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Original Article

Breast Implant Silicones and B Cell-Mediated Immune Responses: A Systematic Review of Literature ☆

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ABSTRACT

Introduction: Breast implants are under recent scrutiny owing to concerns about their potential for inducing immunological diseases, namely breast implant-associated anaplastic large cell lymphoma and breast implant illness. However, the impact of silicone on biologic systems remains unclear. Therefore, we performed a systematic literature review to evaluate the information available on silicone breast implants and their effect on one arm of the adaptive immune response—B lymphocytes and antibody formation.

Methods: We conducted a systematic review in EMBASE/PUBMED in accordance with the PRISMA guidelines, with search entry terms requiring discussion of silicone and immunity. The initial review returned 1079 citations. Manual screening was performed to include studies that were specific to the humoral response after exposure to silicone. Secondary full text review was performed. The extracted data included animal models and findings pertinent to B cells/antibodies in response to breast implant silicones.

Abbreviations: bFGF, Basic fibroblast growth factor; CTL, Cytotoxic T lymphocyte; DA, Dark Agouti; FBR, Foreign body response; KO, Knockout; NK, Natural killer; PDGF, Platelet-derived growth factor; PRISMA, Preferred reporting items for systematic reviews and meta-analyses; TGFβ1, Transforming growth factor beta-1; TIL, Tumor-infiltrating lymphocyte; TLR, Toll-like receptor; TNF- α, Tumor necrosis factor alpha; VEGF, Vascular endothelial growth factor.

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Results: In total, 39 studies on B cells/antibodies and breast-implant-associated silicones were identified. Among them, 23 studies were in humans, 14 in animal models, and 2 were *in vitro*. Common themes included identification of antisilicone antibodies in women with breast implants, anticollagen antibodies, presence of activated B cells or immunoglobulin G in implant capsules, and sensitization of lymphocytes to silicone *in vitro*.
Conclusion: Despite controversial findings in the literature, there is evidence that silicone breast implants activate B cells in the breast implant capsule and may have systemic effects on the production of autoantibodies and/or sensitization of B lymphocytes to silicone. Further research is needed on how breast implants impact other arms of the immune system to understand their long-term biological impact.

Introduction

Silicone has been used in medical devices for over 50 years now. Despite this, its safety in relation to breast implants has long been questioned.[1,2] Although silicone is considered chemically inert, several phenomena have implicated that silicone breast implants are not biologically inert. Breast implant illness is one of the several names given to a complex of symptoms observed in some women with breast implants.[3-5] These symptoms include fever, arthralgia, hair loss, fatigue, chronic pain, headache, chills, and body ache, that are collectively reminiscent of several autoimmune disorders. It is thought that the foreign body response against the silicone implant activates the immune system against self, leading to autoimmune like symptoms, although there is no consensus among the medical community as to whether this is a legitimate diagnosis. Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is another disease observed in association with breast implants that results from T cell activation and proliferation in the capsule.[6] Though it was initially considered rare, approximately 1400 cases are currently reported worldwide.[7] Recently, the Food and Drug Administration (FDA) announced a link between breast implants and various B cell lymphomas.[8,9] Unlike BIA-ALCL, breast implant-associated B cell lymphomas (BIA-BCL) are a heterogenous group of malignancies, comprising various types of B cell lymphomas (approximately 10 different types have been described). Evidently, the implant—whether it is the silicone shell, inner gel, or some other aspect of the foreign body itself—has the ability to activate multiple arms of the immune system.

Most literature surrounding these concerns has focused either on the T cell response (given ALCL is a T cell malignancy) or clinical symptoms of breast implant illness. The basics of B cell-mediated responses to breast implants has largely been only of secondary interest. Our group, however, has found that women with breast implants have elevated antibody responses to certain breast proteins (mammaglobin-A and MUC-1).[10,11] We also identified elevated B cell markers in the breast tissue of women with implants compared to those without.[11]

Given that breast implant illness mimics autoimmune disease (which is often secondary to self-antibody production) and considering the increasing incidences of BIA-BCL, we sought to summarize what is known about the basics of breast implant mediated B cell activation. Our goal was to identify studies that examined the effect of silicone breast implants on B cell immune responses at the cellular and molecular level (rather than clinical symptomatology, which has been more extensively described). Thus, we performed a systematic review to summarize the literature on breast implant-associated B cell and humoral responses. With this review, we aimed to help increase the understanding about the biological impact that silicone breast implants may have and shed light on areas where further research is needed.

Methods

Literature Search

A literature search was conducted on May 28, 2022 in EMBASE and PUBMED for relevant articles with abstracts in English. The search strategy was developed in conjunction with a research librarian from the Galter Library at the Feinberg School of Medicine at Northwestern University. The literature search and subsequent analysis were conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses guidelines. Eligible studies were limited to articles in English language and required to examine the effects of silicone on immune cells in cell culture or animal models. Study selection underwent 2 levels of review by 2 independent researchers. Studies on immune reactions to silicone in specific organs other than the breast were excluded (for instance, several papers reported ocular inflammatory responses to silicone-based contact lenses and nasal capsular contracture around silicone-based nasal implants). The specific search entry terms were "Silicone," "Silicones," or "Breast Implant" in the title or abstract. The journal article also was required to include "Immune response," "Immune system," "Immunity," "Adaptive immunity," "Cellular immunity," "Humoral immunity," "Innate immunity," "Mucosal immunity," or "Active immunity," in the title, abstract, medical search term heading, or as a major topic of the article. We included articles with "contracture" and "capsule."

Titles and abstracts were screened for the following exclusion criteria: publications such as brief communications, correspondence, discussions, letters, conference or lecture manuscripts, case reports, and reviews; publications containing only abstracts; novel modifications of surgical technique; and outcomes about only a specific high-risk population. Additional search methods included a manual review of reference lists of the relevant studies specific to B cells. Details collected from the papers included author, year of publication, cell type or animal model, immune cell characteristics, sample size (for animal models), relevant statistical results, and p-values.

Results

Our search retrieved a total of 1096 articles. Reviewing the initial number in their entirety for inclusion and exclusion criteria resulted in the exclusion of 1065 results. Thus, 39 studies were finally included in this systemic review: All were discovered through computer search and no additional articles were found after reviewing relevant citations (Figure 1). Twenty-three papers used data from human patients, 14 papers were focused on *in vivo* animal models, and 2 studies were conducted using *in vitro* human cell culture models (one of them included both *in vitro* and animal data). Among the studies involving patient data, 4 examined the immune environment in the peri-implant or capsular tissue. These studies represented the local immune response. Nineteen studies from the 23 patient studies described B cell response from serum. These represented the systemic B cell response to silicone. Common themes of studies on the local immune response within the capsule show that intracapsular lymphocytes are predominantly T cells, with B cells representing a minority. The B cells can form reactive germinal centers and plasma cells (activated antibody secreting B cells). With regard to peripheral B cell-mediated immunity, several studies have identified elevated antisilicone and anti-self antibodies. Animal models have demonstrated that it is possible for silicone to act as an adjuvant and induce B cell-mediated responses. Notably, a number of studies have reported negative findings (with no indication of B cell-mediated immunity being upregulated or different compared to women without breast implants). In total, 10 studies were identified with negative findings.

The final list of included studies along with a summary of their findings are presented in Table 1.

Discussion

How the Body "Sees" The Foreign Body Implant

There are 2 ways by which the body "perceives" the breast implant: first, directly through the outer silicone shell and second, through particulate debris shedding (also known as silicone gel bleed).

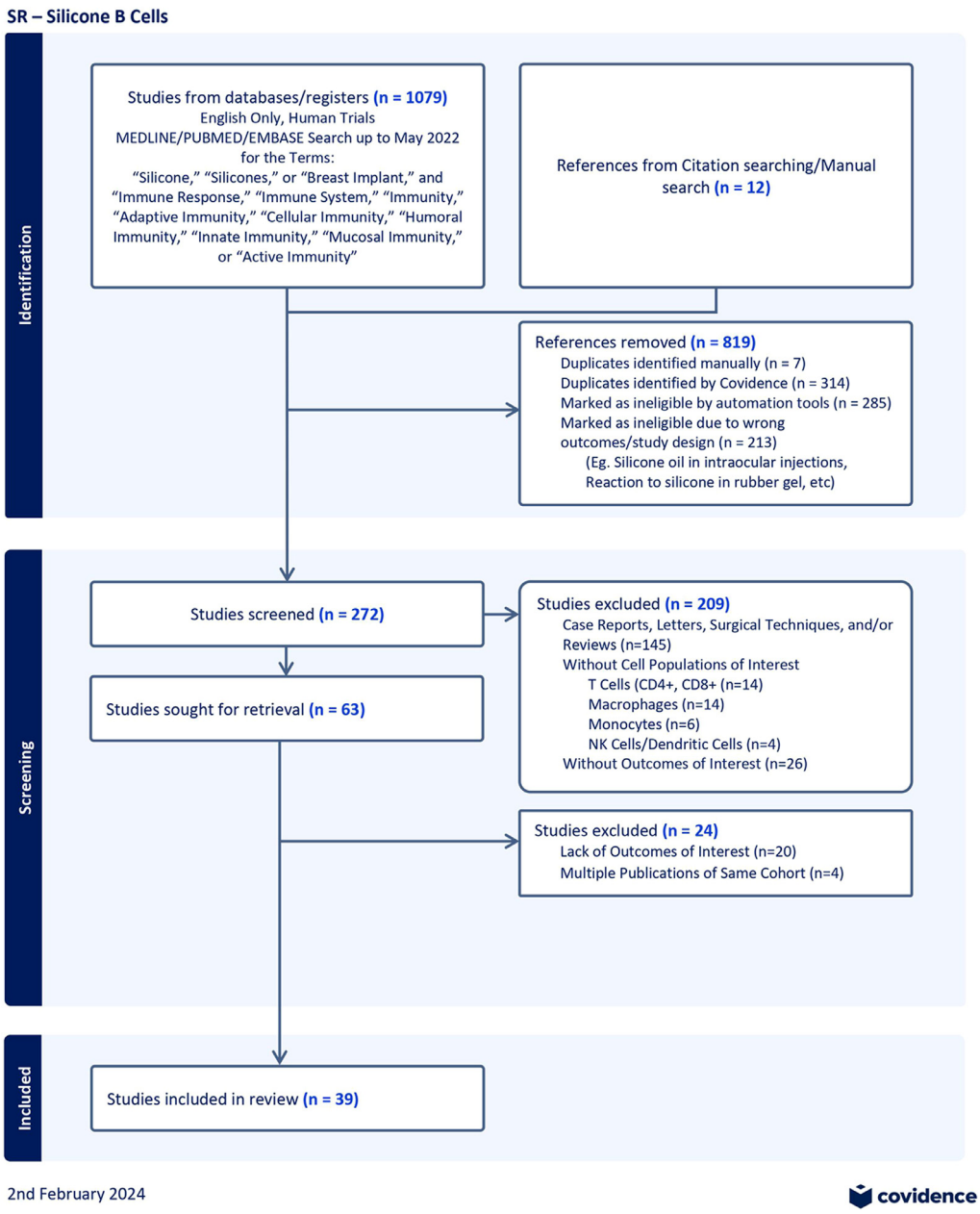

Figure 1. Search strategy. Attrition diagram depicting the search strategy, including manual and computer search results.

Host immune cell responses to the outer silicone shell are the primary drivers of the initial foreign body response and can result in capsule formation.[12] This foreign body response is a highly programmed cascade of events, with each stage defined by specific subsets of immune cells, proteins, and surface interactions. It begins with self-protein deposition on the implant surface, within nanoseconds of its placement in the breast.[12] The most common proteins found adsorbed to the silicone surface include fibronectin, immunoglobulin G (IgG), complement, and fibrinogen.[12] These

Table 1
Retrieved studies and summarized findings. The relevant findings from each of the retrieved studies included in review are documented. Studies are categorized by the model organism, immune environment, and control group used.

Author (Year)	Model Organism	Immune Environment	Control Group	Major findings
Abbondanzo (1999)	Human	Capsular tissue	Not specified	• Reactive germinal centers (CD20+) present in the peri-implant capsule • Plasma cells demonstrated polyclonal immunoglobulin light-chain reactivity, consistent with a reactive process • Conclusion that silicone implants induce chronic inflammatory responses in several adjacent capsules with reactive B-lymphocytes
Bar-Meir (1995)	Human	Serum	Implant-naïve	Compared to 134 control patients, silicone implant patients (n = 116) with rheumatic complaints: • Had elevated responses to 15 of 20 autoantibodies tested • Most striking elevations seen in anti-H2AH2B, HPRPP, SS-A, SS-B, Scl-70, CL, PS, GM2, and NC-1 • 20% of patients had 4 autoantibodies • 8% of patients had 6 autoantibodies
Bekerecioglu (2008)	Human	Capsular tissue	Implant-naïve	SBIs (n = 15) induced: • Strong capsular binding of IgG • Significantly elevated levels of anti-silicone antibody levels • Elevated serum IgE
Brantley (1990)	Rat	Spleen	Placebo-injected, implant-naïve	At 8 months: • No evidence of host sensitization to silicone demonstrated • No measurable systemic lymphocytic recognition/memory expressed with respect to silicone.
Bridges (1993)	Human	Serum	Symptom-free women with SBIs (n = 12), fibromyalgia patients without SBIs (n = 174)	Among the 156 patients with SBI with rheumatic complaints: • 14 had anti-centromere or anti-PM-Sci antibodies and scleroderma-like illness • 10 had anti-BB' polypeptide, but did not meet the clinical criteria for disease • No one in either control group had positive autoantibodies
Brunner (1996)	Human	Serum	Saline-filled implant	At up to 10 years of follow-up: • No difference in IgG/IgM levels • Increased autoantibodies (antithyroglobulin and antimicrosomial) status-postsilicone implant • Correlation between low-grade capsular contracture (Baker I and II) and increased autoantibody levels • Findings not correlated with clinical symptoms

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Table 1 (*continued*)

Author (Year)	Model Organism	Immune Environment	Control Group	Major findings
Ciapetti (1995)	Human	Serum	Implant-naïve	At up to 10 years of follow-up (mean = 4.83): • Increase in proliferation and viability ("functional response") of lymphocytes upon re-exposure to silicone of patients with silicone gel-filled breast implants compared to control
Cuellar (1995)	Human	Serum	None	813 individuals with SBIs were tested for ANAs: • 30% had positive ANAs when tested via mouse-kidney substrate • 57.8% had positive ANAs when tested via a HEp-2 cell line • The most common ANA pattern was speckled (72.5%), followed by homogenous (24%), which can both be indicative of various autoimmune diseases (lupus, Sjogren's)
De Jong (2002)	Human	Serum	Implant-naïve	No difference in the prevalence of anti-polymer antibodies between silicone breast implant and implant-naïve patients. Likewise, clinical symptoms did not correlate with anti-polymer antibody levels.
Ellis (1997)	Human	Serum	Implant-naïve	Silicone implants (n = 26) studied for response against connective tissue proteins and to compounds common to silicone prostheses: • The frequency and intensity of immune responses against collagen I, collagen III, fibrinogen, and fibronectin were significantly increased compared to control.
Fracol (2021)	Human	Serum	Implant-naïve	After an average of 7 to 10 years after implant: • Increased antibody response to breast cancer antigens mammaglobin-A and mucin-1 • No difference in antibody responses to breast cancer susceptibility gene 2, CEA, human EGFR-2, or tetanus.
Granchi (1995)	Human	Serum	Implant-naïve	After 1 year of implantation: • No significant differences in CD19+ B lymphocyte populations seen • After re-exposure to silicone, no difference in antigen expression or the lymphocyte functional activity Involvement of the immune system is local (in the formation of the capsular contracture around the prosthesis) rather than systemic was hypothesized

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Table 1 (*continued*)

Author (Year)	Model Organism	Immune Environment	Control Group	Major findings
Habal (1980)	Mouse	Spleen	Implant-naïve, implant composed of other biomaterials (e.g., polyurethane)	After 1 month, splenic lymphocytes from mice receiving silicone implants showed: • No significant difference in amount of B-cell function (measured in response to LPS stimulation) • Decreased response to tumor antigen (M4 sarcoma) compared to control
Haddad (2007)	Rat	Peri-implant tissue	Implant-naïve	At up to 180 days: • Rats with textured silicone implants had higher levels of lymphocytes at 7 days and 180 days than the control • Acute stage of the inflammatory response was more severe/irregular in the silicone implant • Silicone implant caused greater chronic inflammatory reaction
Heggers (1983)	Guinea pig	Peri-implant tissue, lymph nodes	All received implant. Control did not receive silicone injection pre-implant	After 4 weeks: • Silicone elicits a strong inflammatory cellular immune response • Silicone acts as a hapten-like incomplete antigen (at site of implant, silicone inclusions seen in giant cells surrounded by lymphocytes with cytoplasmic bridges transferring silicone from macrophages to lymphocytes)
Karlson (1999) and Karlson (2001)	Human	Serum	Implant-naïve	After over 10 years postimplant (mean of 11.86 years): • Anti-silicone antibodies not found in any sample (1999) • No difference in frequency of monoclonal immunoglobulins in women with silicone implants (2001) • No evidence of activation of the immune system in women with breast implants.
Klykken (1996)	Mouse, rat	Serum	Placebo-injected	IgM and IgG antibody responses were equivalent between silicone gel-implanted and control animals. No adjutancy was noted in the models tested.
Meza Britez (2012)	Human	Capsular tissue	Textured implants, implants without contracture	Periprosthetic breast implant capsules, textured and smooth (n = 40) showed: • B cells increased in the capsule • Percentages of CD20+ cells were similar in textured vs. smooth • Significantly elevated inflammatory cells with textured implants compared to smooth.

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Table 1 (*continued*)

Author (Year)	Model Organism	Immune Environment	Control Group	Major findings
Naim (1995)	Rat	Serum	PBS-injected	After 108 days from injection of silicone gel from commercial breast implants: • Silicone gel consistently produced a significantly heightened antibody response when compared with the control • Higher antibody response with higher molecular weight of injected silicone gel
Naim (1993)	Rat	Serum	PBS-injected	At up to 56 days postimmunization: • Silicone gel taken from commercial breast implants is a potent immunological adjuvant (significantly higher levels of serum anti-BSA-antibody)
Naim (2000)	Mouse	Serum	PBS-injected	Up to 6 months post silicone exposure: • Persistently higher serum IgM • Suggests that silicone gels are capable of inducing hypergammaglobulinemia.
Naim (1995)	Rat	Serum	PBS-injected	Silicone gel could significantly heighten the antibody response, against: • Heterologous antigens (bovine serum albumin and bovine collagen II) ○ Represents immune response raised non-specifically • Homologous antigens (Rat Tg) ○ Represents specific activation of the immune response
Narini (1995)	Sheep	Lymph nodes	Saline-injected	At one month after silicone gel injection: • After re-exposure to silicone, significantly more lymphocytes were observed in silicone-exposed group than in the control • Suggests delayed-type hypersensitivity (antigen-specific lymphocyte-mediated response to silicone gel)
Peters (1994)	Human	Serum	Implant-naïve	Among the 200 patients with SBI: • No difference in ANAs between groups (26.5% vs. 28%) • No difference in ANAs in those with implant rupture (17.2%) • Among those with positive ANAs, no difference between groups in the frequency or titer of other autoantibodies (anti-DNA, cardiolipin, SSA, SSB, SM, RNP, and Scl-70)
Prantl (2008)	Human	Serum	Implant-naïve	After an average of 34 (SD 11) months of exposure to silicone breast implants: • No statistically significant difference in the distribution of peripheral blood B-lymphocytes compared to the controls • No evidence of systemic proinflammatory effects of silicone • No correlation of B-cell number with clinical Baker score of contracture

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Table 1 (*continued*)

Author (Year)	Model Organism	Immune Environment	Control Group	Major findings
Press (1992)	Human	Serum	None	Among the 23 patients with SBI: • 11 met criteria for various autoimmune disorders • 10 among the 11 had high ANA titers • Implant rupture was associated with accelerated onset of clinical symptoms
Rhie (1998)	*In vitro*	Spleen	Non-coated Petri dishes	After 3 days of silicone exposure: • Direct contact of macrophages with silicone gel was a primary cause of acute immune activation that was related to foreign body reaction → IgM response was enhanced by incubation on silicone gel
Rodriguez (2008)	Rat	Implant Exudate	Empty implant	After 14 days postimplant exposure: • No B cells were detected in the lymphocyte exudate at any timepoint for any group (silicone and control).
Rohrich (1996)	Human	Serum	Implant-naïve	At an average of 6 months postimplant: • No significant difference in anti-silicone antibody levels between test subjects and the controls.
Sanger (1995)	Human	Capsular tissue	n/a	Chronic presence of silicone implant (time not specified): • Did not lead to increased deposition of IgG, IgM, and IgA in the capsular tissue • Did not lead to humoral activation in nearby tissue
Schuler (1978)	Rat	Serum	Implant-naïve	After 16 days of silicone implant exposure: • Early anti-silicone immune response (evidenced by heightened lymphocyte cytotoxicity) at day 7 • Immune response becomes similar to control after 16 days.
Stern (1972)	Rabbit	Serum	Nonsilicone exposed	• Silicone rubber produced a passive hemagglutination with autologous antigen in 1 out of 5 cases • Silicone elastomer induced passive anaphylaxis via autologous antigen in 1 out of 5 cases • Exposure to large surface areas of foreign materials induced immunogenic changes in autologous antibodies
Tenenbaum (1997)	Human	Serum	Implant-naïve	SBI recipients had higher prevalence of positive anti-polymer antibodies than healthy and autoimmune disease patients that were implant-naïve. Antibody levels correlated with more severe clinical symptoms.

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Table 1 (*continued*)

Author (Year)	Model Organism	Immune Environment	Control Group	Major findings
Teuber (1993)	Human	Serum	Implant-naïve	After an average exposure to silicone breast implants for 13.5 years (SD 5.3 years): • Statistically significant incidence of anti-collagen antibodies in women with implants
Vojdani (1994)	Human	Serum	Implant-naïve	• Silicone antibody levels (silicone specific antibodies, IgG, IgA IgM, IgE and IgG + IgA + IgM antibodies) were not significantly different between women with breast implantation vs. breast reduction vs. no breast surgery. • Silicone antibodies were not consistently associated with silicone breast implants in this study.
Wolf (1993)	Human	Serum	Implant-naïve	After exposure to silicone: • Patients with implants had significantly elevated anti-silicone antibodies (specific anti-silicone IgG) compared with the un-implanted control groups.
Zandman-Goddard (1999)	Human	Serum	Asymptomatic SBI patients	Symptomatic (n = 116) and asymptomatic (n = 86) women with SBIs had elevated anti-SSB/La and anti-collagen II antibodies. • 2%-13% of asymptomatic patients with SBI tested positive for various autoantibodies • 20% of symptomatic patients with SBI tested positive for at least 4 autoantibodies • Symptomatic SBIs had longer duration of implant placement compared to asymptomatic SBIs (15.0 vs. 8.2 years)
Zeng (2015)	*In vitro*, mouse	Serum	None (used stiff vs. soft biocompatible organosilicon elastomer)	After 3 days of exposure to polydimethylsiloxane (PDMS) surfaces: • In vitro class switch differentiation of B cells is enhanced with softer substrates • Enhanced antibody response in vivo was observed with softer silicones compared to the stiffer ones • Recruitment of B-cell receptors, pTyr, and pSyk to the B-cell immunological synapse is sensitive to substrate stiffness

ANA, antinuclear antibody; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; LPS, lipopolysaccharide; SBI, silicone breast implant.

proteins then activate the coagulation (fibronectin) and complement (IgG) cascade. The end result of these cascades is an increase in vascular permeability and exposure of integrin binding sites on adsorbed proteins, which signal macrophages and leukocytes to make their way into the peri-implant space and interact with the protein adsorbed surface.[12]

Beyond interacting with the implant through its outer shell surface, the immune system can also perceive the implant through silicone gel bleed.[13] Macrophages are considered the “sentinel cell” of the immune system and one of the key immune cells found in implant capsule. Silicone

debris is taken up by resident macrophages, which subsequently fuse to form multinucleated giant cells and/or granulomas. Silicone debris granulomas can be found in regional lymph nodes, and also in distant organs throughout the body. One study found that in a cohort of 91 women with systemic complaints and silicone breast implants, 90% had silicone debris in regional lymph nodes on biopsy.[14]

In summary, the foreign body response to the breast implant occurs through immune cell interactions with the outer shell protein-coated surface, as well as through particulate debris shedding. It is to be determined which of these are more biologically relevant in causing clinical disease or phenomena and should be a focus of future research.

Breast Implant-Related B Cell-Mediated Immune Responses

B cells are largely associated with the adaptive immune response and have the primary function of creating memory antibodies, cytokine secretion, activation of other immune cells, and antigen presentation. Some question as to the importance of B cells in the peri-capsular environment remain. Although they are only a small percentage of the cells present surrounding biomaterials and implants, they have been shown to play some role in fibrosis around foreign bodies as illustrated in B cell knockout (KO) models that resulted in reduced fibrosis.[15]

Capsular Tissue

Studies on peri-prosthetic breast implant capsules, smooth and textured, have described that CD20+ B cell populations are increased in the area surrounding the capsule. However, they represent the minority of the total cell population in the capsular environment, which is predominantly T cells.[16] However, the B cells present in the capsule, form the reactive germinal centers.[17] Plasma cells (reactive antibody secreting cells) with polyclonal immunoglobulin light chain production are also found in capsules. These two findings indicate activation of B cell-mediated immunity in the capsular environment. Antibody production may be against local proteins, indicated by high binding of IgG to capsular tissue.[18] However, 1 study contradicts these findings. Sanger et al. did not find any increase in deposition of IgG, immunoglobulin M (IgM), or immunoglobulin A in the capsular tissue surrounding long-term breast implants, nor did they find any evidence of humoral activation in the surrounding tissue.[19] Notably, B cells were not present in implant exudate 14 days after implant exposure in a rat model.[20] However, human analysis of reactive late breast implant seromas (not BIA-ALCL) demonstrates a mixed picture of lymphocytic infiltrate that can vary significantly between patients.[21] Other studies on immediate peri-implant response found that when measured at 1-week and 2-week-long exposures to silicone implants, rats had no difference in CD45RA+ B cell levels in exudate compared to controls.[20]

Our group found that B cell expression markers are elevated in human breast tissue surrounding the capsule compared to the breast tissue of women without implants.[11]

Serum

This local B cell response may be diluted when analyzed systemically. Serum studies of approximately 300 women from the national Women's Health Study who had breast implants showed no difference in frequency of overall B cell-produced monoclonal antibodies in the peripheral blood.[22] Moreover, in 41 women with capsular contracture, no statistical difference was observed in the CD19+ B cells as compared to women without implant contracture.[23]

However, several studies have identified the differences in silicone-specific antibody production in women with breast implants. Three studies found heightened levels of antisilicone or antipolymer antibodies in women with breast implants, whereas 4 other studies found no difference between women with and without breast implants.[18,22,24-29] One of these studies found that antipolymer antibody levels correlated with the clinical symptoms.[29] One rat model identified an early antisilicone lymphocyte response that disappeared after 16 days.[30] Probably, the different findings in human antisilicone antibody studies could be attributed to the differences in implant exposure time, implant-specific factors

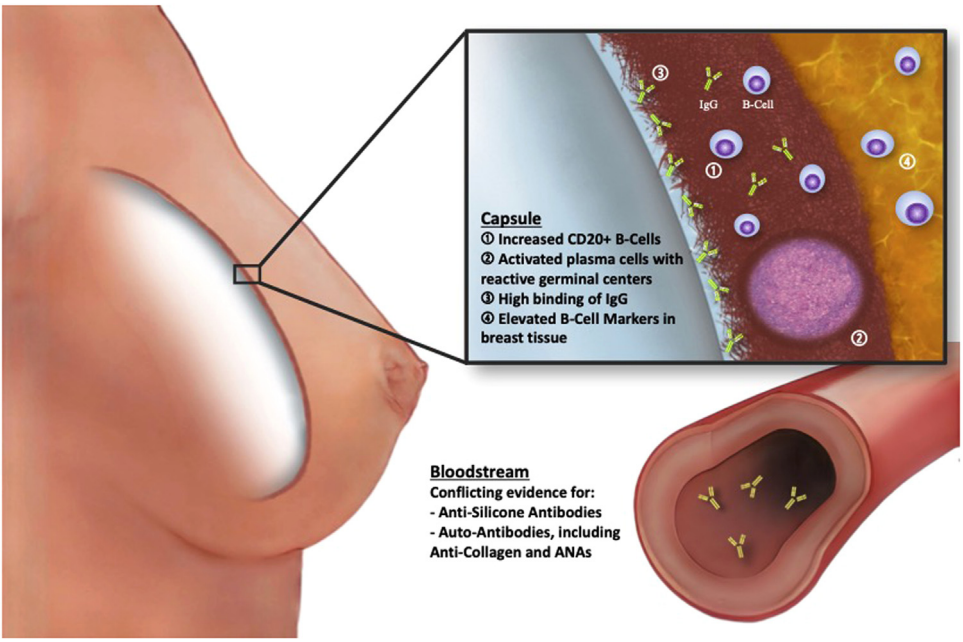

Figure 2. Effect of silicone on B cell immune response. An illustrated example of positive findings in the literature. Findings on the effect of silicone differed in the immediate breast capsule versus that in the serum/blood stream. Notably, 12 of the studies (~1/3rd) reported negative findings (no B cell activation or response to silicone breast implants).

that may elicit an immune response, during which the antibodies were being examined (IgG vs. IgM), or how antibody levels were measured.

Multiple studies have identified the heightened presence of self-antibodies in women with breast implants. These include antithyroglobulin, antimicrosomial, anticollagen, antifibrinogen, and antifibronectin antibodies.[31-33] Other studies have identified the presence of autoantibodies that are more specific to autoimmune disease, such as antinuclear (ANAs), anti-SSA, anti-SSB, anti-Scl70, and anti-dsDNA antibodies.[34-36] One of the largest studies tested 813 women with silicone breast implants and found that 57.8% had positive ANAs, although this study did not have a control group for comparison.[34] Notably, another group observed 200 silicone breast implant patients and found no difference in ANAs compared to an implant-naïve control group.[37] These differences in study outcomes could be attributable to selection bias for symptomatic patients, implant length of time, or testing method.

Animal models showed similar findings and indicated that silicone acts as an adjuvant. Rats injected with silicone produce higher heterologous antibodies (non-specific to the species, binding to bovine serum albumin and bovine collagen) and higher homologous antibodies (specific to the rat, binding to rat thyroglobulin). Mouse models showed higher serum IgM compared to the control. The antibody response in peripheral blood has been observed to be the most potently activated in response to silicone gel, as compared to silicone oil or liquid.[38,39]

In *in vitro* experiments using murine splenic B cells, there was a large increase in antibody-forming B lymphocytes after exposure to mammary implant silicone gel as compared to the control; however, this increase was not statistically significant.[40]

Overall, there is a mixed picture of the B cell response and its role in modulating immune response after silicone breast implant (Figure 2). The cells appear to be important in the initial fibrosis reaction and long-term antibody response, though less significant than other immune cell populations, such as T cells and macrophages.

Limitations

Limitations of this study include the somewhat elusive nature of this topic, potential for bias in study publication, and a paucity of any recent publications. As our primary interest for this topic was to gain a better understanding of the cellular and molecular level interactions between the B cells and silicone breast implants, we purposefully excluded any studies that focused exclusively on clinical symptomatology. Although we could identify several studies with negative findings (no difference in B cell immune responses between women with silicone implants compared to controls), there is certainly a known propensity to not publish studies with negative findings. Thus, the results presented here may be skewed toward positive findings. Lastly, it is notable that besides the author's own work, only one other study has been published on this topic in the last decade. The remaining studies were largely published in the 1990s or early 2000s. It is unclear whether this is due to a lack of interest in the topic or perhaps a general feeling that the topic is not of significance after the Institute of Medicine concluded that silicone breast implants are safe and allowed their return to market in 2006. We feel that the crucial impact of this review is to underscore that contemporary studies are needed to confirm prior findings and help resolve whether silicone breast implants have any impact on systemic B cell-mediated immunity.

Conclusion

Understanding the basic immune cell response to silicone provides the cornerstone of understanding the clinical manifestations of breast implant-associated pathology. Multiple studies point to B cell activation in response to the foreign body breast implant. Shared findings among the various experimental models suggest that silicone breast implants may activate B cells in the implant capsule and may have systemic effects on the production of autoantibodies. They may also play a role in the sensitization of B lymphocytes to silicone. Whether this activation of B cells has far-reaching consequences in affecting an individuals' predilection for systemic disease and cancer development or prevention is still an ongoing area of research. Further research is needed regarding the impact of breast implants on other arms of the immune system to better understand their long-term biological impact.

Acknowledgements and Conflicts of Interest

Iulianna Taritsa, BA: The author has no significant conflicts of interest with any companies or organization whose products or services may be discussed in this article.

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Iulianna Taritsa, BA: Participated in writing, data analysis, and critical revision of the manuscript for important intellectual content and final approval of the manuscript submitted.

Puja M. Jagasia, BA: Participated in writing, data analysis, and critical revision of the manuscript for important intellectual content and final approval of the manuscript submitted.

Michael Boctor BA: Participated in writing, data analysis, and critical revision of the manuscript for important intellectual content and final approval of the manuscript submitted.

John Y. Kim MD: Participated in research design, writing, data analysis and critical revision of the manuscript for important intellectual content and final approval of the manuscript submitted.

Megan Fracol MD: Participated in research design, writing, and critical revision of the manuscript for important intellectual content and final approval of the manuscript submitted.

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