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Deciphering interleukin 10's dual role: insights into B cell dynamics in breast tumor-draining lymph nodes

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Abstract

The immune-modulatory role of interleukin 10 (IL-10) in breast cancer remains controversial, with reports of both pro- and anti-tumor effects. While B cells are important targets of IL-10, the frequency, phenotype, and functional impact of B cells expressing IL-10 receptor (IL-10R) in tumor-draining lymph nodes (TDLNs) of breast cancer patients are still unclear. In this study, we analyzed axillary lymph nodes from 49 breast cancer patients, assessing IL-10R expression on B cells and the effects of recombinant IL-10 (rIL-10) on granzyme B, CD86, and tumor necrosis factor α (TNF-α) production. Flow cytometry revealed that 52.9 ±17.3% of B cells expressed IL-10R, predominantly exhibiting an activated/memory phenotype ($CD27^+CD24^{hi}$). Interestingly, $IL\text{-}10R^+$ B cells were significantly reduced in metastatic lymph nodes (MLNs) compared to non-metastatic lymph nodes (nMLNs), suggesting a protective role in early disease. Paradoxically, $HER2^+$ tumors exhibited higher frequencies of $IL\text{-}10R^+$ B cells, indicating context-dependent functions. Functional assays demonstrated that IL-10 significantly enhanced granzyme B production in B cells but suppressed $TNF\text{-}\alpha^{hi}$ B cells by approximately 40%, without altering CD86 expression. These findings highlight the dual role of IL-10 in modulating B cell-mediated immunity. IL-10 enhances cytotoxic function via granzyme B while dampening antitumor TNF-α responses. The reduced frequency of $IL\text{-}10R^+$ B cells in MLNs suggests their potential role in anti-tumor immunity, while their association with $HER2^+$ tumors may indicate a pro-tumor function in certain contexts. This study emphasizes the complexity of IL-10 signaling in B-cell-mediated immunity, shedding light on its multifaceted effects and the need to clarify the role of IL-10 in cancer immunity.

Key words: *IL-10, IL-10 receptor, B cell, tumor-draining lymph nodes, breast cancer.*

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Introduction

The immune system plays a crucial role in determining the outcome of cancer [1, 2]. During tumor development, the immune profiles of the tumor microenvironment (TME), tumor-draining lymph nodes (TDLN), and peripheral blood undergo significant changes [3-5]. While much research has focused on T cells in cancer, recent studies have highlighted the importance of B cells and their complex roles in tumor immunity [6-8].

Emerging evidence reveals that B cells exhibit dual functions in tumor growth, either supporting or hindering it. On one hand, they promote anti-tumor immunity by recruiting $CD8^+$ T cells *via* chemokines (e.g., CCL3, CCL4, CCL5, CXCL13, CXCL10) [9, 10], activating T cells through antigen presentation and co-stimulatory signals (e.g., CD40/CD40L) [7, 10], and facilitating antibody-dependent tumor destruction through antibody-dependent cellular cytotoxicity (ADCC) or antibody-dependent cellular phagocytosis [10, 11]. Notably,

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a subset of B cells in breast cancer TDLNs can directly kill tumor cells *via* granzyme B [12-14]. Conversely, B cells can suppress immunity by secreting anti-inflammatory cytokines such as IL-10, transforming growth factor β (TGF-β), and IL-35 or by expressing PD-L1 [2, 15]. In breast cancer models, they promote metastasis by generating regulatory T cells (Tregs) in a TGF-β-dependent manner [16]. IL-10-producing B cells, such as IgA^+ $PD\text{-}L1^+$ plasmocytes in prostate cancer, block $CD8^+$ T-cell function [17]. In breast cancer, these B cells make up about 3% of lymph node (LN) B cells and correlate with reduced lymph node involvement, highlighting their dual role in cancer progression [2].

Interleukin 10 regulates immunity by suppressing inflammatory cytokines and antigen presentation [18]. Its receptor, IL-10R, is part of the interferon receptor family and consists of two IL-10R1 and two IL-10R2 chains [19]. While IL-10R1 is found at low levels on resting cells and increases upon activation, emphasizing its importance in inhibitory pathways [20], IL-10R2 is expressed ubiquitously and is not exclusive to IL-10. IL-10 binds directly to IL-10R1, while IL-10R2 supports signaling within the receptor complex [19, 21]. Contrary to common assumptions, IL-10 exhibits antitumor effects by inhibiting angiogenesis *via* suppression of vascular endothelial growth factor (VEGF) and TNF-α [22-24], and enhancing immune responses such as antibody production and $CD8^+/CD4^+$ T-cell activity [25]. It increases interferon γ (IFN-γ) and granzyme B in $CD8^+$ T cells and boosts tumor MHC expression [26, 27]. In clinical trial, pegylated IL-10 enhances tumor-specific $CD8^+$ T-cell function, slowing tumor growth by elevating granzyme B levels [28, 29].

Despite these findings, the role of IL-10 still remains controversial. Breast cancer patients often exhibit elevated serum IL-10 levels [25, 30], yet its prognostic impact is debated. Some studies link IL-10 to poor outcomes through BCL-2-mediated tumor apoptosis inhibition or T-cell suppression [21, 30, 31], while others associate low IL-10 levels with worse survival, suggesting protective effects [32].

Notably, B cells both produce IL-10 and respond to it through IL-10R. However, the frequency of IL-10R-expressing B cells in TDLNs of breast cancer patients, as well as their phenotypic characteristics, remain poorly understood. Additionally, the impact of IL-10 on key antitumor effector molecules in B cells – such as granzyme B, CD86, and TNF-α – has not been fully elucidated. This study aimed to (1) evaluate the prevalence and phenotype of $IL\text{-}10R^+$ B cells in cancer TDLNs and (2) assess whether recombinant IL-10 (rIL-10) modulates granzyme B, CD86, and TNF-α expression in these cells. By addressing these questions, we aimed to elucidate IL-10's dual role in B-cell-mediated antitumor immunity.

Material and methods

Patients

In this study, we analyzed axillary lymph nodes from 49 women with pathologically confirmed breast cancer to evaluate IL-10R expression in B cells (Table 1). Additionally, we investigated the effects of rIL-10 on B cell expression of granzyme B, CD86, and TNF-α, using uninvolved axillary lymph nodes from breast cancer patients.

To ensure data reliability, we excluded patients who had undergone prior radiotherapy or chemotherapy, as well as those with chronic comorbidities such as infectious or autoimmune diseases. Fresh lymph node samples were obtained in collaboration with a pathologist, who prepared the specimens for analysis.

All participants provided written informed consent, and the study was approved by the ethics committees of Mashhad and Shiraz Universities of Medical Sciences (ethic numbers: IR.MUMS.MEDICAL.REC.1398.751 and IR.SUMS.REC.1398.1205, respectively). The research followed the principles outlined in the Declaration of Helsinki (1975, revised 2000).

Isolation of mononuclear cells

To isolate mononuclear cells, we first crushed fresh lymph nodes in complete culture medium (CM10), which contained: RPMI 1640 supplemented with 10% FBS (Gibco, Life Technologies, USA) and 1% penicillin/streptomycin (Bio-Idea, Iran). The cell suspension was passed through a 40 µm cell strainer (SPL, South Korea) to remove debris. We then isolated mononuclear cells by centrifuging the suspension at 600 ×g for 15 minutes over a Ficoll-Hypaque gradient (Lymphodex, inno-train Diagnostik GmbH, Germany) at 24°C. After centrifugation, we carefully collected the mononuclear cell ring and washed it twice in complete culture medium at 1800 rpm for 10 minutes (24°C). The cells were then re-suspended in CM10 for viability assessment and counting using Trypan Blue exclusion. Only samples with > 90% viability were used in experiments.

To separate lymphocytes from monocytes/macrophages, we incubated the cells overnight in a 25 cm^2 culture flask at 37°C with 5% CO_2. After incubation, we washed the cells at 300 ×g for 10 minutes in staining buffer (PBS with 2% FBS) to remove dead cells. Finally, we re-suspended the pellet in CM10 and performed a final cell count using Trypan Blue.

Assessment of IL-10R expression on B cells

To evaluate IL-10R expression on unstimulated B cells, the cells were re-suspended in staining buffer at a concentration of 5×10^5 cells per 50 µl and then stained with the following antibodies:

- APC-conjugated anti-CD19 (clone: HIB19) to identify B cells,
- PE-conjugated anti-IL-10R (clone: 3F9) to detect IL-10 receptor expression,
- PE Rat IgG2a, κ isotype control (clone: RTK2758) to account for nonspecific binding.

All antibodies and reagents were obtained from BioLegend (USA).

Cell activation for analyzing the effect of rIL-10 on B cells

To evaluate the impact of IL-10 on granzyme B expression in B cells, lymphocytes were re-suspended in complete medium at a density of 1×10^6 cells/ml and cultured in a 24-well tissue culture plate. The cells were stimulated with the following reagents for 24 hours:

- Recombinant IL-21 (25 or 50 ng/ml, BioLegend),
- Anti-BCR (3.3 µg/ml, Jackson ImmunoResearch, USA),
- Recombinant IL-10 (25, 50, or 100 ng/ml, BioLegend).

Brefeldin A (1 µl/ml, BioLegend) was added during the last 6 hours of culture to inhibit protein secretion. Cells were maintained at 37°C in a 5% CO_2 incubator throughout the experiment.

Cells stimulated only with rIL-21 and anti-BCR (without IL-10) served as the control group.

To evaluate the impact of rIL-10 on CD86 expression in B cells, lymphocytes were suspended in complete medium at a density of 1×10^6 cells/ml and cultured in a 24-well tissue culture plate. The cells were treated with 25 ng/ml or 100 ng/ml of rIL-10, along with 1 µg/ml CpG (InvivoGen, USA), for 48 hours. During activation, cells were maintained at 37°C in a 5% CO_2 incubator. Cells treated with CpG alone served as the control group.

To evaluate the impact of IL-10 on TNF production by B cells, lymphocytes were re-suspended in complete medium at a density of 1×10^6 cells/ml in a 24-well tissue culture plate. The cells were then treated with recombinant IL-10 (rIL-10) at concentrations of 25, 50, and 100 ng/ml, along with 1 µg/ml CpG (as a stimulatory control), for 48 hours.

During the final 6 hours of culture, the cells were further stimulated with:

- PMA (50 ng/ml, Sigma-Aldrich, Germany),
- Ionomycin (1 µg/ml, Sigma-Aldrich),
- Brefeldin A (1 µl/ml, BioLegend) (to inhibit cytokine secretion and allow intracellular accumulation).

All incubations were performed at 37°C under 5% CO_2. CpG-treated cells (without IL-10) served as the experimental control.

Cell harvesting and staining protocol

After activation, mononuclear cells were harvested and washed with staining buffer (centrifuged at 300 g, 4-8°C for 10 minutes) to assess granzyme B, CD86, and TNF-α

Table 1. Clinicopathological characteristics of breast cancer patients

Characteristic	Value, *n* (%)
Age (years), mean ±SD (range)	49 ±11.3 (23-72)
Lymph node (LN) status	
N0 (free LNs)	23 (46.9)
N1 (1-3 involved LNs)	18 (36.7)
N2 (4-9 involved LNs)	3 (6.1)
N3 (> 9 involved LNs)	5 (10.2)
Lymph node (LN) characteristic	
Involved LNs	20 (40.8)
Uninvolved	29 (59.2)
Tumor size (greatest dimension, cm)	
T1 (≤ 2)	25 (51.0)
T2 (2-5)	19 (38.8)
T3	1 (2.0)
Tx (unknown)	4 (8.2)
Stage	
I	9 (18.4)
II	27 (55.1)
III	9 (18.4)
Unknown	4 (8.2)
Histological grade	
Well differentiated (I)	3 (6.1)
Moderately differentiated (II)	42 (85.7)
Poorly differentiated (III)	1 (2.0)
Unknown	3 (6.1)
Tumor type	
Infiltrating ductal carcinoma (IDC)	41 (83.7)
IDC with medullary features (IDC + M)	5 (10.2)
Unknown	3 (6.1)
Her2 expression	
Positive	5 (10.2)
Negative	22 (44.9)
Equivocal	4 (8.2)
Unknown	18 (36.7)
ER expression	
Positive	24 (49.0)
Negative	7 (14.3)
Unknown	18 (36.7)
PR expression	
Positive	21 (42.9)
Negative	10 (20.4)
Unknown	18 (36.7)

LN – lymph node, ER – estrogen receptor, PR – progesterone receptor, HER2 – human epidermal growth factor receptor 2

production in B cells. The cells were then re-suspended in staining buffer at a concentration of 5×10^5 cells/50 µl in flow cytometry tubes.

Surface staining for CD86: To evaluate CD86 expression, B cells were surface-stained using:

- APC-conjugated anti-CD19 (Clone: HIB19, BioLegend),
- PE-conjugated anti-CD86 (Clone: IT2.2, BioLegend) or its isotype control (PE Mouse IgG2b, κ, Clone: MPC-11, BioLegend).

Intracellular staining for granzyme B and TNF-α: For intracellular detection of granzyme B and TNF-α, cells were first surface-stained with PE- or APC-conjugated anti-CD19 (Clone: HIB19, BioLegend). After fixation with 1% paraformaldehyde (Sigma Aldrich) and permeabilization with Perm/wash buffer (BioLegend), they were then stained with:

- Alexa Fluor 647-conjugated anti-granzyme B (Clone: GB11, BD Biosciences),
- PE-conjugated anti-TNF-α (Clone: MAb11, BD Biosciences),
- Or their respective isotype controls (Alexa Fluor 647 Mouse IgG1, κ, Clone: MOPC-21; PE Mouse IgG1, κ, Clone: MOPC-21).

Finally, cells were washed and analyzed by flow cytometry.

Flow cytometry analysis

We performed flow cytometry using a BD FACSCalibur instrument (BD Biosciences) equipped with four fluorescent detectors. Data were analyzed using FlowJo software (v7.6.2, Tree Star, Ashland, OR).

Gating strategy

As shown in Figures 1A and 5, lymphocytes were first gated based on their forward scatter (FSC) and side scatter (SSC) profiles. From this population, $CD19^+$ B cells were identified for further analysis. The expression of IL-10R, granzyme B, CD86, and TNF-α in B cells was assessed using fluorescence minus one (FMO) controls as the reference.

Statistical analysis

To compare the frequency of B cell subpopulations between two groups, we used the nonparametric Mann-Whitney *U* test. For comparisons involving more than two groups, we applied the Kruskal-Wallis H test, followed by Dunn's posttest for pairwise comparisons. Additionally, we assessed correlations between the frequency of cell subsets, tumor size, and the number of involved lymph nodes using Spearman's rank correlation test.

All statistical analyses were performed using SPSS 16 (SPSS GmbH Software, Germany), with a p-value < 0.05 considered statistically significant. Graphs were generated using GraphPad Prism 6 (GraphPad Software, Inc., San Diego, CA, USA).

Results

Analysis of IL-10R expression on B cells isolated from TDLN of breast cancer patients and its association with clinicopathological characteristics

Association of frequency of IL-10R-expressing B cells with LN involvement in breast cancer patients

To investigate the expression of IL-10R in B cells, we collected axillary lymph nodes from 49 women with pathologically confirmed breast cancer. Clinicopathological characteristics of the patients are summarized in Table 1. In breast tumor-draining lymph nodes (TDLNs), B cells accounted for 34.1 ±13.8% of the lymphocyte population. Among B cells, 52.9 ±17.3% expressed IL-10R (Fig. 1A, Table 2). The proportion of IL-10R-expressing B cells was significantly lower in metastatic lymph nodes (MLN) compared to nonmetastatic lymph nodes (nMLN) ($p = 0.024$). Similarly, the MFI of IL-10R expression in B cells was significantly lower in MLNs ($p = 0.046$). However, the percentage of B cells did not significantly differ between the two types of lymph nodes (Fig. 1B). Additionally, further analysis revealed a positive correlation between the percentage of B cells expressing IL-10R and the intensity of IL-10R expression ($p = 0.009$, $r = 0.4$). However, there was no correlation between IL-10R expressing B cells and the percentage of B cells in TDLNs (Fig. 1C).

There was a significantly lower percentage of B cells expressing IL-10R in patients without LN involvement (LN–) compared to those with at least one involved LN (LN+) ($p = 0.049$), as shown in Figure 2A. However, the frequency of B cells or the MFI of IL-10R on these cells was not significantly different in MLNs and nMLNs in each patient. Furthermore, the percentage of $IL\text{-}10R^+$ B cells showed no significant difference in nMLNs and MLNs of LN+ patients. However, the MFI of IL-10R expression in B cells was significantly lower in MLNs compared to nMLNs of patients with at least one involved LN ($p = 0.021$, Fig. 2B). No significant difference was found in the frequencies of B cells and $IL\text{-}10R^+$ B cells and the intensity of IL-10R expression on B cells in patients classified as N1 (with 1-3 involved LNs) and N2 + N3 (with more than 3 involved LNs). Furthermore, these frequencies did not show any significant correlation with the number of involved lymph nodes (Fig. 2C).

Frequencies of B cells and B cells expressing IL-10R in involved and uninvolved lymph nodes obtained from one patient

We collected both involved and uninvolved lymph nodes from 11 patients. We observed a significantly higher frequency of B cells expressing IL-10R in uninvolved

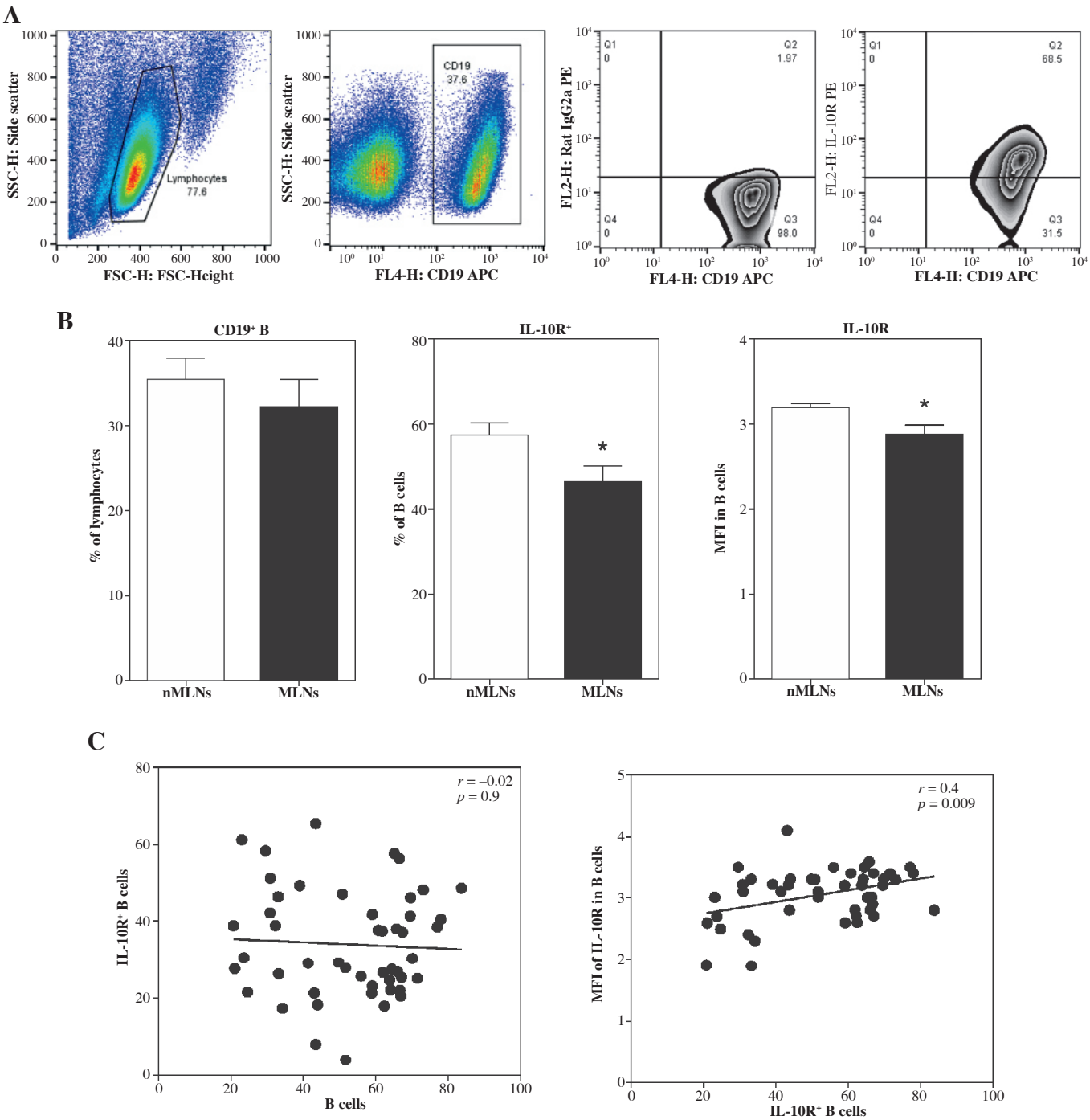

Fig. 1. A) Flow cytometry analysis of IL-10 receptor (IL-10R) expression in B cells derived from breast tumor-draining lymph nodes (TDLNs). Initially, lymphocytes were selected based on their side and forward scatter characteristics. Subsequently, $CD19^+$ cells were gated as B cells. Finally, the expression of IL-10R in B cells was determined using the fluorescence minus one (FMO). **B**) Comparison of frequency of B cells, IL-10R-expressing B cells and the MFI of IL-10R expression on B cells in metastatic lymph nodes (MLNs) and non-metastatic lymph nodes (nMLNs) of breast cancer; data are representative of 29 nMLNs and 20 MLNs. **C**) Correlation of frequency of B cells with IL-10R expressing B cells, frequency of IL-10R expressing B cells, and MFI of IL-10R expression on B cells. Data are presented as mean ±SEM. **P*-value < 0.05. SEM – standard error of the mean, MFI – mean fluorescence intensity

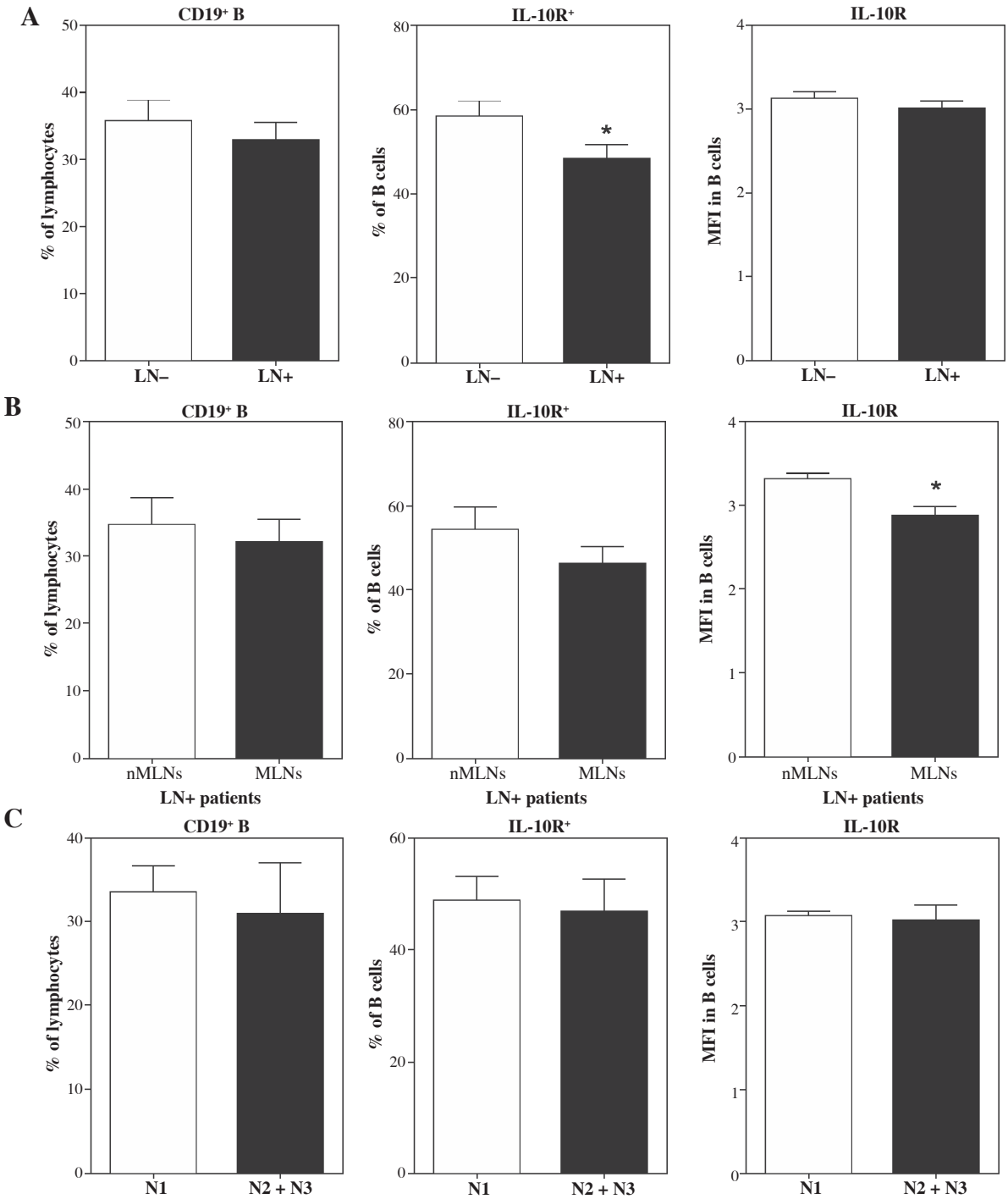

Fig. 2. A) Comparison of frequency of B cells, IL-10 receptor (IL-10R)-expressing B cells and MFI of IL-10R expression on B cells in patients with at least one involved lymph node (LN+) and patients with no involved lymph nodes (LN–) in breast tumor-draining lymph nodes (TDLNs). Data are representative of 21 LN+ patients and 28 LN– patients. **B**) Comparison of frequency of B cells, IL-10R-expressing B cells and MFI of IL-10R expression on B cells in metastatic lymph nodes (MLNs) and non-metastatic lymph nodes (nMLNs) of breast cancer patients with at least one involved lymph node (LN+ patients). Data are representative of 8 nMLNs and 20 MLNs. **C**) Association between frequency of B cells, IL-10R-expressing B cells and MFI of IL-10R expression on B cells with the number of involved lymph nodes. N1 represents 1-3 involved lymph nodes (18 samples), N2 + N3 represents more than 3 involved lymph nodes (8 samples), and data are presented as mean ±SEM. **P*-value < 0.05. SEM – standard error of the mean, MFI – mean fluorescence intensity

Table 2. Percentages of B cells and IL-10R$^+$ B cells in breast cancer draining lymph nodes

Cell subset	Min	Max	Median	Mean ±SD
CD19$^+$ cells (in lymphocytes' gate)	4.0	65.5	30.4	34.1 ±13.8
IL-10R$^+$ cells (in CD19$^+$ cells' gate)	20.7	83.7	59.0	52.9 ±17.3

IL-10R – IL-10 receptor, SEM – standard error of the mean

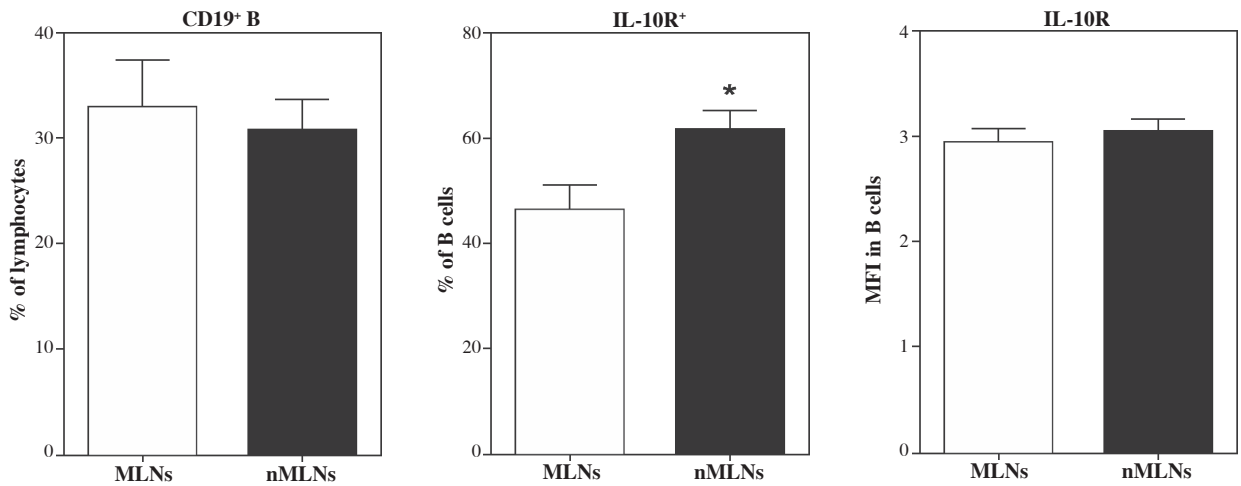

Fig. 3. Comparison of frequency of B cells, IL-10 receptor (IL-10R)-expressing B cells and MFI of IL-10R expression on B cells in metastatic lymph nodes (MLNs) and non-metastatic lymph nodes (nMLNs) from one patient. Data are representative of 11 MLNs and 11 nMLNs. Data are presented as mean ±SEM. **P*-value < 0.05. SEM – standard error of the mean, MFI – mean fluorescence intensity

lymph nodes compared to involved lymph nodes in a patient with breast cancer ($p = 0.040$). However, the frequency of B cells or the MFI of IL-10R on these cells was not significantly different in MLNs and nMLNs in each patient (Fig. 3).

Association between IL-10R expression in B cells and stage, grade, size, and type of breast cancer

The percentage of B cells, IL-10R expressing B cells, and the intensity of IL-10R expression on these cells did not show a significant association with the stage, grade, size, or type of breast cancer (Table 3).

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

According to our results, no significant correlation was found between the frequency of B cells, IL-10R$^+$ B cells, MFI of IL-10R$^+$ B cells with the ER or PR by tumor cells (Fig. 4A). However, it was observed that patients with HER2$^+$ tumors had a notably higher frequency of IL-10R-expressing B cells compared to those in the HER2$^-$ group ($p = 0.023$). However, the intensity of expression of this receptor was not different in these patients (Fig. 4B).

Phenotype of IL-10R-expressing B cells

In one involved and two uninvolved LNs, the phenotype of IL-10R$^+$ B cells was determined based on the expression of CD24 and CD27 markers. The findings revealed that in nMLNs, 85.6% and 61.6% of IL-10R$^+$ B cells were memory/active B cells (CD27$^+$CD24^{hi}), while 11.1% and 32.9% of them showed a naïve phenotype (CD24^{low}CD27$^-$). On the other hand, in the MLN, 49% and 42% of IL-10R$^+$ B cells exhibited memory/active B cells and naïve phenotype, respectively (Fig. 5A). Additionally, we observed that 73.7% and 54.5% of memory B cells in nMLNs expressed IL-10R, while 50.9% of memory B cells in the MLN also expressed IL-10R. Furthermore, 40.7% and 20.8% of naïve B cells in nMLNs and 18.8% of naïve B cells in the MLN expressed IL-10R (Fig. 5B).

Assessing the effect of IL-10 on granzyme B, CD86, and TNF-α expression in B cells

Effect of rIL-10 on production of granzyme B in B cells

The analysis showed that IL-21 (50 ng/ml) and anti-BCR (3.3 µg/ml) can induce B cells to produce granzyme B. However, the addition of 25 ng/ml, 50 ng/ml, and 100 ng/ml of rIL-10 in a 24-hour culture did not sig-

Table 3. Percentages of B cells and IL-10R$^+$ B cells in patients with different stages, grades, tumor sizes, and tumor types

Parameter	Value, *n* (%)	B cell (mean ±SEM)	*P* value	IL-10R$^+$ B cell (mean ±SEM)	*P* value
Tumor size (greatest dimension, cm)			0.7		0.8
T1 (≤ 2)	25 (51.0)	35.7 ±2.5		52.4 ±3.2	
T2 (2-5)	19 (38.8)	35 ±3.6		52 ±4.7	
Stage			0.3		0.6
I	9 (18.4)	29.74 ±3.7		57.8 ±5.1	
II	27 (55.1)	37.6 ±2.4		52 ±3.7	
III	9 (18.4)	33.5 ±6		49.1 ±5.5	
Histological grade			0.2		0.2
Well differentiated (I)	3 (6.1)	44.2 ±9.3		60.5 ±13.8	
Moderately differentiated (II)	42 (85.7)	33.4 ±2		51.8 ±2.7	
Tumor type			0.4		0.6
Infiltrating ductal carcinoma (IDC)	41 (83.7)	34.1 ±2.2		53.4 ±2.6	
IDC with medullary features (IDC + M)	5 (10.2)	40.1 ±5.7		46.9 ±10.9	

IL-10R – IL-10 receptor, SEM – standard error of mean

nificantly affect the production of GrB in these cells. We hypothesized that the lack of effect could be attributed to the use of optimal doses of IL-21 and anti-BCR. The experiment was conducted again, this time using a lower concentration of IL-21 (25 ng/ml) and anti-BCR (3.3 µg/ml), along with 50 ng/ml and 100 ng/ml of rIL-10, for 24 hours. The results of the experiment indicated that the presence of 100 ng/ml of rIL-10 led to a significant increase in the percentage of B cells producing granzyme B ($p = 0.0286$, Fig. 6).

Effect of rIL-10 on expression of CD86 in B cells

Interleukin 10 at concentrations of 25 ng/ml and 100 ng/ml was added to stimulated B cells in the 48-hour culture medium. Subsequent analysis revealed no significant effect on CD86 expression in B cells (Fig. 7).

Effect of rIL-10 on expression of TNF-α by B cells

Following a brief polyclonal stimulation, it was found that 62.8 ±18.1% of B cells obtained from breast TDLNs produced TNF-α. Further investigation showed that 26.1 ±9.3% of B cells expressed this cytokine at a high intensity (TNF^{hi}), while 36.4 ±8.8% expressed TNF at a lower intensity (TNF^{low}). The addition of IL-10 to the culture for 48 hours did not have a significant impact on TNF-α production. However, the presence of 50 ng/ml IL-10 resulted in a 40% decrease in the percentage of TNF^{hi} B cells (16.1 ±4.2%) (Fig. 8).

Discussion

The immune response within tumors and their draining lymph nodes (LNs) is a critical determinant of cancer progression and clinical outcomes. Cytokines such as IL-10 play a pivotal role in shaping this response, with paradoxical effects – both suppressing and stimulating anti-tumor immunity [33, 34]. Our study suggests a context-dependent role for IL-10 in breast cancer immunity. Below, we discuss these findings within the broader framework of IL-10's dual functionality and their potential clinical implications.

IL-10R$^+$ B cells and contrasting associations: nodal involvement vs. HER2$^+$ tumors

B cells make up approximately 30% of lymphocytes in TDLNs, with about half of them expressing IL-10R. This aligns with previous studies that have identified B cells as a primary target of IL-10 [35]. Interestingly, IL-10R$^+$ B cells were more prevalent in nMLNs and LN– patients, while their frequency and intensity of receptor expression were significantly lower in MLNs. This decline was evident even when comparing tumor-involved and uninvolved LNs within the same patient. Our previous study revealed that this reduction extended to the peripheral blood of breast cancer patients, as these cases had a lower percentage of circulating IL-10R$^+$ B cells compared to healthy individuals [36]. Additionally, in nMLNs the majority of IL-10R$^+$ B cells exhibited an active/memory phenotype rather than a naïve one. This suggests that active/memory B cells may be more sensitive to IL-10 compared to naïve B cells, and they upregulate IL-10R upon activation, a pattern that contrasts sharply with what is observed in T cells [18].

The predominance of IL-10R$^+$ cells in nMLNs suggests a protective role for these cells. This protective role of IL-10R$^+$ B cells may stem from their ability to enhance anti-tumor immunity. In nMLNs – a reactive environment

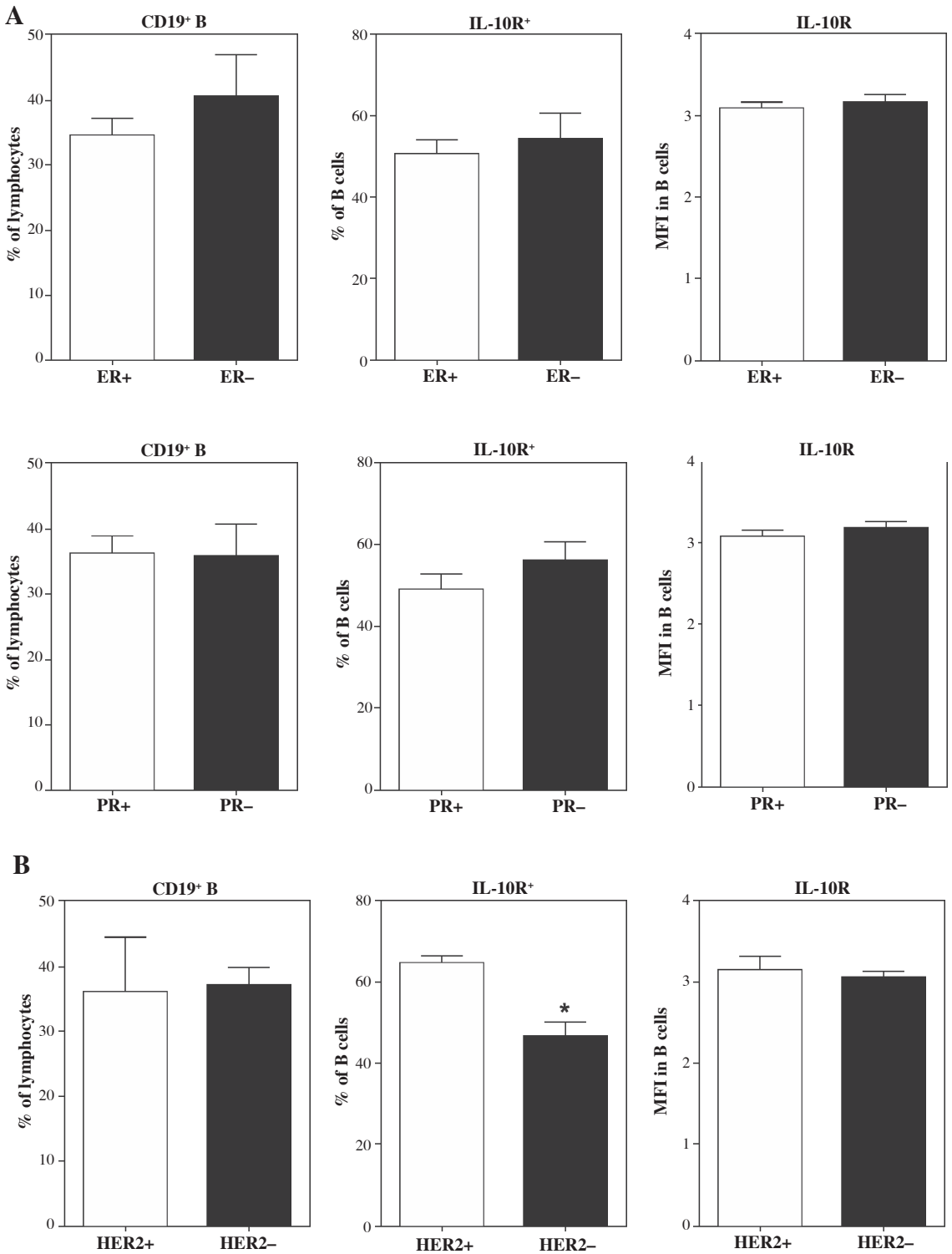

Fig. 4. Association between frequency of B cells, IL-10 receptor (IL-10R)-expressing B cells and MFI of IL-10R expression on B cells with (**A**) expression of estrogen receptor (ER) (24 ER+ patients, 7 ER– patients), **B**) expression of progesterone receptor (PR) on tumor cells (21 PR+ patients, 10 PR– patients), and **C**) human epidermal growth factor receptor 2 (HER2) expression (5 HER+ patients, 22 HER– patients). Data are presented as mean ±SEM. **P*-value < 0.05. SEM – standard error of the mean, MFI – mean fluorescence intensity

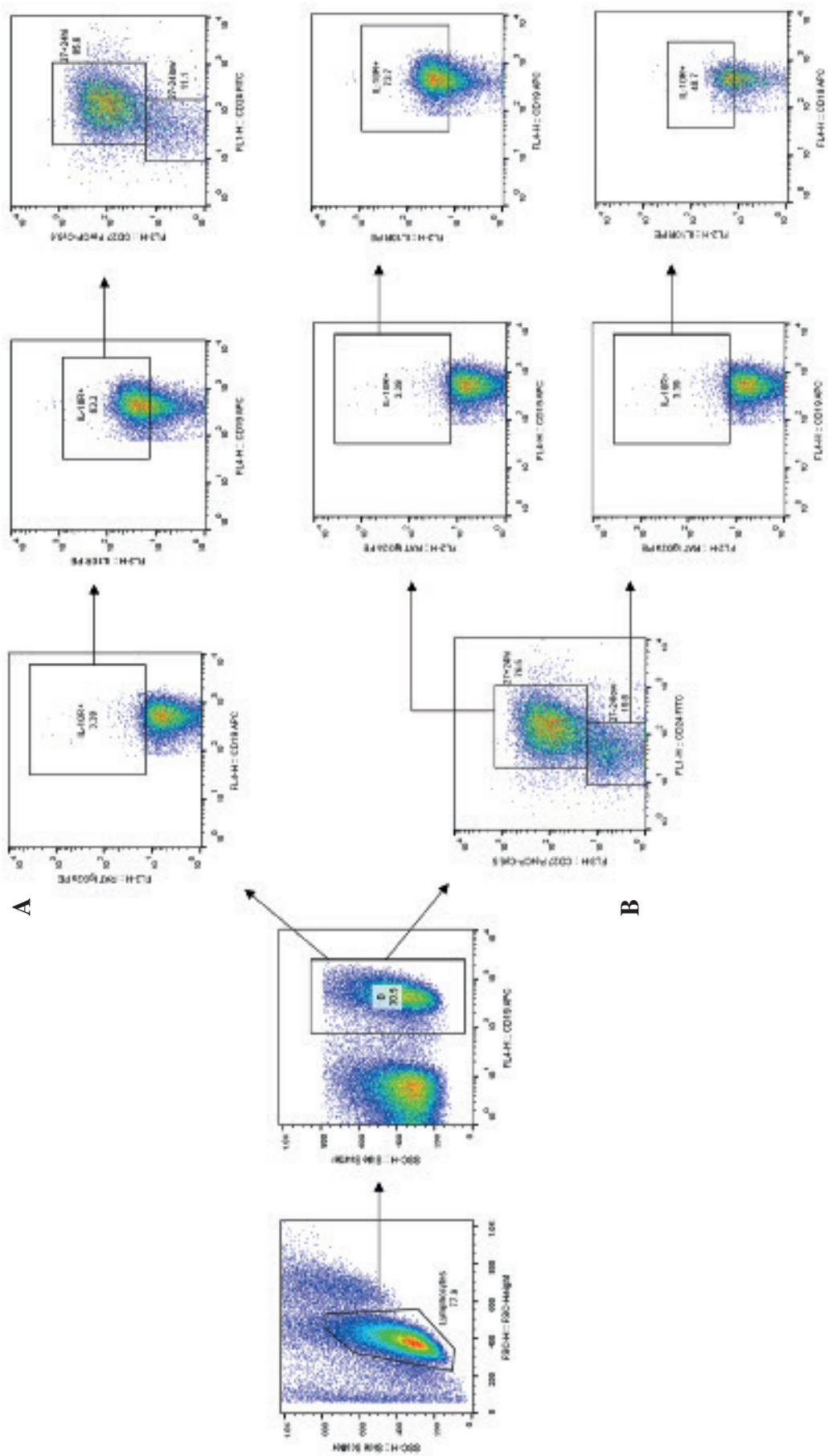

Fig. 5. Assessment of phenotype of IL-10 receptor (IL-10R)-expressing B cells in tumor-draining lymph nodes (TDLNs) of breast cancer patients. First, lymphocytes were gated based on their side and forward scatter features. Then, $CD19^{+}$ cells were identified as B cells. **A**) Presence of IL-10R on B cells was determined using fluorescence minus one (FMO). Finally, the phenotype of B cells expressing IL-10R was evaluated based on expression of CD24 and CD27; active/memory B cells: $CD27^{+}CD24^{hi}$ and naïve B cells: $CD24^{low}CD27^{-}$. **B**) Active/memory and naïve B cells were identified within the B cell population and the expression of IL-10R was then assessed in these cells

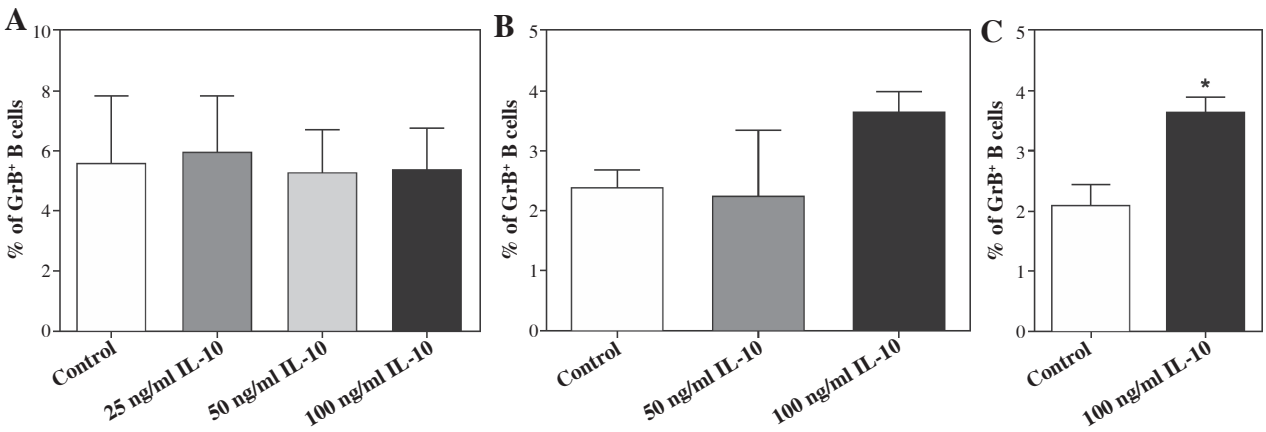

Fig. 6. Comparison of frequency of granzyme B (GrB)-producing B cells in the absence and presence of IL-10. Lymphocytes were stimulated with (**A**) recombinant interleukin (rIL)-21 (50 ng/ml) and anti-B cell receptor (BCR) (3.3 µg/ml) along with 25 ng/ml, 50 ng/ml, and 100 ng/ml of (rIL-10) for 24 hours. Data are representative of 4 independent experiments. **B**) Lymphocytes were stimulated with rIL-21 (25 ng/ml) and anti-BCR (3.3 µg/ml), along with 50 ng/ml and 100 ng/ml rIL-10 for 24 hours. Data are representative of 3 independent experiments. **C**) Lymphocytes were stimulated with rIL-21 (25 ng/ml) and anti-BCR (3.3 µg/ml), along with 100 ng/ml rIL-10 for 24 hours. Data are representative of 4 independent experiments. In all experiments explained above, during the last 6 hours of stimulation, cells received brefeldin A (1 µl/ml) and cells that were treated with IL-21 and anti-BCR were used as controls. After staining with anti-CD19 and anti-GrB antibodies, the cells were analyzed by flow cytometry. Fluorescence minus one (FMO) was used to determine the expression of GrB in B cells. Data are presented as mean ±SEM. **P*-value < 0.05. SEM – standard error of the mean

– tumor antigen exposure may activate IL-10R$^+$ B cells, promoting their survival through BCL-2 upregulation [34, 37]. Additionally, IL-10 signaling in B cells upregulates MHC expression, promotes plasma cell differentiation, and supports class switching [21, 38, 39]. These processes are all critical for effective antigen presentation and T-cell activation.

In contrast, the presence of tumor cells in MLNs creates an immunosuppressive environment that facilitates immune evasion [40]. The reduction of IL-10R$^+$ B cells in MLNs suggests that metastatic tumors may suppress IL-10R expression *via* tumor-derived factors, leading to fewer active/memory and class-switched IL-10R$^+$ B cells. This is consistent with previous findings of reduced IgM$^-$IgD$^-$ class-switched and active/memory B cells in metastatic axillary LNs compared to uninvolved nodes [2], suggesting that decreased IL-10R expression in MLNs may reflect tumor-induced reprogramming. Additionally, the strong correlation between frequency of IL-10R$^+$ B cells and the intensity of their IL-10R expression suggests a tightly regulated mechanism controlling receptor expression. This highlights the importance of downregulating IL-10R in MLNs.

The frequency and expression intensity of IL-10R$^+$ B cells showed no correlation with breast cancer characteristics such as stage, grade, tumor size, or type – except for Her2 status. Patients with Her2$^+$ tumors had significantly higher levels of IL-10R$^+$ B cells compared to those

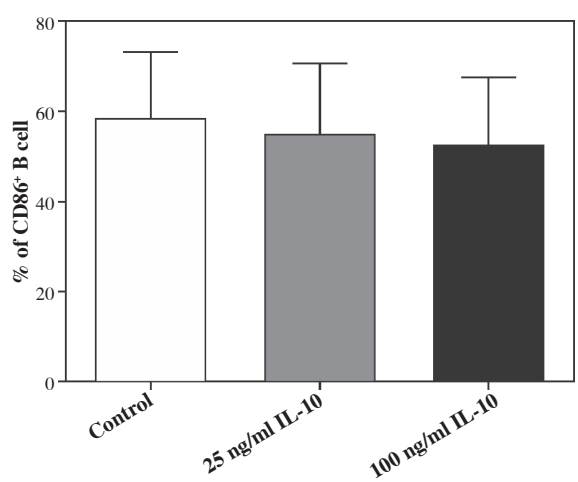

Fig. 7. Comparison of frequency of CD86-expressing B cells in absence and presence of IL-10. Cells were treated with 25 ng/ml and 100 ng/ml of recombinant IL-10 (rIL-10) along with 1 µg/ml of CpG for 48 hours. Cells that were only treated with CpG were used as controls. Cells were analyzed by flow cytometry after staining with anti-CD19 and anti-CD86 antibodies. Finally, expression of CD86 in B cells was determined using fluorescence minus one (FMO). Data are presented as mean ±SEM, and are representative of 3 independent experiments. SEM – standard error of the mean

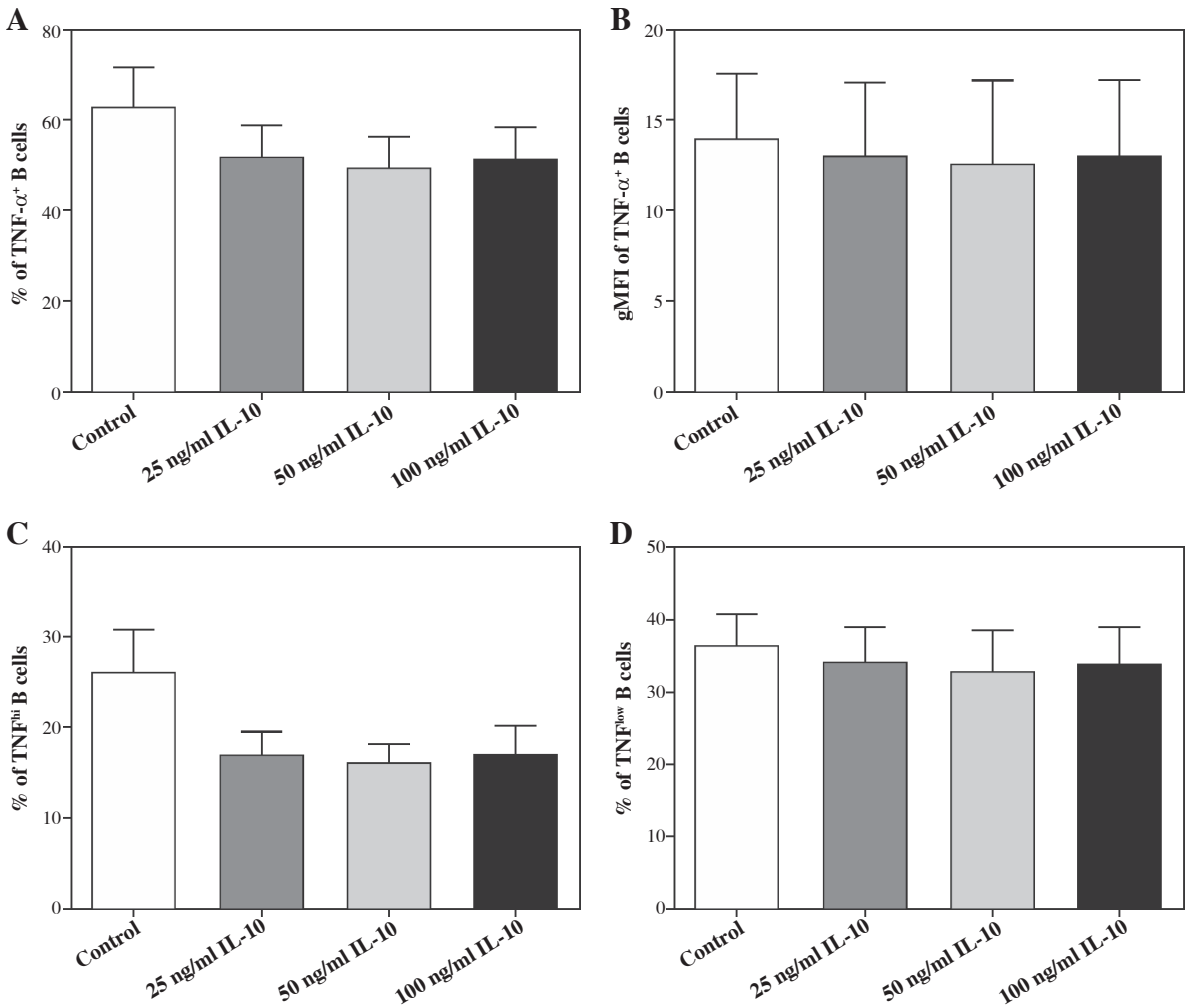

Fig. 8. Comparison of frequency of TNF-α expressing B cells in absence and presence of IL-10. Cells were treated with 25 ng/ml, 50 mg/ml, and 100 ng/ml recombinant IL-10 (rIL-10) in combination with 1 µg/ml of CpG for 48 hours. In the final 6 hours of culture, PMA (50 ng/ml), ionomycin (1 µg/ml), and brefeldin A (1 µl/ml) were added. Cells treated with only CpG were taken as controls. After staining with anti-CD19 and anti-TNF-α antibodies, the cells were evaluated by flow cytometry. Finally, expression of TNF-α in B cells was determined using fluorescence minus one (FMO). The following comparisons are shown: **A**) B cells that express TNF-α, **B**) geometric mean fluorescence intensity (gMFI) of TNF-α expression in B cells, **C**) B cells that express TNFα with high intensity (TNF^{hi} B cells), and **D**) B cells that express TNF-α with low intensity (TNF^{low} B cells). Data are presented as mean ±SEM, and are representative of 4 independent experiments. SEM – standard error of the mean

with $Her2^-$ tumors. Previous studies have shown a positive correlation between $HER2^+$ tumors and the level of IL-10 [40]. Additionally, there is an association between the overexpression of HER2 in breast cancer patients and the presence of *in situ* IgG [41]. Several studies have linked IgG production to tumor promotion through IgG4 subclass or by activating Fc-γ receptors on myeloid cells, which regulate the effector function of TILs [42, 43]. This suggests that a higher frequency of $IL\text{-}10R^+$ B cells supports $HER2^+$ tumor progression by fostering an immunosuppressive microenvironment. The contrast between $IL\text{-}10R^+$ B cell abundance in $HER2^+$ tumors (a poor prognostic marker) and their association with LN– status (a favorable marker) underscores IL-10's context-dependent roles. Since $IL\text{-}10R^+$ B cells are heterogeneous (containing both naďve and active/memory subsets) and IL-10's effects vary by dose and target cell differentiation [26, 28, 29, 44], further research is needed to resolve this discrepancy and elucidate the role of $IL\text{-}10R^+$ B cell subsets in cancer immunity.

IL-10 enhances granzyme B but suppresses TNF-α in B cells: dual immunomodulatory effects

IL-10 promotes granzyme B production in B cells but reduces TNF-α intensity in B cells

Granzyme B-producing B cells represent a unique subset capable of exerting both pro- and anti-tumor effects, depending on the context [45]. In hepatocellular carcinoma, for instance, margin-infiltrating B lymphocytes (MIL-Bs) have demonstrated direct anti-tumor activity through secretion of granzyme B and TRAIL [14]. Previous studies have shown that IL-10, in combination with IL-4, can induce granzyme B expression in anti-BCR-activated B cells, albeit less potently than IL-21 [45]. However, the interplay between IL-10 and IL-21 in modulating granzyme B production remained unexplored. Our study addressed this gap by stimulating B cells with varying concentrations of IL-10 alongside optimal doses of IL-21. While high-dose IL-21 did not significantly alter granzyme B levels, the addition of 100 ng/ml rIL-10 combined with a lower IL-21 dose markedly increased the frequency of granzyme B-producing B cells. This finding challenges the conventional view of IL-10 as a purely immunosuppressive cytokine, suggesting instead that it can enhance cytotoxic B-cell responses under specific conditions.

In contrast, IL-10 exerted a suppressive effect on TNF-α expression. While it did not change overall TNF-α production, it reduced the frequency of TNF-α^{hi} B cells by approximately 1.6-fold across all tested doses. Studies on cancer have shown that TNF-α promotes anti-tumor immunity at high levels but facilitates metastasis at low concentrations [46, 47]. Additionally, research on breast TDLNs has revealed a correlation between TNF-α^{hi} B cells and positive prognostic markers [47]. This finding suggests that IL-10 may decrease the anti-tumor function of B cells by reducing the intensity of TNF-α expression, leading to a weaker immune response against breast cancer.

IL-10 does not modulate CD86 expression

The B7.2 (CD86) co-stimulatory signal enhances B cell activity and is crucial for initiating T-cell activation upon tumor antigen recognition [48, 49]. Previous studies have found that about 23 ±14.3% of B cells in breast TDLNs express CD86. $CD86^+$ B cells have been linked to poor prognosis, potentially due to their association with regulatory B cells that foster immunosuppressive Treg expansion [50-53]. IL-10 has been reported to downregulate CD86 in transitional B cells, thereby dampening $CD4^+$ T-cell responses [54]. Our data revealed that IL-10 had no significant effect on CD86 expression in activated B cells – despite their high baseline CD86 frequency (around 50%). This implies that IL-10's immunomodulatory influence on B cells may be more selective, primarily fine-tuning cytokine production rather than broadly regulating co-stimulatory signals.

Conclusion: IL-10's dual role in B cell function

This study provides novel insights into the role of IL-10R-expressing B cells in breast TDLNs. We found that approximately 50% of B cells in breast TDLNs express IL-10R, with a significant proportion displaying a memory/activated phenotype. These IL-$10R^+$ B cells exhibited a dual association with clinical prognostic markers – negatively correlating with lymph node involvement but positively correlating with HER2 expression – suggesting a context-dependent role in breast cancer progression. Furthermore, we demonstrated that IL-10 exerts a contradictory effect on B cell function, enhancing granzyme B production while suppressing TNF-α expression, underscoring its diverse role in shaping anti-tumor and pro-tumor B cell responses.

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Disclosures

All patients signed the written informed consent. The study was approved by the ethics committees of Mashhad and Shiraz Universities of Medical Sciences (ethics numbers: IR.MUMS.MEDICAL.REC.1398.751 and IR.SUMS.REC.1398.1205), and was in accordance with the 1975 Declaration of Helsinki, as revised in 2000.

The authors declare no conflict of interest.

References

1. Habanjar O, Bingula R, Decombat C, et al. (2023): Crosstalk of inflammatory cytokines within the breast tumor microenvironment. Int J Mol Sci 24: 4002.
2. Mehdipour F, Razmkhah M, Faghih Z, et al. (2019): The significance of cytokine-producing B cells in breast tumor-draining lymph nodes. Cell Oncol (Dordr) 42: 381-395.

3. Anderson NM, Simon MC (2020): The tumor microenvironment. Curr Biol 30: R921-R925.
4. Wang L, Simons DL, Lu X, et al. (2020): Breast cancer induces systemic immune changes on cytokine signaling in peripheral blood monocytes and lymphocytes. EBioMedicine 52: 102631.
5. du Bois H, Heim TA, Lund AW (2021): Tumor-draining lymph nodes: At the crossroads of metastasis and immunity. Sci Immunol 6: eabg3551.
6. Zhang Y, Zhang Z (2020): The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. Cell Mol Immunol 17: 807-821.
7. Laumont CM, Banville AC, Gilardi M, et al. (2022): Tumour-infiltrating B cells: immunological mechanisms, clinical impact and therapeutic opportunities. Nat Rev Cancer 22: 414-430.
8. Fridman WH, Sibéril S, Pupier G, et al. (2023): Activation of B cells in tertiary lymphoid structures in cancer: Anti-tumor or anti-self? Semin Immunol 65: 101703.
9. Hladíková K, Koucký V, Bouček J, et al. (2019): Tumor-infiltrating B cells affect the progression of oropharyngeal squamous cell carcinoma via cell-to-cell interactions with CD8+ T cells. J Immunother Cancer 7: 261.
10. Zhang E, Ding C, Li S, et al. (2023): Roles and mechanisms of tumour-infiltrating B cells in human cancer: a new force in immunotherapy. Biomark Res 11: 28.
11. Gül N, van Egmond M (2015): Antibody-dependent phagocytosis of tumor cells by macrophages: a potent effector mechanism of monoclonal antibody therapy of cancer. Cancer Res 75: 5008-5013.
12. Arabpour M, Rasolmali R, Talei AR, et al. (2019): Granzyme B production by activated B cells derived from breast cancer-draining lymph nodes. Mol Immunol 114: 172-178.
13. Hagn M, Sontheimer K, Dahlke K, et al. (2012): Human B cells differentiate into granzyme B-secreting cytotoxic B lymphocytes upon incomplete T-cell help. Immunol Cell Biol 90: 457-467.
14. Shi JY, Gao Q, Wang ZC, et al. (2013): Margin-infiltrating CD20(+) B cells display an atypical memory phenotype and correlate with favorable prognosis in hepatocellular carcinoma. Clin Cancer Res 19: 5994-6005.
15. Wang JZ, Zhang YH, Guo XH, et al. (2016): The double-edge role of B cells in mediating antitumor T-cell immunity: Pharmacological strategies for cancer immunotherapy. Int Immunopharmacol 36: 73-85.
16. Olkhanud PB, Damdinsuren B, Bodogai M, et al. (2011): Tumor-evoked regulatory B cells promote breast cancer metastasis by converting resting $CD4^+$ T cells to T-regulatory cells. Cancer Res 71: 3505-3515.
17. Shalapour S, Font-Burgada J, Di Caro G, et al. (2015): Immunosuppressive plasma cells impede T-cell-dependent immunogenic chemotherapy. Nature 521: 94-98.
18. Dennis KL, Blatner NR, Gounari F, Khazaie K (2013): Current status of interleukin-10 and regulatory T-cells in cancer. Curr Opin Oncol 25: 637-645.
19. Shouval DS, Ouahed J, Biswas A, et al. (2014): Interleukin 10 receptor signaling: master regulator of intestinal mucosal homeostasis in mice and humans. Adv Immunol 122: 177-210.
20. Thomson AW, Lotze MT. The cytokine handbook. Two-volume set. Elsevier 2003.
21. Moore KW, de Waal Malefyt R, Coffman RL, O'Garra A (2001): Interleukin-10 and the interleukin-10 receptor. Annu Rev Immunol 19: 683-765.
22. Oft M (2014): IL-10: master switch from tumor-promoting inflammation to antitumor immunity. Cancer Immunol Res 2: 194-199.
23. Nazila Fathi M, Elnaz A, Hamid G, et al. (2019): Association of rs1946518 C/A polymorphism in promoter region of interleukin 18 gene and breast cancer risk in Iranian women: A case-control study. Iran J Allergy Asthma Immunol 18: 671-678.
24. Vinod C, Jyothy A, Vijay Kumar M, et al. (2015): A common SNP of IL-10 (-1082A/G) is associated with increased risk of premenopausal breast cancer in South Indian women. Iran J Cancer Prev 8: e3434.
25. Hamidullah, Changkija B, Konwar R (2012): Role of interleukin-10 in breast cancer. Breast Cancer Res Treat 133: 11-21.
26. Mumm JB, Emmerich J, Zhang X, et al. (2011): IL-10 elicits IFNγ-dependent tumor immune surveillance. Cancer Cell 20: 781-796.
27. Jinquan T, Larsen CG, Gesser B, et al. (1993): Human IL-10 is a chemoattractant for CD8+ T lymphocytes and an inhibitor of IL-8-induced CD4+ T lymphocyte migration. J Immunol 151: 4545-4551.
28. Chan IH, Wu V, McCauley S, et al. (2015): IL-10: Expanding the immune oncology horizon. Receptors Clin Investig 2: 1401.
29. Berman RM, Suzuki T, Tahara H, et al. (1996): Systemic administration of cellular IL-10 induces an effective, specific, and long-lived immune response against established tumors in mice. J Immunol 157: 231-238.
30. Llanes-Fernández L, Alvarez-Goyanes RI, Arango-Prado Mdel C, et al. (2006): Relationship between IL-10 and tumor markers in breast cancer patients. Breast 15: 482-489.
31. Venetsanakos E, Beckman I, Bradley J, Skinner JM (1997): High incidence of interleukin 10 mRNA but not interleukin 2 mRNA detected in human breast tumours. Br J Cancer 75: 1826-1830.
32. Li Y, Yu H, Jiao S, Yang J (2014): Prognostic value of IL-10 expression in tumor tissues of breast cancer patients. Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi 30: 517-520.
33. Smyth MJ, Cretney E, Kershaw MH, Hayakawa Y (2004): Cytokines in cancer immunity and immunotherapy. Immunol Rev 202: 275-293.
34. Mannino MH, Zhu Z, Xiao H, et al. (2015): The paradoxical role of IL-10 in immunity and cancer. Cancer Lett 2015; 367: 103-107.
35. Cai G, Nie X, Zhang W, et al. (2012): A regulatory role for IL-10 receptor signaling in development and B cell help of T follicular helper cells in mice. J Immunol 189: 1294-1302.
36. Absalan F, Mehdipour F, Shariat M, et al. (2025): Decreased IL-10R-expressing B Cells in breast cancer patients: a potential biomarker for early cancer detection. Am J Clin Exp Immunol 14: 34-42.
37. Levy Y, Brouet JC (1994): Interleukin-10 prevents spontaneous death of germinal center B cells by induction of the bcl-2 protein. J Clin Invest 1994; 93: 424-428.
38. Iyer SS, Cheng G (2012): Role of interleukin 10 transcriptional regulation in inflammation and autoimmune disease. Crit Rev Immunol 32: 23-63.
39. Saeland S, Duvert V, Moreau I, Banchereau J (1993): Human B cell precursors proliferate and express CD23 after CD40 ligation. J Exp Med 178: 113-120.

40. Bhattacharjee HK, Bansal VK, Nepal B, et al. (2016): Is interleukin 10 (IL10) expression in breast cancer a marker of poor prognosis? Indian J Surg Oncol 7: 320-325.
41. Garaud S, Zayakin P, Buisseret L, et al. (2018): Antigen specificity and clinical significance of IgG and IgA autoantibodies produced in situ by tumor-infiltrating B cells in breast cancer. Front Immunol 9: 2660.
42. Andreu P, Johansson M, Affara NI, et al. (2010): FcRgamma activation regulates inflammation-associated squamous carcinogenesis. Cancer Cell 17: 121-134.
43. Karagiannis P, Gilbert AE, Josephs DH, et al. (2013): IgG4 subclass antibodies impair antitumor immunity in melanoma. J Clin Invest 123: 1457-1474.
44. Emmerich J, Mumm JB, Chan IH, et al. (2012): IL-10 directly activates and expands tumor-resident CD8(+) T cells without de novo infiltration from secondary lymphoid organs. Cancer Res 72: 3570-3581.
45. Hagn M, Schwesinger E, Ebel V, et al. (2009): Human B cells secrete granzyme B when recognizing viral antigens in the context of the acute phase cytokine IL-21. J Immunol 183: 1838-1845.
46. Schweigerer L, Malerstein B, Gospodarowicz D (1987): Tumor necrosis factor inhibits the proliferation of cultured capillary endothelial cells. Biochem Biophys Res Commun 143: 997-1004.
47. Mehdipour F, Razmkhah M, Faghih Z, et al. (2019): The significance of cytokine-producing B cells in breast tumor-draining lymph nodes. Cell Oncol 42: 381-395.
48. Chang CS, Chang JH, Hsu NC, et al. (2007): Expression of CD80 and CD86 costimulatory molecules are potential markers for better survival in nasopharyngeal carcinoma. BMC Cancer 7: 88.
49. Suvas S, Singh V, Sahdev S, et al. (2002): Distinct role of CD80 and CD86 in the regulation of the activation of B cell and B cell lymphoma. J Biol Chem 277: 7766-7775.
50. Shariati S, Mehdipour F, Samadi M, et al. (2020): The balance of regulatory and stimulatory B cell subsets in breast cancer draining lymph nodes correlates with tumor prognostic factors. Life Sci 257: 118117.
51. Wennhold K, Thelen M, Lehmann J, et al. (2021): CD86(+) antigen-presenting B cells are increased in cancer, localize in tertiary lymphoid structures, and induce specific T-cell responses. Cancer Immunol Res 9: 1098-1108.
52. Qiu H, Tian W, He Y, et al. (2021): Integrated analysis reveals prognostic value and immune correlates of CD86 expression in lower grade glioma. Front Oncol 11: 654350.
53. Bao J, Betzler AC, Hess J, Brunner C (2023): Exploring the dual role of B cells in solid tumors: implications for head and neck squamous cell carcinoma. Front Immunol 14: 1233085.
54. Nova-Lamperti E, Fanelli G, Becker PD, et al. (2016): IL-10-produced by human transitional B-cells down-regulates CD86 expression on B-cells leading to inhibition of CD4+T-cell responses. Sci Rep 6: 20044.