Breast Implants Elicit Local and Systemic Immune Response: Evidence for Breast Cancer Immunosurveillance

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Background: Women with cosmetic implants have lower rates of future breast cancer than the general population. The authors hypothesized that the implant foreign body response could induce a local protective anticancer immunosurveillance. The authors expanded on their previous finding, which showed that women with breast implants have elevated antibody responses to certain breast cancer proteins.

Methods: Blood samples and breast tissue were collected from women undergoing first time breast augmentation (implant-naive [IN]) and revision breast augmentation (implant-exposed [IE]). Sera were collected and antibody levels to common breast cancer proteins were quantified by enzyme-linked immunosorbent assay. Reverse transcriptase-polymerase chain reaction was performed on breast tissue samples to quantify immune-related gene expression levels between IN and IE patients. Bulk RNA sequencing was performed to identify differentially expressed genes and altered signaling pathways in the breasts of IN patients versus IE patients.

Results: In total, 188 patients were recruited (IN, $n = 117$; IE, $n = 71$). Data demonstrated that IE patients had higher levels of antibodies to mucin-1, estrogen receptor-α, and mammaglobin A compared with IN patients. Mucin-1 expression was found to be higher in IE compared with IN breast tissue. RNA-sequencing analysis demonstrated up-regulated pathways in IE breast tissue for B-cell activation and development, T-helper cell type 2–related genes, T-cell activation, chemotactic factors, and responses to estrogen.

Conclusions: This is the first study to demonstrate that periimplant inflammation extends beyond the implant capsule to the breast parenchyma. Women with breast implants have more activated B cells in the breast parenchyma and elevated antibody responses to breast cancer antigen. *(Plast. Reconstr. Surg.* 155: 797, 2025.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, V.

Silicone, which is chemically inert, has been used in medical devices for over 50 years.[1,2] However, whether or not it is biologically inert has been the subject of recent controversy, particularly as it relates to silicone breast implants.[3,4]

On implantation, the silicone surface is coated with proteins.[5,6] This protein layer consists predominantly of extracellular matrix proteins (eg, fibrinogen, fibronectin, vitronectin) and mediates an influx of inflammatory cells, including neutrophils, macrophages, T cells, and B cells.[5–8] This results in formation of a fibrotic capsule.[9] The capsule contains a well-characterized immune response to the breast implant.[10,11] Multiple reports have documented an abundance

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of T-helper type 17 (Th17) cells and macrophages contained in the capsule.[10–12] There have been concerns that this could lead to systemic inflammatory symptoms.[13,14] Th17 cells are the primary cell drivers of rheumatoid arthritis disease progression, and concerns have resurfaced that silicone breast implants could predispose patients to autoimmune disease or autoimmune-like symptoms reported with breast implant illness.[15,16]

Inflammation can also be protective, however, particularly as it relates to cancer surveillance and prevention. Women have a baseline level of T-cell activity against "self-protein" human epidermal growth factor receptor-2 (HER-2) that is gradually lost in disease progression from ductal carcinoma in situ to HER-2^{+} invasive breast cancer.[17] T-cell activity against mucin-1 (MUC-1) is found naturally in multiparous women (as opposed to nulliparous women), and antibodies against circulating MUC-1 are inversely correlated with breast cancer disease progression.[18] We hypothesized that the periimplant inflammatory response could induce local immunosurveillance, similar to that which occurs naturally in healthy multiparous women. Epidemiologic studies have indeed shown that women with cosmetic breast implants have lower rates of future breast cancer development compared with implant-naive (IN) women (relative risk, 0.63; 95% CI, 0.56 to 0.71).[19,20]

The inflammatory milieu of the implant capsule has been well characterized.[5–12] However, no studies have examined whether this inflammatory process extends to the local breast parenchyma. Here, we performed a 2-part study. First, we expanded on our prior work by measuring systemic antibody responses to common breast cancer–associated proteins in a larger cohort of implant-exposed (IE) versus IN patients and analyzed responses in a subset of these patients after a longer follow-up period.[21,22] Second, we compared the local immune environment in the breast parenchyma of IE versus IN patients by quantifying expression of immune response–related genes. In addition, bulk RNA-sequencing (RNA-seq) of a subset of patients was performed to identify differentially expressed genes and signaling pathways between these groups.

PATIENTS AND METHODS

Patient Recruitment

After institutional review board approval (protocol no. STU00212926), healthy women presenting with breast-related cosmetic complaints were recruited from the plastic surgery clinic between 2018 and 2022. Inclusion criteria were healthy women aged 18 to 80 years. Exclusion criteria were history of cancer (including breast cancer), autoimmune disease, immunosuppressed status, transplant history, human immunodeficiency virus, or hepatitis.

Antibody Level Quantification

Sera were tested for antibody responses to breast cancer antigens by means of enzyme linked immunosorbent assay. Recombinant human carcinoembryonic antigen (CEA), MUC-1, estrogen receptor (ER)-α, and HER-2 were obtained from Abcam. Recombinant mammaglobin-A was obtained from Abnova, and tetanus toxoid was obtained from List Labs. Tetanus toxoid antibody levels were measured as a control. Control wells incubated with buffer alone were included on each plate and subtracted as background from all sample wells.

Tissue Immune-Related Gene Quantification

Tissue samples were placed in RNAlater (Invitrogen) and stored at −80°C. Samples were homogenized and total RNA was isolated using TRIzol Reagent (ThermoFisher) and RNeasy Mini Kit (Qiagen) according to manufacturer protocols. RNA samples were sent for library preparation and sequencing to the NUSeq core facility at Northwestern University. In addition, quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR) was performed for several differentially expressed genes of interest. RNA samples were converted to complementary DNA using Invitrogen SuperScript IV VILO Master Mix, and qRT-PCR was performed using iTaq Universal SYBR Green Supermix (Bio-Rad) on a StepOnePlus (Applied Biosystems). Immune target gene expression levels were normalized to glyceraldehyde-3-phosphate dehydrogenase for each sample. Nontemplate controls were run with every set of primers to ensure reagents were not contaminated, and melt curves were performed with every run to ensure PCR products were attributable to amplification of a single desired transcript. Table 1 contains sequences for qRT-PCR. Raw RNA-seq data are available at National Center for Biotechnology Information Sequence Read Archive (accession no. PRJNA844984).

Tissue Sample Protein Analysis

Frozen tissue samples were manually homogenized and lysed in Pierce RIPA Buffer. Protein concentration was determined using DC Protein

Table 1. Forward and Reverse Primers for Genes and Encoded Proteins Analyzed with Reverse Transcription-Polymerase Chain Reaction

Gene Name	Encoded Protein	Forward Primer (5'–3')	Reverse Primer (5'–3')
GAPDH	GAPDH	TGTTGCCATCAATGACCCCTT	CTCCACGACGTACTCAGCG
IFNG	IFN-γ	AGTGATGGCTGAACTGTCGC	TGGGATCTTGCTTAGGTTGGC
GATA3	GATA3	TGCCGTTGAGGGTTTCAGAG	TCCGAGCACAACCACCTTAG
CXCR5	CXCR5	AGGTTGTGGGCATTGATGGG	CCAGGTGAGCAAACAAGCAC
RORC	RORγ	CAACAGCAGCAACAGGAACC	GAAGTCCACATCGGTCAGGG
FOXP3	FOXP3	CACCCAGGAAGGACAGCAC	GCTGCTCCAGAGACTGTACC
SDC1	CD138	CAGTAGAGAGCGGACTCCAG	GTCAGAGTCATCCCCAGAGC
IL22	IL-22	CCCTATATCACCAACCGCAC	GCTCACTCATACTGACTCCGT
BATF	BATF	TATTGCCGCCCAGAAGAGC	GCTTGATCTCCTTGCGTAGAG
PAX5	PAX5	GCACACGGATGTTCTCACAC	CAACGGCTTGTGTCCTTTGG
MS4A1	CD20	GCACATACGCACCACATCTC	AGAAGCGTGACAACACAAGC
STAT6	STAT6	GGAAGGGCACTGAGTCTGTC	CTGCCAAAAGGTGAAGCCAC
CD8A	CD8α	TTGAGTCTCCAACGGCAAGG	CGCCTCCACATAGGGGTTTC
ESR1	ERα	TATGTGTCCAGCCACCAACC	TCGTATCCCACCTTTCATCATTCC
MUC1	MUC-1	TACCGATCGTAGCCCCTATG	CTCACCAGCCCAAACAGG

Assay (Bio-Rad) and a SmartSpecPlus spectrophotometer (Bio-Rad). Proteins samples were subjected to Western blot according to standard protocols. Densitometry was performed using ImageJ (National Institutes of Health).

Immunohistochemical Analysis

Tissue samples from capsule and breast parenchyma were fixed in formalin and embedded in paraffin. Five-micron-thick sections were cut with a microtome, and immunohistochemical analysis (IHC) was performed according to standard protocols. The antibody used was MUC-1 antibody (US Biological; E3414-19X). Images were obtained with a Nikon Eclipse 50i light microscope.

Data Presentation and Statistical Analysis

Demographic data are expressed as medians with interquartile ranges, or as sum totals with percentages. Demographic comparisons were performed using an independent samples *t* test for age and body mass index and an analysis of variance analysis for the remaining variables. Antibody levels are expressed as optical density at 450 nm (OD450) values and reported as the median. Data were determined to follow a non-normal distribution after normality tests were completed. Therefore, Wilcoxon rank sum tests were performed to compare antibody levels between cohorts, and Wilcoxon signed rank tests were performed to compare antibody levels over time. Mann-Whitney tests were used to compare ΔCt values. Multivariable regression models used least square means reporting while controlling for variables that were significant on univariate analysis. Statistical analyses were performed with GraphPad Prism version 9.3.0 (GraphPad, San Diego, CA) and significance set at $P < 0.05$.

RESULTS

Patient Demographics

Blood samples were available for 188 patients (IN, $n = 117$; IE, $n = 71$). Table 2 compares demographics between cohorts. IE patients were significantly older (median age, 44 years versus 35 years; $P < 0.001$) and were significantly more likely to be postmenopausal (32% versus 15%; $P = 0.005$). IE patients reported prior pregnancy more often (63% versus 48%; $P = 0.054$). Table 3 describes the breast implant characteristics in the IE cohort. Average implant duration was 13 years.

Antibody Levels

Antibody responses were significantly elevated in IE compared with IN patients to ER (OD450, 0.20 versus 0.17; $P = 0.036$), MUC-1 (OD450, 0.42 versus 0.33; $P = 0.001$), and mammaglobin-A (OD450, 0.33 versus 0.23; $P = 0.001$). There was no difference between cohorts in antibody levels to CEA (OD450, 0.29 versus 0.28; $P = 0.57$) or HER-2 (OD450, 0.19 versus 0.19; $P = 0.57$). There was no difference in response to positive control tetanus (OD450, 1.40 versus 1.42; $P = 0.54$). Figure 1 demonstrates antibody response levels between cohorts.

Univariate analysis indicated that age and menopausal status were significantly different between cohorts. Prior pregnancy was more frequent in IE patients ($P = 0.054$). Because age and menopausal status are related, multivariable

Table 2. Demographic Comparison between the IN and IE Cohorts

Characteristic	IN Cohort	IE Cohort	*P*
No. of patients	17	71	
Median age, yr	35	44	<0.001
BMI, kg/m^2	23.2	23.1	0.88
Race or ethnicity, no. (%)			
White	100 (85.5)	59 (81.9)	0.23
Hispanic	5 (4.3)	6 (8.3)	
Black	4 (3.4)	3 (4.2)	
Asian	4 (3.4)	0 (0.0)	
Declined	4 (3.4)	4 (5.6)	
Smoking history, no. (%)			
Nonsmoker	92 (78.6)	59 (81.9)	0.85
Former smoker	21 (17.9)	10 (13.9)	
Current smoker	3 (2.6)	1 (1.4)	
Unknown	1 (0.9)	1 (1.4)	
Pregnancy history, no. (%)			
Never pregnant	60 (51.3)	26 (36.1)	0.054
Previously pregnant	56 (47.9)	45 (62.5)	
Unknown	1 (0.9)	0 (0.0)	
Menopausal status, no. (%)			
Premenopausal	99 (84.6)	49 (68.1)	0.005
Postmenopausal	17 (14.5)	23 (31.9)	
Unknown	1 (0.9)	0 (0.0)	
Family history of breast cancer, no. (%)			
No	94 (80.3)	56 (77.8)	0.63
Yes	22 (18.8)	14 (19.4)	
Unknown	1 (0.9)	2 (2.8)	

Table 3. Breast Implant Characteristics in the IE Cohort

Characteristic	No. (%)
Implant type	68
Silicone	52 (76.5)
Saline	16 (23.5)
Implant pocket	59
Submuscular/dual-plane	40 (67.8)
Subglandular	19 (32.2)
Implant surface texture	63
Smooth	54 (85.7)
Textured	9 (14.3)
Capsular contracture	69
Grade I	35 (50.7)
Grade II	6 (8.7)
Grade III	16 (23.2)
Grade IV	12 (17.4)
Implant rupture status	68
Ruptured	16 (23.5)
No rupture	52 (76.5)

regression models were used, adjusting only for age and pregnancy history. Antibody levels to MUC-1 (P = 0.0177) and ER (P = 0.0212) remained significantly elevated in the IE cohort. Antibody levels to mammaglobin-A remained marginally significant (P = 0.0513).

Subgroup Analysis of Antibody Levels in IE Patients

Antibody levels to MUC-1 were significantly elevated in women with saline implants compared with silicone (OD450, 0.53 versus 0.40; P = 0.034). There was no difference in antibody levels to CEA (P = 0.19), ER (P = 0.35), HER-2 (P = 0.69), mammaglobin-A (P = 0.26), or tetanus (P = 0.059) by implant type.

Women with implants in place for 10 years or longer (n = 35) had significantly elevated antibody levels to MUC-1 compared with women with implants in place for less than 10 years (n = 31) (OD450, 0.50 versus 0.32; P = 0.002). There was no difference in antibody levels by time since implant placement to CEA (P = 0.94), ER (P = 0.092), HER-2 (P = 0.66), mammaglobin-A (P = 0.40), or tetanus (P = 0.39). There was no difference in antibody levels to any of the proteins tested by implant surface texture, pocket location, rupture history, or capsular contracture (data not shown).

Antibody Levels before and after Implant Placement

Thirty-nine patients had breast implants placed during the study period, with blood drawn before

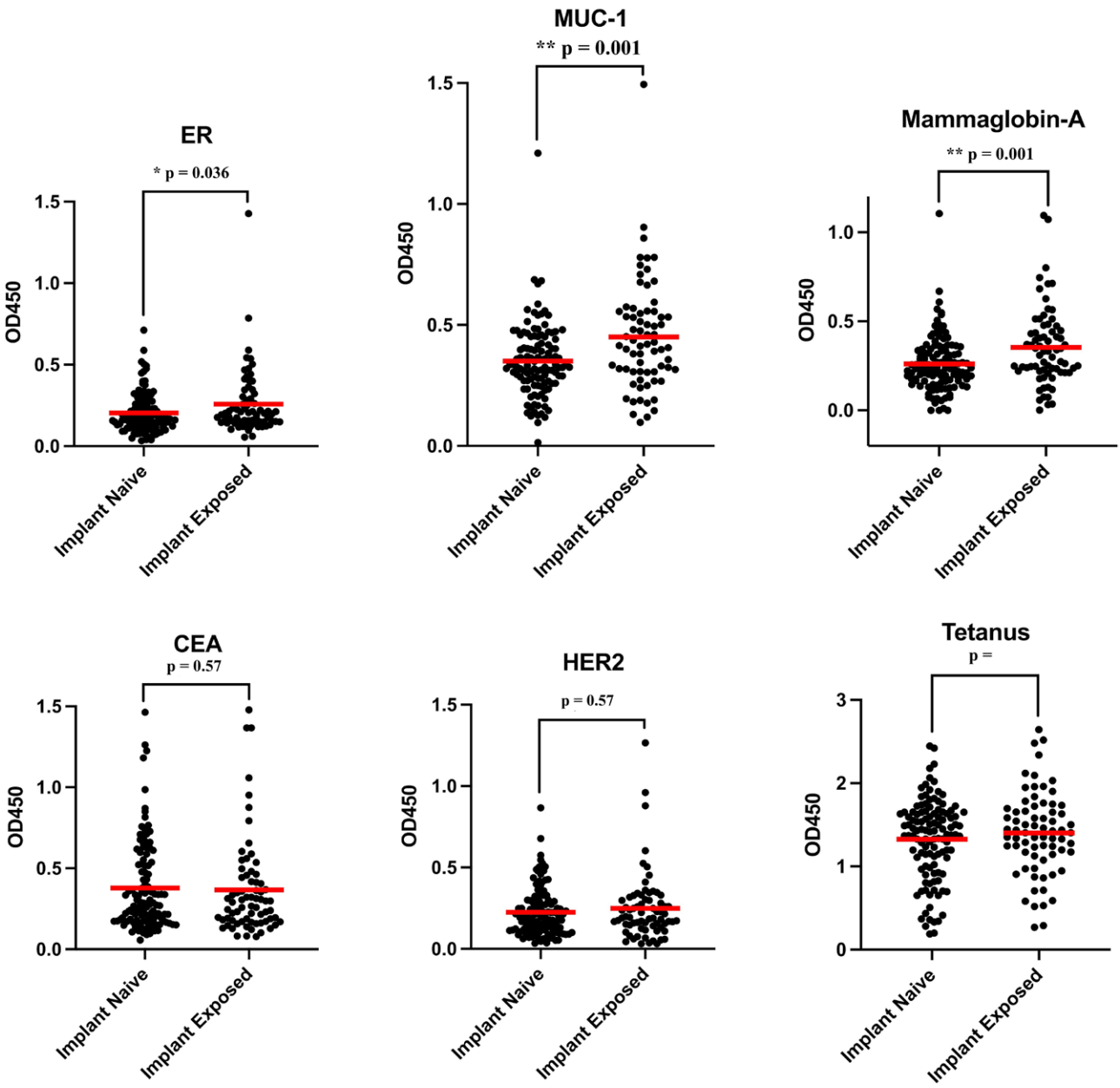

Fig. 1. (*Above*) Statistically significant increase in antibody response (*OD450*) to ER, MUC-1, and mammaglobin-A in IE patients versus IN patients; *red bar* indicates median value. (*Below*) Statistically insignificant changes in antibody response (*OD450*) to CEA, HER2, and tetanus (control) in IE patients versus IN patients; *red bar* indicates median value.

and 1-month after breast implant placement. Antibody levels were significantly elevated 1 month after implant placement to MUC-1 (OD450, 0.31 versus 0.24; $P < 0.001$), ER (OD450, 0.50 versus 0.45; $P < 0.001$), mammaglobin-A (OD450, 0.68 versus 0.56; $P = 0.012$), and HER-2 (OD450, 0.10 versus 0.08; $P = 0.039$). There was no difference in antibody levels before to after implant placement for CEA ($P = 0.10$) or tetanus ($P = 0.56$).

Seventeen patients had blood drawn again 6 months after implant placement. Antibody levels remained significantly elevated at 6 months compared with before implant to MUC-1 ($P < 0.0001$), ER ($P = 0.0079$), and mammaglobin-A ($P = 0.0123$). Antibody levels were not significantly different to CEA ($P = 0.99$), HER-2 ($P = 0.36$), and tetanus ($P = 0.91$). Figure 2 demonstrates antibody level changes before to 1 month and 6 months after implant placement.

Immune Cell–Specific Gene Expression in IE versus IN Breast Tissue

Breast tissue samples were collected from 65 patients (IN, $n = 35$; IE, $n = 30$). Table 4 displays

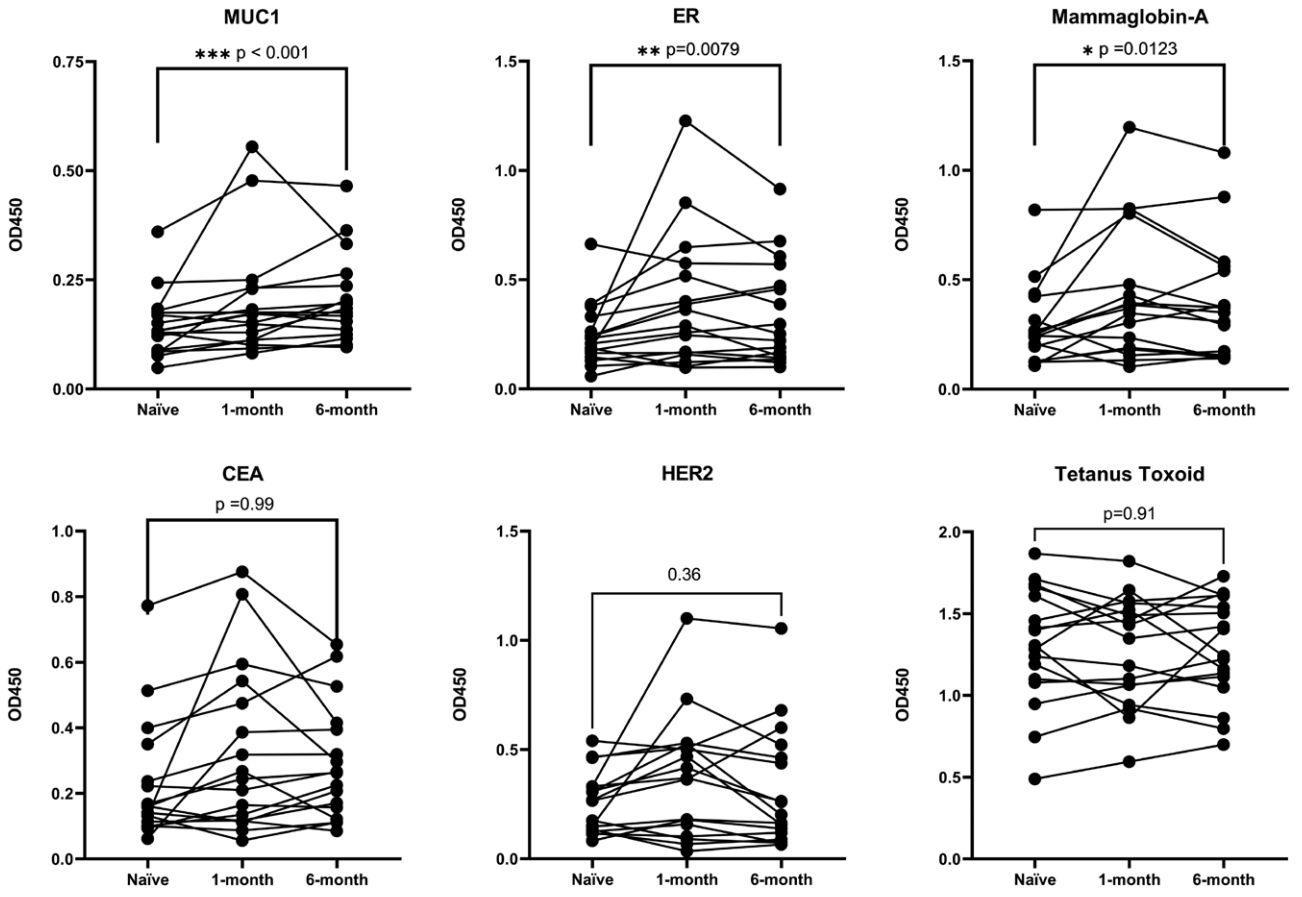

Fig. 2. (*Above*) Statistically significant elevations in antibody response (*OD450*) to MUC-1, ER, mammaglobin-A, and HER2 6 months after implant placement versus before implant placement, with lines connecting an individual patient's antibody levels at distinct time points shown on the *y* axis. (*Below*) Statistically insignificant changes in antibody response (*OD450*) to CEA, HER2, and tetanus (control) 1 month after implant placement versus before implant placement, with lines connecting an individual patient's antibody levels at distinct time points shown on the *y* axis.

and compares demographics between cohorts. Compared with IN patients, breast tissue of IE patients had elevated expression of gene characteristic of plasma cells (antibody-secreting B cells) and Th17 cells. Fold change in IE relative to IN for *SDC1*, the gene encoding CD138 (a plasma cell-associated cell surface proteoglycan) was 1.90x (P = 0.01; SD = 2.06x), whereas expression of *PAX5* (a transcription factor down-regulated in the conversion of B cells to plasma cells) was 0.53x (P = 0.031; S placement D = 0.53x).[23,24] Fold change for expression of Th17-related genes was 2.16x for *IL17A* (P = 0.004; SD = 1.90x), 1.66x for *RORC* (P = 0.024; SD = 1.30x), 2.36x for *BATF* (P < 0.001; SD = 2.09x), and 1.72 for *IL22* (P = 0.064; SD = 1.75x). Gene expression was not significantly different between IE and IN cohorts for Th1, Th2, Tfh, Treg, and $CD8^+$ T-cell–related genes (data not shown).

Univariate analysis indicated that the demographic factors of age and menopausal status were significantly different between cohorts. Because age and menopause are related, multivariable regression models were used adjusting only for age. Gene expression levels remained significantly elevated in IE versus IN breast tissue for *BATF* (P = 0.004) and *SDC1* (P = 0.04).

Subgroup Analysis of Immune Cell–Specific Gene Expression in IE Breast Tissue

Patients with subglandular breast implants had elevated *IL17A* expression (Th17 cells, 2.20x; P = 0.039; SD = 2.03x) and *SDC1* expression (plasma cells, 3.20x; P < 0.017; SD = 2.40x) compared with patients with submuscular or dual-plane breast implants. Compared with patients with grade I/II capsular contracture, patients with grade III/IV capsular contracture had elevated *IL17A* expression (Th17 cells, 3.44x; P < 0.001; SD = 2.57x) and elevated *BATF* expression (Th17 cells, 1.77x; P = 0.054; SD = 1.10x), although the latter did

Table 4. Demographic Comparison between IN and IE Breast Tissue Samples

Characteristic	IN	IE	*P*
No. of patients	35	30	
Mean patient age ± SD, yr	33.2 ± 7.8	45 ± 14.8	0.0002
Mean BMI ± SD, kg/m^2	24.6 ± 5.1	25.2 ± 6.0	0.56
Race/ethnicity, no. (%)			
White	28 (80.0)	25 (83.3)	0.75
Hispanic	0 (0.0)	0 (0.0)	
Black	1 (2.9)	2 (6.7)	
Asian	1 (2.9)	0 (0.0)	
Declined/other	5 (22.9)	3 (10.0)	
Smoking history, no. (%)			
Nonsmoker	27 (77.1)	25 (83.3)	0.36
Former smoker	8 (22.9)	4 (13.3)	
Current smoker	0 (0.0)	0 (0.0)	
Unknown	0 (0.0)	1 (3.3)	
Pregnancy history, no. (%)			
Never pregnant	18 (51.)	14 (46.7)	0.70
Previously pregnant	17 (48.6)	16 (53.3)	
Menopausal status, no. (%)			
Premenopausal	33 (94.3)	20 (66.7)	0.004
Postmenopausal	2 (5.7)	10 (33.3)	
Family history of breast cancer, no. (%)			
No	27 (77.1)	21 (70.0)	0.66
Yes	8 (22.9)	8 (26.7)	
Unknown	0 (0.0)	1 (3.3)	

not reach statistical significance. There were no significant differences in gene expression levels for any of the genes tested based on implant type (saline versus silicone), surface texture (smooth versus textured), implant rupture, or time since implant placement (greater or less than 10 years) (data not shown).

Breast Cancer–Related Gene and Protein Expression in IE versus IN Breast Tissue

Because we detected elevated antibody responses to common breast cancer proteins in IE women (Fig. 1), we next wondered whether there was a difference in expression of these genes and their encoded proteins in the breast tissue of IE women versus IN women. Relative transcription quantification by qRT-PCR demonstrated that *MUC1* expression was elevated in IE compared with IN tissue (2.58x; $P = 0.0015$; SD = 2.67x), whereas no change was detected in expression of ER (0.92x; $P = 0.64$; SD = 0.73x). Up-regulation of MUC-1 expression protein was also confirmed by Western blot (Fig. 3), suggesting that the increased immune response to MUC-1 that we detected in the sera of IE patients may be a consequence of increased local expression of MUC-1 in breast tissue. Specific staining of the MUC-1 antibody used for Western blot was confirmed through immunohistochemical staining of IN and IE breast tissue, of which representative images are depicted in Figure 4.

Histologic Evidence of Increased MUC-1 IHC in IE Breast Tissue

Staining for MUC-1 in ductal epithelium was confirmed by means of IHC of breast tissue specimens. IE breast parenchyma appeared to have more MUC-1 expression than IN breast parenchyma, with representative images shown in Figure 4. This further validates our finding that MUC-1 expression is increased in IE breast tissue.

Immune-Related Gene Expression Pathways Enriched in IE Breast Tissue

We performed a pilot bulk RNA-seq analysis on a subset of 20 patients (IE, $n = 10$; IN, $n = 10$) and compared relative transcriptomic profiles of harvested breast tissue. Demographics can be found in Table 5.

Transcriptomic data were analyzed per sample and visualized using principle component analysis.[25] Inspection of the principle component analysis revealed an outlier from each group. After exclusion of outliers, data were analyzed with DESeq2 and the Benjamini-Hochberg adjustment for multiple comparisons (false discovery adjusted $P < 0.05$).[26,27] This yielded 2040 differentially expressed genes: 892 up-regulated genes

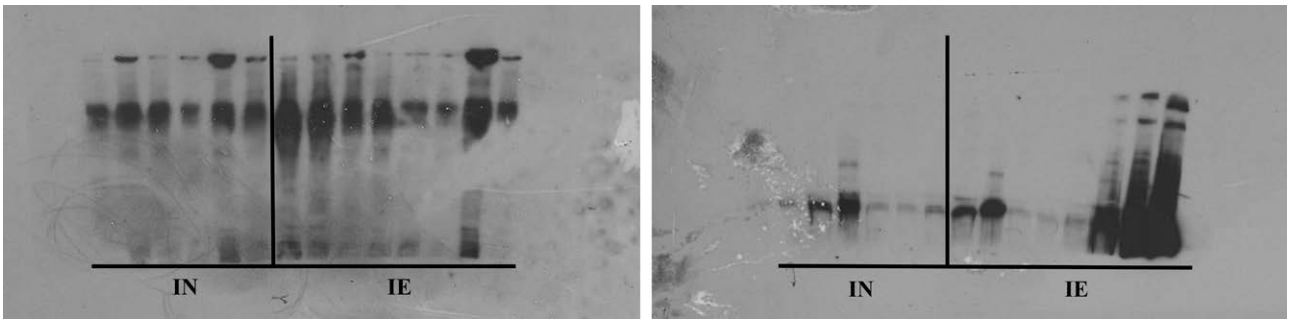

Fig. 3. Western blot results comparing MUC-1 expression between IN and IE cohorts.

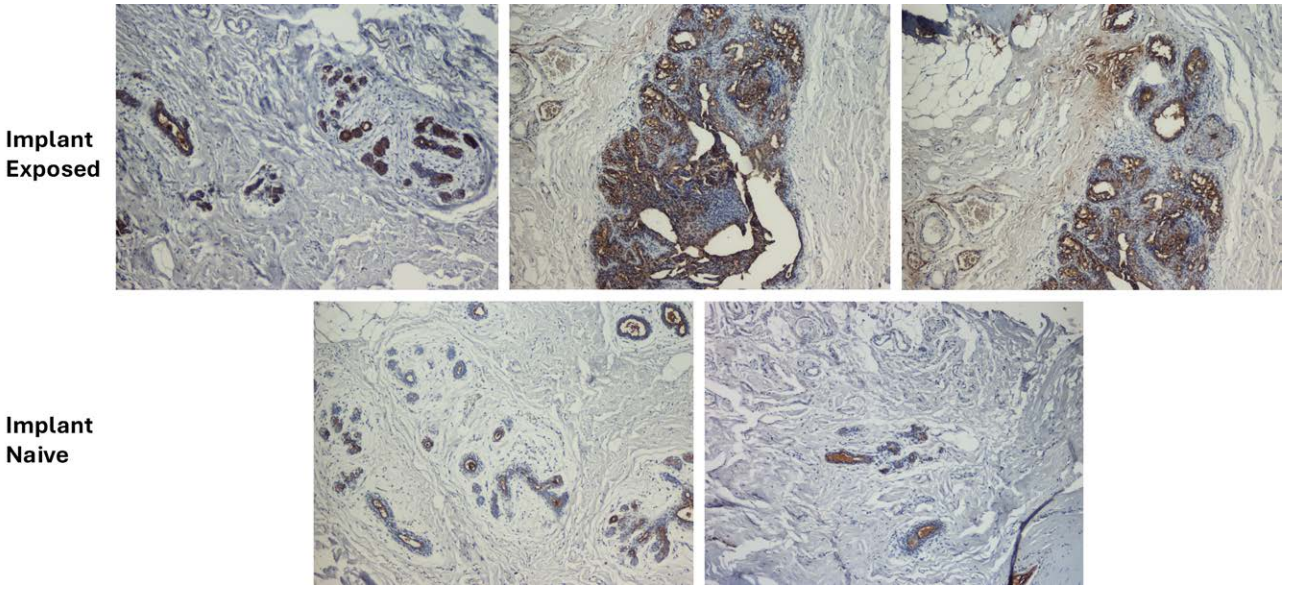

Fig. 4. Immunohistochemical staining of breast tissue for MUC-1 expression showing increased expression in IE ductal epithelium.

and 1148 down-regulated genes in IE versus IN patient tissue. A heat map and volcano plot are presented to visualize differentially expressed genes in Figure 5.

Confirmation of the larger cohort of qRT-PCR data was found for plasma cell–related and Th17-cell–related genes. Plasma cell–related genes that were significantly up-regulated in IE samples included *XBP1* (2.22x; $P < 0.002$), a transcription factor uniquely required for plasma cell differentiation), and *FAS* (1.89x; $P < 0.001$).[28,29] Th17-cell–related genes that were significantly up-regulated in IE samples included *C1QL1* (2.68x; $P < 0.01$), *BATF* (2.44x; $P < 0.01$), and *IL17RB* (2.26x; $P < 0.05$).

Other up-regulated pathways identified in IE compared with IN breast tissue included B-cell activation, Th2-related genes, T-cell activation, chemotactic factors, and responses to estrogen. Up-regulated genes related to B-cell activation included CLCF1 (cytokine belonging to the interleukin (IL) 6 family that induces B-cell expansion and enhances humoral responses; $P = 0.0002$), BCL3 (transcriptional regulator that associates with NFKB ($P < 0.0001$), RELB (also a member of the NFKB family that regulates germinal center B-cell maturation and mediates B-cell survival; $P = 0.004$), and IL7 (important in commitment to B-cell lineage, maturation, and survival; $P < 0.0001$).[30,31] Up-regulated genes related to Th2 cells included IL4R (receptor to the key cytokine that mediates differentiation of Th2 cells; $P = 0.002$) and GATA3 (induced by IL4 binding to IL4R; $P = 0.005$).[32,33] Up-regulated genes related to T-cell activation included CBFB ($P = 0.004$), SEMA4A ($P < 0.0001$), CD44 ($P = 0.001$), and TNFSF14 ($P < 0.0001$). Up-regulated genes related to chemotactic factors included CCL19 ($P < 0.0001$), CCL21 ($P = 0.0001$), CXCL12 ($P = 0.004$), CCR1 ($P = 0.005$), CCL2 ($P < 0.0001$), CXCL1 ($P = 0.0004$), CXCL6 ($P = 0.0004$), and VCAM1 ($P < 0.0001$). Up-regulated genes related to estrogen responses included

Table 5. Patient Characteristics for RNA-Seq Data

Characteristic	Value
All RNA patients, no.	20
Median age, yr	44.8
BMI, kg/m^2	25.7
Race/ethnicity, no. (%)	
White	19 (95.0)
Hispanic	0 (0.0)
Black	1 (5.0)
Asian	0 (0.0)
Smoking history, no. (%)	
Nonsmoker	17 (85.0)
Former smoker	3 (15.0)
Current smoker	0 (0.0)
Pregnancy history, no. (%)	
Never pregnant	9 (45.0)
Previously pregnant	11 (55.0)
Menopausal status, no. (%)	
Premenopausal	16 (80.0)
Postmenopausal	4 (20.0)
Family history of breast cancer, no. (%)	
No	15 (75.0)
Yes	5 (25.0)

ESR1 ($P = 0.005$) and ESR2 ($P = 0.008$). Figure 6 depicts pathways and genes that were upregulated in IE tissues.

DISCUSSION

Although silicone may be chemically inert, it elicits a foreign body response, which makes it biologically relevant.[3,34] The periimplant capsule inflammatory milieu has been extensively characterized, but whether this inflammatory reaction extends beyond the capsule into the breast parenchyma has not yet been elucidated.[5–12] Furthermore, whether these inflammatory changes can have systemic effects continues to be debated.

Autoimmune/inflammatory syndrome induced by adjuvants was first described in 2011, but is starting to gain wider attention. This is a broad group of symptoms that can be caused by a likewise broad group of materials capable of eliciting autoantibody production (including metal and silicone implants). Breast implant illness would be 1 category of disease that falls under autoimmune/inflammatory syndrome induced by adjuvants, and autoantibody dysregulation—specifically against G-protein–coupled receptors—has previously been demonstrated in this patient population and thought to be responsible for autonomic-related symptoms (eg, heart palpitations, dry eyes/mouth, fatigue/depression).[35]

Here, we compared antibody responses to common breast cancer proteins before and after implant placement. This was an extension of our prior work where we showed, in a smaller cohort, that antibody responses to mammaglobin-A and MUC-1 were elevated as early as 1 month after implant placement.[21,22] Antibody levels to mammaglobin-A and MUC-1 were both found to be elevated again at 1 month after implant placement, and these elevated responses were sustained at 6 months after implant placement. Interestingly, women with breast implants in place longer than 10 years had elevated antibody levels to MUC-1 compared with women with breast implants in place less than 10 years. This may also explain the higher MUC-1 antibody levels in saline implant patients (compared with silicone), as average implant duration in the saline group was significantly longer (saline, 17 years; silicone, 11 years). These data suggest that breast cancer antigen-specific immune responses induced by implant placement persist over time, potentially implicating these responses in long-term tumor immunosurveillance, which may explain in part the robust decrease in the incidence of breast cancer in women with breast implants. We do feel it is important to note that other studies have shown that women with cosmetic breast augmentation who go on to develop primary breast cancers present with more advanced stage of disease but have no difference in breast cancer–specific survival compared with women without breast implants.[36] This finding is at odds with our hypothesis, and it is unclear whether the implant may somehow impair detection of the cancer.

Secondarily, based on gene expression analysis, we were able to investigate the immunophenotypes of inflammatory cells present in IE breast tissue compared with IN breast tissue. Elevated levels of target genes for Th17 cells (*IL17A*, *RORC*, and *BATF*) were detected in IE breast tissue.[37,38] In addition, IE breast tissue had elevated levels of the target gene *SDC1* (encoding CD138, specific for plasma cells) and decreased levels of *PAX5* (marker of inactive B cells), suggesting a transition to B-cell activation. Multiple prior studies have documented an abundance of Th17 cells in breast implant capsule.[10–12] This is the first evidence documenting expression signatures indicative of activated B cells in association with periimplant tissue, suggesting that these cells extend beyond capsule to the local breast parenchyma. Interestingly, Th17 cells have the ability to induce B-cell proliferation and can also trigger

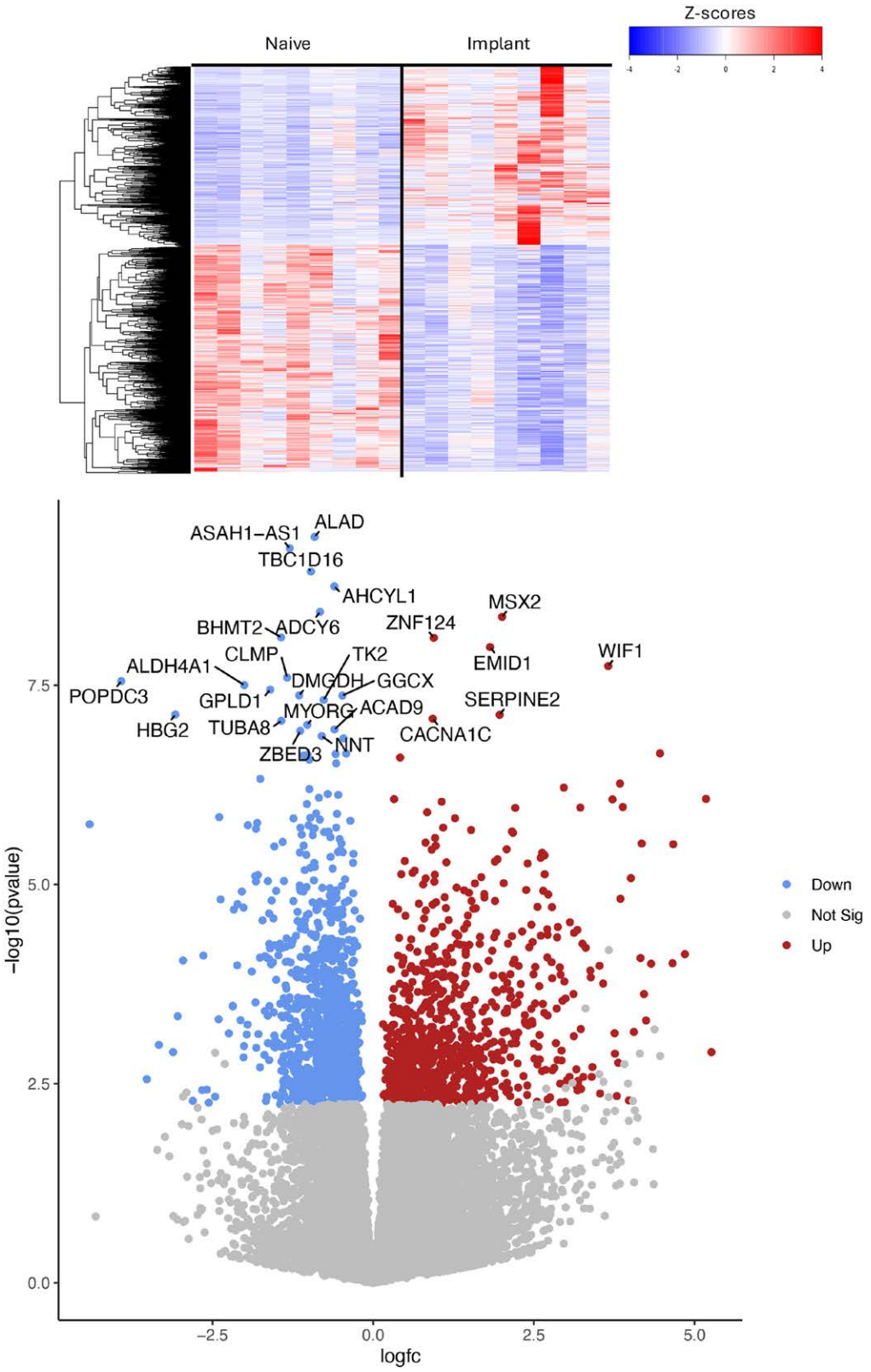

Fig. 5. (*Above*) Two thousand forty differentially expressed genes in the IE compared with IN cohorts: 892 up-regulated genes and 1148 down-regulated genes. (*Below*) Volcano plot demonstrating the differentially expressed genes between IE and IN cohorts: 25 genes with the greatest significance in fold change of gene expression are labeled.

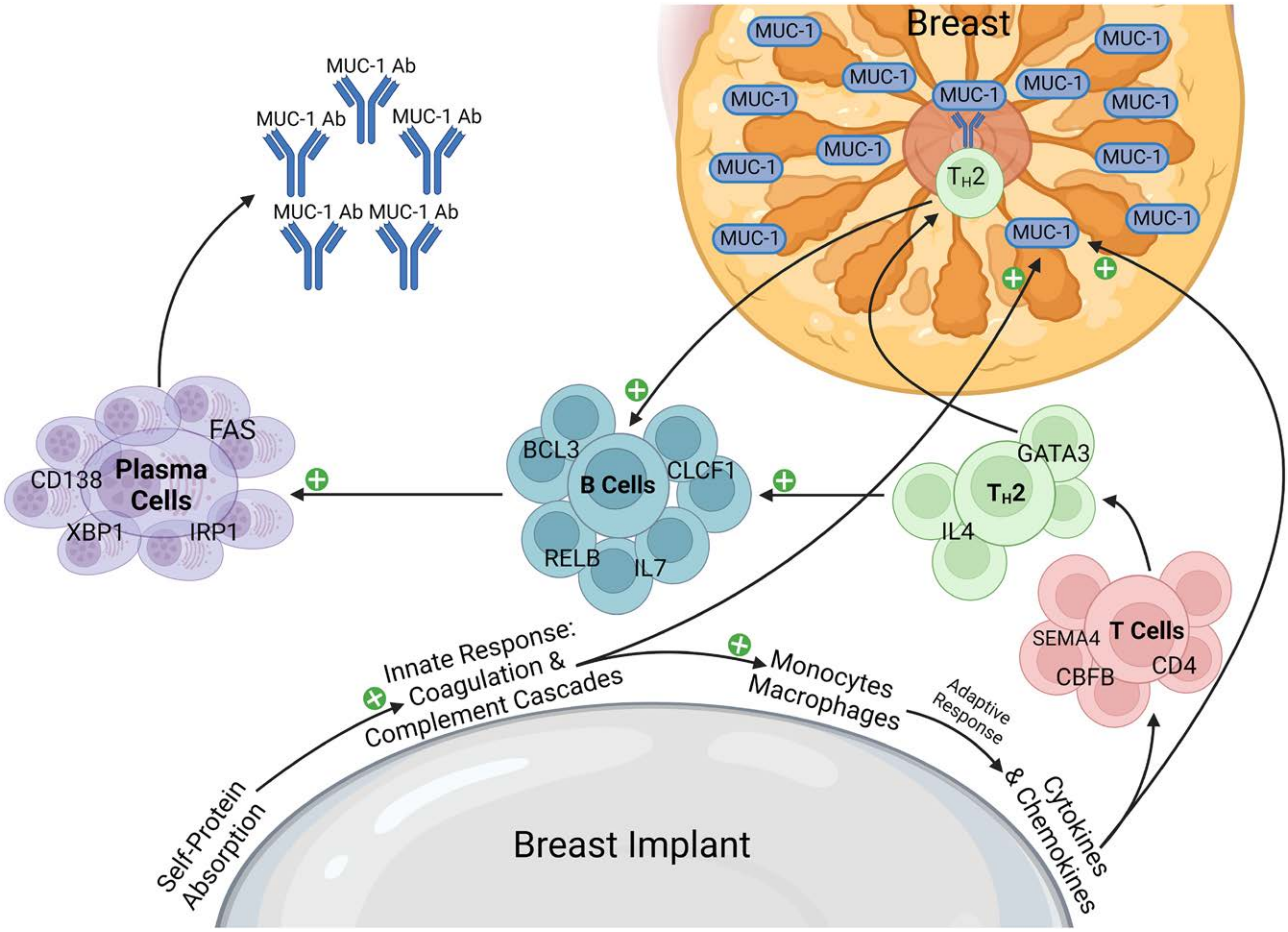

Fig. 6. Hypothesized pathway of immune response to breast implant including capsule formation and infiltration of response into breast parenchyma.

antibody production.[39,40] This may be the link that explains the elevated antibody responses to common breast cancer antigens after implant placement. Thus, we elaborate on our prior hypothesis. The silicone surface gets coated with extracellular matrix protein, initiating an influx of inflammatory cells. Th17 cells predominate and drive the fibrotic response to the implant, resulting in capsule formation. Antigen-presenting cells that abut the implant surface phagocytose the coated protein and present these antigens to other lymphoid cells in the capsule. Activated Th17 cells, in conjunction with antigen presentation, migrate into the breast tissue and activate B cells into antibody-secreting plasma cells, which eventually migrate to the periphery.

It remains to be determined exactly how this immunosurveillance mechanism would work. Th17 cells are a relatively recently described Th subset, and our understanding of their role in cancer is limited. Studies disagree on whether Th17 cells are protumorigenic or antitumorigenic, and their role likely depends on a complex interplay of immune signaling with tumor-specific factors.[41] Future work should include spatial transcriptomics or single-cell RNA-seq to elucidate potential mechanistic pathways.

Limitations of this study include a limited cohort sample size and lack of longer-term follow-up for these patients to determine whether antibody levels are sustained, inability to directly link the breast implant foreign body response to increased antibody levels to breast protein, inability to identify an actual mechanism through which these increased antibody levels may prevent future breast cancer, and lack of documentation of other implantable medical devices. We want to emphasize that our hypothesis that the foreign body response may contribute to breast cancer immunosurveillance is still only a hypothesis, and significant work is needed to further support this idea.

CONCLUSIONS

This study reinforces our prior findings that women with cosmetic breast implants have elevated antibody responses to specific breast tissue proteins that are relevant in cancer immunosurveillance.[21,22] Furthermore, we demonstrate that inflammatory changes around the breast implant extend beyond the capsule into the adjacent breast parenchyma, lending further support to the possibility of local immunosurveillance. These inflammatory changes specifically include B-cell activation into plasma cells, which may explain the increase in antibody levels to breast-specific proteins seen in the peripheral blood of these patients. Further work is needed to understand clinical implications of these inflammatory changes and to elucidate whether a mechanism exists to support our hypothesis that this local immunosurveillance is protective against breast cancer.

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DISCLOSURE

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