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Original Article

Decreased IL-10R-expressing B Cells in breast cancer patients: a potential biomarker for early cancer detection

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Abstract: IL-10 plays a crucial role in regulating B cell function and differentiation, but its effects on B cells depend on its activation state. The frequency of IL-10R$^+$ B cells and how it changes during breast cancer progression have not been studied. This study aimed to evaluate the expression of IL-10R on B cells in the peripheral blood of 50 patients with breast cancer compared to 29 healthy controls. After isolating mononuclear cells, we stained them using anti-CD19 and anti-IL-10R antibodies. We used Flow cytometry to analyze the expression of IL-10R on B cells. We found that over 50% of B cells in both patients with breast cancer and healthy controls expressed IL-10R. However, patients had a significantly lower frequency of IL-10R$^+$ B cells compared to healthy individuals (64±16.0% of patients compared to 78.5±6.6% for healthy individuals, P<0.0001). This decrease was not associated with lymph node involvement or tumor size. Phenotypic analysis revealed that IL-10R-expressing B cells consist of both naive and memory B cells, with the majority of peripheral memory B cells expressing IL-10R. The decrease in IL-10R-expressing B cells in breast cancer patients may be due to apoptosis induced by IL-10 in naive or recently activated B cells, or their migration to lymph nodes to combat tumor cells. Our study suggests that IL-10R could be a potential biomarker for detecting breast cancer in its early stages.

Keywords: IL-10, IL-10R, B cell, flow cytometry, PBMC, breast cancer

Introduction

IL-10 is a homodimeric cytokine with a heterotetrameric transmembrane receptor that belongs to the class II cytokine receptor family (CRF2) and consists of two IL-10R1 subunits and two IL-10R2 subunits [1, 2]. Initially, IL-10R1 subunits, which have a higher affinity for IL-10, bind to IL-10, followed by the binding of IL-10R2 subunits [3]. When IL-10 binds to its receptor, various intracellular proteins interact with it, leading to a variety of effects within the target cells [4].

IL-10 inhibits the activity of NK cells and macrophages, and suppresses cytokine production by Th1 and peripheral blood mononuclear cells. On the other hand, it has the ability to activate and promote the growth of various types of cells, including CD8+ T cells [5]. IL-10 also functions as a powerful stimulator for B cells, boosting their activation, proliferation, and differentiation [6]. A study has shown that the absence of IL-10 in mice is indirectly linked to impaired B cell lymphopoiesis and an increase in B cell damage to DNA [7]. IL-10 is also known as a factor that inhibits cell-mediated immunity and inflammation while enhancing humoral responses [8, 9]. B cells themselves are capable of producing IL-10, which can induce the differentiation of B cells into IgM or IgG plasma blasts [10]. On the other hand, recent studies have shown that IL-10 has varying effects on B cells depending on their activation states [11]. In resting B cells, IL-10 down-regulates the expression of BCL2, leading to apoptosis and growth arrest [12]. Conversely, in pre-activated B cells, it up-regulates the expression of MCL-1, promoting proliferation and differentiation [12, 13].

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Table 1. The information of study groups

Study Group	Age (years)	
	Median (min-max)	Mean ± SD
Patients (n=50)	47 (31-76)	50.6±11.7
Control (n=29)	45 (25-87)	46.1±15.9

Research has shown that cancer functions as a systemic disease, where changes in tumor progression not only affect the quantity and function of immune cells in the tumor-draining lymph nodes (TDLNs) but also impact their responsiveness to cytokines in peripheral blood [14-16]. One crucial component of the adaptive immune system is B cells, which can have both anti-tumor and pro-tumor effects, and have recently gained attention as a potential target in immunotherapy [17]. As mentioned earlier, these cells are directly influenced by IL-10. However, there has been no investigation into the expression of IL-10R on B cells in breast cancer patients. Considering the controversial role of IL-10 in the tumor microenvironment and its impact on B cell function, understanding the differences in IL-10R expression on B cells between breast cancer patients and healthy age-matched controls, along with the associated phenotypes of IL-10R-expressing B cells, will deepen our understanding of how breast cancer can systematically affect B cells. Furthermore, exploring its associations with various clinicopathological features could provide a more comprehensive understanding of the immune landscape in breast cancer and help guide potential therapeutic strategies.

Materials and methods

Patients

We conducted a study to evaluate the expression of IL-10R in B cells. For this purpose, we collected 3 ml of peripheral blood samples from 50 breast cancer patients and 29 age-matched healthy women as controls (**Table 1**). All patients had no history of radiotherapy or chemotherapy, and the control group had no history of cancer. Additionally, both groups had no history of any acute infectious diseases within a month before sampling, autoimmune diseases or chronic infections, and were not taking any medications that could influence their immune profile. Before participating in the study, all patients and controls signed a written informed consent form. The ethics committee of Shiraz University of Medical Sciences approved this study (ethics number: IR.SUMS.REC.1402.289). The Clinicopathological characteristics of the patients are summarized in **Table 2**.

Isolation of mononuclear cells and staining

We used centrifugation on a Ficoll-Hypaque gradient (Histiosep, Iran) to isolate mononuclear cells from a heparinized blood sample. These cells were then resuspended in complete culture medium (RPMI 1640 containing 10% FBS from Gibco, Life Technologies, USA, and 1% penicillin/streptomycin from Bio-Idea, Iran) before being transferred to flasks. After incubating the cells at 37°C for at least 2 hours, their viability was checked using Trypan blue staining. Susequently, we washed the cells with a staining buffer (PBS+FBS 2%) and stained them with APC-conjugated anti-CD19 (clone: HIB19, BioLegend) and PE-conjugated IL-10R (clone: 3F9, BioLegend). The isotype control was stained with APC-conjugated anti-CD19 (clone: HIB19) and PE-conjugated Mouse IgG1κ isotype control, both purchased from BioLegend. After the incubation period, the cells were washed and analyzed using flow cytometry.

Flow cytometry data acquisition and analysis

Flow cytometry was conducted using a four-color FACSCalibur instrument from BD Biosciences. The data were analyzed using FlowJo software (Version 10.1, Ashland, OR, USA). To identify B cells, lymphocytes were first gated based on their side and forward scatters, and then further gated for $CD19^+$ cells (a pan-B-cell marker). The expression of IL-10R was determined in these cells using their respective fluorescence minus one (FMO) control.

Statistical analysis

We compared the frequency of B cell subpopulations in two groups using the nonparametric Mann-Whitney U test. The Kruskal-Wallis H test was utilized for comparisons involving more than two groups. Dunn's posttest was employed for binary comparisons in more than two groups. Statistical analysis was performed us-

Table 2. Clinico-pathological characteristics of breast cancer patients

Characteristics	Value
Age (years)	50.6±11.7% (31-76)
Lymph Node (LN) Status	
N0 (Free LNs)	28 (56.0%)
N1 (1-3 involved LNs)	18 (36.0%)
N2 (4-9 involved LNs)	4 (8.0%)
Tumor Size (greatest dimension, cm)	
T1 (≤2)	31 (62.0%)
T2 (2-5)	16 (32.0%)
T3	1 (2.0%)
T4	1 (2.0%)
Tx (Unknown)	1 (2.0%)
Stage	
I	16 (32.0%)
II	28 (56.0%)
III	5 (10.0%)
Unknown	1 (2.0%)
Histological Grade	
Well differentiated (I)	4 (8.0%)
Moderately differentiated (II)	38 (76.0%)
Poorly differentiated (III)	7 (14.0%)
Unknown	1 (2.0%)
Tumor Type	
Infiltrating ductal carcinoma (IDC)	46 (92.0%)
IDC with medullary features (IDC+M)	1 (2.0%)
Others (Lobular carcinoma, Metaplastic Carcinoma)	2 (4.0%)
Unknown	1 (2.0%)
Her2 Expression	
Positive	10 (20.0%)
Negative	30 (60.0%)
Equivocal	5 (10.0%)
Unknown	5 (10.0%)
ER Expression	
Positive	37 (74.0%)
Negative	9 (18.0%)
Unknown	4 (8.0%)
PR Expression	
Positive	32 (64.0%)
Negative	14 (28.0%)
Unknown	4 (8.0%)

LN: Lymph Node, ER: Estrogen Receptor, PR: Progesterone Receptor, HER2: Human Epidermal Growth Factor Receptor 2.

ing SPSS 16 software (SPSS GmbH Software, Germany), with *P*-values less than 0.05 considered significant. Graphs were created using GraphPad Prism 6 software (Inc, San Diego CA, USA).

Results

Comparison of the frequency of B cells and IL-10R-expressing B cells in the peripheral blood of patients with breast cancer and controls

Table 3 presents the frequency of B cells and B cells expressing IL-10R in PBMC of breast cancer patients and controls. The analysis shows that in contrast to B cells, which showed no difference between patients and controls, the frequency of IL-10R-expressing B cells is significantly higher in controls compared to patients (P<0.0001, **Figure 1A-C**).

Comparison of the frequency of IL-10R-expressing B cells between breast cancer patients with and without lymph node involvement and healthy controls

The percentage of B cells expressing IL-10R was lower in patients with at least one involved lymph node (LN+) and patients without involved lymph nodes (LN-) compared to controls (P=0.004 and P=0.0004, respectively, **Figure 2**). However, there was no significant difference in the proportion of IL-10R+ B cells between LN+ and LN- patients.

Furthermore, the percentage of B cells expressing IL-10R was significantly lower in patients with 1-3 involved lymph nodes (N1) compared to controls (P=0.006). However, there were no differences observed between patients with more than 4-9 lymph nodes involved (N2) and controls.

Table 3. Percentages of B cells and IL-10R+ B cells in the peripheral blood of patients and controls

Cell subsets	Min		Max		Median		Mean ± SD	
	C	Pt	C	Pt	C	Pt	C	Pt
CD19+ cells (In lymphocytes' gate)	4.9	1.9	18.3	17.8	10.6	9.2	10.8±3.5	9.5±4.0
IL-10R+ cells (In CD19+ cells' gate)	65	25.5	93.1	87.7	80.1	65.9	78.5±6.6	64±16.0

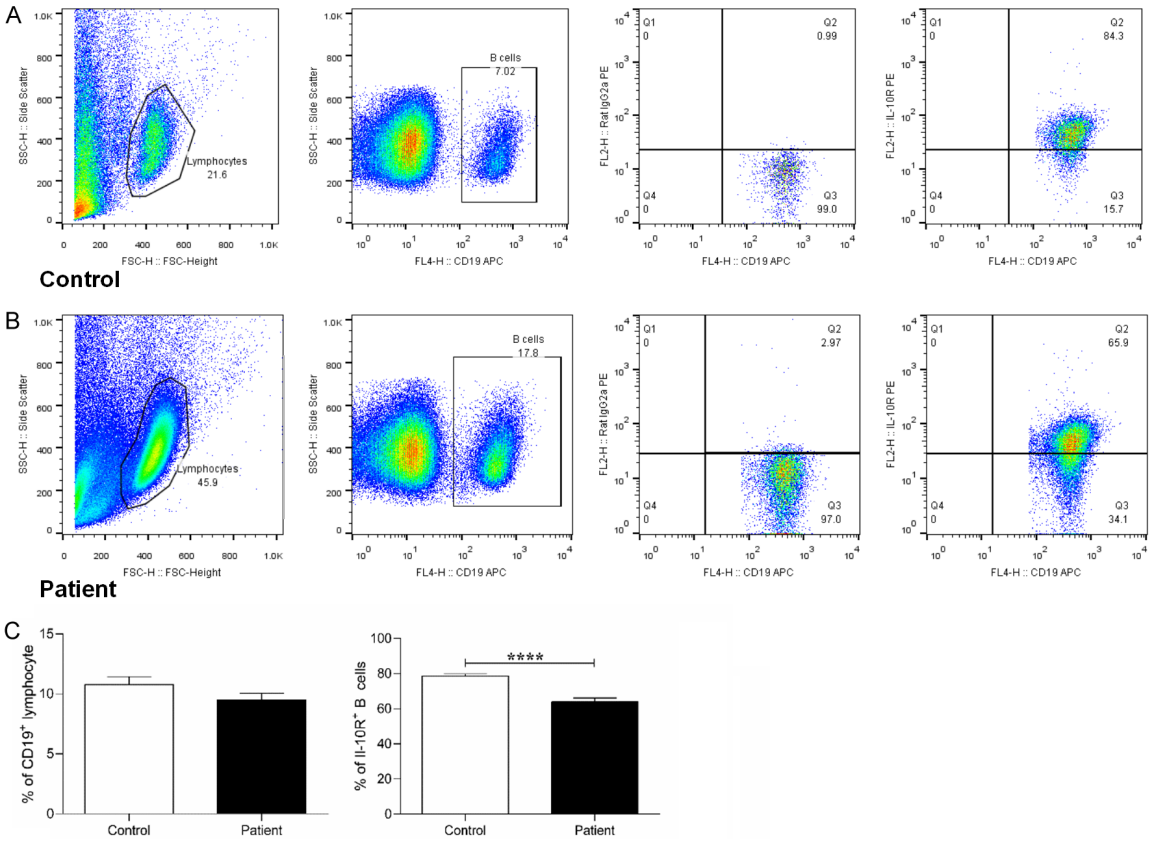

Figure 1. Flow cytometry analysis of the expression of the IL-10 receptor (IL-10R) in B cells derived from peripheral blood samples of (A) a healthy individual (control), and (B) a patient with breast cancer. Firstly, lymphocytes were selected based on their side and forward scatter characteristics. Subsequently, CD19+ cells were gated as B cells. Finally, the expression of IL-10R in B cells was determined using the fluorescence minus one (FMO). (C) Comparison of the frequency of B cells and IL-10 receptor (IL-10R)-expressing B cells in the peripheral blood of patients and controls. Data is presented as Mean ± SEM, ****P-value <0.0001, SEM: standard error of the mean.

Comparison of the frequency of B cells expressing IL-10R in breast cancer patients with different stages, grades or tumor size with healthy controls

The percentage of B cells expressing IL-10R was lower in patients with stage I, II and grade II of the disease compared to the controls (P=0.04, P=0.0001 and P=0.0005, respectively). No significant difference was observed between stage III or grade I and III compared to controls (**Figure 3A** and **3B**).

The proportion of IL-10R-expressing B cells was lower in patients with T1 and T2 tumors compared to controls (P=0.009 and P<0.0001, respectively). However, no difference was seen between the T1 and T2 groups (**Figure 3C**).

Association between the frequency of IL-10R+ B cells and the status of human epidermal growth factor receptor 2 (HER2), estrogen receptor (ER) and progesterone receptor (PR) expression

The frequency of IL-10R-expressing B cells was significantly lower in patients with ER+ (P=0.002) or ER- (P=0.005) and PR+ (P=0.002) or PR- (P=0.008) tumors compared to controls (**Figure 4A**, **4B**).

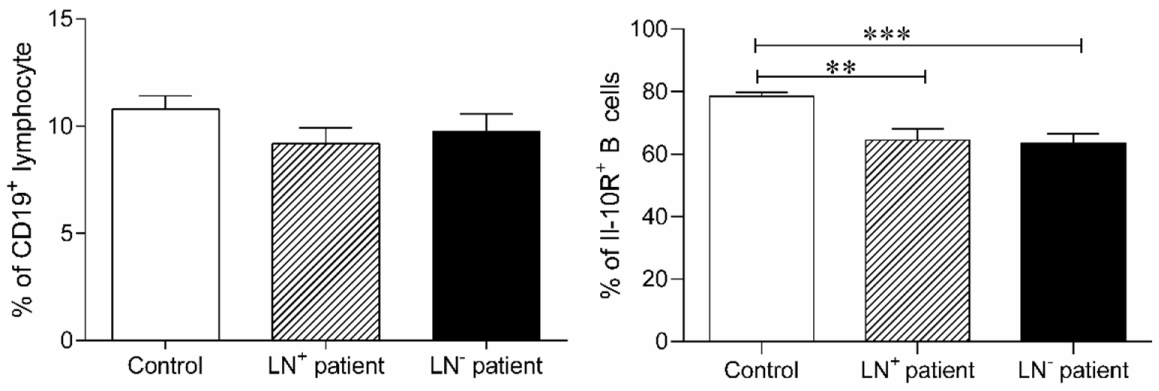

Figure 2. Comparison of the frequency of B cells and IL-10 receptor (IL-10R)-expressing B cells in the peripheral blood of controls, breast cancer patients with at least one involved lymph node (LN+) and those with no involved lymph nodes (LN-). The data is presented as Mean ± SEM, ***P*-value <0.01 and ****P*-value <0.001, SEM: standard error of the mean.

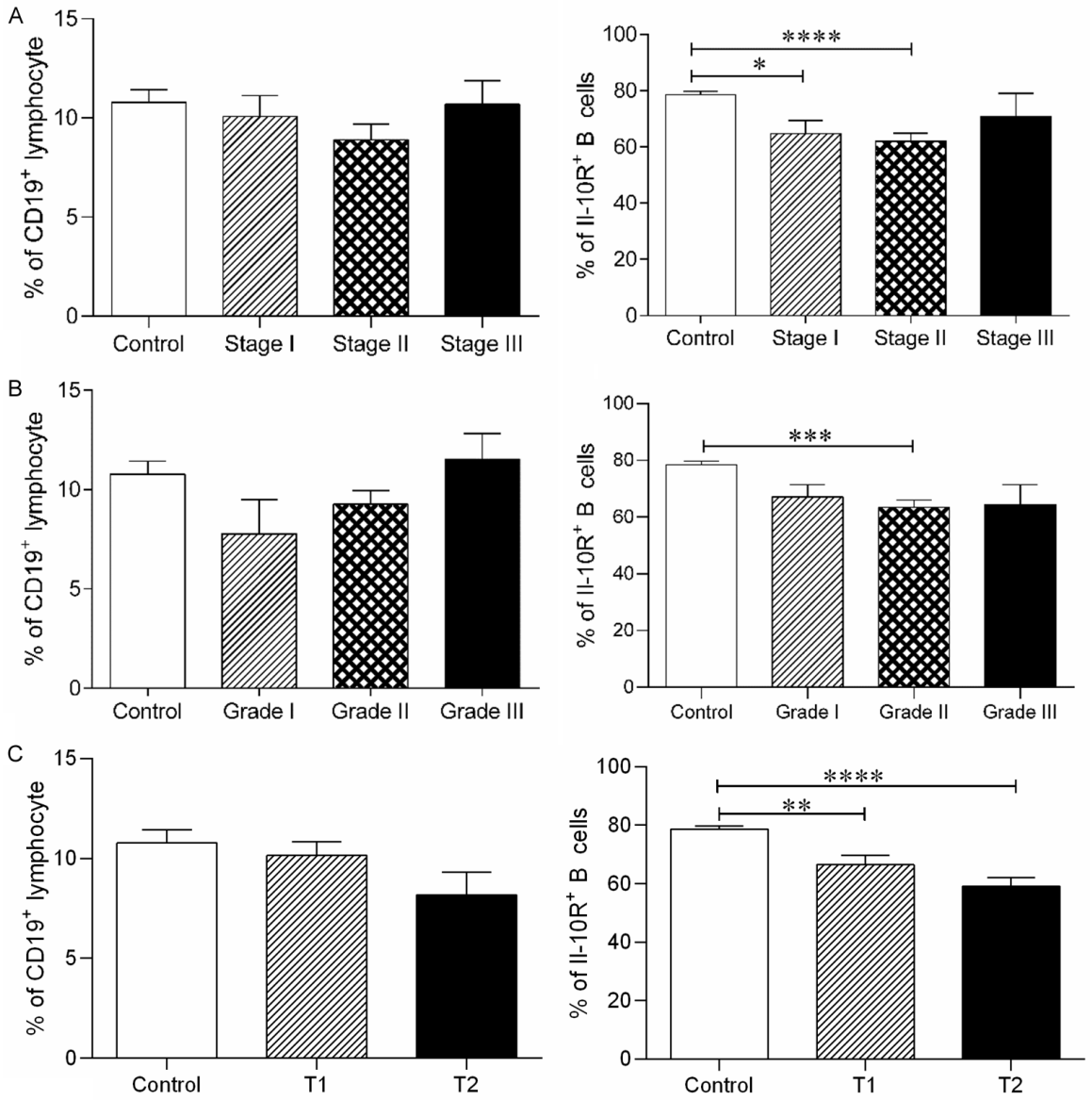

Figure 3. Comparison of the frequency of B cells and IL-10 receptor (IL-10R)-expressing B cells in the peripheral blood of controls versus breast cancer patients with different (A) stages, (B) grades and, (C) tumor sizes (size ≤2 cm (T1) and tumor size >2 cm (T2)). The data is presented as Mean ± SEM, **P*-value <0.05, ***P*-value <0.01, ****P*-value <0.001 and *****P*-value <0.0001, SEM: standard error of the mean.

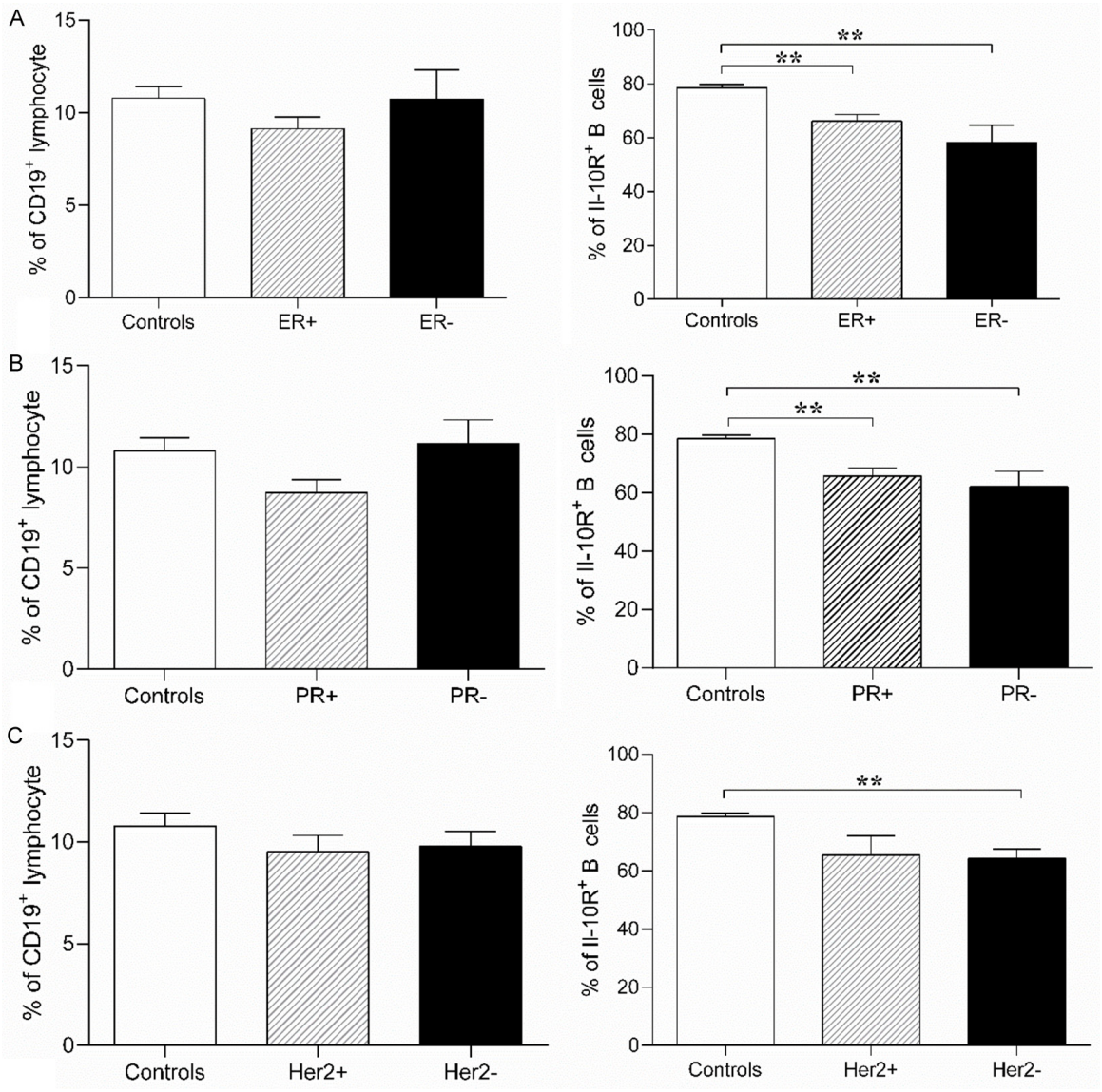

Figure 4. Comparison of the frequency of B cells and IL-10 receptor (IL-10R)-expressing B cells in controls versus breast cancer patients based on (A) the expression of estrogen receptor (ER), (B) the expression of progesterone receptor (PR) and (C) human epidermal growth factor receptor 2 (HER2) expression on tumor cells. Data is presented as Mean ± SEM, ***P*-value <0.01, SEM refers to the standard error of the mean.

Additionally, the frequency of IL-10R-expressing B cells was significantly lower in HER2- patients compared to controls (P=0.001). However, no difference was observed between HER2+ and HER2- patients or between HER2+ patients and controls (**Figure 4C**).

Phenotype of IL-10R-expressing B cell

The phenotype of IL-10R+ B cells was examined in blood samples from three breast cancer patients and three controls. Our results showed that the majority of B cells in peripheral blood,

in both patients and controls are CD27$^-$ naive B cells. Furthermore, the majority of memory B cells express IL-10R, with 88.7±4.4% in patients and 88.2±5.4% in controls, while 56.0±5.5% and 65±8.1% of naïve B cells express IL-10R in patients and controls, respectively. On the other hand, 58.7±7.5% of IL-10R$^+$ B cells in patients were naïve B cells, compared to 61.4±3.7% in controls. 41.3±7.5% of IL-10R$^+$ B cells in patients were memory B cells, while 37.4±4.3% of these cells were memory B cells in controls.

Discussion

B cells, which are an integral part of the immune system, have recently gained significant attention [18]. Research studies have demonstrated that B cells play a dual role in the immune response to tumors. Firstly, B cells can activate T cells by presenting antigens, especially when dendritic cells are unable to do so effectively [19, 20]. Secondly, a subset of B cells, known as B10, can suppress immune responses by producing the cytokine IL-10, which inhibits T cell activation [21, 22]. Studies have shown a higher concentration of IL-10 in the serum of breast cancer patients compared to controls and it plays a controversial role in this context [23]. B cells themselves are one of the main targets influenced by IL-10 through IL-10R [24]. However, there are few studies on the frequency and phenotype of IL-10R-expressing different cell types, including B cells, in the peripheral blood of cancer patients, particularly those with breast cancer. Only one study in patients with multiple myeloma has shown an increase in the expression of IL-10R in the serum of these patients [25]. Therefore, in this study, we investigated the frequency of IL-10R$^+$ B cells in the peripheral blood of patients with breast cancer and compared it with healthy age-matched controls.

Our results revealed that more than half of peripheral B cells expressed IL-10R in both patients with breast cancer and healthy controls. Unlike B cells, which showed no difference between the two groups, breast cancer patients had a significantly lower frequency of peripheral B cells expressing IL-10R compared to healthy individuals. Furthermore, this decrease was not associated with lymph node involvement or tumor size, as it was observed in both LN+ and LN- patients as well as patients with tumor sizes ≤2 cm and >2 cm compared to controls. This suggests that the frequency of IL-10R$^+$ B cells decreases as soon as breast cancer develops.

We found that IL-10R$^+$ B cells are composed of both naïve and memory B cells, but the majority of peripheral memory B cells, not naïve B cells express IL-10R. Interestingly, IL-10 regulates the responses of naive and memory B cells, differentially. Evidence shows that IL-10 induces apoptosis or cell death in naïve B cells but not in memory or activated B cells. Research has shown that when purified B cells from healthy adults are co-cultured with Staphylococcus aureus (SA) Cowan I, IL-10 can induce apoptosis during the initial activation of B cells but support the differentiation of pre-activated B cells [11]. Additionally, IL-10 can cause memory B cells to differentiate into IgM- and IgG-secreting plasmablasts [10, 26]. One possible reason for the decrease in IL-10R-expressing B cells, observed in breast cancer patients, may be attributed to apoptosis induced by IL-10 in naïve or recently activated B cells. Our recent study revealed a significant decrease in the frequency of naïve and unswitched memory B cells in patients compared to controls [27]. It would be beneficial to conduct studies assessing the phenotype of IL-10R-expressing B cells in blood using larger sample size as well as investigating the effect of IL-10 on different subclasses of B cells.

On the other hand, researchers have found that B cells become trapped in lymph nodes that drain tumors, leading to LN enlargement [28]. A study has shown that IL-10 has varying effects on antigen-presenting cells (APCs), including B cell and dendritic cells. Unlike dendritic cells, IL-10 has no impact on the migration, expression of co-stimulatory molecules, or the ability of CD40-activated B cells to stimulate T cells [20]. Therefore, when dendritic cells are not functioning properly due to the effects of IL-10, B cells can effectively assist in presenting antigens to T cells within the TDLNs. Additionally, the presence of IL-10R-expressing B cells may impact the differentiation of B cells into plasma cells, ultimately resulting in the production of antibodies that can help control tumor evasion.

In our unpublished research, we found that the frequency of IL-10R+ B cells was significantly higher in non-metastatic lymph nodes (nMLNs) compared to metastatic lymph nodes (MLNs). It is possible that the reduction in IL-10R-expressing B cells in PBMC of breast cancer patients could be due to their migration to the draining LNs to inhibit tumor spread. This hypothesis should be investigated by simultaneously evaluating the frequency of IL-10R expressing B cells in the peripheral blood as well as nMLNs and MLNs of breast cancer patients.

Despite the numerous research studies conducted on IL-10, there is limited data on the specific effect of IL-10 on B cells in cancers, as well as the frequency and phenotype of B cells expressing IL-10R. To our knowledge this is the first study to investigate the expression of IL-10R on B cells in the context of breast cancer. Our results suggest that the differential expression of this receptor on B cells in the peripheral blood may serve as a potential biomarker for early breast cancer detection. Further research is needed on the function and phenotype of IL-10R+ B cells to determine if targeting IL-10R could enhance the antitumor effects of B cells in breast cancer.

Conclusion

To the best of our knowledge this is the first study to investigate the frequency and phenotype of peripheral IL-10R+ B cells in patients with breast cancer and healthy, age-matched women. Our study revealed that breast cancer patients had a lower frequency of peripheral B cells expressing IL-10R compared to healthy controls. This decrease was not associated with lymph node involvement or tumor size. The majority of memory B cells, but not naïve B cells, expressed IL-10R, however IL-10R-expressing B cells consist of both naïve and memory B cell populations. It remains unclear whether these cells migrate to lymph nodes, or undergo apoptosis due to high levels of IL-10. However, further research is needed to understand the mechanisms behind these changes and explore their implications for cancer immunotherapy.

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Disclosure of conflict of interest

None.

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