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Review Article

Immune evasion and resistance in breast cancer

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Abstract: Breast cancer (BC) is the most common malignancy in females with an increasing incidence in the last decade. The previously observed decline in BC mortality rates has also slowed down recently with an increase in the incidence of invasive BC. BC has various molecular subtypes. Among these subtypes, triple-negative breast cancer (TNBC) represents the most aggressive BC, with a poor prognosis. Because lack of the hormonal or human epidermal growth factor receptor 2 (HER2) receptors, TNBC is resistant to hormonal and HER2 targeted therapy effective for other BC subtypes. The good news is that TNBC has recently been considered an immunologically 'hot' tumor. Therefore, immunotherapy, particularly immune checkpoint inhibitor therapy, represents a promising therapeutic approach TNBC. However, a considerable percentage of patients with TNBC do not respond well to immunotherapy, indicating that TNBC seems to adopt several mechanisms to evade immune surveillance. Thus, it is crucial to investigate the mechanisms underlying TNBC immune evasion and resistance to immunotherapy. In this review, we examine and discuss the most recently discovered mechanisms for BC, with a particular focus on TNBC, to evade the immune surveillance via kidnapping the immune checkpoints, suppressing the immune responses in tumor microenvironment and inhibiting the tumor antigen presentation. Evaluation of these mechanisms in BC will hopefully guide future immunotherapeutic research and clinical trials.

Keywords: Breast cancer, immune evasion, immune privilege, immune resistance

Introduction

Breast cancer (BC) remains a painful clinical challenge. It is estimated that 1 in every 8 women will be diagnosed with BC. BC currently ranks as the most common cancer in females constituting 31% of all reported malignancies in women. Furthermore, BC is the second most common cause of cancer deaths among women, surpassed only by lung cancer; with an estimated 43,170 BC deaths among females in the United States alone [1]. In recent decades, advancements in treatment modalities and screening programs have dramatically improved BC management, and resulted in a decline in its mortality rates, with an overall 43% reduction by 2020. Despite these advancements, however, the reduction in breast cancer mortality has shown a recent downward trend [1].

BC can be classified into various subtypes based on certain molecular characteristics. These subtypes provide insights into the behavior of the tumor and hence the suitable treatment modality for each specific subtype [2]. First, estrogen receptor (ER) and/or progesterone receptor (PR) positive (also known as Luminal A) BC, exhibits a low proliferation rate and a favorable prognosis [2]. The second subtype, known as luminal B, is also ER and/or PR positive but often exhibits higher proliferation rates and may have a less favorable prognosis [3]. The third subtype is the human epidermal growth factor receptor 2 positive ($HER2^+$), characteristic of overexpression of the HER2 receptor that contributes to the aggressive growth of the tumor [3]. Targeted therapies such as HER2 inhibitors have greatly improved outcomes for patients with this subtype [3]. However, the most aggressive subtype, the triple-negative breast cancer (TNBC), lacks expression of ER, PR, and HER2 receptors, and accounts for as many as 15% of invasive BC cases [4]. Thus, TNBC is resistant to the otherwise effective endocrine or hormonal therapy targeting the hormone receptors and HER2 targeted therapy that benefit patients with the other BC sub-

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types. The limited treatment options make TNBC to be more aggressive and poorly prognostic, highlighting the need for novel therapeutic approaches [5].

Immune evasion was first described on discovery of immune privilege. Immune privilege is a phenomenon that some critical tissues such as the brain and testis allow only very low immunity in them, or evade immune surveillance, to avoid accidental autoimmune destruction of the very important cells in them [6]. The concept of immune privilege originally referred to "immune privileged sites" that are specific anatomic sites with structural barriers that restrict immune surveillance by mainly excluding T cells, such as the blood-brain barrier and the trophoblast layer in the placenta [7]. However, it now extends to other tissues and broader biological contexts, such as the tumor microenvironment (TME). Tumors, such as TNBC, are able to establish immune privileged TME by several mechanisms. This allows the tumors to evade immune detection and destruction, and is also referred to as "acquired immune privilege" [8]. Acquired immune privilege involves mechanisms that modulate immune responses that create a protective niche to shield tumors from immune surveillance and attack [9, 10]. Simply speaking, immune privilege takes place by minimizing the activity of patrolling immune cells such as cytotoxic T lymphocytes (CTLs) by preventing the cell recruitment such as T cell exclusion and/or by suppressing the cells already recruited using immunosuppressive cells and factors including the immune checkpoint molecules [11]. In this regard, immune privilege concept is now considered a relative rather than an absolute state of tissues [12]. This might explain the differences in immune responses of different tumors, or different phenotypes of the same tumor (e.g., TNBC patients respond differently to ICI). It has been widely accepted that the anatomic barriers are an important contributor to immune privilege although immune privilege can also happen to certain tissues that lack such structural barriers [6].

Immunotherapy in general works by enhancing immune response in tumor. Many types of tumors kidnap the immune privilege mechanisms to evade immune surveillance. Therefore, immunotherapy typically supplies more tumor killing cells to the tumor, such as the cancer/chimeric antigen receptor T (CAR-T) cell therapy, or activates tumor killing cells that are suppressed albeit already present inside tumor, such as the immune checkpoint inhibitor (ICI) therapy [11]. Some types of cancer such as melanoma respond incredibly well to immunotherapy, and thus are defined to be immunologically "hot". However, other types of cancer do not respond well to immunotherapy and thus are called immunologically "cold", immune privileged or immune resistant.

BC is among a few types of cancer that are immunologically "cold" and thus do not respond well to immunotherapy [13]. Unlike all the other BC subtypes, however, TNBC shows a relatively increased immunogenic properties and thus represents immunologically "hot" cancer, a hopeful target of immunotherapy [14]. Indeed, excitingly, the Food and Drug Administration (FDA) has recently approved pembrolizumab (an ICI antibody) to treat certain patients with the 16 different cancer types including TNBC [15]. Unfortunately, however, only a small subset of patients with TNBC show a good response to immunotherapy [16]. Some TNBC tumors resist to ICI therapy due to genetic and molecular mutations resulting in "cold" TME [17]. For example, a subset of TNBC tumors was found to have less programmed death-ligand 1 (PD-L1) expression. These patients showed poor response to an ICI therapy targeting PD-L1 [18]. A multi-omics study suggests that TNBC tumors might adopt several mechanisms for transforming the TME into a privileged site to evade immune surveillance and attack [19].

Mechanisms underlying immune evasion and resistance in BC, including TNBC remain largely unclear. Identifying molecular and cellular targets is thus imperative to enhance patient response to immunotherapy. Thus, in this review, we highlight the potential mechanisms by which BC is transformed into an immune-privileged site, evades immune surveillance, and becomes resistant to immune therapy, with particular focus on immune checkpoints, TME, and tumor antigen presentation in TNBC [17, 20, 21] as outlined in **Figure 1** and **Tables 1**, **2** and detailed below.

Upregulation of inhibitory immune checkpoints

Immune checkpoints are a mechanism of regulating immune responses and immune toler-

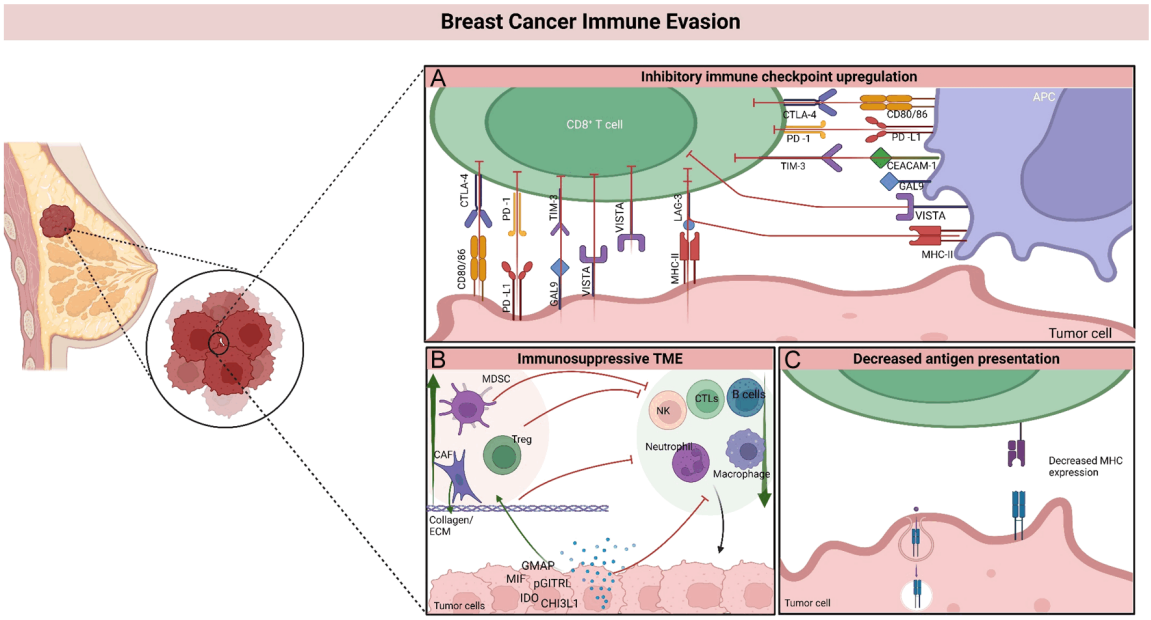

Figure 1. BC immune evasion mechanisms. Tumor can evade immune surveillance through various mechanisms including (A) kidnapping immune checkpoints such as PD-1 thereby inhibiting cytotoxic CD8$^+$ T cells, (B) creating immunosuppressive TME, and (C) decreasing tumor antigen presentation to tumor killing cells such as CD8$^+$ T cells. Abbreviations: APC, Antigen presenting cell; ECM, Extracellular matrix; CHI3L1, chitinase-3-like protein 1; CTL, Cytotoxic T lymphocytes; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; GMAP, galanin message-associated peptide; IDO, Indoleamine-pyrrole 2,3-dioxygenase; MIF, macrophage migration inhibitory factor; NK, Natural killer cells; PD-1, Programmed death-1; PD-L1, Programmed death-Ligand 1; pGITRL, platelet-derived glucocorticoid-Induced TNFR-Related protein ligand; Treg, regulatory T cells; MDSC, myeloid-derived suppressor cells; MHC, Major histocompatibility complex; TIM-3, T cell immunoglobulin and mucin-domain containing-3; TME, Tumor microenvironment; VISTA, V-domain Ig suppressor of T cell activation; LAG-3, Lymphocyte-activation gene 3.

ance, either by interaction of immune stimulatory or inhibitory receptor on immune cells with ligand presented from antigen-presenting cells (APCs). Known inhibitory immune checkpoints include receptor/ligand pairs which normally in physiological conditions function to maintain homeostasis, regulate immune response and prevent the immune system from attacking normal tissues by sending inhibitory signals to the effector immune cells. Cancer cells can kidnap this function of APCs by expressing and presenting the checkpoint ligands to suppress the tumor killing effector immune cells, particularly the CD8$^+$ T lymphocytes expressing the checkpoint receptors. Importantly, this kidnapping often involves changes in expression of both the checkpoint ligands on the cancer cells as well as the checkpoint receptors on the immune cells with the TME. Among the most widely studied inhibitory immune checkpoints are the programmed cell death protein 1 (PD-1, also known as CD279, receptor)/programmed death-ligand 1 (PD-L1, also known as CD274, ligand) and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4, also known as CD152, receptor)/CD80/86 (also known as B7-1/2, ligand) (**Figure 1A**; **Table 1**).

PD-1/PD-L1 immune checkpoint. PD-1 receptor is expressed on the T cell surface, binds to PD-L1 ligand on APCs surface. This binding represents a mechanism of both central and peripheral immune tolerance that suppresses the T cell activity and prevents autoimmune damage of the APCs by the T cell. However, tumor cells can kidnap this mechanism to suppress the T cell immune response to antigen-presenting tumor cell leading to immune evasion [22, 23]. Indeed, TNBC cells express higher levels of PD-L1 than other BC subtypes do [24].

BC cells use several molecular mechanisms involving many factors to upregulate expression of PD-L1 and other immune checkpoint genes to evade immune surveillance (**Figure 1A**; **Table 1**). For instance, annexin A1 (ANXA1), an anti-inflammatory factor, shows higher

Table 1. Factor affecting the expression of immune checkpoints in BC

CP	Effector	Effect	Reference	CP	Effector	Effect	Reference
PD-L1 Expression	ANXA1	+	[26]	PD-L1 Stability	HuR	+	[28]
	Crk	+	[46]		TF-VIIa	+	[30]
	CDK8	+	[53]		GATA3-AS1	+	[37]
	MYC	+	[48, 60]		A11 peptide	-	[27]
		-	[47]				
	ICAM1	+	[50]	PD-1	ICAM1	+	[50, 51]
	GBP5	+	[156]		Crk	-	[46]
	TNFR2	+	[54]		SLC27A2	+	[36]
	TF-VIIa	+	[30]		KLRB1		
	RBMS3	+	[31]		IGHV1-12		
	AKT/mTOR/BTK	+	[33]		IGKV1OR2-108		
	ASPH	+	[34]		Lgals2	+	[77]
					PXDNL	+	[36]
	SLC27A2	-	[36]	CTLA-4	LINC02038		
	KLRB1				MYC	+	[48]
	IGHV1-12				ICAM1	+	[50, 51]
	IGKV1OR2-108						
	Doxorubicin, Abemaciclib, and Dactolisib	+	[42]		GAL	-	[52]
	Anthracycline and taxane	+	[43]		TNFR2	+	[54]
	MDR1	+	[44]		SLC27A2	+	[36]
	BRD4	+	[45]		KLRB1		
	MUC1	+	[49]		IGHV1-12		
	NLRP3	+	[123]		IGKV1OR2-108		
					Chi3l1	+	[60]
	GAL	-	[52]		PXDNL	+	[36]
	ZNF652	-	[29]		LINC02038		
	DMAS	-	[32]	TIM-3	Neoadjuvant chemotherapy	+	[75]
					Lgals2	+	[77]
	GPR81	-	[35]	TIGIT	MYC	+	[48]
	PXDNL	-	[36]		BIRC2	+	[81]
	LINC02038				TNFR2	+	[54]
	miR-195	-	[38]		GAL	-	[52]
	miR-497			GAL-9	Anthracycline and taxane	+	[43]
	miR-4759	-	[39]	LAG-3	MYC	+	[48]
	p53- miR-34a	-	[40]		BIRC2	+	[81]
	Estrogen	-	[41]		TNFR2	+	[54]
	Corticosteroids				Neoadjuvant chemotherapy	-	[75]
	JAK1/2 inhibitors						

(+) indicates a positive association/effect, (-) indicates a negative association. Akt, serine/threonine kinase; ANXA1, annexin A1; ASPH, aspartate β-hydroxylase; BIRC2, Baculoviral IAP Repeat Containing 2; BRD4, bromodomain-containing protein 4; CDK8, cyclin-dependent kinase 8; CP, Checkpoint; DMAS, β, β-Dimethylacrylshikonin; GAL, Galanin And GMAP Prepropeptide gene; GBP5, guanylate binding protein 5; GPR81, G protein-coupled receptor 81; ICAM1, intercellular adhesion molecule 1; IDO-1, indoleamine 2,3-dioxygenase 1; KLRB1, killer cell lectin like receptor B1; MDR1, multidrug resistance 1; mTOR, mammalian target of rapamycin; MUC1, mucin 1; MYC, myelocytomatosis oncogene; RBMS3, RNA binding motif, single-stranded interacting protein 3; TNRF, tumor necrosis factor receptor 2; TF, tissue factor.

expression in TNBC compared to luminal subtypes [25]. ANXA1 was found to upregulate PD-L1 expression via the signal transducer and activator of transcription 3 (STAT3) [26]. On the other hand, the ANXA1-derived peptide A11 was found to decrease PD-L1 stability by competing with the de-ubiquitinase of PD-L1, USP7, thereby exhibiting anti-tumor effects [27]. The human antigen R (HuR) was found to be overexpressed in BC [28]. This RNA-binding protein directly binds to 3'-UTR of PD-L1 mRNA and stabilizes the PD-L1 protein by regulating its glycosylation. A study shows that the FDA-approved HuR inhibitor drug niclosamide can potentially improve TNBC response to ICIs [28]. Another study indicated that the zinc-finger protein 652 (ZNF652) downregulates PD-L1 expression. Loss of ZNF652 observed in TNBC enhances PD-L1 mediated immune evasion [29]. Tissue factor VIIa (TF-VIIa) activates prote-

Table 2. Factors affecting the tumor microenvironment and antigen presenting machinery in BC

Cell type	Effector	Effect	Reference	Cell type	Effector	Effect	Reference
$CD8^+$ T cells	Crk	↓ (infiltration + toxicity)	[46]	B cells	KLRB1	↑	[36, 105]
					IGKV1OR2-108		
					IGHV1-12		
					SLC27A2	↓	
					PXDNL		
					LINC02038		
	Chi3l1	↓ (infiltration + toxicity)	[99]		MUC1	↓ infiltration and function	[97]
	CypA-Crk	↓	[104]		PI3K	↓	[108]
	KLRB1	↑	[36, 105]		MYC	↓	[47]
	IGKV1OR2-108						
	IGHV1-12						
	SLC27A2	↓					
	PXDNL						
	MUC1	↓ (infiltration + toxicity)	[49, 97]		ICAM1	↑	[50]
	MYC	↓	[47, 96, 147]		JMJD8	↓	[112]
	PI3K	↓	[109]		GAL	↓	[52]
		↓	[108]	NK cells	CDK8	↓	[53]
	ICAM1	↑ toxicity	[51]		KLRB1	↑	[36]
					IGKV1OR2-108		
					IGHV1-12		
					LINC02038	↓	
		↑	[50]		MYC	↓	[47, 147]
	JMJD8	↓	[112]		ICAM1	↑	[51]
	RGS1	↓	[113]		BTF3	↓	[139]
	MIF	↓	[117]		BIRC2	↓	[81]
	GAL	↓	[52]		IDO-1	↓ cytotoxicity	[140]
	BIRC2	↓ (infiltration + toxicity)	[81]		NLRP3	↓	[123]
	Lgals2-CSF1	↓ (infiltration + toxicity)	[77]		Mertk	↓	[102]
	TF	↓ (infiltration + toxicity)	[121]		Lgals2-CSF1	↓ toxicity	[77]
	LXR	↓ Toxicity	[122]	Macrophages	Crk	↓	[46, 104]
	NLRP3	↓	[123]		KLRB1	↑ M1, ↓ M2	[36, 105]
					IGKV1OR2-108		
					IGHV1-12		
					SLC27A2	↓	
					LINC02038		
	FGFR	↓	[124]		MUC1	↓	[97]
	Axl/Mertk	↓	[102]		PI3K	↓	[108]
	LOx	↓	[106]		MYC	↓	[47, 147]
	Jagged1	↓ (infiltration + toxicity)	[125]		ICAM1	↑ M1	[50, 51]
	MAL2	↓ toxicity	[127]				
	SOX4	↓ toxicity	[128]		JMJD8	↓	[112]
	ZNF652	↑	[29]		MIF	↓ M1	[117]
	miR-4759	↑	[39]		MP	↓ functionality	[143]
$CD4^+$ T cells	Chi3l1	↓	[99]		Cop1	↓	[144]
	KLRB1	↑	[36, 105]		Chi3l1	↓ M1, ↑ M2	[99]
	IGKV1OR2-108						
	IGHV1-12						
	SLC27A2	↓					
	PXDNL						
	LINC02038						
	MUC1	↓	[97]		CD24-Siglec-10	↑ M2	[142]
	MYC	↓	[47]		Lgals2-CSF1	↑ M2	[77]
	PI3K	↓	[108]		LXR	↑ M2	[122]
	PI3Kβ	↓	[110]		FGFR1	↓ M1, ↑M2	[124]

	ICAM	↑	[50]		Mertk	↓	[102]
	JMJD8	↓	[112]		Jagged1	↑ TAM	[125]
	RGS1	↓	[113]				
	MIF	↓	[117]	Neutrophils	Crk	↓	[46]
					KLRB1	↑	[36, 105]
					IGKV1OR2-108		
					IGHV1-12		
	Chi3l1	↓	[99]		MYC	↓	[47, 147]
	DDR1	↓	[119, 120]		ICAM	↑	[50]
	FGFR	↓	[124]		JMJD8	↓	[112]
	TF	↓ infiltration and activity	[121]		MIF	↑	[117]
	LXR	↓ differentiation	[122]		Chi3l1	↑ infiltration and NETosis	[99]
Regulatory T cells	KLRB1	↑	[36]		Mertk	↓	[102]
	IGKV1OR2-108						
	IGHV1-12						
	SLC27A2	↓					
	PXDNL						
	LINC02038						
	PI3Kδ	↑	[135]	Dendritic cells	CypA-Crk	↓	[104]
	ICAM	↑	[51]		KLRB1	↓	[105]
	MIF	↑	[117]			↑	[36]
					IGKV1OR2-108	↑	
					IGHV1-12		
					SLC27A2	↓	
					LINC02038		
	Lgals2-CSF1	↑	[77]		MYC	↓	[47]
	LXR	↑	[122]		ICAM	↑	[50]
	Acidity	↑	[106]		JMJD8	↓	[112]
	ANXA1	↑	[25]		GAL	↓	[52]
	SRC3	↑	[134]		BIRC2	↓	[81]
CAFs	FGFR	↑	[124]	MDSC	PIK3CA^{mut}	↑	[109]
	MRC2	↑	[126]		NLRP3	↑	[123]
					FGFR	↑	[124]
Antigen presenting machinery (MHC-I)							
	SOX4	↓	[128]		CDK8	↑ expression	[53]
	MYC	↓ expression	[47]		MAL2	↓	[127]

(↑) indicates increased and (↓) indicates decreased TME infiltration. A11, ANXA1 derived peptide; ASPH, aspartate β-hydroxylase; BIRC2, Baculoviral IAP Repeat Containing 2; BRD4, bromodomain-containing protein 4; CAF, cancer associated fibroblast; CDK8, cyclin-dependent kinase 8; Chi3l1, chitinase-3-like1; COP1, constitutive photomorphogenesis 1; CSF1, colony Stimulating Factor 1; DDR1, discoidin domain receptor 1; FGFR, Fibroblast growth factor receptor; GAL, Galanin And GMAP Prepropeptide gene; ICAM1, intercellular adhesion molecule 1; JMJD3, jumonji domain-containing protein-3; KLRB1, killer cell lectin like receptor B1; LXR, liver X receptor; MAL2, myelin and lymphocyte protein 2; MDR1, multidrug resistance protein 1; MerTK, Mer tyrosine kinase; MHC-I, major histocompatibility complex; MIF, macrophage migration inhibitory factor; MP, microparticles; Mrc2, mannose receptor, C type 2; MUC1, mucin 1; MYC, myelocytomatosis oncogene; NK, natural killer; NLRP3, NLR family pyrin domain containing 3; PI3K, phosphoinositide 3-kinases; RBMS3, RNA binding motif, single-stranded interacting protein 3; RGS1, regulator of G-protein signaling 1; Siglec-10, sialic Acid Binding Ig Like Lectin 10; SOX4, SRY-related HMG-box-4; SRC3, steroid receptor coactovator-3; TAM, tumor associated macrophages; TAN, tumor associated neutrophils; TF, tissue factor.

ase-activated receptor 2 (PAR2). PAR2 signaling mediates tumor immune evasion by both enhancing PD-L1 expression and stabilizing PD-L1 protein via glycosylation in BC cells [30]. Similarly, the RNA binding motif, single-stranded interacting protein 3 (RBMS3) was also found to enhance PD-L1 expression in TNBC by binding to the 3'UTR of PD-L1 mRNA and stabilizing it [31]. Some natural compounds might exhibit therapeutic potential in BC by modulating PD-L1 expression. For instance, β, β-Dimethylacrylshikonin (DMAS), an active compound extracted from Comfrey root, exhibits antitumor activity by inhibiting the Y705 phosphorylation and thus activity of STAT3 and subsequent downregulation of PD-L1 in TNBC [32]. Similarly, activation of STAT3 appears to mediate PD-L1 upregulation by the protein kinase B (Akt), mammalian target of rapamycin (mTOR), and Bruton's tyrosine kinase (BTK) signaling pathways [33].

Additionally, overexpression of aspartate β-hydroxylase (ASPH) found in many tumors includ-

ing BC, has been found to affect tumor immune response mainly by upregulating PD-L1 expression and thus mediating immune evasion [34]. The lactate receptor GPR81, a PD-L1 downregulator, is found less expressed in BC which contributes to immune evasion [35]. A TME-related prognostic signature recently identified in immunosuppressive BC TME indicates that the upregulation of the peroxidasin like (PXDNL) gene and downregulation of the solute carrier family 27 member 2 (SLC27A2), killer cell lectin like receptor B1 (KLRB1), immunoglobulin heavy variable 1-12 (IGHV1-12), and immunoglobulin kappa variable 1/OR2-108 (IGKV1OR2-108) genes contributed to immune evasion via modulating the expression of several immune checkpoints including PD-1, PD-L1, and CTLA-4 [36]. This study also identified the long noncoding RNA (lncRNA) 2038 (LINC02038) upregulation to be a contributor to the immunosuppressive TME [36]. In addition, other lncRNAs and microRNAs (miRNAs) also play a significant role in BC immune evasion. In TNBC, the lncRNA, GATA3-AS1, is upregulated and mediates immune evasion through deubiquitinating and stabilizing PD-L1 protein [37]. Several miRNAs including miR-195/miR-497 [38], miR-4759 [39], and miR-34a [40] have been shown to be a negative regulator of PD-L1 expression and their downregulation in TNBC contributes to immune evasion.

Some non-immunological anticancer therapeutics were also found to affect response to immunotherapy. For example, estrogen was found to negatively regulate PD-L1 expression by its effect on JAK/STAT and nuclear factor κB (NF-κB) signaling pathways. Estrogen deprivation, thus, resulted in an immunosuppressive phenotype in ER^+ BC cells [41]. Similarly, corticosteroids and JAK inhibitors also downregulate PD-L1 expression. Several chemotherapeutic agents and steroid receptor coactivator (SRC) inhibitors were also found to upregulate PD-L1 expression in ER^+ and TNBC cell lines. Specifically, treatment with anthracycline, taxane, doxorubicin, abemaciclib, and dactolisib resulted in substantial increase in PD-L1 expression in human TNBC cell line [42, 43]. PD-L1 upregulation in BC was found to be positively associated with the expression of multidrug resistance protein 1 (MDR1) in TNBC patients [44]. These results suggest an immunosuppressive mechanism of chemotherapy resistance and the benefit of chemo-ICI combined therapy.

Some protooncogenes are also upregulated in TNBC and play a role for immune evasion. For example, the bromodomain-containing protein 4 (BRD4), Crk and Myc protooncogenes were all reported to be elevated and associated with the upregulated PD-L1 expression in TNBC and blocking their signaling were shown to successfully decrease PD-L1 expression [45-48]. Indeed, the mucin 1 protein signaling through Myc and NF-κB was linked to the increased PD-L1 expression [49]. Additionally, several other molecular factors including the intercellular adhesion molecule-1 (ICAM1) [50, 51], galanin and galanin message-associated peptide (GMAP) [52], cyclin-dependent kinase 8 (CDK8) [53], and tumor necrosis factor receptor 2 (TNFR2) [54] were found to upregulate the expression of PD-L1 and PD-1 as well as other checkpoint molecules such as CTLA-4, lymphocyte activation gene 3 (LAG3), and the T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domain (TIGIT) in TNBC.

ICI therapy targeting the PD-1/PD-L1 pathway using PD-1 or PD-L1 blocking antibody drugs enhances T cell's cytotoxicity and anti-tumor immune surveillance [55]. The FDA has approved the anti-PD-1 antibody, pembrolizumab (KEYTRUDA, Merck & Co), in combination with chemotherapy for the treatment of patients with locally recurrent unresectable or metastatic TNBC tumors with high PD-L1 expression as determined by an FDA-approved test (when a combined positive score is 10 or higher). The de-glycosylated PD-L1 level is considered a biomarker for predicting the patient response to the anti-PD-L1 (or anti-PD-1) therapy [56].

CTLA-4/CD80/86 immune checkpoint. CTLA-4 is another important immune checkpoint receptor expressed on T cells and negatively regulates their activation (**Figure 1A**). CTLA-4 binds to its ligand CD80 (also known as B7-1) or CD86 (also known as B7-2) on APCs. This interaction results in blockage of the stimulatory binding of CD28 to the same ligands, which eventually leads to T cell suppression and dampened immune response [57].

CTLA-4 was also found to be most highly expressed in TNBC compared to other BC sub-

types [58], suggesting availability of cytotoxic T cells for a promising anti-CTLA-4 therapy for TNBC patients. Indeed, anti-CTLA-4 therapy using therapeutic monoclonal antibodies (e.g., ipilimumab) has been used to enhance antitumor immune responses and improve BC patient response as a monotherapy or in combination with anti-PD-1/PD-L1 therapy [59]. Like PD-1, CTLA-4 expression on T cells is also upregulated in the context of TNBC by an array of molecular regulators (**Table 1**). Interestingly, most of the known regulators of CTLA-4, including ICAM1, Myc, TNRF2, GAL, SLC27A2, KLRB1, IGHV1-12, IGKV1OR2-108, PXDNL, and LINC02038, also regulate PD-1 expression in TNBC in a similar manner as described above [36, 48, 52, 54, 60]. A recent study has demonstrated that the cytokine chitinase-3-like 1 (Chi3l1) derived from TNBC cancer stem cells activates the CTLA-4 signaling in $CD8^+$ T cells via the protooncogene MAF for immune escape [60].

Other immune checkpoints that are emerging include B7-H3 (also known as CD276) and B7-H4 (ligands; receptors unknown), T-cell immunoglobulin and mucin domain 3 (TIM-3, receptor)/galectin-9 (GAL-9, ligand), T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domain (TIGIT, ligand)/nectins (CD155, CD112, CD113 or Nectin-4, receptor), V-domain immunoglobulin suppressor of T cell activation (VISTA, ligand and receptor), and Lymphocyte-activation gene 3 (LAG-3, ligand)/major histocompatibility complex II (MHC II, receptor). These molecules were also found to be modulated in TNBC and are associated with altered prognosis and survival (**Figure 1A**; **Table 1**).

B7-H3 and B7-H4 are emerging immune checkpoint ligands although their receptors remain unidentified. B7-H3 is expressed on APCs, CTLs, natural killer cells (NKs), and tumor cells and is considered an orphan ligand. B7-H3 is enriched in the tumor associated macrophages (TAMs) in TNBC and highly associated with metastasis rate and poor prognosis [61]. B7-H3 upregulation contributes to immunosuppressive TME [62, 63]. B7-H3 blockade treatment with an anti-B7-H3 antibody results in improved patient response to other ICI therapy such as anti-PD-L1 therapy [62]. B7-H4 is another member of the co-inhibitory B7 family ligands. Its upregulation contributes to the epithelial to mesenchymal transition associated with the immunosuppressive TME in TNBC [64-66].

TIM-3/GAL-9 interaction is also thought to play a role as an immune checkpoint. TIM-3 is a type I transmembrane protein that is known to trigger inhibitory signals in immune cells and is known to be involved in immune tolerance and T cell exhaustion. TIM-3 is expressed on CTLs, monocytes, macrophages, NKs, and dendritic cells (DCs). Despite being considered an orphan ligand, the carcinoembryonic antigen cell adhesion molecule 1 (CEACAM1) was discovered to be a potential receptor for TIM-3 [67]. CEACAM1 is expressed on the surface of active T cells and its activation induces inhibitory signals [67]. GAL-9 is another potential signaling pathway by which TIM-3 acts. TIM-3/GAL9 negatively regulate $CD4^+$ T helper cells and their expression is upregulated in response to anti-PD-1/PD-L1 therapy in TNBC [68-70]. While co-positivity of both PD-L1 and TIM-3 indicates bad prognosis [71], several studies indicate that expression of TIM-3 and Gal-9 is associated with more favorable prognosis in TNBC patients with increased number of tumor infiltrating lymphocytes [43, 72-76]. Galectin 2 encoding gene Lgals2 was found associated with the increase in the $TIM3^+$ CTL cells in the TME [77].

TIGIT is another inhibitory checkpoint expressed on T cells and NK cells [78, 79], In melanoma, TIGIT blockage showed beneficial therapeutic outcomes, particularly when combined with ICI targeting other checkpoints (such as PD-L1 and CTLA-4) [80]. It is thus plausible that TIGIT could represent a potential therapeutic target in TNBC. It was found that overexpression of Myc, TNRF2 or the baculoviral IAP repeat-containing 2 (BIRC2) is associated with TIGIT upregulation [48, 54, 81], and GAL expression is associated with TIGIT downregulation [52].

VISTA expressed on tumor cells as well as several immune cells, has also been identified as a checkpoint molecule that inhibits CTLs activation and induces immunosuppressive TME [82]. However, VISTA might act as a ligand on APCs and a receptor on T cells. Hence, its role in immunoregulation in cancer is still controversial. In TNBC, VISTA is downregulated, and its expression is positively correlated with good prognosis [83, 84]. On the other hand, other

reports suggest its inhibitory effect on tumor immune surveillance in BC [85, 86]. Similarly, blocking aldehyde dehydrogenase 2 (ALDH-2) results in enhanced $CD8^+$ T cell cytotoxicity via inhibition of tumor VISTA expression [87].

LAG-3 is another negative immune checkpoint protein that is expressed on immune cells [88]. The mechanism of LAG-3 inhibitory function on cancer immune surveillance is still poorly understood. In TNBC, LAG-3 is highly expressed [89], co-expressed with PD-L1, and is associated with a better prognosis [90, 91], MYC oncogene, BIRC2, and TNFR2 are factors that are known to contribute to upregulation of LAG-3 in TNBC [48, 54, 81]. LAG-3 expression in TNBC is reduced following neoadjuvant chemotherapy [75].

Ongoing clinical trials are evaluating the efficacy of simultaneous targeting of multiple immune checkpoints, such as the combination of anti-CTLA-4 [58, 59] or anti-B7-H3 monoclonal antibodies with PD-1/PD-L1 blockade [61, 62], to tackle immune resistance and enhance BC patients' response.

Immune suppressive tumor microenvironment (TME)

The TME is a complex entity that encompasses different components. TME includes the extracellular matrix (ECM) and signaling molecules secreted, immune cells, and other types of stromal cells surrounding the tumor cells such as T lymphocytes, B lymphocytes, NK cells, myeloid cells, TAMs, DCs, and myeloid dendritic suppressor cells (MDSCs), cancer associated fibroblasts (CAFs), and tumor vascular endothelial cells [92]. The complex interaction between TME components contributes to cancer immune response and immune evasion (**Figure 1B**; **Table 2**) [93]. In fact, the limited response to ICI therapy is attributed to immunosuppressive TME in which there are more number/activity of immune suppressive cells such as MDSC, regulatory T lymphocytes (T_{reg}) and CAF, and/or less number/activity of tumor clearing cells including cytotoxic T lymphocytes (CTLs), NK cells, and TAMs. Notably, TME is highly dependent upon cancer type and stage that mandates context-specific therapeutic intervention. For example, molecules under $CD8^+$ T cells may not primarily suppress CTLs. Below, we update on the cellular and molecular details in TNBC TME that contribute to immune evasion and resistance. Nonetheless, it is important to recognize that due to the complexity and interdependence of the TME, it is challenging to separate the distinct role of individual components. Factors that affect one component will likely have a broader impact on the entire TME and/or affect all components simultaneously. Therefore, herein, we focus on the factors that affect specific TME components and are predicted to contribute to TNBC immune evasion.

$CD8^+$ cytotoxic T lymphocytes (CTLs) are by far the most important contributors to immune response to pathogens and tumors. They mediate target cell death from apoptosis. CTLs are activated when T cell receptors (TCR) recognize the target cell antigens presented by class I major histocompatibility complex (MHC-1) on APCs. Interestingly, CTL infiltration into the TME signals highly positive prognosis in TNBC compared to other BC subtypes [94]. Many factors play a role in CTL infiltration into and activity inside TNBC TME as detailed below.

Myc is the most frequently mutated oncogene in TNBC [95]. Reduction of several immune cell populations in Myc-driven immunosuppressive TME was reported [47, 95]. Myc plays a critical role for immunosuppressive TME by regulating important inflammatory factors such as IFN and JAK/STAT [95], STING and chemoattractants such as Ccl5, CXCL10, and CXCL11 [96]. This makes TNBC with Myc mutations, highly resistant to ICI therapy. A combinatory therapy of cytosine-phosphate-guanine oligodeoxynucleotide, CpG with anti-OX40 was found to reverse this immunosuppressive TME in TNBC with Myc mutations and increase $CD8^+$ T cell infiltration and cytotoxicity [47]. Targeting mucin 1 (MUC1)/Myc axis has been shown to enhance the cytotoxicity of CTLs against TNBC cells [49]. MUC1 activated IFN-γ signaling has also been associated with reduced number of tumor infiltrating leukocytes (TILs) [97] supporting a notion that IFN-γ signaling can be either immune activating or suppressive dependent upon TME context which deserves further investigation [98].

Chi3l1 expression was found to contribute to T cell exclusion from the TME and is upregulated in TNBC tumors [99]. Mechanistically, the cytokine Chi3l1 induces T cell exclusion by inducing neutrophils recruitment and the formation of

neutrophil extracellular trap (referred to as NETosis) that prevents CTL infiltration [99]. Chi3l1 secreted by TNBC stem cells can also interact with the transcription factor "MAF" to upregulate CTLA-4 expression and consequently suppress CTL functions in TME [60].

The Tyro-3, Axl, and Mertk belong to a family of receptor protein kinases that play an important role in immune tolerance and maintains the immune suppressive state in the immune privileged sites such as the brain and testis [100]. One of their functions is to mediate the cell clearance by efferocytosis to avoid undesired inflammatory reaction [101]. TNBC can kidnap this immune privilege mechanism to evade immune response. Targeting inactivation of MerTK or Axl in the TME has been shown to enhance tumor immune response with increased tumor infiltration of the tumor clearing immune cells, particularly CTLs [102]. It is important to recognize that these TAM receptors involved may predominantly target macrophages' efferocytosis, resulting in dampened T-cell infiltration.

The Crk proto-oncogene is overexpressed in many tumors including TNBC, and is associated with tumor aggressiveness [103]. In addition to inducing PD-L1 upregulation [46], Crk was found to contribute to TNBC immune evasion by inhibiting tumor infiltration of effector immune cells including CTLs. Crk knockout leads to increased CTL tumor infiltration and toxicity. Disruption of Crk/CypA interaction using CypA inhibitors results in reduced tumor growth and metastasis and improved response to anti-PD-L1 therapy in TNBC patients through increased tumor infiltration of the effector immune cells including the $CD8^+$ CTLs, macrophages, and DCs [104].

Killer cell lectin receptor B1 (KLRB1, also known as CD161) is downregulated in TNBC. Its expression decreases progressively with tumor advancement and is positively associated with an anti-tumor TME phenotype and active filtration of TILs and thus favorable outcomes [36, 105].

The intercellular adhesion molecule-1 (ICAM1) expression decreases with TNBC progression and is associated with a favorable tumor immune response with increased number of TILs [50] and higher cytotoxicity of CTLs [51].

The lactate oxidase (Lox) catalyzes oxidation of lactate and thus reduces acidity inside TME. Its expression was found to enhance the activity of CTLs, decrease the activity of the immunosuppressive T_{regs} cells and enhance tumor response to anti-PD1/PD-L1 therapy [106].

The phosphatidylinositol 3-kinase (PI3K) signaling plays a crucial role in tumorigenesis and tumor progression in TNBC [107, 108]. Its p110α subunit protein shows immunosuppressive. Inhibition of this subunit increases TILs, and synergizes this effect when combined with anti-PD-L1 therapy [108]. In line with this evidence, a recent report showed that a mutation of this subunit contributed to CTL exclusion [109]. Consistently, loss of PTEN that counteracts against PI3K is associated with immune evasion [110]. Not surprisingly, mutational activation of PI3k signaling in TNBC plays a critical role for the resistance to immune therapy [111], making the PIK3 pathway a therapeutic target in combination with immune therapy.

The Jumonji domain containing 8 (JMJD8) protein is localized endoplasmic reticulum. Upregulation of JMJD8 was found to promote immune evasion in TNBC by inhibiting the STING signaling to the interferon (IFN)-stimulated gene (ISG), resulting in decreased type I IFN responses and thereby inhibition of the infiltration and activation of $CD8^+$ CTLs as well as multiple other immune cell types including $CD4^+$ T cells [112].

Regulator of G-protein signaling 1 (RGS1) expression in T cells is negatively associated with their infiltration to the TME and was found to be upregulated by IFN-STAT1 signaling. RGS1 expression reduced CTL chemotaxis and survival in BC TME [113]. However, its specific role in TNBC TME has not been investigated yet.

The macrophage migration inhibitory factor (MIF) plays an inflammatory role by binding to its CD74 receptor and other chemokine receptors such as CXCR2, CXCR4 and CXCR7 involved in leukocyte migration [114]. MIF is reported to contribute to immunosuppressive TME in melanoma, bladder cancer and TNBC [115, 116]. The inhibition of MIF gives rise to increased infiltration of cytotoxic $CD8^+$ T cells and M1 macrophages and decreased number of T_{regs} and tumor-associated neutrophils within the TNBC TME [117].

GMAP, encoded by galanin and GMAP prepropeptide (GAL) gene, is overexpressed in TNBC and is well associated with decreased CTL infiltration into the TME of TNBC rather than other BC subtypes [118].

CXCL9 is a cytokine, and its secretion is inhibited in TNBC. This inhibition is mediated by the NF-κB signaling involving the BIRC2, an E3 ubiquitin-protein ligase. BIRC2 expression is found high in TNBC that comes along with decreased secretion of CXCL9 and reduced infiltration of CTLs and NK cells that express CXCR3, the receptor for CXCL9 [81]. BIRC2 knockdown improves TNBC response to ICI therapy [81].

Discoidin domain receptor 1 (DDR1), a collagen tyrosine kinase receptor, is upregulated in TNBC and is associated with immunosuppressive TME. DDR1 contributes to BC immune evasion by modulating the ECM collagen fibers in the TME, resulting in physical immune exclusion of TILs in TNBC [119, 120].

Lectin galactoside-binding soluble 2 (Lgals2) gene encoding for galectin-2 protein was found to promote tumor immune evasion in TNBC through colony stimulating factor 1 (CSF1) signaling-mediated recruitment of TAMs. Its inhibition using a neutralizing antibody causes immune activation and tumor arrest. This study suggests that Lgals2 plays an immunosuppressive role in TNBC and is a potential immunotherapeutic target [77].

Tissue factor has been demonstrated to contribute to immunosuppressive TME in TNBC. In addition to what is mentioned earlier that TFVIIa overexpression in TNBC patients promotes immune evasion by modulation PD-L1 expression, another recent study has shown that tissue factor is upregulated in TNBC, inhibits tumor infiltration of TILs including $CD8^+$ and $CD4^+$ T cells and promotes recruitment of TAMs [121].

The liver X receptor (LXR) on the CTL surface seems to play a role like an inhibitory immune checkpoint protein. Indeed, LXR is highly activated in TNBC tumors where it interacts with ligands secreted from the cancer cells, resulting in the suppression of CTL activation, expansion, and cytotoxicity [122]. The inhibition of LXR leads to activation of $CD8^+$ CTLs, reduction of both immune suppressive cell populations including myeloid-derived suppressor cells (MDSCs) and T_{reg} cells, and inhibition of tumor growth [122].

The nucleotide-binding domain, leucine-rich containing family, pyrin domain-containing 3 (NLRP3) inflammasomal protein is found to be activated in the immune suppressive TME of TNBC [123]. One particular impact of NLRP3 activation in TNBC is decreasing CTL infiltration by affecting MDSCs [123]. In addition to MDSCs, other tumor stromal cells can also be utilized to form immune suppressive TME. For example, the upregulation of the fibroblast growth factor receptor (FGFR) in CAFs contributes much to the immune suppressive TME in TNBC, and FGFR blockade enhances CTL infiltration and tumor immune response [124]. Similarly, upregulation of Jagged1/Notch signaling boosts TAM recruitment and eventually leads to CTL exclusion and inactivation in TNBC TME [125, 126].

Myelin and lymphocyte protein 2 (MAL2), a protein involved in membrane trafficking and sorting is highly overexpressed in TBNC tumors and associated with decreased CTL cytotoxicity and poor survival [127]. The transcription factor SRY-related HMG-box-4 (SOX4) also contributes to immunosuppressive TME and thus to TNBC immune evasion. SOX4 inhibition increases CTL infiltration and enhances TNBC response to anti-PD-L1 therapy [128].

The zink finger protein 652 (ZNF652) loses its expression in TNBC. This progressive loss is associated with reduced CTL infiltration into the TME as well as poor prognosis and survival. In fact, ZNF652 acts as a transcriptional repressor of PD-L1 [29]. By similar mechanism, miR-4759 promotes immune surveillance. Notably, miR-4759 expression is much lower in TNBC than in other BC subtypes, suggesting a selective mechanism of PD-L1 upregulation in TNBC [39].

$CD4^+$ helper T lymphocytes are another subset of T cells that are important in maintaining activity and function of CTLs and other immune cells. In fact, many factors that affect CTLs in the TNBC TME modulate $CD4^+$ helper T cell infiltration and/or function. As shown in **Table 2**, most of the factors studied in the context of TME reduce $CD4^+$ helper T cells infiltration, and

thus contribute to immunosuppressive TME. However, as in CTLs, ICAM and KLRB1 play an immune protective role and increase $CD4^+$ helper T cell presence in the TNBC TME [50, 105]. It is important to note that the T helper 2 (Th2) subset of $CD4^+$ helper T cells may play an immunosuppressive role in the TME that is worth of more investigation [129, 130].

Regulatory T lymphocytes (T_{regs}) are a key small subset of $CD4^+$ (or even smaller subpopulation of $CD8^+$) T cells that are immunosuppressive against the $CD4^+$ T helper cells or $CD8^+$ CTLs and play a vital role in maintaining physiological immune self-tolerance mechanisms. T_{regs} can be hijacked to TME where they play a critical role in cancer immune evasion. T_{regs} are specifically abundant in TNBC TME compared to other BC subtypes [25]. T_{regs} were found to activate TGF-β1 secretion by BC cells, which result in repression of the cytotoxicity of $CD8^+$ CTLs and subsequent immune escape [131]. TGF-β secreted by cancer cells is known to modulate both innate and adaptive tumor immune response [132]. Additionally, T_{regs} also secrete TGF-β into the TME and work together with cancer cells for TGF-β mediated repression of $CD8^+$ CTLs [131]. In TNBC, T_{reg} infiltration into the TME is a major prognostic factor and is associated with poor ICI response [133]. Steroid receptor coactivator 3 (SRC3) is highly expressed in T_{regs} and plays a role for the immunosuppressive effects of T_{regs}. Treating tumors in mouse models with T_{regs} lacking SRC3 induces $CD8^+$ CTLs and NK cells mediated immune surveillance [134]. BC cells also modulate T_{reg} proliferation, infiltration and activity in the TME using other molecular mechanisms. For example, the upregulation of ANXA1 protein in BC and especially TNBC, results in boosting T_{reg}-mediated immune suppression [25]. Modulation of TME acidity using nanoparticles resulted in the reduction of the T_{reg} population in TNBC TME [106]. As described above, MIF secretion contributes to immunosuppressive TME by reducing CTL infiltration. MIF also was found to increase T_{reg} infiltration [117]. Surprisingly, KLRB1 and ICAM1-induced antitumoral immune response by increasing CTL infiltration was found to be accompanied by increased T_{regs} in the TME [36, 51]. PI3Kδ, Lgals2/CSF1, and LXR also play a role in T_{reg} infiltration into TNBC TME [77, 122, 135].

B lymphocytes (B cells) can also play both an immunosuppressive and immune-activating role in the TME [129]. TNBC TME is rich in B cells compared to other cell subtypes [136]. Anti-tumoral immune-activating role of B cells is mediated by antibody production, complement activation, and antigen presentation. However, a small subset of B cells, named B_{regs} play an immunosuppressive role in TNBC TME [129], an interesting new area under investigation. Several factors were found to reduce B cell infiltration into TME, including MUC1, PI3K, MYC, JMJD8, and GAL [47, 52, 97, 108, 112]. KLB1 and ICAM1, however, help B cell infiltration into BC TME [36, 105].

Natural killer (NK) cells are part of the innate immune response and are the first responders to stressed cells. NK cells play an important role in immune surveillance and their number in the TME has a prognostic value. Tumors adopt several mechanisms to evade NK-mediated immune surveillance by reducing their infiltration and cytotoxicity [129]. In TNBC, NK cell infiltration is correlated with favorable immune response and improved outcomes [137]. Interestingly, however, a recent study showed that while TNBC exhibits high infiltration of NK cells into the TME, their tumor infiltration is associated with poor survival and immunosuppressive phenotype. This study further demonstrated that the NK cells enriched in TNBC are in fact immature and can induce immune evasion by upregulating PD-L1 [138]. CDK8, an activator of the JAK-STAT pathway, plays an important role in regulating NK cell cytotoxicity. In TNBC, CDK8 was found to contribute to immune evasion by inducing epithelial-to-mesenchymal transition (EMT) and preventing NK cell immune surveillance [53]. KLRB1 was reported to inhibits the cytotoxicity of NK cells by promoting the IFNγ [36]. The basic transcription factor 3 (BTF3) was found to induce immune evasion by down-regulating the interferon regulatory factor 7 (IRF7) and thus decreasing NK cell infiltration into TNBC TME [139]. BIRC2 decreases $CXCR3^+$ NK cell recruitment into TNBC TME by inhibiting the secretion of the chemokine CXCR9 [81]. Upregulation of the tryptophan-kynurenine metabolic pathway enzyme, indoleamine 2,3 dioxygenase-1 (IDO-1) in TNBC contributes immune evasion. IDO-1 induces HLA-G resulting in inhibition of NK cell cytotoxicity [140]. IDO-1 is normally expressed

by placental trophoblast cells and is a mechanism of immune suppression in such immune privileged site. Like what they impact CTLs, MertK, CSF1 and NLRP3 also inhibit NK cell infiltration into the TME [77, 102, 123].

Myeloid cells are components of the innate immune system, and macrophages, neutrophils, dendritic cells (DCs), and MDSCs are all examples of myeloid cells. These cells seem to play a major role in cancer immunity and immune evasion mechanisms (**Table 2**). TAMs in the TME might play a dual immune role (either pro- or anti-tumoral role). Several factors impact the phenotype (immunosuppressive vs. anti-tumoral) of the TAMs [141]. Interestingly, the origin of the TAM seems to be a major factor. For example, yolk-sac derived TAMs tend to be immunosuppressive whereas monocyte derived TAMs tend to be immune supportive [141]. Furthermore, macrophages can be divided into two subsets based on the role they play in the TME. M1 macrophages are considered inflammatory and play an anti-tumoral role whereas M2 macrophages are immunosuppressive and pro-tumoral [141].

In BC TME, several factors affect the predominance of the macrophage types and thus represent a therapeutic target to enhance ICI response. KLRB1 exhibits an immune protective role by increasing the inflammatory M1 and reducing M2 macrophages [36, 105]. ICAM1 also favors the M1 microphages in TNBC TME [50, 51]. Mertk supports the immunosuppressive role of M2 macrophages [102], and inhibition of macrophages' efferocytosis by MerTK blockade, in TNBC resulted in more favorable TME marked by increased T cell infiltration and cytotoxicity [102]. Lgals2 mainly affects the TME via enhancing the colony stimulating factor 1 on TAMs inducing M2 polarization and proliferation [77]. Other factors that were found to induce M2 polarization and thereby contribute to TNBC immune evasion include MIF, Chi3l1, CD24-Siglec10, LXR, and FGFR1 [99, 117, 122, 124, 142]. Drug resistant BC cells secrete microparticles (MPs) that disrupt macrophage's chemotactic function resulting in immune evasion [143]. Cop1, an E3 ligase, interferes with macrophage infiltration by inhibiting the secretion of Ccl2 and Ccl7 chemokines [144]. TNBC shows increased activation of Jagged1-Notch pathway, increased TAM infiltration and inhibited T cell proliferation and cytotoxicity [125]. Heparan sulfate proteoglycan 2 (HSPG2) is an important component of the tumor ECM. It plays a role in T cell exclusion and EMT. TNBC TAMs were found to express high levels of HSPG2, which was associated with T cell exclusion, reduced tumor immunity, aggressive metastasis and poor prognosis. At the molecular level, HSPG2 was found to be a target of the NF-kB signaling in TAMs, and thus its expression can be manipulated by inhibiting the NF-kB signaling in TAMs [145].

Neutrophils in the TME are diverse and can be either pro- or anti-tumoral [129]. In TNBC, neutrophils exhibit pro-tumoral role and induce tumor metastasis [146] mainly via the formation of extracellular traps. Chi3l1, overexpressed in TNBC increases neutrophil infiltration into the TME, thereby inducing the NETosis process [99]. MIF overexpression is another mechanism that TNBC uses to enhance neutrophil infiltration to evade the immune surveillance [117]. Interestingly however, KLRB1 and ICAM can also promote neutrophil infiltration into the TME [50, 105]. MYC oncogene induces immunosuppressive TME phenotype, but it is not known why it seems to reduce neutrophil infiltration [47, 147].

Dendritic cells (DCs) are APCs that play an important role in regulating immune responses by affecting other immune cells, specifically T lymphocytes [129]. Dendritic cells exert antitumor effects, and some tumors alter their recruitment into the TME, fostering immune privilege [129]. Molecular factors that modulate DCs recruitment and activity in TNBC [36, 47, 50, 52, 81, 104, 105, 112] are outlined in **Table 2**. A subtype of myeloid dendritic cells is found to have tolerogenic properties and thus induce tumor growth and suppress the immune response, these are the MDSCs. Studies predict that targeting these cells represent a potential therapeutic approach to enhance anti-tumor immunity in TNBC [148]. CD84 is a surface marker of MDSCs in TNBC [149]. TNBC TME was found to be enriched with MDSCs [150]. TNBC cells can induce the activation of NLRP3 inflammasome in MDSC [123] which induces the secretion of IL-1β thereby triggering the expansion of MDSCs [151] and decreasing $CD8^+$ CTLs and NK cells [123]. Furthermore, in luminal BC subtypes, PIK3CA mutations that

results in PI3K hyperactivation also cause immunosuppressive TME by recruiting MDSCs and reducing cytotoxicity of CTLs [109] through STAT3 signaling [109].

Cancer associated fibroblasts (CAFs) belong to stromal cells and participate in ECM remodeling to affect other components of TME and play an important role in TNBC immune evasion. CAF infiltration into the TME is associated with poor response to ICI therapy (anti-PD-L1 and anti-CTLA-4) independently of tumor intrinsic genetic differences [126]. Interestingly, CAFs do not affect proliferation or cytotoxicity of $CD8^+$ CTLs within the TME, but rather promote T cell exclusion [126]. Mechanistically, the expression of mannose receptor C type 2 (MRC2), a protein that play an important role in ECM remodeling, on CAFs was associated with immunosuppressive TME and is specifically upregulated in TNBC but not in luminal BC subtypes [126]. Hence, CAFs seem to play an important role in immune evasion and poor response to immunotherapy in TNBC. CAFs induce $CD8^+$ CTL exhaustion and exclusion by physically excluding T cell access to the tumor cells through producing extracellular matrix components and expressing CXCL12, the ligand for CXCR4. CAFs also induce tumor suppressive TME by recruiting MDSCs and protumoral neutrophils and macrophages [20]. Fibroblast growth factor receptor (FGFR) on CAFs also contributes to T cell exclusion and immune evasion by modulating vascular cell adhesion protein 1 (VCAM-1) expression, which plays a role in leukocyte infiltration to the TME. Furthermore, FGFR inhibitors have been proven to be effective in enhancing ICI response. FGFR-1 was found to be upregulated in immune-excluded (immunologically cold) TNBC tumors, which is associated with poor prognosis [124].

Downregulation of antigen-presenting machinery

An important part of immune surveillance is the recognition of foreign antigens. Hence antigen presentation by tumor cells either directly or through APCs represents the most crucial step in tumor immune activation. BC, like other types of cancer, can evade the immune surveillance by downregulating the antigen-presenting machinery molecules such as MHC-I [152] (**Figure 1C**; **Table 2**). Myelin and Lymphocyte 2 (MAL2) protein, a protein involved in membrane trafficking and sorting, was found to be highly expressed in TNBC and was associated with decreased $CD8^+$ cytotoxicity via disrupting MHC-I on cancer cells [127]. Inhibition of SOX4 was shown to enhance cancer antigen presentation and reduce PD-L1 expression [128]. Epigenetic inhibitors such as GSK-LSD1, CUDC-101 and BML-210 have shown to enhance MHC-I expression and augment ICI therapy in BC [153]. TRAF3 and SMAC mimics downregulated MHC-1 expression on cancer cells, but their role in TNBC has not been investigated yet [154]. Blockade of NK2GA, an inhibitory receptor expressed on NK cells and $CD8^+$ CTLs, has been shown to markedly enhance tumor immune response when combined with anti-PD-L1 therapy [155].

Conclusions

ICI therapy has shown some effect on TNBC. However, TNBC adopts several mechanisms to evade the immune system which likely results in poor patient response to ICI therapy. Further understanding of the mechanisms of immune evasion and resistance at signaling and molecular levels will help identify ideal therapeutic targets and strategies for designing effective immunotherapy including ICI therapy and facilitate clinical trials for TNBC patients.

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Disclosure of conflict of interest

None.

Abbreviations

ALDH-2, aldehyde dehydrogenase 2; ANXA1, Annexin A1; APC, antigen presenting cell; ASPH, aspartate β-hydroxylase; BC, breast cancer; BIRC2, Baculoviral IAP Repeat Containing 2; BRD4, bromodomain-containing protein 4; BTF3, basic transcription factor 3; BTK, Bruton's tyrosine kinase; CAF, cancer-associated fibroblasts; CAR-T, chimeric antigen receptor T;

CDK8, cyclin-dependent kinase 8; CEACAM1, carcinoembryonic antigen cell adhesion molecule 1; CHI3L1, chitinase-3-like protein 1; CSF1, colony Stimulating Factor 1; CTL, cytotoxic lymphocytes; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; DC, dendritic cells; DDR1, Discoidin domain receptor 1; DMAS, β-Dimethylacrylshikonin; ECM, extracellular matrix; EMT, epithelial mesenchymal transition; ER, estrogen receptor; FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; GAL, galanin and GMAP prepropeptide; GAL9, galectin-9; GMAP, galanin message-associated peptide; GPR81, G protein-coupled receptor 81; HER2, human epidermal growth factor receptor 2; HuR, human antigen R; ICAM1, Intercellular adhesion molecule-1; ICI, Immune checkpoint inhibitors; IDO, Indoleamine-pyrrole 2,3-dioxygenase; IFN, interferon; IGHV1-12, immunoglobulin heavy variable 1-12; IGKV1OR2-108, immunoglobulin kappa variable 1/OR2-108w; IRF7, Interferon regulatory factor 7; ISG, IFN-stimulated gene; JMJD8, Jumonji domain containing 8; KLRB1, killer cell lectin like receptor B1; LAG3, lymphocyte activation gene 3; Lgals2, lectin galactoside-binding soluble 2; lncRNA, long non-coding RNA; Lox, lactate oxidase; LXR, liver X receptor; MAL2, Myelin and lymphocyte protein 2; MDSC, myeloid-derived suppressor cell; MDR1, multidrug resistance 1; MIF, macrophage migration inhibitory factor; MHC-I, major histocompatibility complex I; miRNA, microRNA; MRC2, mannose receptor C type 2; mTOR, mammalian target of rapamycin; MUC1, mucin 1; MYC, myelocytomatosis oncogene; NF-κB, nuclear factor κB; NK, natural killer cells; NLRP3, nucleotide-binding domain, leucine-rich containing family, pyrin domain-containing 3; PAR2, protease-activated receptor 2; PI3K, phosphatidylinositol 3-kinase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PR, progesterone receptor; RBMS3, RNA binding motif, single-stranded interacting protein 3; RGS1, regulator of G-protein signaling 1 SLC27A3, solute carrier family 27 member 2; SOX4, SRY-related HMG-box-4; SRC3, steroid receptor coactivator 3; STAT3, signal transducer and activator of transcription 3; TAM, Tumor associated macrophage; TF, tissue factor; Th2, T helper 2; TIGIT, T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domain; TIL, tumor infiltrating leukocytes; TIM-3, T-cell immunoglobulin and mucin domain 3; T_{reg}, regulatory T cells; TNBC, triple-negative breast cancer; TME, Tumor microenvironment; TNFR, tumor necrosis factor receptor 2; VISTA, V-domain immunoglobulin suppressor of T cell activation; ZNF652, zinc-finger protein 652.

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References

[1] Siegel RL, Miller KD, Wagle NS and Jemal A. Cancer statistics, 2023. CA Cancer J Clin 2023; 73: 17-48.

[2] Yersal O and Barutca S. Biological subtypes of breast cancer: prognostic and therapeutic implications. World J Clin Oncol 2014; 5: 412-424.

[3] Prat A, Pineda E, Adamo B, Galván P, Fernández A, Gaba L, Díez M, Viladot M, Arance A and Muñoz M. Clinical implications of the intrinsic molecular subtypes of breast cancer. Breast 2015; 24 Suppl 2: S26-S35.

[4] Foulkes WD, Smith IE and Reis-Filho JS. Triple-negative breast cancer. N Engl J Med 2010; 363: 1938-1948.

[5] Yin L, Duan JJ, Bian XW and Yu SC. Triple-negative breast cancer molecular subtyping and treatment progress. Breast Cancer Res 2020; 22: 61.

[6] Mellor AL and Munn DH. Creating immune privilege: active local suppression that benefits friends, but protects foes. Nat Rev Immunol 2008; 8: 74-80.

[7] Niederkorn JY. See no evil, hear no evil, do no evil: the lessons of immune privilege. Nat Immunol 2006; 7: 354-359.

[8] Cobbold SP, Adams E, Graca L, Daley S, Yates S, Paterson A, Robertson NJ, Nolan KF, Fairchild PJ and Waldmann H. Immune privilege induced by regulatory T cells in transplantation tolerance. Immunol Rev 2006; 213: 239-255.

[9] Joyce JA and Fearon DT. T cell exclusion, immune privilege, and the tumor microenvironment. Science 2015; 348: 74-80.

[10] Forrester JV, Xu H, Lambe T and Cornall R. Immune privilege or privileged immunity? Mucosal Immunol 2008; 1: 372-381.

[11] Bonaventura P, Shekarian T, Alcazer V, Valladeau-Guilemond J, Valsesia-Wittmann S, Amigorena S, Caux C and Depil S. Cold tumors: a therapeutic challenge for immunotherapy. Front Immunol 2019; 10: 168.

[12] Ichiryu N and Fairchild PJ. Immune privilege of stem cells. In: Zavazava N, editors. Embryonic Stem Cell Immunobiology: Methods and Protocols. Totowa, NJ: Humana Press; 2013. pp. 1-16.
[13] Das S and Johnson DB. Immune-related adverse events and anti-tumor efficacy of immune checkpoint inhibitors. J Immunother Cancer 2019; 7: 306.
[14] Debien V, De Caluwe A, Wang X, Piccart-Gebhart M, Tuohy VK, Romano E and Buisseret L. Immunotherapy in breast cancer: an overview of current strategies and perspectives. NPJ Breast Cancer 2023; 9: 7.
[15] Kim MS and Prasad V. Pembrolizumab for all. J Cancer Res Clin Oncol 2023; 149: 1357-1360.
[16] Valencia GA, Rioja P, Morante Z, Ruiz R, Fuentes H, Castaneda CA, Vidaurre T, Neciosup S and Gomez HL. Immunotherapy in triple-negative breast cancer: a literature review and new advances. World J Clin Oncol 2022; 13: 219-236.
[17] Jacob SL, Huppert LA and Rugo HS. Role of immunotherapy in breast cancer. JCO Oncol Pract 2023; 19: 167-179.
[18] Cortes J, Cescon DW, Rugo HS, Nowecki Z, Im SA, Yusof MM, Gallardo C, Lipatov O, Barrios CH, Holgado E, Iwata H, Masuda N, Otero MT, Gokmen E, Loi S, Guo Z, Zhao J, Aktan G, Karantza V and Schmid P; KEYNOTE-355 Investigators. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. Lancet 2020; 396: 1817-1828.
[19] Xiao Y, Ma D, Zhao S, Suo C, Shi J, Xue MZ, Ruan M, Wang H, Zhao J, Li Q, Wang P, Shi L, Yang WT, Huang W, Hu X, Yu KD, Huang S, Bertucci F, Jiang YZ and Shao ZM; AME Breast Cancer Collaborative Group. Multi-omics profiling reveals distinct microenvironment characterization and suggests immune escape mechanisms of triple-negative breast cancer. Clin Cancer Res 2019; 25: 5002-5014.
[20] Gao D, Fang L, Liu C, Yang M, Yu X, Wang L, Zhang W, Sun C and Zhuang J. Microenvironmental regulation in tumor progression: interactions between cancer-associated fibroblasts and immune cells. Biomed Pharmacother 2023; 167: 115622.
[21] Solinas C, Gombos A, Latifyan S, Piccart-Gebhart M, Kok M and Buisseret L. Targeting immune checkpoints in breast cancer: an update of early results. ESMO Open 2017; 2: e000255.
[22] Zitvogel L and Kroemer G. Targeting PD-1/PD-L1 interactions for cancer immunotherapy. Oncoimmunology 2012; 1: 1223-1225.
[23] Han Y, Liu D and Li L. PD-1/PD-L1 pathway: current researches in cancer. Am J Cancer Res 2020; 10: 727-742.
[24] Oner G, Önder S, Karatay H, Ak N, Tükenmez M, Müslümanoğlu M, İğci A, Dincçağ A, Özmen V, Aydiner A, Yavuz E and Cabioğlu N. Clinical impact of PD-L1 expression in triple-negative breast cancer patients with residual tumor burden after neoadjuvant chemotherapy. World J Surg Oncol 2021; 19: 264.
[25] Bai F, Zhang P, Fu Y, Chen H, Zhang M, Huang Q, Li D, Li B and Wu K. Targeting ANXA1 abrogates Treg-mediated immune suppression in triple-negative breast cancer. J Immunother Cancer 2020; 8: e000169.
[26] Xiao D, Zeng T, Zhu W, Yu ZZ, Huang W, Yi H, Lu SS, Feng J, Feng XP, Wu D, Wen Q, Zhou JH, Yuan L, Zhuang W and Xiao ZQ. ANXA1 promotes tumor immune evasion by binding PARP1 and upregulating Stat3-induced expression of PD-L1 in multiple cancers. Cancer Immunol Res 2023; 11: 1367-1383.
[27] Yu ZZ, Liu YY, Zhu W, Xiao D, Huang W, Lu SS, Yi H, Zeng T, Feng XP, Yuan L, Qiu JY, Wu D, Wen Q, Zhou JH, Zhuang W and Xiao ZQ. ANXA1-derived peptide for targeting PD-L1 degradation inhibits tumor immune evasion in multiple cancers. J Immunother Cancer 2023; 11: e006345.
[28] Zhang Q, Yang Z, Hao X, Dandreo LJ, He L, Zhang Y, Wang F, Wu X and Xu L. Niclosamide improves cancer immunotherapy by modulating RNA-binding protein HuR-mediated PD-L1 signaling. Cell Biosci 2023; 13: 192.
[29] Liu Y, Peng Y, Du W, Yu C, Peng Z, Qin L, Ma Y, Wu X, Peng Y, Cheng X, Xia L, Fa H, Wu Y, Sun L, Liu J, Liu Z, Shang Y, Wang S and Liang J. PD-L1-mediated immune evasion in triple-negative breast cancer is linked to the loss of ZNF652. Cell Rep 2023; 42: 113343.
[30] Paul S, Das K, Ghosh A, Chatterjee A, Bhoumick A, Basu A and Sen P. Coagulation factor VIIa enhances programmed death-ligand 1 expression and its stability in breast cancer cells to promote breast cancer immune evasion. J Thromb Haemost 2023; 21: 3522-3538.
[31] Zhou Y, Liang Z, Xia Y, Li S, Liang J, Hu Z, Tang C, Zhao Q, Gong Q and Ouyang Y. Disruption of RBMS3 suppresses PD-L1 and enhances antitumor immune activities and therapeutic effects of auranofin against triple-negative breast cancer. Chem Biol Interact 2023; 369: 110260.
[32] Wu Z, Wu H, Wang Z, Li H, Gu H, Xia E, Yan C, Dai Y, Liu C, Wang X, Lv L, Bao J, Wang O and Dai X. β, β-Dimethylacrylshikonin potentiates paclitaxel activity, suppresses immune evasion and triple negative breast cancer progression via STAT3Y705 phosphorylation inhibition

based on network pharmacology and transcriptomics analysis. Phytomedicine 2023; 114: 154769.
[33] Soltanshahi M, Taghiloo S and Asgarian-Omran H. Expression modulation of immune checkpoint molecules by ibrutinib and everolimus through STAT3 in MCF-7 breast cancer cells. Iran J Pharm Res 2022; 21: e127352.
[34] Bai X, Zhou Y, Yokota Y, Matsumoto Y, Zhai B, Maarouf N, Hayashi H, Carlson R, Zhang S, Sousa A, Sun B, Ghanbari H, Dong X and Wands JR. Adaptive antitumor immune response stimulated by bio-nanoparticle based vaccine and checkpoint blockade. J Exp Clin Cancer Res 2022; 41: 132.
[35] Guo S, Zhou J, Lou P, Weng L, Ye X, Guo J, Liu H and Ma R. Potentiated effects of lactate receptor GPR81 on immune microenvironment in breast cancer. Mol Carcinog 2023; 62: 1369-1377.
[36] Zhao H, Yin X, Wang L, Liu K, Liu W, Bo L and Wang L. Identifying tumour microenvironment-related signature that correlates with prognosis and immunotherapy response in breast cancer. Sci Data 2023; 10: 119.
[37] Zhang M, Wang N, Song P, Fu Y, Ren Y, Li Z and Wang J. LncRNA GATA3-AS1 facilitates tumour progression and immune escape in triple-negative breast cancer through destabilization of GATA3 but stabilization of PD-L1. Cell Prolif 2020; 53: e12855.
[38] Yang L, Cai Y, Zhang D, Sun J, Xu C, Zhao W, Jiang W and Pan C. miR-195/miR-497 regulate CD274 expression of immune regulatory ligands in triple-negative breast cancer. J Breast Cancer 2018; 21: 371-381.
[39] Lin YZ, Liu SH, Wu WR, Shen YC, Wang YL, Liao CC, Lin PL, Chang H, Liu LC, Cheng WC and Wang SC. miR-4759 suppresses breast cancer through immune checkpoint blockade. Comput Struct Biotechnol J 2022; 20: 241-251.
[40] Deng S, Wang M, Wang C, Zeng Y, Qin X, Tan Y, Liang B and Cao Y. p53 downregulates PD-L1 expression via miR-34a to inhibit the growth of triple-negative breast cancer cells: a potential clinical immunotherapeutic target. Mol Biol Rep 2023; 50: 577-587.
[41] Hühn D, Martí-Rodrigo P, Mouron S, Hansel C, Tschapalda K, Porebski B, Häggblad M, Lidemalm L, Quintela-Fandino M, Carreras-Puigvert J and Fernandez-Capetillo O. Prolonged estrogen deprivation triggers a broad immunosuppressive phenotype in breast cancer cells. Mol Oncol 2022; 16: 148-165.
[42] Gilad Y, Eliaz Y, Yu Y, Han SJ, O'Malley BW and Lonard DM. Drug-induced PD-L1 expression and cell stress response in breast cancer cells can be balanced by drug combination. Sci Rep 2019; 9: 15099.
[43] Yoon HK, Kim TH, Park S, Jung H, Quan X, Park SJ, Han J and Lee A. Effect of anthracycline and taxane on the expression of programmed cell death ligand-1 and galectin-9 in triple-negative breast cancer. Pathol Res Pract 2018; 214: 1626-1631.
[44] Antony GR, Augustine P, Parambil ST, Littleflower AB, Kattoor J, Krishna KMJ and Subhadradevi L. Immunohistochemical expression of PD-L1 and MDR1 in breast tumors: association with clinico-pathological parameters and treatment outcome. Clin Exp Med 2023; 23: 859-869.
[45] Jing X, Shao S, Zhang Y, Luo A, Zhao L, Zhang L, Gu S and Zhao X. BRD4 inhibition suppresses PD-L1 expression in triple-negative breast cancer. Exp Cell Res 2020; 392: 112034.
[46] Kumar S, Davra V, Obr AE, Geng K, Wood TL, De Lorenzo MS and Birge RB. Crk adaptor protein promotes PD-L1 expression, EMT and immune evasion in a murine model of triple-negative breast cancer. Oncoimmunology 2017; 7: e1376155.
[47] Lee JV, Housley F, Yau C, Nakagawa R, Winkler J, Anttila JM, Munne PM, Savelius M, Houlahan KE, Van de Mark D, Hemmati G, Hernandez GA, Zhang Y, Samson S, Baas C, Kok M, Esserman LJ, van't Veer LJ, Rugo HS, Curtis C, Klefström J, Matloubian M and Goga A. Combinatorial immunotherapies overcome MYC-driven immune evasion in triple negative breast cancer. Nat Commun 2022; 13: 3671.
[48] Li X, Tang L, Chen Q, Cheng X, Liu Y, Wang C, Zhu C, Xu K, Gao F, Huang J, Wang R and Guan X. Inhibition of MYC suppresses programmed cell death ligand-1 expression and enhances immunotherapy in triple-negative breast cancer. Chin Med J (Engl) 2022; 135: 2436-2445.
[49] Maeda T, Hiraki M, Jin C, Rajabi H, Tagde A, Alam M, Bouillez A, Hu X, Suzuki Y, Miyo M, Hata T, Hinohara K and Kufe D. MUC1-C induces PD-L1 and immune evasion in triple-negative breast cancer. Cancer Res 2018; 78: 205-215.
[50] Chen H, Pu S, Mei N, Liu X, He J and Zhang H. Identification of prognostic biomarkers among ICAMs in the breast cancer microenvironment. Cancer Biomark 2022; 35: 379-393.
[51] Zhou Q, Xu J, Xu Y, Sun S and Chen J. Role of ICAM1 in tumor immunity and prognosis of triple-negative breast cancer. Front Immunol 2023; 14: 1176647.
[52] Wu M, Yuan K, Lyu S and Li Y. Screening potential immune signatures for early-stage basal-like/triple-negative breast cancer. World J Surg Oncol 2022; 20: 214.
[53] Knab VM, Gotthardt D, Klein K, Grausenburger R, Heller G, Menzl I, Prinz D, Trifinopoulos J, List J, Fux D, Witalisz-Siepracka A and Sexl V.

Triple-negative breast cancer cells rely on kinase-independent functions of CDK8 to evade NK-cell-mediated tumor surveillance. Cell Death Dis 2021; 12: 991.

[54] Liao P, Jiang M, Islam MS, Wang Y and Chen X. TNFR2 expression predicts the responses to immune checkpoint inhibitor treatments. Front Immunol 2023; 14: 1097090.

[55] Ai L, Chen J, Yan H, He Q, Luo P, Xu Z and Yang X. Research status and outlook of PD-1/PD-L1 inhibitors for cancer therapy. Drug Des Devel Ther 2020; 14: 3625-3649.

[56] Ou-Yang F, Li CL, Chen CC, Shen YC, Moi SH, Luo CW, Xia WY, Wang YN, Lee HH, Wang LH, Wang SC, Pan MR, Hou MF and Hung MC. Deglycosylated membrane PD-L1 in tumor tissues as a biomarker for responsiveness to atezolizumab (Tecentriq) in advanced breast cancer patients. Am J Cancer Res 2022; 12: 123-137.

[57] Van Coillie S, Wiernicki B and Xu J. Molecular and cellular functions of CTLA-4. Adv Exp Med Biol 2020; 1248: 7-32.

[58] Peng Z, Su P, Yang Y, Yao X, Zhang Y, Jin F and Yang B. Identification of CTLA-4 associated with tumor microenvironment and competing interactions in triple negative breast cancer by co-expression network analysis. J Cancer 2020; 11: 6365-6375.

[59] Rupp T, Genest L, Babin D, Legrand C, Hunault M, Froget G and Castagné V. Anti-CTLA-4 and anti-PD-1 immunotherapies repress tumor progression in preclinical breast and colon model with independent regulatory T cells response. Transl Oncol 2022; 20: 101405.

[60] Ji S, Yu H, Zhou D, Fan X, Duan Y, Tan Y, Lang M and Shao G. Cancer stem cell-derived CHI3L1 activates the MAF/CTLA4 signaling pathway to promote immune escape in triple-negative breast cancer. J Transl Med 2023; 21: 721.

[61] Pizon M, Schott DS, Pachmann U and Pachmann K. B7-H3 on circulating epithelial tumor cells correlates with the proliferation marker, Ki-67, and may be associated with the aggressiveness of tumors in breast cancer patients. Int J Oncol 2018; 53: 2289-2299.

[62] Cheng N, Bei Y, Song Y, Zhang W, Xu L, Zhang W, Yang N, Bai X, Shu Y and Shen P. B7-H3 augments the pro-angiogenic function of tumor-associated macrophages and acts as a novel adjuvant target for triple-negative breast cancer therapy. Biochem Pharmacol 2021; 183: 114298.

[63] Mei J, Cai Y, Zhu H, Jiang Y, Fu Z, Xu J, Chen L, Yang K, Zhao J, Song C, Zhang Y, Mao W and Yin Y. High B7-H3 expression with low PD-L1 expression identifies armored-cold tumors in triple-negative breast cancer. NPJ Breast Cancer 2024; 10: 11.

[64] Zhou L, Wu J, Ruan M, Xiao Y, Lan H, Wu Q, Yu CW and Zhang Q. The loss of B7-H4 expression in breast cancer cells escaping from T cell cytotoxicity contributes to epithelial-to-mesenchymal transition. Breast Cancer Res 2023; 25: 115.

[65] Sanuki F, Mikami Y, Nishimura H, Fujita Y, Monobe Y, Nomura T, Taira N and Moriya T. Immunohistological analysis of B7-H4, IDO1, and PD-L1 expression and tumor immune microenvironment based on triple-negative breast cancer subtypes. Breast Cancer 2023; 30: 1041-1053.

[66] Altan M, Kidwell KM, Pelekanou V, Carvajal-Hausdorf DE, Schalper KA, Toki MI, Thomas DG, Sabel MS, Hayes DF and Rimm DL. Association of B7-H4, PD-L1, and tumor infiltrating lymphocytes with outcomes in breast cancer. NPJ Breast Cancer 2018; 4: 40.

[67] Huang YH, Zhu C, Kondo Y, Anderson AC, Gandhi A, Russell A, Dougan SK, Petersen BS, Melum E, Pertel T, Clayton KL, Raab M, Chen Q, Beauchemin N, Yazaki PJ, Pyzik M, Ostrowski MA, Glickman JN, Rudd CE, Ploegh HL, Franke A, Petsko GA, Kuchroo VK and Blumberg RS. CEACAM1 regulates TIM-3-mediated tolerance and exhaustion. Nature 2015; 517: 386-390.

[68] Zhu C, Anderson AC, Schubart A, Xiong H, Imitola J, Khoury SJ, Zheng XX, Strom TB and Kuchroo VK. The Tim-3 ligand galectin-9 negatively regulates T helper type 1 immunity. Nat Immunol 2005; 6: 1245-1252.

[69] Saleh R, Toor SM, Khalaf S and Elkord E. Breast cancer cells and PD-1/PD-L1 blockade upregulate the expression of PD-1, CTLA-4, TIM-3 and LAG-3 immune checkpoints in CD4(+) T cells. Vaccines (Basel) 2019; 7: 149.

[70] Miao X, Guo Q, Pan Z, Xu X, Shao X and Wang X. The characteristics and novel clinical implications of CD4+CXCR5+Foxp3+ follicular regulatory T cells in breast cancer. Ann Transl Med 2021; 9: 1332.

[71] Cabioglu N, Onder S, Oner G, Karatay H, Tukenmez M, Muslumanoglu M, İgci A, Eralp Y, Aydiner A, Saip P, Yavuz E and Ozmen V. TIM3 expression on TILs is associated with poor response to neoadjuvant chemotherapy in patients with locally advanced triple-negative breast cancer. BMC Cancer 2021; 21: 357.

[72] Ju MH, Byun KD, Park EH, Lee JH and Han SH. Association of galectin 9 expression with immune cell infiltration, programmed cell death ligand-1 expression, and patient's clinical outcome in triple-negative breast cancer. Biomedicines 2021; 9: 1383.

[73] Byun KD, Hwang HJ, Park KJ, Kim MC, Cho SH, Ju MH, Lee JH and Jeong JS. T-cell immunoglobulin mucin 3 expression on tumor infiltrating lymphocytes as a positive prognosticator in

triple-negative breast cancer. J Breast Cancer 2018; 21: 406-414.
[74] Yoshikawa K, Ishida M, Yanai H, Tsuta K, Sekimoto M and Sugie T. Prognostic significance of the expression levels of T-cell immunoglobulin mucin-3 and its ligand galectin-9 for relapse-free survival in triple-negative breast cancer. Oncol Lett 2022; 23: 197.
[75] Sarradin V, Lusque A, Filleron T, Dalenc F and Franchet C. Immune microenvironment changes induced by neoadjuvant chemotherapy in triple-negative breast cancers: the MIMOSA-1 study. Breast Cancer Res 2021; 23: 61.
[76] Liu J, Li Y, Li Q, Liang D, Wang Q and Liu Q. Biomarkers of response to camrelizumab combined with apatinib: an analysis from a phase II trial in advanced triple-negative breast cancer patients. Breast Cancer Res Treat 2021; 186: 687-697.
[77] Ji P, Gong Y, Jin ML, Wu HL, Guo LW, Pei YC, Chai WJ, Jiang YZ, Liu Y, Ma XY, Di GH, Hu X and Shao ZM. In vivo multidimensional CRISPR screens identify Lgals2 as an immunotherapy target in triple-negative breast cancer. Sci Adv 2022; 8: eabl8247.
[78] Stanietsky N, Simic H, Arapovic J, Toporik A, Levy O, Novik A, Levine Z, Beiman M, Dassa L, Achdout H, Stern-Ginossar N, Tsukerman P, Jonjic S and Mandelboim O. The interaction of TIGIT with PVR and PVRL2 inhibits human NK cell cytotoxicity. Proc Natl Acad Sci U S A 2009; 106: 17858-17863.
[79] Harjunpää H and Guillerey C. TIGIT as an emerging immune checkpoint. Clin Exp Immunol 2020; 200: 108-119.
[80] Tang W, Chen J, Ji T and Cong X. TIGIT, a novel immune checkpoint therapy for melanoma. Cell Death Dis 2023; 14: 466.
[81] Samanta D, Huang TY, Shah R, Yang Y, Pan F and Semenza GL. BIRC2 expression impairs anti-cancer immunity and immunotherapy efficacy. Cell Rep 2020; 32: 108073.
[82] Huang X, Zhang X, Li E, Zhang G, Wang X, Tang T, Bai X and Liang T. VISTA: an immune regulatory protein checking tumor and immune cells in cancer immunotherapy. J Hematol Oncol 2020; 13: 83.
[83] Zhang M, Zhang J, Liu N, Wang B, Zhou Y and Yang J. VISTA is associated with immune infiltration and predicts favorable prognosis in TNBC. Front Oncol 2022; 12: 961374.
[84] Zong L, Mo S, Yu S, Zhou Y, Zhang M, Chen J and Xiang Y. Expression of the immune checkpoint VISTA in breast cancer. Cancer Immunol Immunother 2020; 69: 1437-1446.
[85] Rezouki I, Zohair B, Ssi SA, Karkouri M, Razzouki I, Elkarroumi M and Badou A. High VISTA expression is linked to a potent epithelial-mesenchymal transition and is positively correlated with PD1 in breast cancer. Front Oncol 2023; 13: 1154631.
[86] Xie X, Zhang J, Shi Z, Liu W, Hu X, Qie C, Chen W, Wang Y, Wang L, Jiang J and Liu J. The expression pattern and clinical significance of the immune checkpoint regulator VISTA in human breast cancer. Front Immunol 2020; 11: 563044.
[87] Chen Y, Sun J, Liu J, Wei Y, Wang X, Fang H, Du H, Huang J, Li Q, Ren G, Wang X and Li H. Aldehyde dehydrogenase 2-mediated aldehyde metabolism promotes tumor immune evasion by regulating the NOD/VISTA axis. J Immunother Cancer 2023; 11: e007487.
[88] Goldberg MV and Drake CG. LAG-3 in cancer immunotherapy. Curr Top Microbiol Immunol 2011; 344: 269-278.
[89] Tahtacı G, Günel N, Sadioğlu A, Akyürek N, Boz O and Üner A. LAG-3 expression in tumor microenvironment of triple-negative breast cancer. Turk J Med Sci 2023; 53: 142-148.
[90] Heimes AS, Almstedt K, Krajnak S, Runkel A, Droste A, Schwab R, Stewen K, Lebrecht A, Battista MJ, Brenner W, Hasenburg A, Gehrmann M, Hengstler JG and Schmidt M. Prognostic impact of LAG-3 mRNA expression in early breast cancer. Biomedicines 2022; 10: 2656.
[91] Stovgaard ES, Kümler I, List-Jensen K, Roslind A, Christensen IJ, Høgdall E, Nielsen D and Balslev E. Prognostic and clinicopathologic associations of LAG-3 expression in triple-negative breast cancer. Appl Immunohistochem Mol Morphol 2022; 30: 62-71.
[92] Anderson NM and Simon MC. The tumor microenvironment. Curr Biol 2020; 30: R921-R925.
[93] Gupta I, Hussein O, Sastry KS, Bougarn S, Gopinath N, Chin-Smith E, Sinha Y, Korashy HM and Maccalli C. Deciphering the complexities of cancer cell immune evasion: mechanisms and therapeutic implications. Adv Cancer Biol Metastasis 2023; 8: 100107.
[94] Liu S, Lachapelle J, Leung S, Gao D, Foulkes WD and Nielsen TO. CD8+ lymphocyte infiltration is an independent favorable prognostic indicator in basal-like breast cancer. Breast Cancer Res 2012; 14: R48.
[95] Zimmerli D, Brambillasca CS, Talens F, Bhin J, Linstra R, Romanens L, Bhattacharya A, Joosten SEP, Da Silva AM, Padrao N, Wellenstein MD, Kersten K, de Boo M, Roorda M, Henneman L, de Bruijn R, Annunziato S, van der Burg E, Drenth AP, Lutz C, Endres T, van de Ven M, Eilers M, Wessels L, de Visser KE, Zwart W, Fehrmann RSN, van Vugt MATM and Jonkers J. MYC promotes immune-suppression in triple-negative breast cancer via inhibition of interferon signaling. Nat Commun 2022; 13: 6579.

[96] Lee KM, Lin CC, Servetto A, Bae J, Kandagatla V, Ye D, Kim G, Sudhan DR, Mendiratta S, González Ericsson PI, Balko JM, Lee J, Barnes S, Malladi VS, Tabrizi S, Reddy SM, Yum S, Chang CW, Hutchinson KE, Yost SE, Yuan Y, Chen ZJ, Fu YX, Hanker AB and Arteaga CL. Epigenetic repression of STING by MYC promotes immune evasion and resistance to immune checkpoint inhibitors in triple-negative breast cancer. Cancer Immunol Res 2022; 10: 829-843.

[97] Yamashita N, Long M, Fushimi A, Yamamoto M, Hata T, Hagiwara M, Bhattacharya A, Hu Q, Wong KK, Liu S and Kufe D. MUC1-C integrates activation of the IFN-γ pathway with suppression of the tumor immune microenvironment in triple-negative breast cancer. J Immunother Cancer 2021; 9: e002115.

[98] Alspach E, Lussier DM and Schreiber RD. Interferon γ and its important roles in promoting and inhibiting spontaneous and therapeutic cancer immunity. Cold Spring Harb Perspect Biol 2019; 11: a028480.

[99] Taifour T, Attalla SS, Zuo D, Gu Y, Sanguin-Gendreau V, Proud H, Solymoss E, Bui T, Kuasne H, Papavasiliou V, Lee CG, Kamle S, Siegel PM, Elias JA, Park M and Muller WJ. The tumor-derived cytokine Chi3l1 induces neutrophil extracellular traps that promote T cell exclusion in triple-negative breast cancer. Immunity 2023; 56: 2755-2772, e2758.

[100] Lu Q, Gore M, Zhang Q, Camenisch T, Boast S, Casagranda F, Lai C, Skinner MK, Klein R, Matsushima GK, Earp HS, Goff SP and Lemke G. Tyro-3 family receptors are essential regulators of mammalian spermatogenesis. Nature 1999; 398: 723-728.

[101] Doran AC, Yurdagul A Jr and Tabas I. Efferocytosis in health and disease. Nat Rev Immunol 2020; 20: 254-267.

[102] Davra V, Kumar S, Geng K, Calianese D, Mehta D, Gadiyar V, Kasikara C, Lahey KC, Chang YJ, Wichroski M, Gao C, De Lorenzo MS, Kotenko SV, Bergsbaken T, Mishra PK, Gause WC, Quigley M, Spires TE and Birge RB. Axl and mertk receptors cooperate to promote breast cancer progression by combined oncogenic signaling and evasion of host antitumor immunity. Cancer Res 2021; 81: 698-712.

[103] Fathers KE, Bell ES, Rajadurai CV, Cory S, Zhao H, Mourskaia A, Zuo D, Madore J, Monast A, Mes-Masson AM, Grosset AA, Gaboury L, Hallet M, Siegel P and Park M. Crk adaptor proteins act as key signaling integrators for breast tumorigenesis. Breast Cancer Res 2012; 14: R74.

[104] Davra V, Saleh T, Geng K, Kimani S, Mehta D, Kasikara C, Smith B, Colangelo NW, Ciccarelli B, Li H, Azzam EI, Kalodimos CG, Birge RB and Kumar S. Cyclophilin a inhibitor Debio-025 targets crk, reduces metastasis, and induces tumor immunogenicity in breast cancer. Mol Cancer Res 2020; 18: 1189-1201.

[105] Xu N, Meng X, Chu H, Yang Z, Jiao Y and Li Y. The prognostic significance of KLRB1 and its further association with immune cells in breast cancer. PeerJ 2023; 11: e15654.

[106] Tang Y, Chang Q, Chen G, Zhao X, Huang G, Wang T, Jia C, Lu L, Jin T, Yang S, Cao L and Zhang X. Tumor immunosuppression relief via acidity modulation combined PD-L1 siRNA for enhanced immunotherapy. Biomater Adv 2023; 150: 213425.

[107] Yang J, Nie J, Ma X, Wei Y, Peng Y and Wei X. Targeting PI3K in cancer: mechanisms and advances in clinical trials. Mol Cancer 2019; 18: 26.

[108] Sai J, Owens P, Novitskiy SV, Hawkins OE, Vilgelm AE, Yang J, Sobolik T, Lavender N, Johnson AC, McClain C, Ayers GD, Kelley MC, Sanders M, Mayer IA, Moses HL, Boothby M and Richmond A. PI3K inhibition reduces mammary tumor growth and facilitates antitumor immunity and Anti-PD1 responses. Clin Cancer Res 2017; 23: 3371-3384.

[109] Li X, Chen G, Wang F, Guo X, Zhang R, Liu P, Dong L, Yu W, Wang H, Wang H and Yu J. Oncogenic PIK3CA recruits myeloid-derived suppressor cells to shape the immunosuppressive tumour microenvironment in luminal breast cancer through the 5-lipoxygenase-dependent arachidonic acid pathway. Clin Transl Med 2023; 13: e1483.

[110] Bergholz JS, Wang Q, Wang Q, Ramseier M, Prakadan S, Wang W, Fang R, Kabraji S, Zhou Q, Gray GK, Abell-Hart K, Xie S, Guo X, Gu H, Von T, Jiang T, Tang S, Freeman GJ, Kim HJ, Shalek AK, Roberts TM and Zhao JJ. PI3Kβ controls immune evasion in PTEN-deficient breast tumours. Nature 2023; 617: 139-146.

[111] Basho RK, Zhao L, White JB, Huo L, Bassett RL, Mittendorf EA, Thompson A, Litton JK, Ueno N, Arun B, Lim B, Valero V, Tripathy D, Zhang J, Adrada BE, Santiago L, Ravenberg E, Seth S, Yam C, Moulder SL and Damodaran S. Comprehensive analysis identifies variability in PI3K pathway alterations in triple-negative breast cancer subtypes. JCO Precis Oncol 2024; 8: e2300124.

[112] Yi J, Wang L, Du J, Wang M, Shen H, Liu Z, Qin Y, Liu J, Hu G, Xiao R, Ding J, Chen X, Wang H, Huang H, Ouyang G and Liu W. ER-localized JmjC domain-containing protein JMJD8 targets STING to promote immune evasion and tumor growth in breast cancer. Dev Cell 2023; 58: 760-778, e766.

[113] Huang D, Chen X, Zeng X, Lao L, Li J, Xing Y, Lu Y, Ouyang Q, Chen J, Yang L, Su F, Yao H, Liu Q,

Su S and Song E. Targeting regulator of G protein signaling 1 in tumor-specific T cells enhances their trafficking to breast cancer. Nat Immunol 2021; 22: 865-879.
[114] Soumoy L, Kindt N, Ghanem G, Saussez S and Journe F. Role of macrophage migration inhibitory factor (MIF) in melanoma. Cancers (Basel) 2019; 11: 529.
[115] Zhang H, Ye YL, Li MX, Ye SB, Huang WR, Cai TT, He J, Peng JY, Duan TH, Cui J, Zhang XS, Zhou FJ, Wang RF and Li J. CXCL2/MIF-CXCR2 signaling promotes the recruitment of myeloid-derived suppressor cells and is correlated with prognosis in bladder cancer. Oncogene 2017; 36: 2095-2104.
[116] Charan M, Das S, Mishra S, Chatterjee N, Varikuti S, Kaul K, Misri S, Ahirwar DK, Satoskar AR and Ganju RK. Macrophage migration inhibitory factor inhibition as a novel therapeutic approach against triple-negative breast cancer. Cell Death Dis 2020; 11: 774.
[117] Yan L, Wu M, Wang T, Yuan H, Zhang X, Zhang H, Li T, Pandey V, Han X, Lobie PE and Zhu T. Breast cancer stem cells secrete MIF to mediate tumor metabolic reprogramming that drives immune evasion. Cancer Res 2024; 84: 1270-1285.
[118] Wu M, Yuan K, Lyu S and Li Y. Screening potential immune signatures for early-stage basal-like/triple-negative breast cancer. World J Surg Oncol 2022; 20: 214.
[119] Lian B, Yan S, Li J, Bai Z and Li J. HNRNPC promotes collagen fiber alignment and immune evasion in breast cancer via activation of the VIRMA-mediated TFAP2A/DDR1 axis. Mol Med 2023; 29: 103.
[120] Sun X, Wu B, Chiang HC, Deng H, Zhang X, Xiong W, Liu J, Rozeboom AM, Harris BT, Blommaert E, Gomez A, Garcia RE, Zhou Y, Mitra P, Prevost M, Zhang D, Banik D, Isaacs C, Berry D, Lai C, Chaldekas K, Latham PS, Brantner CA, Popratiloff A, Jin VX, Zhang N, Hu Y, Pujana MA, Curiel TJ, An Z and Li R. Tumour DDR1 promotes collagen fibre alignment to instigate immune exclusion. Nature 2021; 599: 673-678.
[121] Ren Z, Xue Y, Liu L, Zhang X, Pei J, Zhang Y, Wang Y and Yu K. Tissue factor overexpression in triple-negative breast cancer promotes immune evasion by impeding T-cell infiltration and effector function. Cancer Lett 2023; 565: 216221.
[122] Carpenter KJ, Valfort AC, Steinauer N, Chatterjee A, Abuirqeba S, Majidi S, Sengupta M, Di Paolo RJ, Shornick LP, Zhang J and Flaveny CA. LXR-inverse agonism stimulates immune-mediated tumor destruction by enhancing CD8 T-cell activity in triple negative breast cancer. Sci Rep 2019; 9: 19530.
[123] Tengesdal IW, Li S, Powers NE, May M, Neff CP, Joosten LAB, Marchetti C and Dinarello CA. Activation of host-NLRP3 inflammasome in myeloid cells dictates response to Anti-PD-1 therapy in metastatic breast cancers. Pharmaceuticals (Basel) 2022; 15: 574.
[124] Wu Y, Yi Z, Li J, Wei Y, Feng R, Liu J, Huang J, Chen Y, Wang X, Sun J, Yin X, Li Y, Wan J, Zhang L, Huang J, Du H, Wang X, Li Q, Ren G and Li H. FGFR blockade boosts T cell infiltration into triple-negative breast cancer by regulating cancer-associated fibroblasts. Theranostics 2022; 12: 4564-4580.
[125] Meng J, Jiang YZ, Zhao S, Tao Y, Zhang T, Wang X, Zhang Y, Sun K, Yuan M, Chen J, Wei Y, Lan X, Chen M, David CJ, Chang Z, Guo X, Pan D, Chen M, Shao ZM, Kang Y and Zheng H. Tumor-derived Jagged1 promotes cancer progression through immune evasion. Cell Rep 2022; 38: 110492.
[126] Jenkins L, Jungwirth U, Avgustinova A, Iravani M, Mills A, Haider S, Harper J and Isacke CM. Cancer-associated fibroblasts suppress CD8+ T-cell Infiltration and confer resistance to immune-checkpoint blockade. Cancer Res 2022; 82: 2904-2917.
[127] Fang Y, Wang L, Wan C, Sun Y, Van der Jeught K, Zhou Z, Dong T, So KM, Yu T, Li Y, Eyvani H, Colter AB, Dong E, Cao S, Wang J, Schneider BP, Sandusky GE, Liu Y, Zhang C, Lu X and Zhang X. MAL2 drives immune evasion in breast cancer by suppressing tumor antigen presentation. J Clin Invest 2021; 131: e140837.
[128] Bagati A, Kumar S, Jiang P, Pyrdol J, Zou AE, Godicelj A, Mathewson ND, Cartwright ANR, Cejas P, Brown M, Giobbie-Hurder A, Dillon D, Agudo J, Mittendorf EA, Liu XS and Wucherpfennig KW. Integrin αvβ6-TGFβ-SOX4 pathway drives immune evasion in triple-negative breast cancer. Cancer Cell 2021; 39: 54-67, e59.
[129] de Visser KE and Joyce JA. The evolving tumor microenvironment: From cancer initiation to metastatic outgrowth. Cancer Cell 2023; 41: 374-403.
[130] Tokumaru Y, Le L, Oshi M, Katsuta E, Matsuhashi N, Futamura M, Yoshida K and Takabe K. Association of Th2 high tumors with aggressive features of breast cancer. J Clin Oncol 2020; 38: e12584.
[131] Lainé A, Labiad O, Hernandez-Vargas H, This S, Sanlaville A, Léon S, Dalle S, Sheppard D, Travis MA, Paidassi H and Marie JC. Regulatory T cells promote cancer immune-escape through integrin αvβ8-mediated TGF-β activation. Nat Commun 2021; 12: 6228.
[132] Batlle E and Massagué J. Transforming growth factor-β signaling in immunity and cancer. Immunity 2019; 50: 924-940.
[133] Huang P, Zhou X, Zheng M, Yu Y, Jin G and Zhang S. Regulatory T cells are associated with

the tumor immune microenvironment and immunotherapy response in triple-negative breast cancer. Front Immunol 2023; 14: 1263537.
[134] Han SJ, Jain P, Gilad Y, Xia Y, Sung N, Park MJ, Dean AM, Lanz RB, Xu J, Dacso CC, Lonard DM and O'Malley BW. Steroid receptor coactivator 3 is a key modulator of regulatory T cell-mediated tumor evasion. Proc Natl Acad Sci U S A 2023; 120: e2221707120.
[135] Li Y, Li Y, Yang Y, Deng Y, Ni X, Zhao B, Yan Z, He W, Li Y, Li S, Liu L and Lu D. Synergistic efficacy of PI3Kδ inhibitor with anti-PD-1 mAbs in immune-humanized PDX model of endocrine resistance hormone receptor-positive advanced breast cancer. Heliyon 2023; 9: e18498.
[136] Hu Q, Hong Y, Qi P, Lu G, Mai X, Xu S, He X, Guo Y, Gao L, Jing Z, Wang J, Cai T and Zhang Y. Atlas of breast cancer infiltrated B-lymphocytes revealed by paired single-cell RNA-sequencing and antigen receptor profiling. Nat Commun 2021; 12: 2186.
[137] Liu Z, Ding M, Qiu P, Pan K and Guo Q. Natural killer cell-related prognostic risk model predicts prognosis and treatment outcomes in triple-negative breast cancer. Front Immunol 2023; 14: 1200282.
[138] Thacker G, Henry S, Nandi A, Debnath R, Singh S, Nayak A, Susnik B, Boone MM, Zhang Q, Kesmodel SB, Gumber S, Das GM, Kambayashi T, Dos Santos CO and Chakrabarti R. Immature natural killer cells promote progression of triple-negative breast cancer. Sci Transl Med 2023; 15: eabl4414.
[139] Wang H, Gao L, Qi M, Su P, Xiong X, Zhao J, Hu J and Han B. BTF3 promotes stemness and inhibits Type I Interferon signaling pathway in triple-negative breast cancer. Biochem Biophys Res Commun 2021; 537: 22-28.
[140] Jing R, Bai S, Zhang P, Ren H, Jia L, Li W and Zheng G. IDO-1 impairs antitumor immunity of natural killer cells in triple-negative breast cancer via up-regulation of HLA-G. Breast Cancer 2024; 31: 135-147.
[141] Binnewies M, Roberts EW, Kersten K, Chan V, Fearon DF, Merad M, Coussens LM, Gabrilovich DI, Ostrand-Rosenberg S, Hedrick CC, Vonderheide RH, Pittet MJ, Jain RK, Zou W, Howcroft TK, Woodhouse EC, Weinberg RA and Krummel MF. Understanding the tumor immune microenvironment (TIME) for effective therapy. Nat Med 2018; 24: 541-550.
[142] Barkal AA, Brewer RE, Markovic M, Kowarsky M, Barkal SA, Zaro BW, Krishnan V, Hatakeyama J, Dorigo O, Barkal LJ and Weissman IL. CD24 signalling through macrophage Siglec-10 is a target for cancer immunotherapy. Nature 2019; 572: 392-396.
[143] Jaiswal R, Johnson MS, Pokharel D, Krishnan SR and Bebawy M. Microparticles shed from multidrug resistant breast cancer cells provide a parallel survival pathway through immune evasion. BMC Cancer 2017; 17: 104.
[144] Wang X, Tokheim C, Gu SS, Wang B, Tang Q, Li Y, Traugh N, Zeng Z, Zhang Y, Li Z, Zhang B, Fu J, Xiao T, Li W, Meyer CA, Chu J, Jiang P, Cejas P, Lim K, Long H, Brown M and Liu XS. In vivo CRISPR screens identify the E3 ligase Cop1 as a modulator of macrophage infiltration and cancer immunotherapy target. Cell 2021; 184: 5357-5374, e5322.
[145] De Paolis V, Maiullari F, Chirivì M, Milan M, Cordiglieri C, Pagano F, La Manna AR, De Falco E, Bearzi C, Rizzi R and Parisi C. Unusual association of NF-κB components in tumor-associated macrophages (TAMs) promotes HSPG2-mediated immune-escaping mechanism in breast cancer. Int J Mol Sci 2022; 23: 7902.
[146] Zheng C, Xu X, Wu M, Xue L, Zhu J, Xia H, Ding S, Fu S, Wang X, Wang Y, He G, Liu X and Deng X. Neutrophils in triple-negative breast cancer: an underestimated player with increasingly recognized importance. Breast Cancer Res 2023; 25: 88.
[147] Zimmerli D, Brambillasca CS, Talens F, Bhin J, Linstra R, Romanens L, Bhattacharya A, Joosten SEP, Da Silva AM, Padrao N, Wellenstein MD, Kersten K, de Boo M, Roorda M, Henneman L, de Bruijn R, Annunziato S, van der Burg E, Drenth AP, Lutz C, Endres T, van de Ven M, Eilers M, Wessels L, de Visser KE, Zwart W, Fehrmann RSN, van Vugt MATM and Jonkers J. MYC promotes immune-suppression in triple-negative breast cancer via inhibition of interferon signaling. Nat Commun 2022; 13: 6579.
[148] Mehdizadeh R, Shariatpanahi SP, Goliaei B and Rüegg C. Targeting myeloid-derived suppressor cells in combination with tumor cell vaccination predicts anti-tumor immunity and breast cancer dormancy: an in silico experiment. Sci Rep 2023; 13: 5875.
[149] Alshetaiwi H, Pervolarakis N, McIntyre LL, Ma D, Nguyen Q, Rath JA, Nee K, Hernandez G, Evans K, Torosian L, Silva A, Walsh C and Kessenbrock K. Defining the emergence of myeloid-derived suppressor cells in breast cancer using single-cell transcriptomics. Sci Immunol 2020; 5: eaay6017.
[150] Dawod B, Liu J, Gebremeskel S, Yan C, Sappong A, Johnston B, Hoskin DW, Marshall JS and Wang J. Myeloid-derived suppressor cell depletion therapy targets IL-17A-expressing mammary carcinomas. Sci Rep 2020; 10: 13343.
[151] Shi H, Qin Y, Tian Y, Wang J, Wang Y, Wang Z and Lv J. Interleukin-1beta triggers the expan-

sion of circulating granulocytic myeloid-derived suppressor cell subset dependent on Erk1/2 activation. Immunobiology 2022; 227: 152165.
[152] Pedersen MH, Hood BL, Beck HC, Conrads TP, Ditzel HJ and Leth-Larsen R. Downregulation of antigen presentation-associated pathway proteins is linked to poor outcome in triple-negative breast cancer patient tumors. Oncoimmunology 2017; 6: e1305531.
[153] Zhou Z, Van der Jeught K, Fang Y, Yu T, Li Y, Ao Z, Liu S, Zhang L, Yang Y, Eyvani H, Cox ML, Wang X, He X, Ji G, Schneider BP, Guo F, Wan J, Zhang X and Lu X. An organoid-based screen for epigenetic inhibitors that stimulate antigen presentation and potentiate T-cell-mediated cytotoxicity. Nat Biomed Eng 2021; 5: 1320-1335.
[154] Gu SS, Zhang W, Wang X, Jiang P, Traugh N, Li Z, Meyer C, Stewig B, Xie Y, Bu X, Manos MP, Font-Tello A, Gjini E, Lako A, Lim K, Conway J, Tewari AK, Zeng Z, Sahu AD, Tokheim C, Weirather JL, Fu J, Zhang Y, Kroger B, Liang JH, Cejas P, Freeman GJ, Rodig S, Long HW, Gewurz BE, Hodi FS, Brown M and Liu XS. Therapeutically increasing MHC-I expression potentiates immune checkpoint blockade. Cancer Discov 2021; 11: 1524-1541.
[155] Taylor BC, Sun X, Gonzalez-Ericsson PI, Sanchez V, Sanders ME, Wescott EC, Opalenik SR, Hanna A, Chou ST, Van Kaer L, Gomez H, Isaacs C, Ballinger TJ, Santa-Maria CA, Shah PD, Dees EC, Lehmann BD, Abramson VG, Pietenpol JA and Balko JM. NKG2A is a therapeutic vulnerability in immunotherapy resistant MHC-I heterogeneous triple-negative breast cancer. Cancer Discov 2024; 14: 290-307.
[156] Cheng SW, Chen PC, Lin MH, Ger TR, Chiu HW and Lin YF. GBP5 repression suppresses the metastatic potential and PD-L1 expression in triple-negative breast cancer. Biomedicines 2021; 9: 371.