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Review Article

Interleukin-10: A double-edged sword in breast cancer

Chun-Ming Chang[a,b], Ho Yin Pekkle Lam[b,c], Hao-Jen Hsu[c,d], Shinn-Jong Jiang[c]**

[a]Department of General Surgery, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan, [b]Institute of Medical Sciences, Tzu Chi University, Hualien, Taiwan, [c]Department of Biochemistry, School of Medicine, Tzu Chi University, Hualien, Taiwan, [d]Department of Life Sciences, College of Medicine, Tzu Chi University, Hualien, Taiwan

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Abstract

Breast cancer (BC) is a frequently diagnosed cancer among women worldwide. Currently, BC can be divided into different subgroups according to the presence of the following hormone receptors: estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2. Each of these subgroups has different treatment strategies. However, the presence of new metastatic lesions and patient deterioration suggest resistance to a given treatment. Various lines of evidence had shown that cytokines are one of the important mediators of tumor growth, invasion, metastasis, and treatment resistance. Interleukin-10 (IL-10) is an immunoregulatory cytokine, and acts as a poor prognostic marker in many cancers. The anti-inflammatory IL-10 blocks certain effects of inflammatory cytokines. It also antagonizes the co-stimulatory molecules on the antigen-presenting cells. Here, we review the current knowledge on the function and molecular mechanism of IL-10, and recent findings on how IL-10 contributes to the progression of BC.

Keywords: *Breast cancer, Cytokine, Interleukin-10, Tumor microenvironment*

Introduction

Breast cancer (BC) is the most common cancer among women worldwide. According to the World Cancer Research Foundation and the American Cancer Institute, it accounts for 25.4% of the total number of new cancer cases in 2018 [1]. Currently, BC can be divided into different categories based on the presence of the following three hormone receptors: estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2) [2]. BC lacking expression of all the three types of hormone receptors is classified as triple-negative BC (TNBC) [3], which makes up 12%–17% of all BC cases, and has a discouraging clinical outcome due to the lack of targeted therapy [4]. In addition, TNBC is characterized by high nuclear grade, high mitotic activity, high metastasis rate, and low overall survival rate [5].

Tumor cells have the ability to escape immune surveillance and evade apoptosis [6,7]. Tumor microenvironment (TME) is one of the reasons tumor can escape host immune response. The TME comprises of many immunosuppressive cells including regulatory T (Treg) cells, T helper type 2 (Th2) cells, tumor-associated macrophages (TAMs), myeloid-derived suppressor cells, and, in some case, Th17 cells [8-10]. Therefore, immunotherapy that modulates host immune response and restores immune surveillance may be a promising strategy for treating BC, particularly TNBC.

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The relative low survival rate of BC has been suggested to be associated with lymph node (LN) metastasis. In a multivariate analysis, lymphatic invasion, but not vascular invasion, was identified as a poor prognostic factor in patients with BC [11,12]. In addition, lymphatic vessel proliferation and LN metastasis, which are the events related with BC malignancy, were associated with dense infiltration of inflammatory cells [11,13], particularly tumor infiltrating lymphocytes (TILs) and TAMs [14,15].

More currently, the presence of TILs has been used to predict patient's response to chemotherapy in different subtypes of BC and other cancers [15-18]. For example, increased TILs are associated with better prognosis in HER2-positive BC and TNBC, while it is associated with a worse prognosis in luminal-HER2-negative BC. TILs consist predominantly of T cells. CD8+ T cells and natural killer (NK) cells usually correlate with favorable outcomes as these cells aid in tumor cell destruction [8,19]. CD4+ T cells enhance penetration of CD8+ T cells by producing Th1 cytokines and activate antigen-presenting cells (APCs) such as dendritic cells to

Address for correspondence:
Prof. Shinn-Jong Jiang,
Department of Biochemistry, School of Medicine, Tzu Chi University, 701, Section 3, Zhongyang Road, Hualien, Taiwan.
E-mail: sjjiang@mail.tcu.edu.tw

Prof. Hao-Jen Hsu,
Department of Biochemistry, School of Medicine, Tzu Chi University, 701, Section 3, Zhongyang Road, Hualien, Taiwan.
E-mail: hjhsu32@mail.tcu.edu.tw

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participate in anti-tumor responses [9]. M0 (nonactivated type) macrophages can polarize to M1 (pro-inflammatory, anti-tumor type) and M2 (anti-inflammatory type) states and produce certain cytokines. The cytokines produced by these cells can affect various stages of tumor progression, including initiation, promotion, proliferation, tumor cell transition, angiogenesis, invasion, immune surveillance escape, metastasis, and drug resistance [20]. BC is not a cold tumor that contains only few infiltrating T cells. Instead, immune cells usually infiltrate the tumors and its TME. However, the TME is generally in an immunosuppressive state.

Various lines of evidence had shown that increased Treg cells in BC confer a more aggressive phenotype, which is characterized by decreased survival rate and increased relapse rate [21-23]. Tumor shrink was observed in a Treg depletion BC model, suggesting that the presence of Treg cells can promote tumor cell growth and metastasis [24-27]. In an oncogene-driven BC model, transient removement of Treg cells led to the reduction of both primary and metastatic tumors [28]. The existence of Treg cells in the TME has been found to be associated with human tumors' development and metastasis including BC [29-32]. Although experiments have demonstrated that Treg cell can be used as a therapeutic target, the nature of Treg cells in human tumors remains unclear.

Treg cells have shown to be associated with many cytokines that are known to survey BC [33,34]. Interleukin 10 (IL-10), of all, plays an important coordination role in the occurrence of BC [35]. IL-10 is one of the anti-inflammatory cytokines, and can inhibit inflammatory responses by antagonizing the co-stimulatory molecules expressed on the APCs [36]. Here, we review the function and molecular mechanism of IL-10, and how IL-10 contributes to the progression of BC.

Interlukin-10

The gene of IL-10 locates on chromosome 1 at q31-32 [37] and is composed of five exons [38]. IL-10 protein encoded by this gene consists of 160 amino acids with a molecular weight of 18 kDa and forms a dimer to exert its function [39]. Human IL-10 shows 73% amino acid sequence similarity with murine IL-10 [39]. IL-10 is expressed by many immune cells including macrophages, T cells, and NK cells [40], and is a pleiotropic cytokine that has both immunomodulatory [41-43] and antiangiogenic properties [41]. IL-10 is expected to play a key role in limiting the host immune response during infection, inflammation, autoimmunity, transplantation, and tumorigenesis [44,45]. IL-10 is also known as the cytokine synthesis inhibitory factor [39] which can inhibit the production of IL-1α, IL-1β, IL-6, IL-8, IL-12, and IL-18, as well as TNF-α and granulocyte macrophage-colony-stimulating factor in T cells and macrophage. In addition, IL-10 diminishes the expression of interferon (IFN)-γ in Th cells and peripheral blood mononuclear cells and stimulates the proliferation of mast cells.

Interlukin-10 signaling pathways

The receptor of IL-10 is a tetrameric transmembrane receptor complex containing two IL-10RA (also known as IL-10R1) and two IL-10RB (also known as IL-10R2) proteins [36]. Both receptors are classified as class II cytokine (CRF2) family which is composed of an intracellular domain, a transmembrane domain, and an extracellular domain [36]. IL-10RA has higher affinity for IL-10 than IL-10RB. IL-10 binds to the extracellular domain of IL-10RA and causes phosphorylation of Janus kinase-1 (JAK1) and tyrosine kinase-2 (TYK2). Once phosphorylated, JAK1 further phosphorylates the signal transducer and activator of transcription-3 (STAT3) and STAT3, then translocases to the nucleus, and turns on the transcription of anti-apoptotic and cell cycle-related genes [36]. Conversely, STAT3 silencing and the suppressor of cytokine signaling 3 (SOCS3) protein reduces the expression of IL-10 [39]. In addition to the JAK/STAT3 pathway, IL-10 activates the phosphoinositide 3-kinase (PI3K)/Akt/GSK3 β signaling cascade and modulates downstream transcription in macrophages [46,47]. Moreover, IL-10 modulates mTOC1 activity in PI3K-mediated monocytes [46]. Meanwhile, the activation of PI3K/Akt/mTOC1 and STAT3 pathways by IL-10 requires AMPK signaling [48]. Notably, IL-10R activation also stimulates STAT1 and STAT5 pathways [49-52].

Along with IL-10, IL-6 is also involved in STAT3 activation [Figure 1]. Although pro-inflammatory and anti-inflammatory cytokines can work within the same cell or through the same signaling pathway, they perform very distinct functions and their downstream mechanisms are different [53-55]. A reasonable explanation may depend on the synergistic effect of STAT3 and other transcriptional cofactors that provide different gene expression programs. For

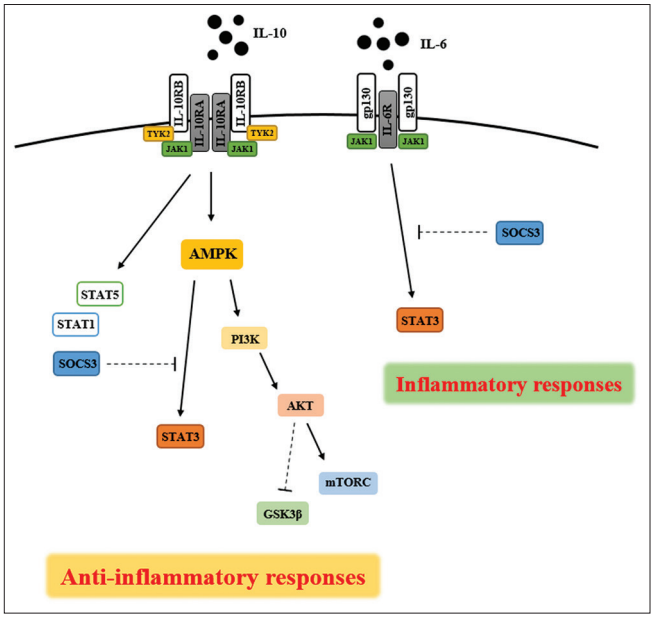

Figure 1: Interleukin-10 signaling pathway. Binding of interleukin-10 to its receptor causes phosphorylation of JAK1 and TYK2. Once phosphorylated, JAK1 further phosphorylates signal transducer and activator of transcription-3 through AMPK. The signal transducer and activator of transcription-3 translocates into the nucleus and upregulates anti-inflammatory genes. Interleukin-10 also activates PI3K/Akt/mTOC pathway and inhibits GSK3β to promote anti-inflammatory responses. Interleukin-6, on the contrary, also activates signal transducer and activator of transcription-3 pathway. However, it upregulates pro-inflammatory genes and causes inflammatory response. The signal transducer and activator of transcription-3 signaling can be inhibited by the suppressor of cytokine signaling 3

example, in macrophages, both IL-10 and IL-6 induce the activation of SOCS3, but SCOS3 only inhibits the activity of IL-6R (gp130) [56,57]. In addition, IL-10-stimulated-heme oxygenase 1 contributes to the anti-inflammatory response triggered by macrophages [58]. Recently, Khan *et al*. found that SOCS3 and STAT-3 activities were regulated by downstream regulated gene 2 product (NDRG2) which suppresses IL-10 expression [39].

The association of interlukin-10 with tumor-associated macrophage and regulatory T cells

TAM has been found as the most abundant infiltrating leukocyte in most tumors and is thought to be correlated with a worse outcome in many tumors [59,60]. TAM facilitates tumor progression by its immunosuppressive effects. Many immunosuppressive products such as IL-10, cathepsin B, and cathepsin S were produced by TAM in tumor sites [61]. IL-10 produced by TAM has been reported to contribute to therapeutic resistance in BC including irradiation, chemotherapy, and immunotherapy [62]. TAM-associated BC drug resistance is frequently associated with increased BCL2 expression and activation of STAT3 signaling [63]. Because TAM may lead to therapeutic resistance, finding new and efficient therapies for BC is important. Currently, the use of IL-10 neutralizing antibody has been discussed and may be effective in TAM-induced BC. Tumor infiltrating Treg cells and macrophages were reported to be the origin of IL-10 production in murine tumor model [64]. Therefore, chemotherapy-induced TAM which infiltrates the BC may recruit IL-10/IL-10R pathway and play a role in tumor pathogenesis. By targeting the IL-10 signaling pathway, we may expect a decreased therapeutic resistance and a better clinical outcome [62].

IL-10 brings into its immunosuppressive function at many aspects: suppression of T cell proliferation [65], modulation of APCs [66], and preservation of the activity/stability of Treg cells [67,68]. It is still unclear about the effect of IL-10 on Treg cells, even though it is already known that IL-10 plays a major role in Treg suppression [69,70]. A previous study indicated that IL-10 magnifies IL-10 expression (in a classic feedback loop regulation) on Treg cells via STAT3 activation, which, conversely, is significant for the inhibition of Th17 cell-induced inflammation [67]. The role of IL-10 on Treg was also confirmed in another study with murine colitis model. When IL-10 is expressed on gut APCs, it preserves Foxp3 expression on Treg cells [68]. There are two types of Treg cells: natural Treg (nTreg) and induced Treg (iTreg). nTreg cells are naturally produced in the thymus, whereas iTreg cells are produced when our immune response encounters a tumor antigen. However, most of the studies focused on the existed IL-10 on Treg but not in the course of iTreg production. Although the majority of Treg cells accumulating in tumors are nTreg cells, in some cases, iTreg cells are produced in spontaneous tumors or tumors without a defined tumor antigen [71]. BC has an increased presence of Treg cells [72,73], yet little is known about the role of nTreg or iTreg cells in BC development. Fascinatingly, even though both IL-10 and IL-6 play different roles in inflammation, they deliver signals through STAT3 phosphorylation, with IL-6 being more crucial for the induction of Th17 cells [74] and detrimental for iTreg recruitment [75,76]. However, the role of IL-10 in iTreg recruitment still remains controversial.

Mechanism of interlukin-10 in the process of breast cancer and other tumors

IL-10 paradoxically affects tumor development and pathogenesis [77]. Currently, three biological activities of IL-10 that contribute to the pleiotropic effect have been revealed [Figure 2]. First, IL-10 can promote CD8+ T cell activation and proliferation, which has a direct or indirect cytotoxic effect on the cancer cells. Second, IL-10 inhibits T cell-stimulated tumor-killing immunity by suppressing antigen presentation by APCs. Lastly, IL-10 can inhibit tumor-promoting inflammation [78]. Although high serum IL-10 is highly prevalent in end-stage cancer patients and correlates negatively with the survival [79], high IL-10 is generally accompanied by other cytokines and can dramatically affect the patients' overall immunity.

Both the pro- and anti-tumor effects of IL-10 have been well characterized [80]. The role of IL-10 in modulating the immune response appears to depend on the TME and the number of IL-10 receptors expressed on the immune cells [81]. Depleted IL-10 in mouse model has shown a positive relationship with the expression of inflammatory cytokine, IL-1, which facilitates tumor progression [36]. IL-10 also suppresses the proliferation and activity of T cells [82] and therefore stimulates tumor cell proliferation and metastasis [83]. Thence, IL-10 production can diminish cell-modulated inflammatory response in metastatic cancer cells [39] and can be a latent biomarker for human cancers in forecast and prognosis [84]. Moreover, IL-10 shortage contributes to the rejection of ultraviolet-induced tumorigenesis [85]. In addition, the expression of IL-10 mRNA is detected in >50% of BC samples [86]. In many cancer patients, the existence of IL-10 in the TME has been depicted as a poor prognostic factor [77,87,88]. In addition, several evidences suggested a contrasting role for IL-10 in cancers. Both the expression and consumption of IL-10 have shown to be associated with tumor shrinkage and therapy resistance [89-91]. In contrast to the inhibition of cancer-facilitating inflammatory mediators (reviewed in [80]), IL-10 also promotes tumor angiogenesis [92].

The BC risk associated with chronic mastitis has been well documented [84]. It appears that the toll-like receptors (TLRs) play a role in BC pathogenesis and recurrence [93-95]. TLRs can be activated through pathogen-associated molecular patterns (PAMPs) exogenously and endogenously, which, in turn, leads to the activation of inflammatory pathways [95]. It was established that TLRs are highly expressed in BC samples [93-96], and is even higher in recurrence BC samples [96,97]. Inflammatory markers such as serum C-reactive protein and amyloid A are correlated to poor clinical outcome in BC patients [98]. TLR activation has an important role in IL-10 production. PAMPs can induce IL-10 production in macrophages by various pathways including

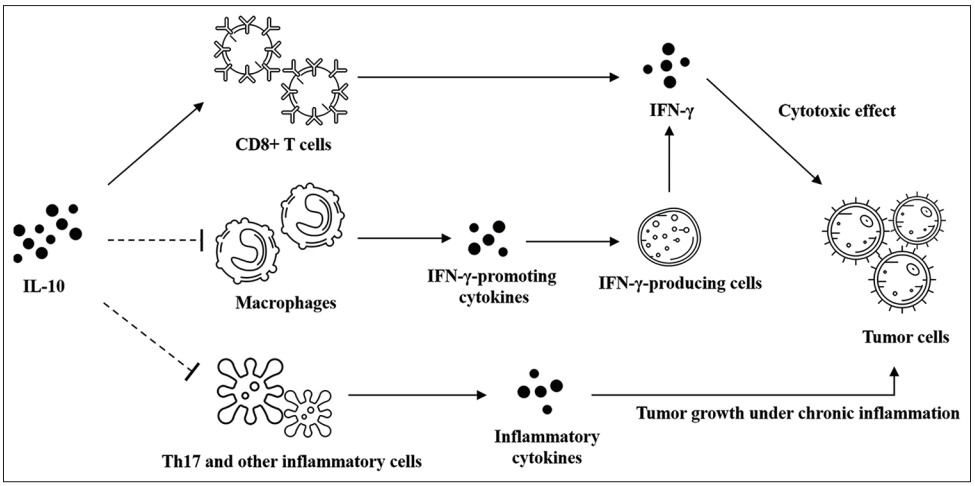

Figure 2: Paradoxical effect of interleukin-10 on cancers. Interleukin-10 paradoxically affects tumor development by three pathways. First, interleukin-10 promotes CD4+ T cell activation and proliferation, which promote interferon-γ secretion and induce tumor cell death. Next, interleukin-10 inhibits the effect of antigen-presenting cells, thereby allowing tumor cell to survive. At last, interleukin-10 can inhibit certain inflammatory cells and inhibit inflammation-related tumor cell growth

TLR2/MSK/CREB and TPL2/ERK. The signaling pathways also produce type I IFNs, which promote IL-10 production and synergize with IL-10 in regulating downstream inflammatory process [78].

The function of IL-10 is controversial in BC. Studies investigating the relationship between IL-10 and BC are shown in Table 1. Overexpression of IL-10 leads to a defect in dominating and immunogenic tumors [113], while IL-10RA inhibition improves therapeutic outcome in BC model [114]. Currently, very little is known about the *in vitro* function of IL-10 on the phenotypic conduct of BC cells, in terms of tumor cell migration and adherence to lymphatic and vessel endothelium. IL-10 has been reported to positively correlate with the overall survival rates in patients with colorectal cancer [115] and BC [99], but negatively correlate with patients with non-small cell lung carcinoma [116] and gastric cancer [92]. In addition, higher serum IL-10 concentration was detected in BC patients than in healthy individuals [39, 81,104], which is correlated with a bad clinical outcome [117]. It is indicated that IL-10 displayed an anti-metastatic function in murine model of BC and melanoma [100]. One recent study showed that IL-10 suppresses MDA-MB-231 cell migration in a dose-dependent manner [118]. The effect of IL-10 on MCF-7 cell was also observed in the same study, in which IL-10 can slightly but not significantly reduce the migration at 24 h after treatment. Because the migration rate of MDA-MB-231 is higher than that of MCF-7, a longer time would be required to observe the effect of IL-10 on MCF-7. IL-10 also causes immunosuppression by inducing TNF, IL-1, and IL-12 and certain chemokine production [119]. In addition, IL-10 reduces the production of CD80 and CD86 which are the two co-stimulatory molecules on cancer cells. IL-10 refrains APCs uptaking tumor antigens [119] and provokes upregulation of certain factors which plays significant role in BC progression. [37] Administration of anti-tumor vaccine before IL-10 treatment has been shown to induce tumor development [89,91,120,121]. IL-10 induces the production of tissues inhibitor of metalloproteinase and reduces the production of matrix metalloproteinase (MMP), thereby stimulating angiogenesis in BC [37]. Treatment of IL-10 also accelerates inflammatory response by inducing the production of IFN-γ, IFN-γ-inducible protein-10 (IP-10, also known as CXCL10), and other monokines [122]. As IL-10 promotes the progression of cancer cells, treatment with IL-10 antagonist may achieve a promising therapeutic efficacy and outcome [123].

Mechanism of interlukin-10 in anti-tumor activity

IL-10 in the TME has also been shown to correlate with anti-tumor immunity in both human and animal models. IL-10 exerts its anti-tumor effect by inhibiting angiogenesis [37]. This anti-angiogenic effect was due to the reduction of vascular endothelial growth factor, TNF-α, IL-1β, IL-6, and MMP-9 [119]. IL-10 can activate B cell differentiation into plasma cells which produce tumor cell-specific antibodies and mediate antibody-dependent cell cytotoxicity [124,125]. IL-10 suppresses the translocation of nuclear factor-κB into the nucleus and inhibits the signaling for inflammation [39]. IL-10 as well activates TILs and inhibits tumor development. Thence, IL-10 in the TME may protect tumor cell destruction by modulating host immune responses [81,89,91,120,121]. The contribution of IL-10 to the anticancer activity of NK cells is also well elucidated [38]. IL-10 dose-dependently aided target cell vandalization by activating NK cells in an animal study [122], while another study demonstrated that IL-10 can activate CD4+ or CD8+ T cell to prevent the destruction of tumor cells [39]. Therefore, IL-10 immunotherapy that modulates immunosuppression at the TME may be beneficial in treating BC and may be thought as a novel therapeutic approach [122]. Accumulating successful of PEGylated IL-10 treatment to cancer models further supports the use of IL-10 immunotherapy in BC [126]. IL-10 performs its anti-tumor function by enhancing the infiltration of CD8+ T cells in tissue, promoting T cell memory and upregulating IFN-γ expression [52,126]. PEGylated IL-10 was therefore created [127] to stimulate such anti-tumor

Table 1: The relationship between interleukin-10 and breast cancers

Study summary	Effects of IL-10	References
IL-10 is associated with good prognosis in early-stage invasive BC patients	Anti-tumor	[99]
IL-10 is a good prognosticator in terms of DFS in nonbasal, nontriple negative, ER+, PR+ BC	Anti-tumor	[99]
IL-10 suppresses tumorigenicity in BALB/cByJ mice and C.B-17/IcrCrl-SCID/Beige mice	Anti-tumor	[100]
IL-10 in stroma cells is associated with overall survival and DFS	Anti-tumor	[101]
IL-10 released by transfected mouse mammary adenocarcinoma cells enhances antitumor reaction and elicits a strong antibody-dependent immunity	Anti-tumor	[102]
IL-10 released by transfected mouse mammary adenocarcinoma cells results in delayed tumor rejection	Anti-tumor	[103]
IL-10 and Bcl-2 proteins in the TME may represent an increased aggressiveness of BC, even in the early stages	Pro-tumor	[82]
IL-10 in serum is strongly associated with BC and correlates with the clinical stage of BC	Pro-tumor	[104]
IL-10 stimulates carboxypeptidase B2 expression and is positively correlated with lymphovascular invasion of BC	Pro-tumor	[105]
IL-10 overexpression downregulates T cell response in sentinel lymph node with BC	Pro-tumor	[106]
IL-10 increases during paclitaxel chemotherapy and correlates with the related adverse effect	Pro-tumor	[107]
IL-10 is inversely correlated to ER and PR status and is more abundant in high-grade BC	Pro-tumor	[108]
IL-10 gene hypomethylation is involved in the process of BC carcinogenesis	Pro-tumor	[109]
IL-10 mRNA is detected in most BC samples	N*	[86,110]
IL-10 transcripts are expressed in most primary breast adenocarcinomas and BC cell lines	N*	[111]
IL-10 proteins are localized to tumor cells of primary breast adenocarcinomas and to occasional infiltrating mononuclear cells	N*	[111]
No significant difference in serum IL-10 was detected between BC patients and controls	N*	[112]

*N: Not otherwise specified. IL-10: Interleukin-10, BC: Breast cancer, PR: Progesterone receptor, ER: Estrogen receptor, DFS: Disease-free survival, TME: Tumor microenvironment

responses in cancer patients [128]. Growing evidences point to the fact that IL-10 can promote tumor destruction and its potential can serve as a key agent for cancer patients' immunotherapy [78,129,130].

Interlukin-10 and programmed cell death-1 programmed cell death ligand 1

Programmed cell death-1 (PD-1) and programmed cell death ligand 1 (PD-L1) are known to inhibit anti-tumor immunity [131]. Therefore, increasing attention has been focused on treating cancers with therapeutic PD-1 and PD-L1 antibodies. Studies concerning the release of IL-10 in patients resisting anti-PD-1/anti-PD-L1 monotherapies revealed that IL-10 is linked to PD-1/PD-L1 signaling pathways. Blockage of PD-1 and IL-10 improves the survival by reducing tumor burden and augments anti-tumor immune responses [131]. Pembrolizumab (PD-1 inhibitor) and atezolizumab (PD-L1 inhibitor) are two immune checkpoint inhibitors that are heavily utilized in BC immunotherapy. The use of a single inhibitor has shown to produce durable responses and favorable survival in TNBC patients [132,133]. The inhibitors are also augmented with chemotherapy agents such as nanoparticle albumin-bound paclitaxel (nab-paclitaxel) to treat PD-L1+ patients with metastatic TNBC [133]. Neoadjuvant chemotherapy, when combined with cytotoxic chemotherapy, achieves higher rates of pathological complete response and significantly increases the event-free survival [134]. Several literatures have already suggested that IL-10 and PD-1 pathways intersect in many cancers [135,136]. Considering that IL-10 could paradoxically affect patients' immune responses, combination therapy that target IL-10 signaling to augment immune responses is compelling.

Conclusion

One characteristic feature of BC is immune infiltration. Although the TME of BC is constantly immunosuppressive, infiltrated immune cells can exhibit both pro- and anti-tumor activities. IL-10 is one of the cytokines produced by these immune cells and displays both tumor-promoting and -inhibiting activities. A broad range of IL-10-expressing and IL-10-replying cells take part in modulating the immune response under different circumstances and at different sites. However, the opposing effects of IL-10 make therapeutic manipulation challenging. A profound comprehension of the molecular mechanisms and cellular functions of IL-10 may enable us to design potential therapeutic agents to manipulate IL-10-related immune response to tumor cells. At last, the use of IL-10 agonists and antagonists may have advantages in treating BC.

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Conflicts of interest

There are no conflicts of interest.

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