Università degli Studi di Padova
Dipartimento di Scienze del Farmaco

Scuola di Dottorato di ricerca in BIOLOGIA E MEDICINA DELLA RIGENERAZIONE
Indirizzo: INGEGNERIA DEI TESSUTI E DEI TRAPIANTI
CICLO XXV

THE IMMUNOLOGICAL RESPONSE TO BREAST IMPLANT: THE ROLE OF CELLS AND CYTOKINES IN THE PERIPROSTHETIC CAPSULE AND THEIR INVOLVEMENT IN THE ONSET OF THE AUTOIMMUNE DISEASES

(LA RISPOSTA IMMUNOLOGICA ALLA PROTESI MAMMARIA: RUOLO DI CELLULE E CITOCHINE NELLA FORMAZIONE DELLA CAPSULA PERIPROTESICA E LORO COINVOLGIMENTO NELL'INSORGENZA DI MALATTIE AUTOIMMUNI)

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Dottoranda: dott.ssa Carlotta Scarpa

To my teachers

THIS WORK RECOVERS PART OF THE STUDIES ABOUT THE PERIPROSTHETIC CAPSULE THAT I'VE DONE IN THE LAST TEN YEARS:

C. Scarpa, *La reazione periferica alle protesi mammarie riempite con silicone e con olio di soia: studio istologico*, Graduation (Padua University 2001-2002)

Scarpa 2010[1] = Bassetto F., Vindigni V., Scarpa C., Doria A., *Breast prostheses and connective tissue disease (CTD): myth or reality?* Aesthetic Plast Surg 2010; 34 (3): 257-63.

Scarpa 2010[2] = Bassetto F, Scarpa C, Caccialanza E, Montesco M. C., Magnani P., *Histological features of periprosthetic mammary capsules: silicone vs polyurethane.* Aesth Plast Surg 2010; 34 (4): 481-85.

Scarpa 2012 = Bassetto F., Scarpa C., Vindigni V., Doria A., *The periprosthetic capsule and connective tissue diseases: a piece in the puzzle of autoimmune/autoinflammatory syndrome induced by adjuvants*, Experimental Biology and Medicine (EBM) 2012; 237: 1117-122

ABSTRACT

Since their discovery breast prostheses have been criticized for being responsible for triggering systemic autoimmune disease. The presence of breast implants causes a natural foreign body reaction characterized by the infiltration of macrophages and T-cells. In order to understand which immunological pathways could be responsible for giving rise to, and the development of, connective tissue disease such as systemic sclerosis, I considered the cells and cytokines involved, focusing on the relationship between tissue growth factor-β, interleukin (IL)-1, IL-6 and T helper 17 and/or T regulatory cells, and their effects on the different steps of capsular tissue formation. A disturbance in the modulation of these key cytokines may be responsible, in susceptible individuals, for a perpetuation of the inflammatory reaction which can locally lead to capsular contracture and at the systemic level may contribute to triggering autoimmune diseases.

Sin dalla loro creazione le protesi mammarie sono state considerate responsabili della possibile insorgenza di malattie autoimmuni sistemiche. La presenza di protesi mammarie provoca una reazione naturale da corpo estraneo caratterizzata dall'infiltrazione di macrofagi e linfociti T. Al fine di capire i meccanismi immunologici che stanno alla base dell'insorgenza e dello sviluppo di malattie, come la sclerodermia, ho considerato le cellule e le citochine coinvolte, focalizzando l'attenzione sulla relazione tra il TGF-β, l'interleuchina (IL)-1, IL-6, i T helper 17 e/o le cellule T regolatrici, e il loro effetto sulle diverse fasi di formazione del tessuto capsulare. Un disturbo nella modulazione di queste citochine chiave può essere responsabile, in soggetti sensibili, di una cronicizzazione della reazione infiammatoria, che può localmente portare a contrattura capsulare e a livello sistemico può contribuire a innescare malattie autoimmuni.

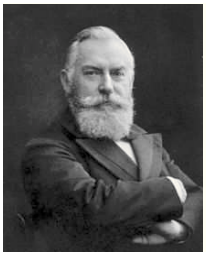
INDEX

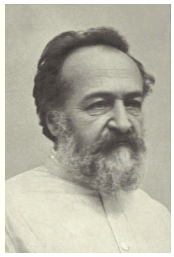
INTRODUCTION

Almost ten years ago, during my medical graduation, I started to consider that in these last centuries, especially in the latter, the chemical development promotes the research of biologically compatible materials which could permit to restore the body image, and consequently the psychological point of view, of patients affected by any kind of impairments.

In this atmosphere many scientists tried to find a good substitute of the breast with the aim of restore its natural shape, firstly using external prostheses which could give back only the aesthetic point of view and later using implants, inserted in women's body, which could restore not only the tactile sensation, but also the psychological image.

The history of the actual mammary implants begun at the end of nineteenth century when Vincenz Czerny and Robert Gersuny used the adipose autologous tissue (the first) and liquid paraffin (the second one) as filler for breast augmentation but unfortunately the presence of cysts, due to the liquid material, provoked the abandon of this late solution. The upcoming silicone and polyurethane foam would have changed everything.



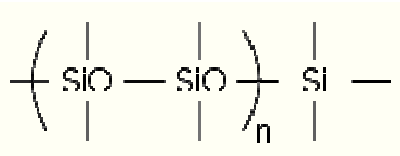


Vincenz Czerny ***Robert Gersuny***

1.

AN OLD PROBLEM: WHICH MATERIAL FOR BREAST PROSTHESES?

1.1 SILICONE:

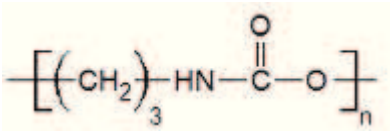


Discovered in 1907 by Frederick Kipping and chemically known as **polydimetilsiloxane,** the silicone is a polymer, heat stable, microscopically visible as a refractive material.

Initially not used for medical devices, in 1948, Dow Corning Industries created the "Silastic" medical grade that is silicone for medical purpose. Since that moment silicone has been used in many medical devices, including artificial valves, joints, needles and teats, becoming, in the sixties, the major component of breast implants as for the surface as for the content.

Frederick Kipping

1.2 POLYURETHANE:



Discovered in 1947 by Otto Bayer the polyurethane is a polymeric material derived by MDI (methylene-diphenil-isocyanate). It can be straight, elastic, adhesive, foam etc.

Being biologically compatible the polyurethane has been used in many medical devices as vascular prostheses, inner room of artificial hearts and, in plastic surgery, as prosthetic surface of some breast implants.

Otto Bayer

2.

SILICONE BREAST IMPLANTS: MORPHOLOGICAL FEATURES

2.1 Breast implants:

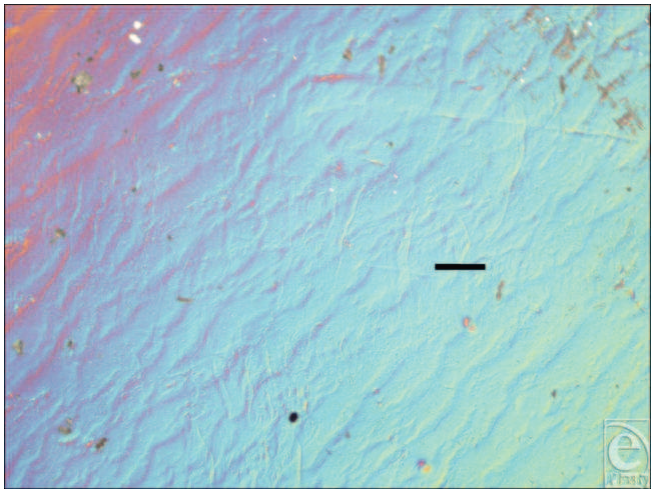
Appeared in 1963 as a smooth silicone implant filled by liquid silicon, nowadays on the market there are three types of prosthetic surface, round or anatomical in shape, featured by the presence of silicon outside and inside.

The surface:

1) **Smooth surface** characterized by a smooth silicone outside and soft cohesive gel for the content.

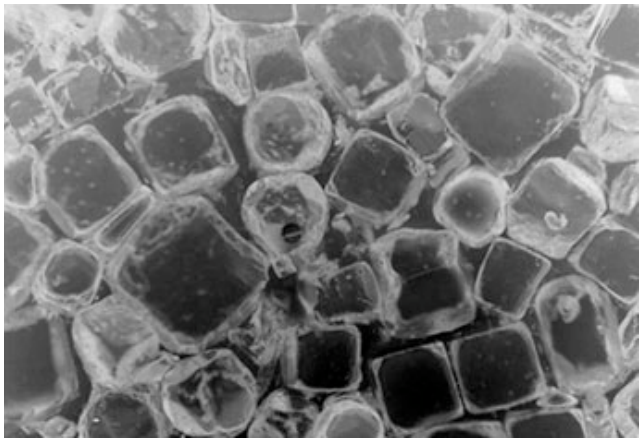
Nowadays it's used mostly as sizer during the surgery, abandoned as definitive implant because of the strong foreign body reaction, with consequent increased risk of capsular contracture, due to the smoothness of the surface.

Smooth surface: E=External side, I=Internal side

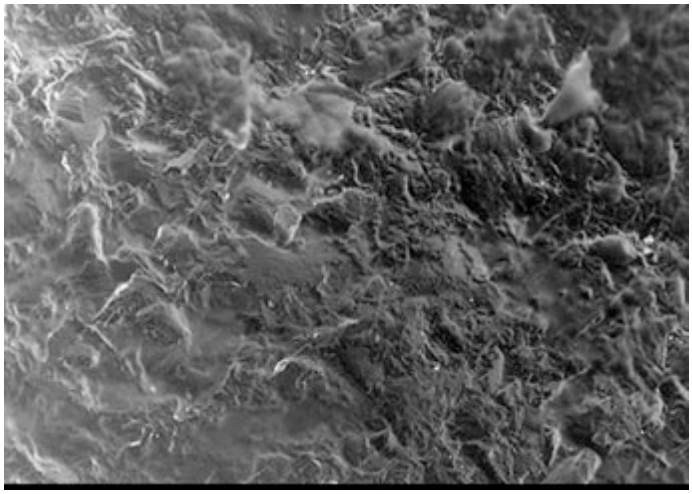


Smooth surface

2) **Textured surface,** featured by pores or microvilli (depending on home manufacturer), allows the implant to be anchored to the surrounding tissue and thus to remain in place. These kinds of implants have been created in the nineties with the aim of avoiding or reducing the inflammatory response to the prostheses. In the first years after surgery, the texturization disarranges the collagen fibers and reduces the possibility of circular contraction of the capsule.

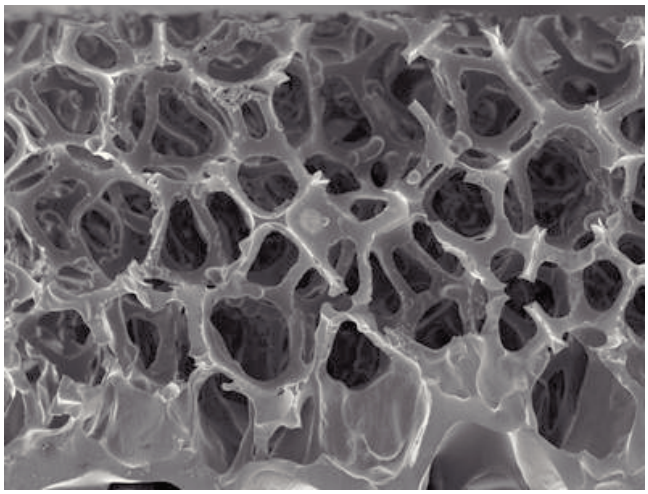


Allergan texturization



Mentor texturization

3) **Textured silicone surface coated with polyurethane foam** characterized by a double surface and cohesive silicone gel inside. Made for the recurrence of capsular contracture (the presence of the polyurethane supports a longer young inflammatory response featured by macrophages and neovascularization).



Polyurethane surface

The content

Many researches have been made to find the ideal content featured by the compatibility and the right firmness to give a natural breast[1]. Firstly being liquid, the silicone was banned in 1992 in USA because of the frequent bleeding from the implants and the potential induction of autoimmune connective tissue diseases (CTD). To avoid bleeding the manufactures created new kinds of contents, as silicone cohesive gel, soft cohesive gel, jaluronic acid, soybean oil and finally

[1] **Some reference 'history':** Giachero, taking Mutou, recalls how a sort of silicone implants have been used in 1949 by the Japanese scholar Akiyama, who used two different types of implants: the first pre-filled with silicone gel, the second can be intraoperatively filled with semi-fluid silicone. Mutou himself used these prostheses and in a period of 4 years (from 1966 to 1970) submitted 79 patients to breast augmentation surgery, and obtained encouraging results in 68 cases. The first silicone breast implant appeared on the market in 1963 when Cronin and Gerow, having consulted Braley and remembering the suggestion of Brown et al. (1960) of using the silicone breast implants, developed the first silicone implants as we know them. This prosthesis, the Cronin implant, presented a silicone shell with 4 smooth Dacron disks of Dacron with the aim of allowing the adherence to the surrounding tissues. The front and rear disks, however, created an intense inflammatory response, "recommending" the presence of the only rear one. In 1965 Arion created the silicone implants filled with saline. In the same years were also introduced devices without Dacron, but with a higher mobility; in addition, the manufactures made several changes and to the outer surfacehe and to its contents; they increased the viscosity of the silicone gel. Industries like Dow Cornig, McGhan, etc.., tried to find new shapes: from a round implant to a drop featured by low, medium or high profile and round or oval base. Another industry named Koken invented a ruse with the aim of decreasing the periprosthetic capsule, but the solution was soon abandoned. The idea was of incorporating silicone together with oxygen, so the progressive loss of the latter would have reduced the volume and the tension of the prosthetic surface and of the capsule itself. Considerable efforts were made to improve the volume of filling, just think about Arion (1965) and his saline implants; or Becker, who, in 1984, combined the pre-filled and refillable implants to obtain the double-lumen ones. These implants were featured by two pockets, one filled with a silicone gel and one fillable with saline. All these efforts and others have always had the primary purpose of avoiding, or at least reducing, the formation of periprosthetic capsule and the risk of its contracture / retraction. In 1970 Ashley et al., introduced the polyurethane, decreasing the rate of contraction / capsular retraction. Later, in 1989, after the success of this new polymer, microstructured or textured implants have been launched on the market. These are the devices that the plastic surgeons use in daily practice. Finally, two other kind of shells were studied: the prosthesis covered with a film of Carbofilm and those in PVP (polyvinylpyrrolidone). The first was based on the belief of the extreme biocompatibility of carbon and its consequent ability to reduce the capsule. The second has been studied by Menke et al. In a period of 2 years, during a perspective survey, the authors observed as the implants filled with PVP were a good alternative to the saline ones both for their increased viscosity, both for the very satisfactory aesthetic results.

saline (the latter widely used in these years in USA)[2]. Having abandoned the soybean oil because of its carcinogenicity not only for the patients but also for their children (biodegrading products could be eat by the babies during breast feeding)[3], and recently having excluded jaluronic acid (Macrolane) because of the radiological difficulties in cancer diagnoses due to the possible microcalcification of the material, nowadays the most frequent content in Europe, and since 2011 in USA, is represented by the silicone cohesive gel that avoid bleeding from the implant even in rupture cases.

2.2 Breast prostheses and human body

Since their introduction many authors have dedicated their studies to understand the exact relationship between silicone breast implants and human body in order to verify the real compatibility of

[2] For a discussion of this topic see also Scarpa C., *La reazione periferica alle protesi mammarie riempite con silicone e con olio di soia: studio istologico*, Graduation (Padua University 2001-2002) pp.13-37.

[3] The 'life' of implants filled with soybean oil was very short: in 1995 the company Lipomatrix, thinking of the biodegradability of the content, produced a new type of prosthesis, called Trilucent (for the presence of a mixture of triglycerides and an implant surface radiolucent) filled no more than silicone gel, but of soybean oil. Immediately Young (1996) noted how the oil "bleeded" by the prosthesis was easily absorbed and metabolized without causing inflammation or foreign body reaction. These observation haven't been confirmed later. Choudhary (2000) found not only a foreign body reaction and a significant inflammatory response, due to the bleeding and the breaking of Trilucent, but showed that the oil wasn't easily absorbed staying in place. In the same year Williams published a study on the toxicity of soybean oil, indicating the formation of an aldehyde (and other products), due to the peroxidation of fatty acids, with potential risk for the patients. McArthur (2001) confirmed these measurements suggesting and demonstrating the possible genotoxicity of the material that was intact and leaked through the wall of the prostheses. Simultaneously Munker (2001) reported that the 55% (56 out of 88!), of explanted Trilucent, showed a thickening or a change in the color of the surface, due to lipid peroxidation. It's very important, the observation of a remarkable adherence of the periprosthetic capsule to the surrounding tissues, especially the pectoralis major muscle. Finally McGregor (2002) has highlighted the risk of rupture during their removal, due to the 'Velcro effect'.

the materials. From this point of view we can find studies about the possibility of infection, cancer risk, but most of all about the foreign body reaction and the possibility of triggering autoimmune diseases.

2.2.1 The possibility of infection: due to the presence of microorganism as Staphylococcus aureus, Staphylococcus epidermidis etc.[4], it could be promoted by the insertion of the implants. A "non sterile" technique or an incision in the axillary fold can cause this complication. To avoid this problem many authors[5] have proposed the use of antibiotic solution, with or without disinfectant or saline, on the prostheses or locally inserted in the

[4] Since the end of the seventies the commensal bacteria of the human skin were identifies to be introduced during surgery. Already in 1979 Coutiss (see http:// www.silicone-review.gov.uk/infection/index.htm) recorded the presence of, Staphylococcus aureus, a commensal of the human skin and potentially pathogenic bacterium, in the 72% of the cases. In the following years Ransjo (1983), Freedman (1989), Virden (1992), Brand (1993), and still Poblete (1994), Dobke (1995), Ahn (1996) have identified in bacteria, as Staphylococcus aureus, epidermidis, Streptococci A and B etc., the cause of implant infection. So it was clear the correlation between infection and the formation of periprosthetic capsule and its contraction. Initially it was thought that the presence of bacteria could cause the formation of periprosthetic capsule: 10 units that form colonies of bacteria are sufficient to give the capsule and 107 to cause the extrusion of the implants, but investigators as Kossovsky (1984) showed that the infection could accelerate or exacerbate the formation of the capsule, but wasn't the cause. In 1992 Virden identified the presence of bacteria (Staphylococcus epidermidis) in the 56 % of implants affected by capsular contracture (15 implants out of 27). Dobke (1995) confirmed the previous data, establishing the presence of bacteria with a predominance of Staphylococcus epidermidis in 54% of the analyzed implants (81 of 150). In the 76% of the contracted capsule (62 of 82) were found bacteria. Unfortunately the relationship between the implants, the capsule and the bacteria is still unclear.

[5] In this regard, in 1981 and then in 1994 Burkhardt noted that the use of antibiotics, such as gentamicin and cephalothin, and/or the irrigation with Betadine decrease the number of bacteria conducing to the reduction of the capsular contracture, also if severe.

breast pocket, or the administration of antibiotic therapy during the pre, intra and postoperative period. Unfortunately there are no unique guide lines for this complication, and the plastic surgeons can act following their preferences.

2.2.2 The cancer risk: hypothesized for years because of the silicone products consequent to its fragmentation, it has been considered not only for the silicone but also for the polyurethane foam and for the soybean oil.

Nowadays it's been confirmed only for the Trilucent soybean oil prostheses that were abandoned in 1997 causing the necessity of substituting the implants with silicone ones.

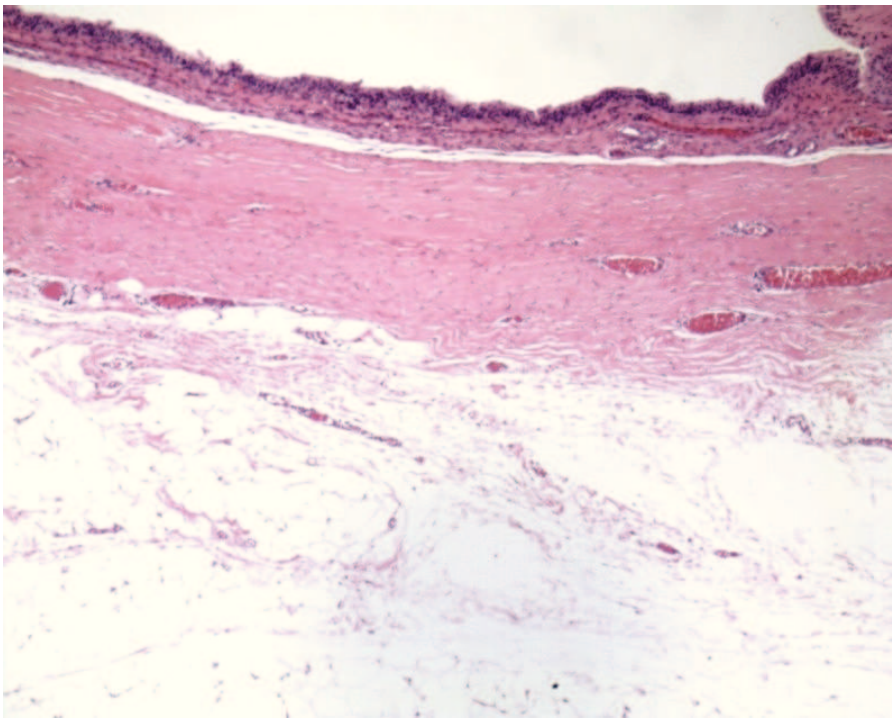
Regarding silicone, this material has been studied for years and recently reintroduced in USA by the FDA, The American Food and Drugs Administration, because of the absence of evidence of an increased cancer incidence.

Same destiny has been reserved for polyurethane foam considered responsible for the triggering of cancer due to 2,4 toluendiamine, derived by the polyurethane fragmentation.

Nowadays the "cancer risk-polyurethane related" has been abandoned: the amount of 2,4 toluendiamine is too low to trigger cancer in humans.

2.2.3 The foreign body reaction

The periprosthetic capsule:



"The formation of a fibrous capsule around a silicone breast implant is part of a physiologic reaction….In contrast the formation of capsule contracture is a local complication of unknown causes" this in Poeppl 2007. Well known as periprosthetic capsule, it is a dynamic inflammatory reaction, appeared in the first 20 days after surgery and present with any kind of foreign body with the aim of isolating the implant from the surrounding tissues. At the beginning it's featured by a macrophagic reaction becoming lymphocytic and finally collagenous during the maturation of the capsule, as we see later.

Histologically we can distinguish three layers:

1) the intimal zone,

2) the intermediate zone,

3) the transition zone.

The intimal zone: inner compartment directly related to the surface of the implant; it is featured by a mono o multilayered inflammatory reaction composed by macrophages, fibroblasts and, in some cases, a pseudoepithelium named synovial metaplasia.

The intermediate zone: characterized by a variable thickness and the presence of collagen fibers, parallel aligned or disarranged dependently by prosthetic surface and the age of the implant. At the beginning the texturization promotes the disarrangement but, in the older capsules, the fibers are parallel aligned increasing the risk of capsular contraction.

The transition zone: outer compartment related with the surrounding tissues (pectoralis major muscle or mammary gland).

The synovial metaplasia

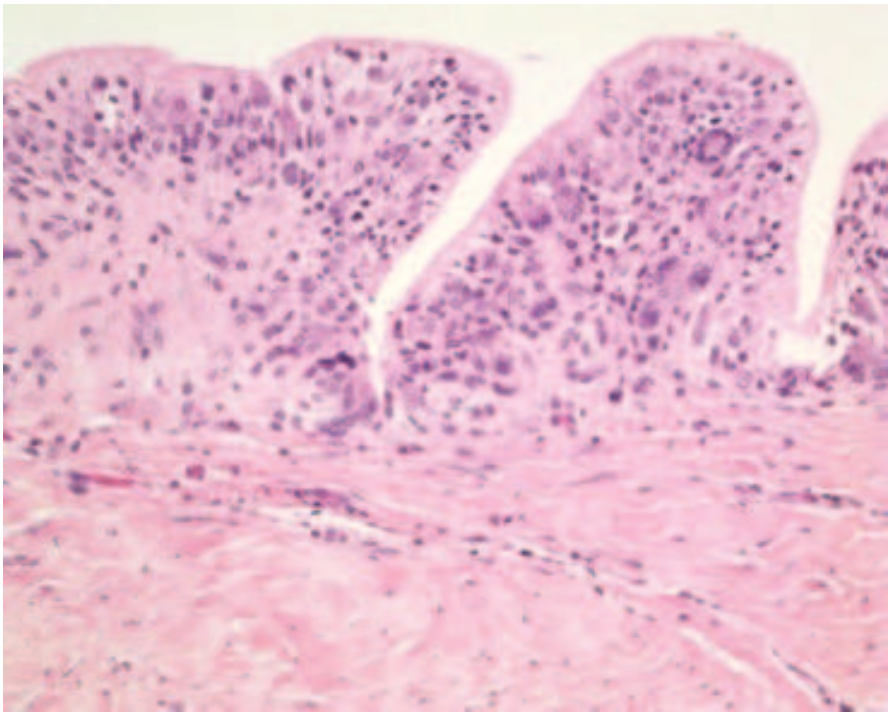
In the last 40 years authors like Chase et al., Copeland et al., Raso et al., Del Rosario et al., and Wyatt et al. described the synovial metaplasia as a typical feature more evident in capsules from textured and polyurethane breast prostheses.

According to Chase, Ko and Wyatt the synovial metaplasia can be related with the age of the implant, decreasing as the age of the implant increase. At the time, the synovial metaplasia was seen as having a protective effect against the capsular contracture thanks to a biofilm produced by the capsular synovial cell layer at the interface with the implant and consisting of chondroitin 4 sulfate and keratin sulfate.

Authors, like Ko and Poeppl found no correlation between the presence of this pseudoepithelium and the chemical and physical features of the implant's surface, hypothesizing that only the mechanical stress, exerted by the implant on the surrounding tissues, could cause it.

Histologically, in accordance with Raso et al. the synovial metaplasia is a proliferation of synovia-like cells arranged in a palisade manner in the interface between capsule and implant. Using an electronic microscope the cells can be distinguished in: macrophage like and fibroblast like. The cells are featured by round to oval nuclei and an abundant eosinophilic cytoplasm. Multinucleated forms were also found. This membrane may be everted on the capsular surface, giving rise to villous hyperplasia.

The cells are positive to vimentin, lysozyme, CD68, anti-trypsin, anti-chymotrypsin.



Synovial Metaplasia

The Collagen Fibers

Many authors (as Ginsbach, Brand, Bucky, Batra and Wyatt) have described a random or multidirectional orientation of the collagen bands, associated with textured and polyurethane prostheses, becoming parallel with the age of the implant and/or sometimes with the mammary massage, a common practice in patients after breast reconstruction. This act could cause a separation between the capsule and the textured surface of the implant, with a consequent straightening of the connective fibers.

As Giachero described in 1992, and also in mine studies[6], the change in the density of the collagen fibers, or fibrosis, is a common feature of both silicone and polyurethane implants and increases with the age of the prostheses, replacing the inflammatory reaction.

Autoimmune disease:

Known as connective tissue diseases, these pathologies are not physiological and have been recently correlated with the siliconosis in a new syndrome, described by Shoenfeld et colleagues, called ASIA Syndrome.

ASIA is the acronym for autoimmune/autoinflammatory syndrome induced by adjuvants and it comprehends the siliconosis mediated by the exposure to silicone (the adjuvant) and featured by immune phenomena and clinical symptoms of autoimmune diseases such as, for example, body ache, morning stiffness, dry eyes and mouth and unexplained fever.

In a recent paper[7] I've reviewed the literature since sixties 'till today with the aim of finding if the correlation between SBI (silicone breast implant) and CTD has been clarified. At the beginning there have been few case reports that correlated SBI with CTD describing clinical symptoms of unspecified and/or well-defined autoimmune diseases such as systemic sclerosis (SSc) or

[6] See Scarpa 2002 and 2010[2].

[7] See Scarpa 2010[1].

Sjogren's syndrome (SS), conditions in which anti-silica antibodies or other autoantibodies were detected.

Later, from 1990 to 2000, there have been experimental studies using also animal models (e.g. New Zealand Black mice vs BALB/c albino mice). These papers were mostly cross sectional or case control based on large groups of patients. In this last group of studies autoimmune symptoms, immune cells, including T cells, and autoantibodies were analyzed in order to explore the relationship between SBIs and the occurrence of CTD.

Some autoimmune diseases such as the human adjuvant disease (HAD), SSc, Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), morphea, SS, and fibromyalgia were reported in association with SBI.

Notably, some immune abnormalities were found including changes in CD4+ T cells and macrophages, autoantibodies such as anti-silica and anti-collagen, and to a lesser extent antinuclear antibodies (ANA), anti-cardiolipin, anti-tireoglobulin, and anti-thyroid antibodies and rheumatoid factor.

However, the studies on the association between breast implants and CTD are contradictory and failed to explain why in some patients SBI may stimulate CTD and the removal of these implants may reverse the disease after a long time ranging from months to years.

Proinflammatory biomarkers, including Heat Shock Protein (HSP) 60, Myeloid Related Proteins (MRP) 8-14, procollagen III,

circulating immune complexes and antiphospholipid antibodies, were demonstrated in the serum or adhering to the surface of SBI. This finding is in keeping with the development of massive capsular fibrosis and contracture as well as with the induction of autoimmune syndromes, especially in predisposed patients.

3.

BREAST IMPLANTS AND CTD

3.1 On the aim of this study

Considering that the presence of the breast implants causes a natural foreign body reaction characterized by the infiltration of macrophages and T cells, and that these cells are involved in the development of CTD in implant carriers, I created a cartoon explicating every steps of capsule formation and the cells involved in order to understand which immunological pathways can be responsible for triggering and developing CTD in predisposed patients.[8]

3.2 The periprosthetic capsule and CTD

As I said earlier, the capsular formation is a dynamic inflammatory process. Nowadays it's clear that the mechanical presence of the implant can transform a "normal foreign body reaction" to a chronic inflammatory reaction. This theory is confirmed by many histological studies that have described the development of granuloma even years later after implantation.

[8] I had the idea for this theory three years ago and the long period, taken to develop it and to publish the article related, is due to 1) the numerous discussions and revisions with Prof. Doria and my supervisors in order to verify the goodness of the theory, 2) the numerous attempts done to find a financial supports to the project that I presented, in 2011, to the Ethic Committee for animal testing of Padua University.

If in normal subjects this process can lead to capsular contracture, in genetically predisposed individuals, chronic inflammation could give rise not only to a fibrotic capsule with subsequent capsular contracture, but may also stimulate an autoimmune response characterized, for example, by anti-collagen autoantibodies[9].

3.2.1 The immunologic steps of the capsule

Since the discovery of mammary capsule it was clear that the first cells involved in a foreign body reaction are the macrophages. Their presence has been seen by Raso in 1994 and 1995 that described numerous mithocondria, cytoplasmatic process and vacuole. In 1995 Del Rosario confirmed the presence of CD68+ cells known macrophages.

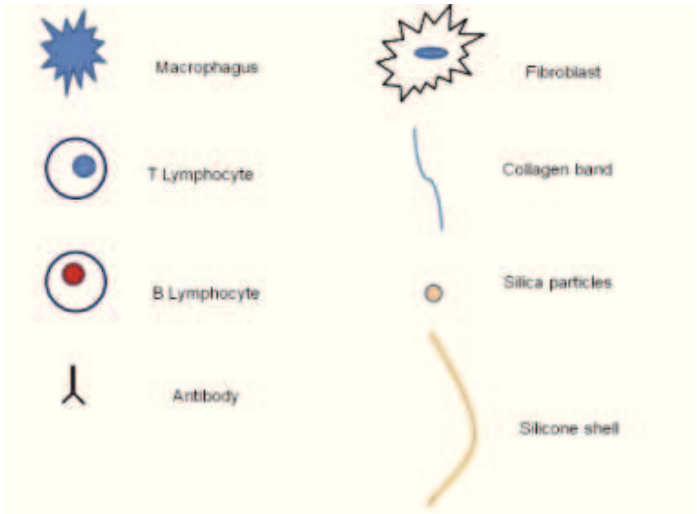
These observations have been confirmed later in 1999 and 2001 by Abbondanzo and Kamel. Finally, Raso described, in macrophages cytoplasm, silicon material pointing out the phagocytic attempt.

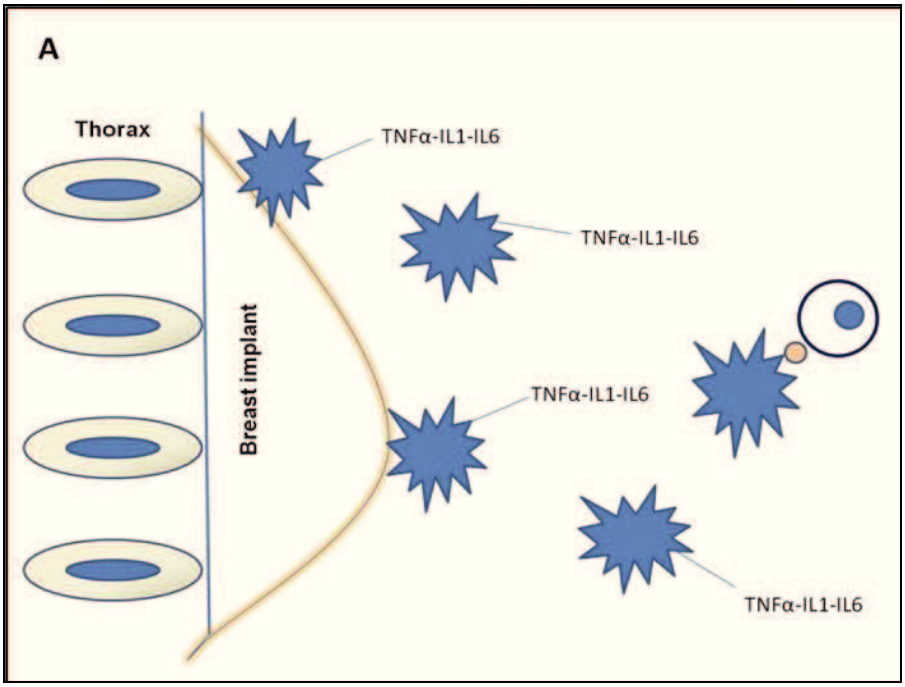
But these are only the first cells, later the lymphocytic cells (T and B) take place. The first evidence has been described in 1991 by Picha et al, but only 5 ys later Katzin, using the three colours

[9] The capsule and its thickness depend on the material used for the SBI and, most important, on the characteristics of the patients, which may present a predisposition to an excessive fibroplasia. It is therefore clear, in the final analysis, as the periprosthetic fibrous capsule is a physiological and inevitable reaction and that the plastic surgeons can only try to delay or avoid the contraction keeping a thin and soft capsule and searching for a valid medical and drug therapies.

flowcytometry, studied their phenotype noting CD4+ T cells. This observation has been considered very important because it indirectly demonstrated the possible activation of B cells to produce antibodies. Recently Wolfram noticed two classes of cells in periprosthetic capsule: Treg and Th17 that, as we see later, could be very important in the onset of CTDs.

3.2.2 The first step:



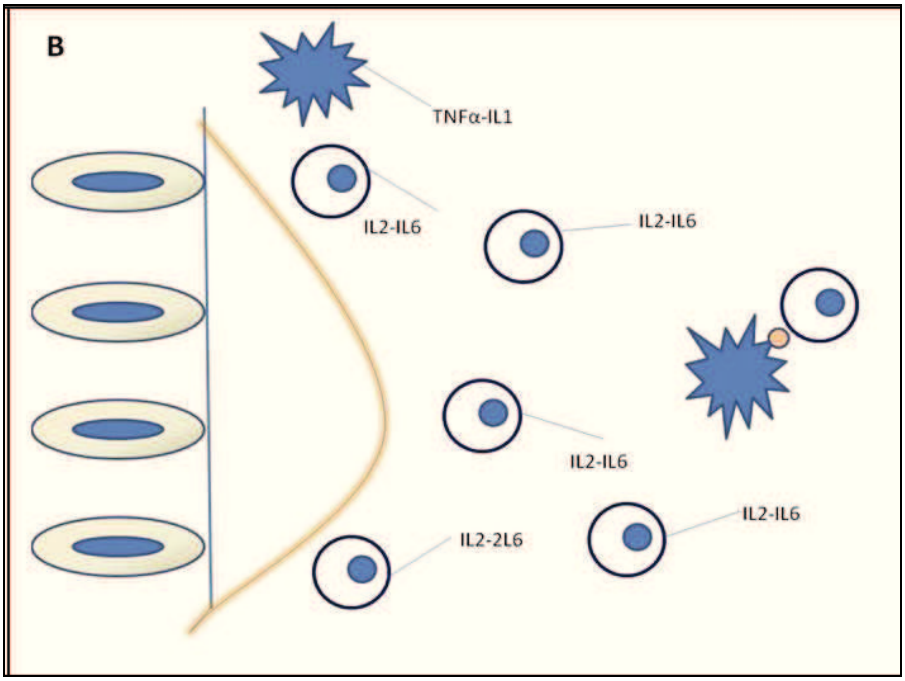


Initially the immune system tries to reject the implant, inducing a foreign body reaction that due to the implant's size isolates the implant from surrounding tissue making a new tissue (a granulation tissue).

This first step is characterized by infiltration of CD68+ macrophages mixed in the inner layer with secretory cells producing proteoglycans in order to lubricate the space between the capsule and the implant.

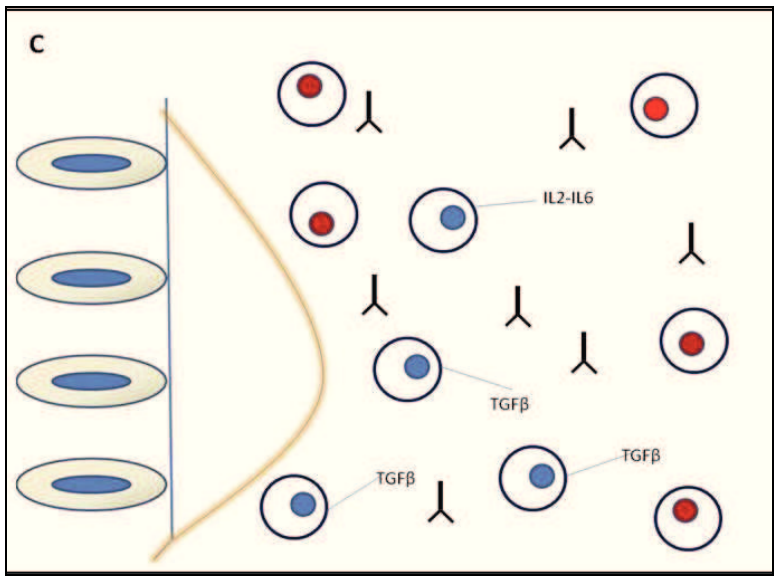
In this stage macrophages produce cytokines such as tumor necrosis factor α (TNF-α), interleukin 1 (IL-1) and interleukin 6 (IL-6), leading to an acute inflammatory response and recruitment of other immune cells including T lymphocytes.

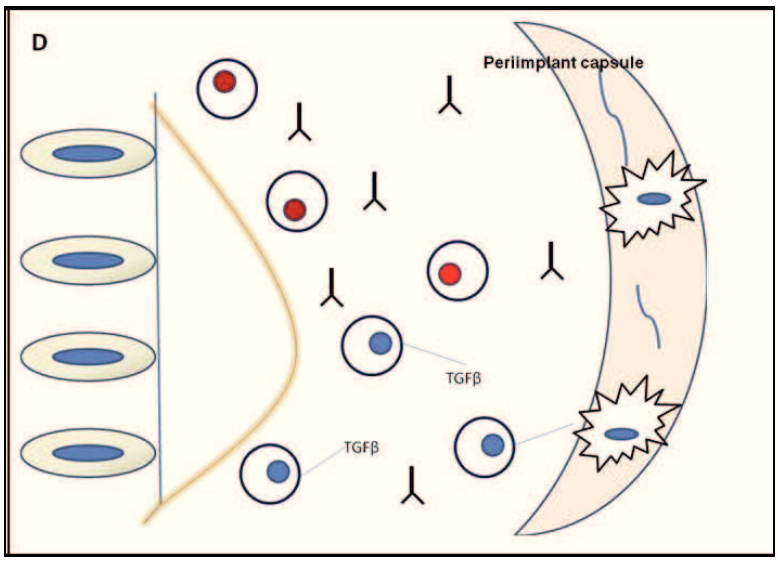
3.2.3 The second step:



The T Lymphocytes are reported as CD4+ T helper (Th) cells which could be activated by antigens like silica particles derived from the implant surface to produce IL-2 and probably IL-6 with the consequent activation of B cells and the production of anti-silica antibodies observed in capsular biopsies by some authors.

3.2.4 The third and fourth steps:





TNF-α and tissue growth factor-β (TGF-β), produced by macrophages and activated T cells, may stimulate neoangiogenesis and fibroblast growth with the formation of proteins such as collagen and connective tissue, leading to the transformation of the foreign body reaction in a fibrotic capsule.

3.3 The cells and cytokines involved

3.3.1 The cells

1) Macrophages: monocytes featured by CD68+, the macrophages are very mobile phagocytic cells, firstly involved in a foreign body reaction.

Histologically they can be distinguish in two forms depending on their state of activation: a) *not activated macrophages:* round, stars-like or fusiform cells with basophil cytoplasm, lysosomes and abundant rough endoplasmic reticulum; in this phase they are very similar to fibroblasts and recognizable only with a colloidal coloration; b) *activated macrophages:* recognizable for the bigger dimension and the presence of phagocytosed material in their cytoplasm. They are featured by membrane extensions that allow their migration to the inflammatory site.

Macrophages' rule is to phagocyte pathogens and to present, as APC cells, the antigen to lymphocytes with the aim of avoiding infections and stimulating an immunitary response.

They produce cytokines like IL-1, IL-6, IL-23 and TNF-α that are responsible for the maintenance of the inflammation calling other cells like T and B cells.

In the periprosthetic capsule the macrophages isolate the implants from surrounding tissues, and in some cases they are present in synovial metaplasia and, producing IL-6, they induce the differentiation of T naïve cells into T helper 17.

2) T lymphocytes: histologically featured by an important nucleus surrounded by a little cytoplasm, in the capsule these cells can be responsible for recognizing the antigens and regulating the inflammation.

Treg: having a peripheral differentiation, they are stimulated by TGF-β and IL-2 and inhibited by IL-6. Usually they represent 2-3% of human CD4+ T cells.

These cells are featured by Foxp3+ and are responsible for turning off the inflammatory response and it has been demonstrated their reduction or dysfunction in autoimmune disease like Rheumatoid Arthritis.

Th17: T helper cells that produce Th17 stimulated by IL-1β, IL-6, IL-23 and TGF-β. However the role of the latter is very controversial: some authors pointed out a possible, in vitro, differentiation without TGF but only in presence of IL-6 and IL-1β.

Th17 stimulate the synoviocytes to produce VEGF and the IL-17 activates IL-6 in synovial compartment creating a positive feedback that continuously produce Th17 converting the inflammation from acute to chronic.

In Miastenia Gravis they represent the key for the production of autoantibodies. In 2011 Peters et al. demonstrated that the Th17 derived only by IL-6 and IL-1β could be more pathogenic because of the interaction with IL-23 (derived by APC cells like macrophages), keeping the inflammation.

In the last months a possible conversion of Treg into Th17 has been hypothesized, due to the presence of a high amount of IL-6 and IL-1β.

3) B cells: responsible for the production of antibodies, after the stimulation by the antigen (silicon material in our case), they differentiate in plasmablasts and later in plasmacells. The plasmacells are histologically featured by bigger dimension, excentric oval or round nucleus with a typical chromatine whell-shaped and the presence of nucleoli. These last two features reflect the active production of antibodies.

3.3.2 The cytokines*:*

1) IL-1: is a pleiotropic mediator of the response to injuries and infections. Produced by macrophages, dendritic cells, B and T cells in peripheral circulation, it stimulates the secretion of G-CSF,

TNF-α, IL-6, IL-17 and others. Locally IL-1 is an autocrin and paracrin costimulator in the early innate inflammatory and in adaptive immune responses. It's also responsible for the activation of autoreactive T cells and stimulates them to migrate thanks to the expression of matrix metalloproteinases (MMPs), CD40L and OX40. In 2009 IL-1 has been considered the key of the autoimmune response Th17 mediated: the IL-1R1 induced by IL-6 is necessary for the early differentiation of Th17.

2) IL-6: produced by T cells and macrophages and taking part to the acute phase response, this cytokine is historically considered proinflammatory and directly fibrotic activating fibroblasts to produce collagen and it is directly correlated with skin thickness in skin fibrosis.

It's responsible for the differentiation of T naïve cells in Th17 inhibiting the differentiation in Treg cells and it has been involved in autoimmune diseases, as SSc, where IL-6 is a marker and has been found to be elevated in the bronchoalveolar lavage fluid.

Finally, notably in 2005 Febbraio M et al. described IL-6 as a myokine produced by the muscles cells, expecially during the muscular contraction.

3) IL-17: identified as a transcript from a rodent model of T cell hybridoma in 1993, IL-17A is a member of IL-17 family which

is composed by 6 isoforms from A to F, but only IL-17A and F are produced by Th17.

IL-17 is a proinflammatory cytokine acting as a potent mediator in delay type responses; it increases the production of other cytokines, as IL-6 or IL-1β, and kemokine, as IL-8, with the aim of recruiting immunologic cells, as monocytes, to the site of inflammation.

IL-17 can also activate matrix metalloproteinases (MMPs) and inhibit matrix production in chondrocytes and osteoblasts. Its overproduction causes a consequent damage of the articulations in patients affected by Rheumatoid Arthritis where IL-17 has been found in the synovia.

4) TGF-β: the transforming growth factor β exists in 3 isoforms but the first (TGF-β1) is the most common in immunitary response. Its role is to regulate inflammation recruiting cells like monocytes, lymphocytes, neutrophils and fibroblasts and stimulating the differentiation of T naïve cells into Treg and Th17 (in this latter case TGF interacts with other cytokines as IL-6 and IL-1β). In the meantime it can inhibit GMCSF (Granulocyte Macrophage colony stimulating factor) with a consequent downregulation of monocytes' response.

It's also profibrotic:

1) it induces the Fibroblast Growth Factor;

2) it activates fibroblasts to produce collagen;

3) it reduces the production of enzymes that are responsible for the degradation of the Extracellular Matrix.

Using indirect immunohistochemistry, Kuhn et al. detected TGF-β1 and TGF-β2 in all of the fibrotic capsules.

5) TNF-α: involved in the acute phase of the inflammation, it's produced by macrophages and other cells like CD4+ T cells and fibroblasts. This cytokine is involved in the production of IL-6 and its presence can increase IL-17.

It interacts with IL-1 and IL-6 with the aim of stimulating chemotaxis and phagocytosis.

In 2010 TNF-α has been involved in capsular contracture: Tan et al described an increased expression of this cytokine in the inflammatory response correlated with capsular contracture. In this article TNF-α was localized in fibroblasts, macrophages and extracellularly close to the breast implant.

4.

THE 'THEORY'

4.1 Normal Subjects and predisposed patients

Based on the immunological steps of the capsular formation, cytokines, especially TGF-β, and the new class of lymphocytes Th17 seem to play a major role in the development of CTD induced by SBI. In fact, IL-1 and IL-6 have been implicated in the differentiation of Th cells into Th17, which produce IL-17, and seem to be responsible not only for the transformation from acute to chronic inflammatory responses, but also for the onset and maintenance of autoimmune diseases such as Rheumatoid Arthritis.

The balance between Treg and Th17 cells is a critical issue in maintaining an inflammatory process and preventing an autoimmune response. In a normal subject the activation of fibroblasts, resulting in deposition of extracellular matrix (ECM), leads to a down regulation of the inflammatory reaction and its transformation into a fibrotic reaction. However, in genetically predisposed individuals the continuous stimulation, due to the presence of the implant, leads to a perpetuation of an immune inflammatory response.

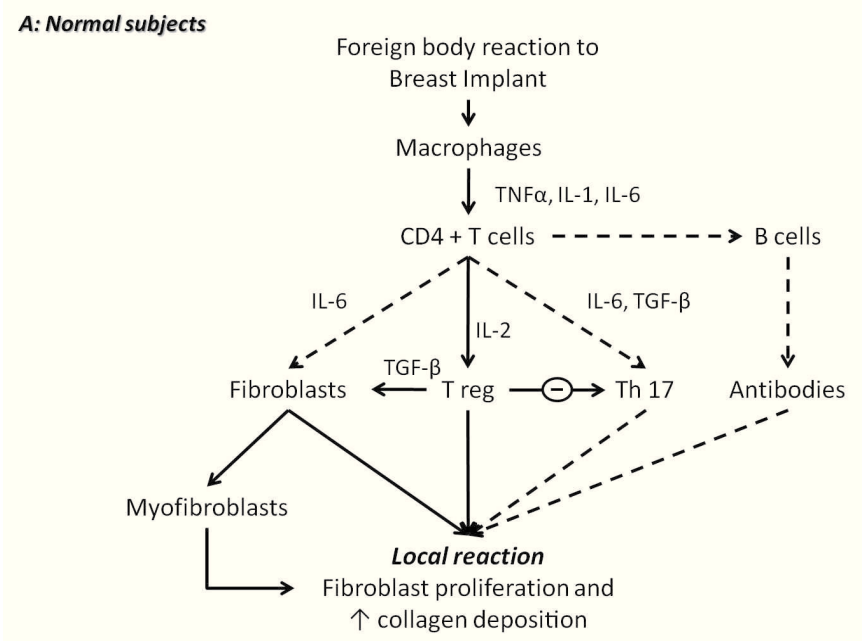
The continuous activation of macrophages and production of TNF-α, IL-1, IL-6 prolongs the inflammatory response with production of large amounts of Th17. Production of IL-1 and IL-2 promotes the switch in Treg/Th17 cell balance in favor of Th17 cells.

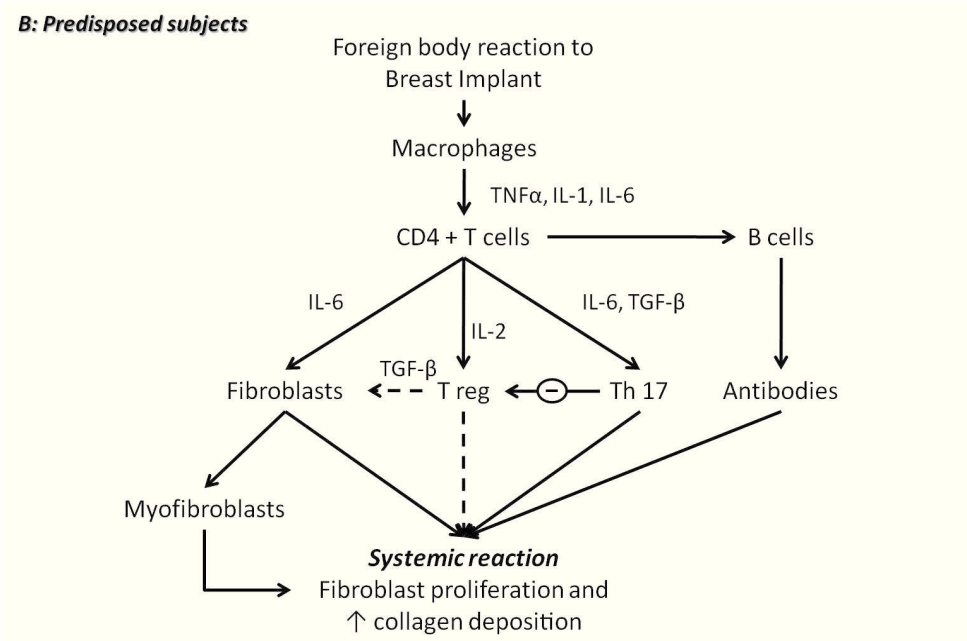
TGF-β stimulates the overproduction of IL-6 and fibroblast growth factor (FGF), resulting in fibroblast proliferation and ECM deposition. Specifically, TGF-β, in addition to stimulating macrophages with positive feedback, is able to induce the differentiation of fibroblasts into myofibroblasts which present alpha smooth muscle actin in the cytoskeleton and are responsible for contraction of the scar and deposition of proteoglycans and collagen III. Activated macrophages and fibroblasts produce angiotensin II, which, by means of Nicotinamide Adenine Dinucleotide Phosphate (NADPH), leads to further production of TGF-β1 and subsequent reactivation of the inflammatory process described above.

TGF-β1 and IL-6 can, in turn, induce the differentiation of naïve Th cells, which have never come into contact with silicone before, into Th17 by activating RORC2 gene.

Notably, the presence of Th17, the over expression of TGF-β1, and the overproduction of fibroblasts and ECM (collagen and proteoglycans III), may be responsible, in susceptible individuals, for a perpetuation of the inflammatory reaction which locally can lead to capsular contracture and at the systemic level may contribute to triggering autoimmune diseases, especially SSc.

This autoimmune disease is characterized by the deposition of procollagen III and proteoglycans in the skin, lungs, heart and other organs, and seems to be related to fibroblast proliferation and TGF-β gene over-expression which could stimulate fibroblasts, in an autocrine fashion, to produce more collagen.


A: Normal subjects
Foreign body reaction to
Breast Implant
Macrophages
TNFα, IL-1, IL-6
CD4 + T cells
B cells
IL-6
IL-6, TGF-β
IL-2
TGF-β
Fibroblasts
T reg
Th 17
Antibodies
Myofibroblasts
Local reaction
Fibroblast proliferation and
↑ collagen deposition


B: Predisposed subjects
Foreign body reaction to
Breast Implant
Macrophages
TNFα, IL-1, IL-6
CD4 + T cells
B cells
IL-6
IL-6, TGF-β
IL-2
TGF-β
Fibroblasts
T reg
Th 17
Antibodies
Myofibroblasts
Systemic reaction
Fibroblast proliferation and
↑ collagen deposition


Temporary/lower inflammatory reaction
Continuous/overstimulation
Inhibitory process

Legenda: Immunological response following breast implants depends on genetic background of patients:

A) **normal subjects** with local reaction: notice the temporary stimulation of immune inflammatory reaction and the subsequent marked response of Treg cells with moderate production of collagen fibers and inhibition of Th17 production;

B) **genetically predisposed subjects** with systemic reaction: notice the continuous stimulation of the immune inflammatory reaction with consequent overproduction of collagen fibers and lower activation of Treg cells and their inhibition by Th17

4.2 Potential treatment

The involvement of TGF-β could open many new approaches to the therapy of fibrotic capsule and surrounding inflammation. Using a rat model, it has been shown that the local application of oligonucleotides targeting Connective Tissue Growth Factor (CTGF) and TGF-β can reduce CTGF and capsular formation.

More recently Zimman et al. have noted a reduction of TGF-β1, anticollagen III monoclonal autoantibodies and periprosthetic fibrosis, in rats treated with angiotensin converting enzyme inhibitors (enalapril) which block the renin-angiotensin system and consequently the inflammatory and profibrotic effects of angiotensin II.

Notably, 9-cis-retinoic acid, an antifibrotic drug, increased COX_2 expression and PGE2 production, inhibiting the expression of CTGF as well as type-I and -III collagen in scleroderma cultured fibroblasts.

The use of leukotriene receptor antagonists, zafirlukast and montelukast, which showed antifibrotic potential, is controversial. Initially developed as a treatment for asthma, zafirlukast was demonstrated to reduce capsular thickness impairing collagen density. Even this effect could be useful in order to prevent capsular fibrosis and contracture. However, there are some reports on the occurrence of Churg-Strauss syndrome in patients treated with leukotriene receptor antagonists and a direct immunomodulatory role for these drugs in the development of vasculitis, has been postulated.

Recently, Lina et al. reported a reverse in the Th1/Th2, Th17/Treg imbalance in patients with RA treated with a therapeutic strategy based on the combined treatment with Methotrexate (MTX) and Etanercept. The authors demonstrated that Etanercept and MTX play an immunomodulatory role on the cytokines involved in the capsular process (IL-1, IL-6, TNF-α, TGF-β and IL-17), ameliorating RA by normalizing the imbalance between Th17 and Treg.

Thus, some drugs might play a role by inhibiting not only the local but also the systemic inflammatory responses.

5.

CONCLUSION

Although the causal role of SBI on CTD cannot be considered conclusive, it can be speculated that some genetically predisposed individuals may develop CTD because of the stimulation provided by a foreign body. The continuous stimulation of the immune system might also explain why the lag-time between SBI and CTD onset can vary from months to years. The possibility of using new therapeutic strategies could reduce both the risk of capsular contraction and autoimmune diseases[10].

[10] **MY PROJECT:** in order to demonstrate in vivo the goodness of the 'theory' exposed above and to find a therapeutic target, in 2011 I presented an experimental research, based on an animal model, that has been approved by the Ethic Committee for animal testing of Padua University. Unfortunately the lack of financial supports and of cooperation (proposed by prof. Doria) with Dr. Shoenfeld, who received the text of the project, don't allow me to complete the study.

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