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Review

Breast cancer genomics and immuno-oncological markers to guide immune therapies

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ABSTRACT

There is an increasing awareness of the importance of tumor – immune cell interactions to the evolution and therapy responses of breast cancer (BC). Not surprisingly, numerous studies are currently assessing the clinical value of immune modulation for BC patients. However, till now durable clinical responses are only rarely observed. It is important to realize that BC is a heterogeneous disease comprising several histological and molecular subtypes, which cannot be expected to be equally immunogenic and therefore not equally sensitive to single immune therapies. Here we review the characteristics of infiltrating leukocytes in healthy and malignant breast tissue, the prognostic and predictive values of immune cell subsets across different BC subtypes and the various existing immune evasive mechanisms. Furthermore, we describe the presence of certain groups of antigens as putative targets for treatment, evaluate the outcomes of current clinical immunotherapy trials, and finally, we propose a strategy to better implement immuno-oncological markers to guide future immune therapies in BC.

1. Introduction

Cancer immunotherapy is a rapidly emerging field, which has proven successful in the treatment of various tumor types, such as lymphoma, melanoma, renal cell carcinoma, and non-small cell lung cancer [1]. Initially, breast cancer (BC) has been considered a poorly immunogenic tumor type and has therefore not been extensively investigated for its susceptibility to immune therapies. During the past years, however, it became evident that certain cases of BC are strongly infiltrated by immune cells and that the presence of these immune cells has significant prognostic and predictive value. Although many studies are currently examining immune therapies for BC, still only a minority of patients appear to respond, and little is known about the underlying mechanisms of treatment efficacy. Thus, there is an unmet need to get better understanding of the interaction of breast cancer and the immune system in order to identify potential immuno-oncological prognostic and predictive markers as well as novel leads for effective mono or combination immune therapies.

Genomics has improved our understanding of BC biology and revealed 4 intrinsic molecular subtypes: luminal A (resembling the histological phenotype: ER+, PR+, HER2-, Ki67-), luminal B (ER+, PR+, HER+/−, Ki67+), HER2 (ER-, PR-, HER2+), and basal-like subtype (ER-, PR-, HER2-). The classification of BC into subtypes bears clinical relevance. For instance, in the treatment of the hormone receptor (HR) positive subtypes (those that are positive for ER and/or PR) endocrine therapy, including aromatase inhibitors or selective estrogen receptor mediators such as Tamoxifen, play an important role. HER2 over-expressing tumors are generally treated with HER2-targeting drugs such

Abbreviations: APC, antigen presenting cell; APOBEC, apolipoprotein B mRNA editing enzyme catalytic polypeptide-like; BRCA1/2, breast cancer 1/2; BCSS, breast cancer specific survival; B2M, β-2-microglobulin; CAF, cancer associated fibroblast; CCL, chemokine ligand; CD, cluster of differentiation; CMV, cytomegalo virus; CTLA4, cytotoxic T lymphocyte associated protein 4; CR, Complete response; CXCL, CXC-motif chemokine ligand; DC, dendritic cell; DCIS, ductal carcinoma in situ; DFS, disease free survival; EBV, epstein-barr virus; ECM, extracellular matrix; ELF5, E75 like ETS transcription factor 5; EMT, epithelial − mesenchymal transition; GBP1, interferone induced guanylate binding protein 1; GRZM, granzyme; H & E, hematoxylin and eosin; HER2, human epidermal growth factor receptor 2; HERV-K, human endogenous retrovirus K; HLA, human leucocyte antigen; HPV, human papiloma virus; HR, hormone receptor or hazard ratio; hTERT, telomerase reverse transcriptase; IDC, invasive ductal carcinoma; IDO1, indoleamine-pyrrole 2,3-dioxygenase; IFN, interferon; IGK, immunoglobin kappa locus; IGLL5, immunoglobin lambda like polypeptide 5; JAK1/2, Janus kinase 1/2; LAG3, lymphocyte activation gene 3; MDSC, myeloid derived suppressor cell; MEK, map kinase kinase; MFS, metastasis free survival; MHC, major histocompatibility complex; MMTV, mouse mammary tumor virus; MUC1, mucin 1; MV, measles virus; NK, natural killer cell; NO, nitric oxide; OCLN, occludin; OR, objective response or odds ratio; OS, overall survival; PC, plasma cell; PD1, programmed cell death protein 1; PDL1, programmed death ligand; PI3K, phosphoinositol 3-kinase; PR, progesteron receptor; PTEN, phosphatase and tensin homolog; RFS, relapse-free survival; ROS, reactive oxygen species; SD, stable disease; STAT1, signal transducer and activator of transcription 1; TAA, tumor associated antigen; TAP, transport associated protein; TIL, tumor infiltrating leukocytes; TLS, tertiary lymphoid structures; TGFB, transforming growth factor beta; TNBC, triple negative breast cancer; TNFa, tumor necrosis factor alpha; Treg, Regulatory T cell; Tγδ, gamma delta T cell

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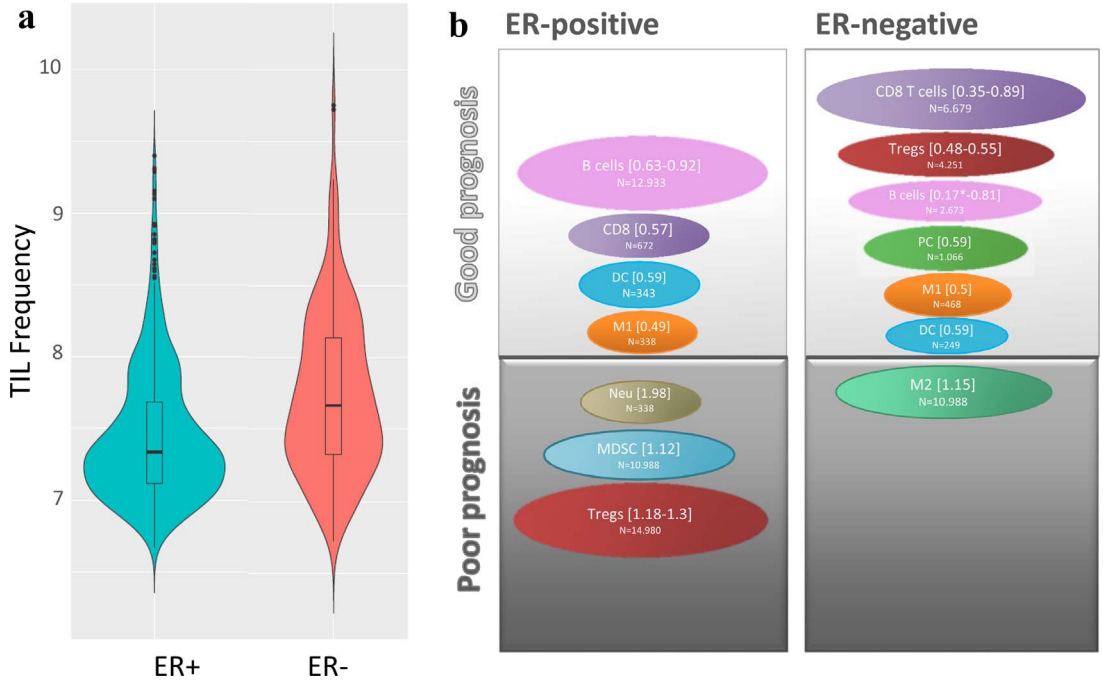

Fig. 1. TIL frequencies and prognosis in ER+ and ER- BC: Violin plots based on average RNA expression of TIL gene signature [> 100 leukocyte related genes, manuscript in preperation] on a log scale, per patient based on ER-status. (Data from NCBI's Gene Expression Omnibus, accessions GSE2034, GSE5327, GSE2990, GSE7390 and GSE11121.) (A). Leukocyte subsets which are significantly correlated ($p < 0.05$) with overall survival, or metastasis free survival (*), in ER+ and ER- tumors. Hazard ratios of multivariant regression analyses are shown between brackets [HR]. Circle sizes are indicative of cohort-size (N), based on numbers of patients evaluated in one or more studies [15, 20–23, 26–46] . Studies include gene expression based analysis, immunohistochemistry and/or flow cytometry (B).

as trastuzumab and pertuzumab, whereas triple negative BC (TNBC, largely resembling the basal-like BC subtype) is mostly treated with standard cytotoxic therapies.

Notably, and the focus of the current review, these molecular subtypes also differ with respect to quantity and composition of tumor infiltrating leukocytes (TILs). In BC, an enormous number of studies have been performed in order to evaluate the prognostic and predictive values of TILs, and their specific subsets. Although mononuclear cells can easily be identified by H & E-stainings upon routine diagnostics, this technique does not allow accurate assessment of different immune subsets. Immune stainings have enabled the phenotypic distinction of various cell types, but are often limited to those markers for which well-characterized antibodies are available. Recent advances in immunogenomics have paved the way towards enhanced understanding of specific immune subsets and their interactions with tumor cells based on gene expression data [2–5]. In addition, emerging DNA sequencing data has made it possible to explore mutational landscapes of BC and investigate their relationship with TILs and immune pathways. Here, we discuss TIL profiles, prognosis and prediction based on TIL subsets, antigenicity, immune evasive mechanisms, and current immunotherapy trials. Finally, we propose a strategy to select and implement immune-oncological markers to improve therapy choices for BC patients.

2. Normal breast versus (pre)malignant breast tissues: quantity and quality of TILs

2.1. Normal breast tissue

Immune cells in the healthy mammary gland form an active and dynamic barrier against microbes in the mucosal layer [6]. In addition, immune cells take part in mammary gland remodeling and are considered to play a role in cancer immune surveillance [7]. In normal breast tissue, one generally finds low numbers of leukocytes, including T cells (typically expressing the markers CD3, CD4 or CD3, CD8), B cells (CD20), macrophages (CD68) and dendritic cells (CD11c) [6]. These immune cells are not found in interlobular stroma but are restricted to the lobules, where T cells directly associate with the epithelial layer [8]. While frequencies of macrophages and CD4 T cells are rather constant, frequencies of CD8 T cells depend on hormonal changes and peak within the luteal phase of the menstrual cycle, coinciding with epithelial cell turnover [9].

2.2. Pre-malignant breast tissue

BC formation is a multistep process, including premalignant stages of hyperplasia and ductal carcinoma in situ (DCIS) and the malignant stage of invasive ductal carcinoma (IDC) [10]. The transition from normal breast tissue to malignancy is typically accompanied by an increased infiltration of leukocytes, including myeloid cells, B cells and cytotoxic CD8 T cells [8]. First, in premalignant DCIS, an increased lymphocytic infiltration is observed [11], which is significantly higher in HER2+ and TN DCIS compared to HR+ DCIS [12]. In DCIS, numbers of neutrophils are significantly increased compared to normal tissue, however in this tumor stage activated T cells represent the dominant lymphocyte population [13], followed by B cells and the immune suppressive regulatory T cells (Tregs: CD4, CD25, FOXP3) [14]. While in normal and premalignant BC the CD4/CD8 T cell-ratio is approximately 2, in IDC this ratio is shifted towards 0.3 [15,16].

2.3. Malignant breast tissue

A common feature in IDC is a high overall quantity of TILs. Interestingly, high lymphocytic numbers relate to better prognosis and predict a favorable response to neo-adjuvant chemotherapy [17–19] (see also Sections 3 and 4). In fact, in highly inflamed tumors, TIL frequency was found to be a superior prognostic marker in comparison to HR status and lymph node involvement in patients with primary operable BC [15]. Notably, characteristics of TILs vary across molecular subtypes of BC [20,21]. The frequency of TILs is usually high in the more aggressive types of BC, including the ER- subtypes (HER2 and