

# Mechanism of immune evasion in breast cancer

Mozhi Wang<sup>1,\*</sup>  
 Changwang Zhang<sup>2,\*</sup>  
 Yongxi Song<sup>2</sup>  
 Zhenning Wang<sup>2</sup>  
 Yaojia Wang<sup>1</sup>  
 Fang Luo<sup>1</sup>  
 Yujie Xu<sup>1</sup>  
 Yi Zhao<sup>1</sup>  
 Zhonghua Wu<sup>2</sup>  
 Yingying Xu<sup>1</sup>

<sup>1</sup>Department of Breast Surgery,  
<sup>2</sup>Department of Surgical Oncology  
 and General Surgery, The First  
 Affiliated Hospital of China Medical  
 University, Shenyang, People's  
 Republic of China

\*These authors contributed equally  
 to this work

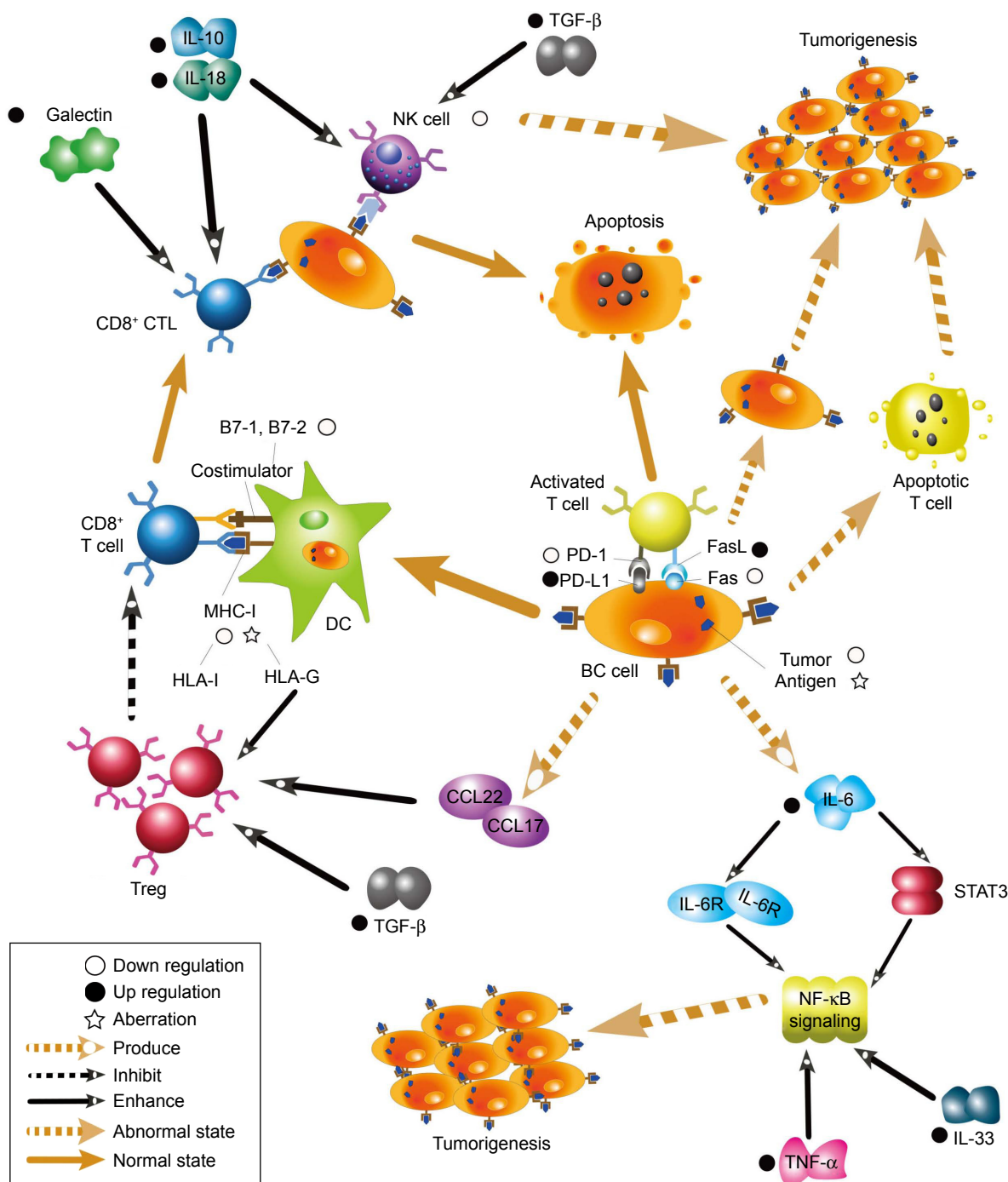
**Abstract:** Breast cancer (BC) is the most common malignant tumor among women, with high morbidity and mortality. Its onset, development, metastasis, and prognosis vary among individuals due to the interactions between tumors and host immunity. Many diverse mechanisms have been associated with BC, with immune evasion being the most widely studied to date. Tumor cells can escape from the body's immune response, which targets abnormal components and foreign bodies, using different approaches including modification of surface antigens and modulation of the surrounding environment. In this review, we summarize the mechanisms and factors that impact the immunoeediting process and analyze their functions in detail.

**Keywords:** immune evasion, mechanism, breast cancer, cytokines, apoptosis, PD-L1

## Introduction

Breast cancer (BC) has become the leading cause of death from malignant tumors among women worldwide in the past few decades.<sup>1,2</sup> It has an extremely high morbidity and mortality, and the molecular mechanisms of BC have attracted a large number of researchers. Cancer immunoeediting is a dynamic process by which the immune system attempts to destroy tumors, and it comprises three stages: elimination, equilibrium, and escape.<sup>3,4</sup> During the elimination stage, host immune factors respond to progressive tumors and destroy them early before clinical changes appear. In the long-lasting equilibrium stage, meager residual tumor cells survive and keep in quiescence.<sup>3</sup> Ultimately in the immune evasion stage, tumor cells gain the capacity to evade identification and attack by host immune responses using diverse mechanisms to survive and develop in the host.<sup>5</sup> As a significant part of immunoeediting, immune evasion has been recognized as a promising hallmark of BC in recent years. Gene mutations occasionally occur in somatic cells either spontaneously or owing to the combined action of various carcinogenic factors. Some mutated cells can recover through self-repair, whereas others undergo apoptosis. A few mutated cells express neoantigens on their membrane surface. These mutated cells with neoantigens are then identified as heterologous components and killed by innate and adaptive immunity components, and then cleared before tumors develop.<sup>6</sup> However, some primary tumors can escape host immunosurveillance and establish, develop, migrate, and relapse. It has been shown that the mechanisms adopted by tumor cells to escape immunosurveillance include the modification of surface antigens and alterations of their surrounding environment. These aspects converge at the microenvironment, which includes cancer cells and the environment by which they are surrounded. Herein, we review the current knowledge on immune evasion and the factors and pathways affecting this process during interactions between the immune system and tumors with the view of elucidating mechanisms of immune evasion and improving current immunotherapies. A summarized net of mechanisms is presented in Figure 1.

Correspondence: Yingying Xu  
 Department of Breast Surgery, The  
 First Affiliated Hospital of China Medical  
 University, 155 North Nanjing Street,  
 Shenyang 110001, Liaoning, People's  
 Republic of China  
 Tel +86 24 8328 2741  
 Fax +86 24 2270 3578  
 Email xuyingying@cmu.edu.cn



**Figure 1** A summarized network of immune evasion mechanisms and their interactions.  
**Abbreviations:** IL, interleukin; TGF-β, transforming growth factor type beta; NK, natural killer; CTL, cytotoxic T lymphocyte; MHC, major histocompatibility complex; DC, dendritic cell; PD-1, programmed death receptor 1; PD-L1, PD-1 ligand; FasL, Fas ligand; Fas, factor-associated suicide; HLA, human leukocyte antigen; BC, breast cancer; Treg, regulatory T cell; CCL, C-C motif chemokine ligand; STAT, signal transducer and activator of transcription; NF-κB, nuclear factor-kappa B; TNF-α, tumor necrosis factor alpha.

## Tumor-related immune evasion Types of tumor-associated antigens

The hypothesis that tumor cells are recognized as non-autogenous cells by T cells to induce host immune responses underlies the concept of tumor immunosurveillance.<sup>5</sup> BC cells can express specific surface antigens, distinct

from those expressed by normal somatic cells, to impair the innate and acquired immune system and trigger a series of immune responses.<sup>7</sup> There are three groups of tumor-associated antigens (TAAs): autoantigens or embryonic antigens, which are expressed excessively or abnormally; modified autoantigens, which are expressed specifically in

the presence of tumors; and neoantigens, which are derived from gene mutations, chromosomal aberrations, and viral transformation.<sup>8,9</sup> Because of these antigenic aberrations and the influence of host immunity, cells from the filial generation can become low-immunogenic tumor cells and compose the predominant cell types involved in resistance to the immune system.<sup>10</sup> Melanoma-associated antigens (MAGEs) are a family of cancer/testis antigens which play roles as TAAs, and MAGE-A9 and MAGE-A11 are reported to be less expressed in estrogen-receptor-negative and HER2-negative BC.<sup>11</sup> Inversely, MAGE-A9 is found to be significantly upregulated in invasive ductal BC and is positively correlated to unfavorable outcomes.<sup>12</sup> Tchou et al discovered that mesothelin is overexpressed in triple-negative breast cancer (TNBC) via modifying the T cell receptor (TCR).<sup>13</sup> Protein HER2/neu, known to be overexpressed in Her2-positive BC, is located primarily on the membrane of tumor cells. In addition, the expression of its extracellular domain is significantly higher in the sera of BC patients compared with tumor-free individuals, and its expression levels are positively correlated with histological tumor grade, suggesting that HER2/neu is overexpressed in and leads to the poor prognosis of Her2-positive BC.<sup>14</sup> The low expression of HER2/neu might restrict the immune-cell-mediated destruction of tumor cells; thus, TCR gene therapy that encodes for TCR and enhances the immune response has been profoundly studied and tested in clinical trials.<sup>13,15</sup> Additionally, a specially designed nanobody can selectively bind to TAA receptors.<sup>16</sup> Therefore, loss or modification of surface antigens may promote immune evasion via lack of tumor cell recognition. These mechanisms may become potential targets to broaden our immunotherapeutic strategies.

## Abnormal expression of major histocompatibility complex class I

Another type of antigen found on the membrane of tumors cells is presented by the major histocompatibility complex (MHC) class I, a subgroup of the MHC family. After interaction with MHC-I molecules, tumor antigens are presented on the surface of antigen-presenting cells for the tumor cells to be recognized, killed, and cleared by effector T lymphocytes.<sup>17</sup> Therefore, the loss or modification of MHC-I on the surface of tumor cells allows these cells to escape immunosurveillance. Tumor cells silence *MHC-I* genes and downregulate their transcription levels to circumvent the immune system. The indispensable MHC-I antigen-processing machinery (APM) is reported to be deficient in tumors, including in BC.<sup>18</sup> Furthermore, the beta-2 microglobulin, calnexin, and transporter-associated

antigen processing 1 are downregulated in metastatic brain lesions of BC and negatively associate with cytotoxic T lymphocytes (CTLs) infiltration.<sup>19</sup> Expression levels of human leukocyte antigen (HLA) class I molecules are significantly downregulated in BC, and this downregulation is necessary for the transformation of normal cells into abnormal cells. Gene mutation, loss of heterozygosity, and disturbance of transcriptional control can all be responsible for the low expression of HLA-I; this decreased expression of HLA-I lowers immunity and consequently is positively correlated with malignancy, metastasis, and prognosis of the tumor as a result of attenuated immunity.<sup>8</sup>

To obviate the potential for attack by CTLs and natural killer (NK) cells, HLA-G, the non-classical HLA-I antigen involved in immune mediation, is expressed on the surface of tumor cells.<sup>20</sup> Expression levels of HLA-G increase in BC,<sup>21</sup> which associates with poor prognosis.<sup>22</sup> Following studies on a 14 bp InDel polymorphism in the *HLA-G* gene, Haghgi et al performed genotyping and found that patients with higher BC stages had a higher frequency of allele deletion compared with patients with lower stages, indicating that the 14 bp InDel polymorphism in the *HLA-G* gene was a risk factor for the development of BC.<sup>23</sup> In addition, the area under the curve for receiver operating characteristic values of the soluble form of HLA-G (sHLA-G) can help identify metastasis, suggesting that sHLA-G may be utilized as a biomarker for the diagnosis of BC, particularly at the metastasis stage.<sup>24</sup> Furthermore, HLA-G may be present in exosomes to spread from tumor cells to other cells.<sup>25</sup> König et al found that distinct sHLA-G subcomponents differentially affected the prognosis of neoadjuvant chemotherapy-treated BC.<sup>21</sup> Due to the relationship between HLA-G expression and worsened BC prognosis, immunotherapeutic strategies to target HLA-G, and the DNA methyltransferase known to upregulate its expression are suggested.<sup>22</sup>

## Antiapoptosis function

The control and reduction of apoptosis, the highly selective and programmed form of cell death, have been considered a fundamental strategy for evading the immune response in cancer development.<sup>26</sup> Any part of the apoptosis pathway can be disturbed, causing endless proliferation of almost all types of cancers, including BC.<sup>27</sup> All factors discussed are listed in Table 1.

## Factor-associated suicide and its ligand

Factor-associated suicide (Fas) is a type II transmembrane protein from the tumor necrosis factor (TNF) family, also known as CD95 and Apo-1.<sup>28</sup> Fas is an important suicide

**Table 1** Factors influencing the cellular apoptosis in breast cancer

Factors	Expression level	Impact on tumor development	Detailed impact on mechanism	References
Fas/FasL	Fas↓	Induce apoptosis	Activate apoptosis signaling and induce apoptosis in the cells in which this receptor interacts with its ligand – FasL	28
	FasL↑	Decrease immunity	Maintain a proapoptotic environment Induce effector T lymphocytes to death and stimulate activation-induced cell death and escape immune recognition and interference	29 8, 30
PD-1/PD-1L	↑	Inhibit apoptosis	Inhibit the activation of effector T cells, which induce FasL and interleukin-10	32
			Attenuate T cell apoptosis	34
			Stimulate tumor regression, improve the outcomes, and prove clinically effective when PD-1/PD-L1 pathway is targeted and PD-1 is blocked	46, 49–51
Bcl-2	↑	Inhibit apoptosis	Inhibit the release of cytochrome C from mitochondria to the cytoplasm and the TRAIL-induced cellular apoptosis	55, 56
		Promote growth	Promote neoplastic transformation and prolong the life span of tumor cells by allowing them to accumulate oncogene mutations and stimulate the growth of BC cells	57, 58
Survivin	↑	Inhibit apoptosis	Associated with poorer outcome, advanced tumor grade, worse metastasis, and lower survival rate	59, 60
Caspase	↓	Promote apoptosis	Resist apoptosis by the downregulation of caspase activation	61

**Notes:** Various factors that can influence the programmed apoptosis are listed in the table along with their impacts on the cellular apoptosis in breast cancer. ↑ means upregulation and ↓ means downregulation.

**Abbreviations:** Fas, factor-associated suicide; FasL, Fas ligand; PD-1, programmed death receptor 1; PD-1L, PD-1 ligand; TRAIL, TNF-related apoptosis-inducing ligand; BC, breast cancer.

receptor because it can activate apoptosis signaling and induce apoptosis in cells in which the receptor interacts with its ligand–Fas ligand (FasL).<sup>28</sup> FasL expresses on the activated T lymphocytes, and its presence has been implied to maintain a proapoptotic environment.<sup>29</sup> T lymphocytes normally trigger apoptosis in Fas-expressing cells through the interaction of Fas and FasL, to limit rapid cell amplification and stimulate overactivated immune cells to downregulate the immune response (Figure 2). Increased FasL levels in BC cells induce effector T lymphocytes to die. Therefore, BC cells can stimulate activation-induced cell death and escape immune recognition and interference.<sup>8,30</sup> Another strategy adopted by tumor cells to resist Fas-mediated apoptosis is to silence or downregulate Fas and Fas/FasL signaling pathways. The specific intracellular signaling domain of Fas, the death domain, is deficient in BC.<sup>8</sup> Bębenek et al also demonstrated that loss of Fas and FasL was associated with worse prognosis. For this reason, these authors indicate that the Fas/FasL system can be used as a prognostic hallmark in BC.<sup>28</sup>

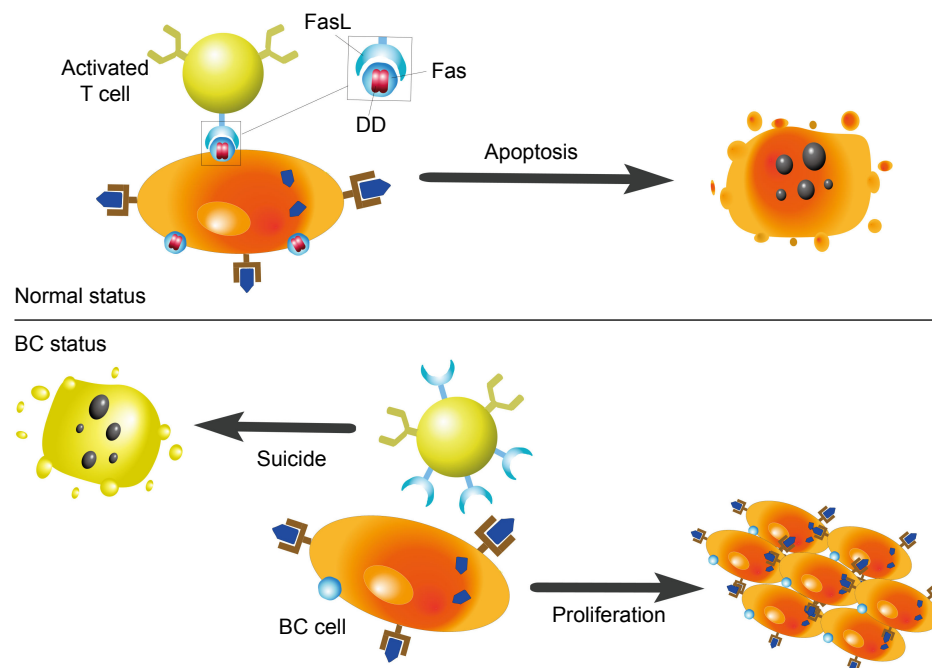
### Programmed death receptor 1 and its ligand

Programmed death receptor 1 (PD-1) is a crucial immunosuppressive molecule found in CTLs, BC cells, and antigen-presenting cells.<sup>31</sup> The interaction between PD-1 and its ligand, PD-L1, on the surface of tumor cells, inhibits the activation of effector T cells, which induce FasL and interleukin

(IL) 10. PD-L1 has been found on the surface of BC cells<sup>32</sup> and circulating tumor cells (CTCs).<sup>33</sup> The blockade of PD-L1 can significantly attenuate T cell apoptosis in tumor models, which might be due to the important role that PD-L1 plays on regulatory T cell (Treg) induction and maintenance.<sup>33,34</sup> While PD-L1 has been shown to directly synergize with FOXP3+ Tregs,<sup>34</sup> it has also been revealed to be modulated by several other factors. Ubiquitination and N-glycosylation have known effects on the immunosuppressive activity of PD-L1.<sup>35</sup> Also, increased expression of stem cell antigens Ly6K and Ly6E is reported to facilitate the activation and expression of cytokine-induced PD-L1, subsequently promoting drug resistance.<sup>36</sup> The alimentary nutrient apigenin and its essential component luteolin have both been shown to indirectly inhibit interferon (IFN)- $\gamma$ -induced PD-L1 expression via depression of signal transducer and activator of transcription (STAT) 1 phosphorylation, while not affecting constitutive PD-L1.<sup>31</sup>

The expression of PD-1/PD-L1 shows significant heterogeneity.<sup>37</sup> It has frequently been found to be upregulated in various types of BCs, including inflammatory BCs, small-cell carcinomas of the breast, and basal tumors.<sup>37–39</sup> Many researchers claim PD-L1 is overexpressed in TNBC,<sup>40–42</sup> and that it is related to tumor grade,<sup>43</sup> the local cytotoxic immune response, and prognosis.<sup>38,44</sup> Although Mazel et al also proved that CTCs of hormone-receptor-positive and HER2-negative BCs express higher level of PD-L1,<sup>45</sup> no specific studies on





**Figure 2** Influences of Fas/FasL system on apoptosis.

**Note:** This figure shows the way that Fas/FasL system applies to influence the apoptosis. In natural status, cells that can express Fas go through apoptosis after its combination to FasL in activated T cells. However, Fas is less expressed in BC cells and its specific intracellular signaling domain, the death domain (DD), is deficient. And the overexpression of FasL in activated T cells leads to T cells' suicide.

**Abbreviations:** FasL, Fas ligand; Fas, factor-associated suicide; DD, death domain; BC, breast cancer.

HER2-positive BC draw a similar conclusion. Moreover, PD-1/PD-L1-targeted therapies efficiently stimulate tumor regression and improve patient outcomes.<sup>46</sup> Two agents, the PD-1 inhibitor pembrolizumab and the PD-L1 inhibitor atezolizumab, have been tested in clinical trials and are shown to increase the lasting local antitumor response to therapies<sup>40</sup> with promising clinical benefit.<sup>47,48</sup> As immune checkpoint inhibitors, PD-1/PD-L1 antagonists can be combined with other targeting therapies, including inhibitors of MAP2K and glucocorticoid-induced tumor necrosis factor receptor (GITR). These combinatory approaches have proven effective in clinical trials for TNBC,<sup>49-51</sup> with the combination therapy improving outcome in vivo.<sup>52</sup> Nevertheless, Mall et al found that the repeated use of PD-1/PD-L1 monoclonal antibodies might exacerbate an as yet uncharacterized fatal xenogeneic hypersensitivity reaction observed in a BC murine model.<sup>53</sup> As the US Food and Drug Administration has admitted immunotherapeutic antibodies against PD-L1,<sup>54</sup> further research and development of novel therapeutic methods are promising and necessary to elucidate the role of PD-1/PD-L1 in distinctive BC.

### Bcl-2, survivin, and caspase

Other proteins are known to play significant roles in apoptosis in BC. The Bcl-2 protein encoded by the *bcl-2* oncogene is involved in the endogenous apoptosis pathway by inhibiting

the release of cytochrome C from mitochondria to the cytoplasm and consequently preventing tumor cell apoptosis.<sup>55</sup> High levels of Bcl-2 in BC cells inhibit the cellular apoptosis induced by TNF-related apoptosis-inducing ligand.<sup>56</sup> Bcl-2 promotes neoplastic transformation and prolongs the life span of tumor cells by allowing them to accumulate oncogenic mutations.<sup>57</sup> Studies using a double-transgenic murine model reported that overexpression of both Bcl-2 and c-Myc stimulated the growth of BC cells.<sup>58</sup> The expression of survivin, a prominent member of the family of antiapoptotic molecules, also increases in BC and is associated with poorer outcome, advanced tumor grade, worse metastasis, and lower survival rate.<sup>59,60</sup> The decrease in caspase activation is another mechanism used by cancer cells to resist apoptosis. Accordingly, the expression of caspase-3 is downregulated in BC.<sup>61</sup> However, the altered expression pattern of caspase-3 and caspase-7 was not strongly correlated with the clinicopathologic features of BC, indicating that the dysregulation of cellular apoptosis was much more complex than once thought.<sup>62</sup>

## Tumor microenvironment

The onset and metastasis of tumors are closely correlated with the tumor microenvironment. The microenvironment is influenced by the specific structures, functions, and metabolism of neoplastic lesions, and by the inner environment of tumor cells. Tumor cells use autocrine and paracrine mechanisms

to alter and maintain conditions essential for tumor survival, development, proliferation, and progression.<sup>63</sup> Recent advancements in the areas of oncology and molecular biology have helped elucidate the association between malignant breast tumor and the immune factors around the tumors.

## Tumor-infiltrating lymphocytes

Tumor-infiltrating lymphocytes (TILs) are a group of heterogeneous immune cells that primarily acquire immunosuppressive or immunomodulatory phenotypes and exert antitumor activity in the tumor environment. The synthesis and activation of TILs depend on the presence of chemokines and cytokines produced by tumor cells and immune cells that are present in tumor lesions.<sup>63</sup>

### Effector CD8<sup>+</sup> T lymphocytes

It is well supported that effector CD8<sup>+</sup> T lymphocytes which identify TAAs may serve as biomarkers and improve the outcomes in various tumor types.<sup>64</sup> However, these benefits depend on the interaction between the protective function of effector CD8<sup>+</sup> T lymphocytes and the deleterious function of regulatory immune cells that are produced to help tumors escape immunity. Due to the impact of the inhibitory environment and the xenogeneic immunogenicity of antigens, T lymphocytes may ignore tumor antigens in some tumor types, including BC. Peripheral antitumor CD8<sup>+</sup> T lymphocytes, which were different from those obtained from bone marrow, did not trigger an immune response in BC.<sup>65</sup> Additionally, CD8<sup>+</sup> T cells are able to restrain the anti-immune response capabilities of tumor cells. Thus, therapeutic strategies to evade or attack CD8<sup>+</sup> T cells might provoke strong immune responses.<sup>66</sup>

### Regulatory T cells

Tregs play a crucial role in immunosuppression.<sup>67</sup> Tregs can inhibit the proliferation and activation of effector T lymphocytes and the secretion of helper T lymphocyte 1 (Th1) cytokines, resulting in the suppression of antitumor immune responses.<sup>68</sup> Infiltration of Tregs is suggested to be significantly higher in TNBC than estrogen receptors/progesterone receptors-positive BC.<sup>69</sup> Tregs accumulate in BC, indicating that the multiplication of these cells may be the result of both the natural circulatory system and a local trigger.<sup>8,30,70</sup> The recruitment of Tregs to tumor lesions is dependent on C–C motif chemokine receptor (CCR) 4, modulated by several CCR family members such as CCR2,<sup>71</sup> and induced by compounds secreted by BC cells, macrophages, and dendritic cells (DCs).<sup>70</sup> C–C motif chemokine ligand (CCL) 22 and

CCL17 are specifically attractive to Tregs, as well.<sup>72</sup> Tregs can protect CTC from immune attack, alleviate the killing capacity of CTLs, and trigger larger quantity of myeloid-derived suppressor cells (MDSCs).<sup>33</sup> Immune infiltration of Tregs is related to clinical prognosis,<sup>72</sup> and can be augmented by Ly6E and Ly6K.<sup>36</sup> The upregulation of GITR-related protein with Treg-inhibiting activity increases the proliferation, activation, and synthesis of cytokines.<sup>49</sup> Recent studies found that the transforming growth factor type beta (TGF- $\beta$ )-SMAD3/SMAD4-mediated induction of CD25/IL-2 receptor alpha on the surface of CD4<sup>+</sup> T lymphocytes is blocked by inhibitors of MEK/ERK signaling in BC patients. In addition, the aberrant activation of Janus kinase 1/3-mediated STAT3/STAT5 decreased the expression of FOXP3.<sup>73</sup> Due to the synergistic action of FOXP3<sup>+</sup> Tregs and PD-L1, immune evasion is intensified when FOXP3<sup>+</sup> Tregs and PD-L1 are both upregulated.<sup>34</sup> Therefore, a combination therapy strategy against both FOXP3<sup>+</sup> Tregs and PD-L1 might be promising.

## Antigen presentation

T lymphocytes induce cellular immunity and target immunogenic tumor cells. The activation of non-sensitized T lymphocytes requires a secondary signal, which is triggered by the interaction of antigen-presenting cells or costimulating factors with the costimulatory molecules receptor as well as by the primary signaling.

### Dendritic cells

DCs are myeloid- and plasmacytoid-derived professional antigen-presenting cells that initiate immune escape, activate naïve T cells, and induce memory T cells.<sup>74</sup> A few mature DCs have been found in BC, revealing the complexity of antigen presentation and activation of the immune response against these tumors.<sup>75</sup> The large number of immature DCs and the dysfunction of DCs promote immune tolerance and hinder the effective activation of cytotoxicity.<sup>76,77</sup> The mechanisms mentioned constitute novel approaches of a clinical therapeutic method. The increased use of DC vaccine for BC patients in the past few years has increased the number of clinical adverse reactions and reminded the scientific community that important mechanisms other than dysregulation of DCs and immune escape may be occurring.<sup>74</sup> da Cunha et al proposed that immunoinhibitory regulatory DCs are polarized by the tumor microenvironment, changing to a tolerogenic phenotype to promote tumor development and growth.<sup>78</sup> The dysfunction of DCs is due to the abnormal differentiation of myeloid cells, and decreases the number of mature DCs and the expression of MHC-II, colony-stimulating factor (CSF),

and adhesion molecules. Accordingly, tumor antigens are not adequately presented, and CSFs and adhesion molecules are downregulated on the surface of DCs.<sup>77</sup> It has been recently shown that the differentiation of myeloid cells into DCs can be blocked by the tumor-dependent activation of STAT3 signaling in myeloid progenitor cells.<sup>79</sup> In summary, DCs and their mechanisms of action and differentiation should be the focus of future studies.

### NK group 2, member D

NK group 2, member D (NKG2D) receptors are located on the surface of NK cells and in some T cells to recognize ligands on the cellular surface.<sup>80</sup> Tumors can exploit this by using sustained enhanced ligand production to downregulate the expression levels of NKG2D receptors and can directly blunt NKG2D via production of TGF- $\beta$  as well.<sup>81,82</sup> Crane et al also reported that tumor cells may produce soluble factors which induce expression of the NKG2D ligand on the surface of immune cells, thereby circumventing immunity.<sup>83</sup> The results of a tumorigenicity test using an orthotopic xenotransplant BC model indicated that the self-stimulation of NKG2D could promote BC by increasing angiogenesis and promoting tumor growth, intravasation, and dissemination; however, NKG2D expression did not affect tumor proliferation or survival.<sup>84</sup>

### Costimulators

T lymphocytes are activated by costimulators including the classical B7 family and the non-classical B7 homologous family.<sup>85</sup> Tumors lack the classical costimulators CD80 and CD86 cells and, for this reason, weakly recognize HLA-II antigens.<sup>86</sup> Therefore, T lymphocyte-activated signals would not reach the threshold for antitumor signals necessary to subvert the immune system.<sup>87</sup> Tumor cells can thwart the expression of B7-1 and B7-2 molecules to inactivate T lymphocyte clones, and stimulate the expression of B7-H1 and B7-H4 molecules to enhance the secretion of IL-10 and trigger apoptosis in CTLs via upregulation of activated Fas/FasL on the surface of T lymphocytes. CTL-associated antigen 4 (CTLA-4) is a transmembrane receptor on T cells which shares the same B7 ligand with CD28.<sup>88</sup> CTLA-4 transduces an intrinsic negative signal in effective T cells and directly negatively regulates the immune response.<sup>89</sup> Accordingly, CTLA-4 has been regarded as the other essential immune checkpoint inhibitor besides PD-L1.<sup>90</sup> Single-dose and combination therapies of the anti-CTLA-4 monoclonal antibody ipilimumab are under evaluation in clinical trials.<sup>91</sup> Engel et al demonstrated that expression

levels of B7-H1 increased in TNBC but were similar to those found in other BC subgroups.<sup>69</sup> However, the elevated expression level of B7-H4 was correlated with the negative status of receptors and the positive state of Her2/neu.<sup>92</sup> In addition, mechanistic studies of BC indicated that the presence of B7x correlated with a reduction in general and tumor-specific T cell cytokine responses as well as with increased infiltration of immunosuppressive cells to escape local antitumor immune responses via inhibition of the proliferation of both CD4 and CD8 T cells.<sup>93</sup> Therefore, targeting the costimulatory pathway holds promise for improving the efficacy of immunotherapy for BC.

### Inflammation and inflammatory mediators

Host immunity can affect tumors growth both in promotive and suppressive ways, and this immunoediting is a dynamic process that involves tumors and the host immune response and consists of three stages: elimination, equilibrium, and escape.<sup>3,4</sup> During the elimination stage, inflammation is acute and tumor-inhibitory, and characterized by the infiltration of effector cells and antitumor cytokines. In contrast, during the immune escape stage, inflammation is chronic and tumor-promoting and characterized by the infiltration of inhibitory immune cells and soluble cytokines.<sup>5</sup> Therefore, inflammation is critical for tumor onset, development, angiogenesis, and migration in BC, and cytokines play a unique role in each event.<sup>85</sup>

### Transforming growth factor type beta

TGF- $\beta$  is a functional bidirectional cytokine and the most studied immunosuppressive cytokine induced by BC.<sup>94</sup> TGF- $\beta$  belongs to the TGF- $\beta$  superfamily and has antiproliferative activity in the early phases of cancer, acting through cell cycle arrest. TGF- $\beta$  inhibits estrogen receptor alpha-mediated cancer proliferation.<sup>95,96</sup> Mutations responsible for the antitumor effect and alterations of TGF- $\beta$  signaling have been detected in BC.<sup>97</sup> In activated T cells, TGF- $\beta$  is translocated to the nucleus and induces c-Myc to promote tumor-associated inflammation in the later BC stage.<sup>98</sup> TGF- $\beta$  is a microtubule-destabilizing agent that targets p53 in human BC.<sup>99</sup> Additionally, TGF- $\beta$  was implied to interact with Wnt signaling, Her2, and focal adhesion kinase for epithelial-to-mesenchymal transition (EMT) and allows for the development of cancer stem cells.<sup>99-101</sup> In recent years, some factors associated with TGF- $\beta$  have been identified and examined. Small molecules such as galunisertib inhibit the TGF- $\beta$  receptor I kinase by inhibiting the phosphorylation of SMAD2

and activation of the classical TGF- $\beta$  signaling pathway.<sup>94</sup> A subset of inducible or adaptive Tregs is enhanced by TGF- $\beta$  and suppresses antitumor immunity.<sup>102</sup>

### Interleukins

IL-6 can be produced by BC cells and by fibroblasts in BC. IL-6 regulates BC stem cells by activating STAT3 and the IL-6 receptor/GP130 complex.<sup>103–105</sup> In the initiation stage, when nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) signaling is activated by IL-6 and STAT3, NF- $\kappa$ B can change from a normal phenotype to an aberrant phenotype via self-regulation and inflammatory cytokines involved in NF- $\kappa$ B signaling.<sup>9</sup> Increased invasion and EMT were also found to occur via IL-6 upregulation.<sup>106</sup>

IL-33 stimulates the expression and activation of MDSCs, and induces the autocrine production of granulocyte-macrophage CSF in the tumor microenvironment. Therefore, IL-33 mitigates apoptosis and promotes the survival of MDSCs. In addition, it also causes immunosuppression via activation of NF- $\kappa$ B and mitogen-activated protein kinase signaling.<sup>107</sup>

IL-18 is an antitumor inflammatory factor that activates CTLs and NK cells, induces antitumoral IFN- $\gamma$  expression and osseous metastasis,<sup>108</sup> and promotes tumorigenesis.<sup>109</sup> IL-18 is essential for distal metastasis in BC.<sup>110</sup> IL-19 and IL-20 provide a favorable microenvironment for tumor growth and foster the proliferation and progression of BC

via synthesis of matrix metalloproteinases.<sup>111,112</sup> IL-23 can modulate CD8<sup>+</sup> T cell infiltration and promote inflammation-related development in the BC microenvironment.<sup>113</sup> IL-10 can activate both NK cells and CTLs to inhibit development and metastasis of BC cells, and a few researchers have described its negative effect on tumorigenicity.<sup>114</sup> The mentioned studies are summarized in Table 2.

### Tumor necrosis factor alpha

TNF- $\alpha$  is an inflammatory cytokine induced by toll-like receptors (TLRs) which stimulates the NF- $\kappa$ B signaling pathway to promote tumor development via modulation of antiapoptotic effects, tumor cell proliferation, angiogenesis, and metastasis.<sup>115</sup> The expression level of TNF- $\alpha$  increases significantly in malignant breast tumors possibly due to gene polymorphisms.<sup>116</sup> Owing to the dual effects of TNF- $\alpha$ , its synergic association with NF- $\kappa$ B is important. TNF- $\alpha$  stimulates cyclin D1 via activation of NF- $\kappa$ B to induce the proliferation of BC T47D cells;<sup>117</sup> however, it also induces apoptosis of T47D cells in vitro.<sup>118</sup> Activation of the TNF- $\alpha$ /NF- $\kappa$ B pathway enhances the invasion and malignancy of BC,<sup>119</sup> whereas inhibition has the opposite effect.<sup>120</sup> Altogether, these results indicate that TNF- $\alpha$  promotes apoptosis and tumorigenesis concurrently. It acts as an antitumor agent locally and induces cellular proliferation and metastasis in the tumor microenvironment.<sup>55</sup> In addition, the increased susceptibility of TNF- $\alpha$  triggered by the loss

**Table 2** Interleukins associated with the immune evasion in breast cancer

Interleukins	Action on BC	Impact on tumor development	Impact on mechanism	References
IL-6	Promotion	Invasion $\uparrow$ EMT	Take part in the activation of NF- $\kappa$ B signaling pathway by the activation of STAT3 and IL-6 receptor/GP130 complex, thus changing its phenotype to variants	103–105
IL-10	Promotion	Angiogenesis $\uparrow$ Invasion $\uparrow$	Activate CTL and NK cells, increase tumor infiltration, and inhibit metalloproteinase	114
	Inhibition	Growth $\downarrow$ Metastasis $\downarrow$	Induction of NK-mediated lysis of BC	
IL-18	Promotion	Tumorigenesis $\uparrow$ Distal metastasis $\uparrow$	Activate CTL and NK cells and induce IFN- $\gamma$	109, 110
	Inhibition	Local impact		
IL-19 and IL-20	Promotion	Growth $\uparrow$ Proliferation $\uparrow$ Progression $\uparrow$	Synthesis of matrix metalloproteinase	111, 112
IL-23	Promotion	Inflammation $\uparrow$	Modulate infiltration of CD8 <sup>+</sup> T cells and inflammation-related development of breast cancer microenvironment	113
IL-33	Tumor	Apoptosis of MDSC $\downarrow$	Induce the autocrine production of GM-CSF Activate NF- $\kappa$ B and mitogen-activated protein kinase signaling	107

**Notes:** Different interleukins are listed in the table along with their influences on the immune evasion in breast cancer.  $\uparrow$  means increase and  $\downarrow$  means decrease.

**Abbreviations:** BC, breast cancer; IL, interleukin; NF- $\kappa$ B, nuclear factor-kappa B; STAT, signal transducer and activator of transcription; EMT, epithelial-to-mesenchymal transition; CTL, cytotoxic T lymphocyte; NK, natural killer; IFN- $\gamma$ , interferon gamma; MDSC, myeloid-derived suppressor cell; GM-CSF, granulocyte-macrophage colony-stimulating factor.



of the anti-HER2 Th1 response may reflect a mechanism of immune evasion in HER2-driven tumorigenesis.<sup>121</sup>

### Galectin and indoleamine-2,3-dioxygenase

Galectin is an evolutionarily conserved glycan-binding protein that contains a recognition domain identical to that of  $\beta$ -galactosidase and is involved in the proliferation, adhesion, migration, apoptosis, and angiogenesis of tumor cells. An analysis of BC specimens indicated that galectin-1 can be used in tumor grading.<sup>122</sup> Stannard et al evaluated galectin inhibitor disaccharides and observed that galectin-1 could promote tumor progression by blocking the antitumor function of CD8<sup>+</sup> CTLs.<sup>123</sup> In addition, other studies were performed to prove that the silencing of galectin-1 could markedly reduce tumor growth and lung metastasis by decreasing the expression and immunosuppressive activity of CD4<sup>+</sup>CD25<sup>+</sup>FOXP3<sup>+</sup> Tregs.<sup>124,125</sup>

Indoleamine-2,3-dioxygenase (IDO) is an immune inhibitor in malignant tumors.<sup>126</sup> IDO causes tryptophan catabolism, resulting in biostatic tryptophan starvation and l-kynurenine production, the latter helping to control the interaction between BC and host immunity.<sup>127</sup> Levina et al discovered that the immune response was enhanced when IDO1 was not expressed or expressed at low levels, demonstrating that the enhanced immune evasion associated with tumor cell proliferation and cell cycle increase as well as apoptosis resistance was due to the upregulation of IDO.<sup>128</sup> These results indicate that the increased expression of IDO can help counterbalance host immunity and BC aggression.

### Myeloid-derived suppressor cells

MDSCs are a group of heterogeneous bone marrow-derived immature cells that significantly suppress the immune response.<sup>129</sup> MDSCs must be amplified, recruited, and activated before they successfully differentiate into DCs, macrophages, and granular leukocytes. MDSC accumulation can inhibit mature DCs and the antitumor immune response. Additionally, the enhanced stem-like qualities of BC cells and lower activation of T cells modulated by MDSCs were revealed recently.<sup>130</sup> Mononuclear MDSCs can differentiate into macrophages and mature DCs via modulation of nitric oxide, inhibitory cytokines, and arginase-1. Granular MDSCs, the other subset of MDSCs, inhibit the immune response via direct intracellular contact and production of reactive oxygen species/intermediate nitrogen species. Cancer-associated fibroblasts, a subset of MDSCs with a similar phenotype, are an important group of interstitial

tumor cells characterized by low expression of CD80 and MHC-II in BC, suggesting their involvement in immune evasion.<sup>86</sup> In addition to these subsets, the location of MDSCs also influences their suppressive ability. Tumor-infiltrating MDSCs are more strongly inhibited by tumor-producing cytokines such as IL-33 compared to peripheral MDSCs.<sup>107</sup> Several factors and agents targeting MDSCs have been investigated in recent years. Polyinosinic-polycytidylic acid, a ligand for TLR-3, decreases the number of MDSCs and the immunosuppressive activity in BC by augmenting the T cell response.<sup>131</sup> In addition, previous studies have suggested that, in addition to its cytotoxicity against tumor cells, doxorubicin plays a major role in the reduction of MDSC-induced immunosuppression.<sup>132</sup>

### Discussion

BC has become a major research focus because of its high susceptibility and malignancy in women. The traditional therapy of surgical excision has limited effects due to frequent distal metastasis and invasion, while chemotherapy and radiotherapy leave a great burden on the normal tissues of body.<sup>133</sup> Thus, it is urgent to exploit promising therapeutic strategies. Since cancer immunotherapy was prized as a breakthrough,<sup>134</sup> immune evasion has become one of the most important topics to be investigated. Herein, we reviewed the latest findings in mechanisms of immune evasion in BC. Tumor-related immune evasion includes the deficiency and modification of TAAs, the abnormal expression of MHC-I, and antiapoptosis functions. TAAs, including autoantigens, modified antigens, and neoantigens, can express in both BC cells and host immune cells when the microenvironment of tumor comes into being. Any modification or mutation of antigens might alter tumor cells' immunogenicity, resulting in the various characteristics of different subtypes of BCs. MHC-I molecules help in antigens presentation and identification by T cells; hence, absence of MHC-I and MHC-I APM in BC might attenuate immune responses. In addition, HLA-G, normally presented on the host immune cells, is overexpressed on BC cells to escape destruction via CTLs and NK cells, and associates to poor prognosis. Inhibition of cellular programmed apoptosis might accelerate tumor cell proliferation. Targeting Fas/FasL and PD-L1/PD-1 axes can disturb the endless proliferation of tumor cells and is a potential immunotherapeutic strategy on which researchers have focused in recent years. In the tumor microenvironment, there are numerous factors such as TILs, processes related to antigen presentation, and inflammation-related cytokines. TILs play essential roles in antitumor function and

the process of antigen presentation to ensure the detectability of tumor cells. Numerous stages of immunoeediting show different types of inflammation, and inflammatory mediators are involved in various key pathways, while MDSCs are heterogeneous and immunosuppressive.

## Limitations

It should be noted that there are still limitations existing in this review. Although these individual mechanisms are known, their joint functions remain unclear. Tumor growth and progression are associated with complex and systemic pathological processes, which must be connected in some manner. The integrity of the human body should not be disconnected from the tumor environment. This correlation will need to be determined and summarized clearly so that immunotherapeutic strategies can be designed effectively. This approach is promising to avoid clinically adverse reactions and reduce metastasis and the mortality rate.

## Conclusion

Mechanisms of immune evasion in BC have been studied for decades and provide numerous promising targets for immunotherapy. The two significant immune checkpoint inhibitors, PD-L1/PD-1 ligand–receptor pairs and CTLA-4, have been studied and intervened with through immunotherapy. The improvement of basic researches and clinical trials aiming at checkpoint inhibitors might indicate applicable preclinical detection and diagnostic approaches as well as their clinically therapeutic strategies.

## Acknowledgments

This work was supported by the National Natural Science Foundation of China (81372550), Program of Education Department of Liaoning Province (L2014307), and the Key Laboratory Programme of Education Department of Liaoning Province (LZ2015076, LZ2015080).

## Disclosure

The authors report no conflicts of interest in this work.

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