the enhanced responsiveness of BRCA1/2-mutated tumors to platinum-based chemotherapy [18]. However, it is possible that alternative intrinsic biologic properties of BRCA1/2-mutated HGSOCs (e.g., increased immunogenicity) contribute to the improved outcomes observed in these patients. In this regard, it has been shown that HR deficient HGSOCs (including those with BRCA1/2-mutations) depend on alternative, low fidelity mechanisms for double-strand break (DSB) repair, such as the Polθ/PARP1-mediated alternative end-joining (alt-EJ) pathway [19]. DSB repair via alt-EJ utilizes microhomology at rearrangement junctions to rejoin DSBs and is mediated by the error-prone Polθ polymerase, which produces point mutations as well as random insertions and deletions (indels) at sites of microhomology [20]. Not surprisingly, BRCA1/2-mutated HGSOCs have been shown to possess a higher number of mutations compared to non-BRCA1/2-mutated tumors [21], with an elevated number of larger indels (up to 50 bp) with overlapping microhomology at breakpoint junctions [22]. Given their higher mutational load and unique mutational signature, in one study has been hypothesized that BRCA1/2-mutated tumors may harbor more tumor-specific neoantigens, and, therefore, increased tumor-infiltrating lymphocytes (TILs) as well as demonstrate increased expression of the immune checkpoint modulators, PD-1 and PD-L1. In this study, authors formally evaluated the association of BRCA1/2-mutation status with neoantigen load, number of TILs and expression of PD-1 and PD-L1 in HGSOC [23]. Furthermore, given that both BRCA1/2-mutation status and number of TILs are known favorable prognostic factors in this disease, authors also assessed whether BRCA1/2-mutated HGSOCs are independently associated with survival after adjusting for neoantigen load or number of TILs. In this study authors reported significantly higher predicted neoantigens in BRCA1/2-mutated tumors compared to tumors without alterations in homologous recombination (HR) genes (HR-proficient tumors). Tumors with higher neoantigen load were associated with improved overall survival and higher expression of immune genes associated with tumor cytotoxicity such as genes of the TCR, the IFN-gamma and the TNFR pathways. Furthermore, immunohistochemistry studies demonstrated that BRCA1/2-mutated tumors exhibited significantly increased CD3+ and CD8 + TILs, as well as elevated expression of PD-1 and PD-L1 in tumor-associated immune cells compared to HR-proficient tumors. Survival analysis showed that both BRCA1/2-mutation status and number of TILs were independently associated with outcome. Of note, two distinct groups of HGSOCs, one with very poor prognosis (HR proficient with low number of TILs) and one with very good prognosis (BRCA1/2-mutated tumors with high number of TILs) were defined. These findings support a link between BRCA1/2-mutation status, immunogenicity and survival, and suggesting that BRCA1/2-mutated HGSOCs may be more sensitive to PD-1/PD-L1 inhibitors compared to HR-proficient HGSOCs.

2.3. Tumor infiltrating lymphocytes in cervical cancer

The detection of significant numbers of tumor-infiltrating lymphocytes [TIL] in cervical carcinoma tissues underlines the importance of cell mediated immune response in this malignancy [24]. Bethwaite et al. found an association among low density of TIL, risk of pelvic