The Foreign Body Response, Topography, and Silicone Breast Implants

The foreign body response is a fundamental part of healing, especially once a biomaterial is implanted into the body. When the response starts, leukocytes migrate to the implant and express cytokines that are key during acute inflammation (notes). Fibrin, produced during coagulation, is an important part of the process. During the proliferation phase, collagen and fibroblasts are present. Fibroblasts are useful for matrix production and contraction, but attach more to textured surfaces than smooth surfaces (8). Remodeling occurs after many of these processes are complete.

Altering the topography of an implant has been shown to have an effect on the foreign body response. Macrophages, which play a prominent role in the foreign body response, are necessary for healing, but they also release cytokines that can lead to inflammation and fibrous encapsulation (4). This encapsulation effectively seals off the implant. There can be a number of adverse effects from the foreign body response and sometimes, the capsule can contract if the body is rejecting the implant at all. This can lead to further complications. Changing the topography of an implant has an effect on proinflammatory cytokine production in vivo, as well as capsule thickness (4). It has been proven that collagen fibers on textured surfaces are less likely to align than those on smoother surfaces (nano level) (8). Since the response is so microscopic, alterations in topography at the nano and micrometer levels have been shown to change the behavior of macrophages which makes altering the topography a viable way to try and manipulate the foreign body response (4).

One example of a material that shows this under conditions of ideal surface chemistry is PTFE (4), however, there are a variety of materials that can be manipulated. One specific experiment studied SilkSurface implants, which are nanotextured, and VelvetSurface implants, which are microtextured to see which had a higher rate of infection (6). Over a span of three years, the nanotextured implants were found to have a lower rate of infection. This supports the idea that implants with smoother textures have a lower risk of infection (6). The results of many such studies can be analyzed using the common technique of scanning electron microscopy (SEM) (4). SEM makes it easy for results to be seen after the experiment's duration has passed, and helps researchers decide if a change is statistically significant. There are ISO 14607 categories which use SEM to categorize implants into smooth, microtextured, and macrotextured (8). Implants with roughness below 10 μm are classified as smooth surfaces (8).

The foreign body response is a complex bodily reaction that is taken into consideration whenever putting a material into the body. There are many factors that influence the way the body heals and the response to different materials that are implanted. Silicone, commonly used in breast implants, has its own unique interaction with the body. It is important to understand how the body interacts with silicone implants in order to make procedures safer for patients. Breast augmentation is one common medical procedure. Some choose to have an implant for cosmetic

reasons, sometimes temporarily, while other procedures are done after a mastectomy. Whether the procedure is cosmetic or not, it is important to ensure such a common procedure is as safe as possible. Any physician can implant a breast device regardless of training which means the implant must be as safe and function as possible for the high number of individuals who interact with it (8). Around 30% of those who have a breast augmentation also have some sort of complication, which is why something should be done to make the foreign body response less problematic post-op. Studies have shown that recently there has been an increasing number of women who have complications or anaplastic large cell lymphoma (ALCL) due to their implants (5). One common reason for these complications is surface texture, and cancerous cells can form due to complications with capsule formation and contracture (CC) after an implant procedure (3). Even implants that appear to be smooth have ~5μm between ripples in their surfaces which can be seen using electron microscopy (8). CC occurs when the periprosthetic capsule tightens and hardens, eventually leading to distortion of the implant (7). .

Some other possible reasons for complications in breast implants include reactions to implant particles, allergies, genetic factors, or reactions to certain bacteria that grow on the implant surface, which is usually made out of silicone. The capsule that forms around the implant consists of three layers. The first is the fibroblast containing tissue that comes in contact with the implant. The second is composed of loosely arranged connective tissue and internal vascular supply. The third layer is made up of dense connective tissue with the external vascular supply (3).

There have been reports of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL), particularly in women who received textured breast implants. The immune cancer starts in the fibrous scar capsule formed during the foreign body response and in some cases can spread to surrounding areas (1). The lymphoma cells are typically found in the seroma around the implant (2). The cancer usually spreads slowly and can be removed with the problematic implant, but it can be more dangerous as it spreads to other areas of the body. Aside from this cancer, there are often other complications from breast implants, including those due to infection, capsule formation, or prosthesis rupture (3). Changing the surface properties and topography of a breast implant may alter the capsule around it, which could lead to fewer complications.

The topography of breast implants has been categorized by parameters such as roughness, density of peaks, SA, and ISO 14607:2018 surface classification and a variety of silicone breast implant surfaces. The textures that were found to have the lowest SA were Allergan Smooth, Motiva SilkSurface, and Motiva Velvetsurface (8). The collagen fibers of the implant capsule aligned parallel to the surface in flatter textures (8). Mimicking the environment for fibroblasts on the surface of the implant is important (3).

Electrospun silk fibroin or polyethylene oxide (PEO) can be used as a coating in breast implants to improve biocompatibility (3). This coating increases the elastic modulus, making the implant surface more flexible (3). This is important because during implantation, the material

chosen for use must be easily manipulated and mechanically strong (3). The experiment used implants with a surface made of PDMS. Increasing the microbial properties of new implants could minimize the inflammatory response and reduce bacterial adhesion (8). In the future, implants will be designed to decrease the foreign body response by making them as antibacterial as possible. SEM has been used to confirm the presence of a biofilm on implants that caused complications (7). The amount of silicon in the macrophages can cause an increased negative response (7).

It is hypothesized that smooth electrospun silk coatings with modified surfaces can be used on silicone breast implants in order to decrease harmful capsule formation around silicone breast implants, which will decrease the risk of lymphoma and other complications when compared to implants considered to be micro or macro textured according to ISO standards.

One possible experiment that could be conducted in order to support the hypothesis is based on research that found that the pattern of shark skin has antimicrobial properties (9). Surface topographies can limit bacterial adhesion, so a silk coating using the Sharklet micropattern, which is a shark-inspired micro-pattern, could be used on silicone breast implants in hopes of decreasing complications from the implant. ISO biocompatibility would be referenced during the experiment to make sure the implant was viable. SEM would be used in order to determine the roughness, SA and ISO classification of the material pattern. The silk would be sterilized by boiling in distilled water as necessary. The silk fibers would then be dissolved in a solution containing PEO in order to increase viscosity for electrospinning. During electrospinning, the Sharklet micropattern would be implemented. Tensile tests would occur periodically during processing in order to make sure the implant was strong enough for manipulation. The implant would have a roughness of ~5μm, putting it in the smooth category according to ISO standards. The Sharklet micropatterned implant would be compared to an unpatterned implant of identical size and processing, around 15mm in diameter. This implant serves as the control, and control and test groups would be the same size (~20). Statistical analysis will be performed and when p values are <0.05 the difference will be regarded as statistically significant. The implant would be easy to use and durable. It would pass all tensile and compressive strength tests with significance in order to be considered a success. The implant could first be analyzed in vitro in order to ensure biocompatibility while replicating human body conditions, but eventually implanted into larger animals to assess success. Human trials would be conducted if there were no extreme adverse effects during these trials.

Another possible experiment involves seeding fibroblasts into the electrospun silk. These fibroblasts could be derived from the breast tissue that they would be inhabiting in order to minimize rejection. Since the tissue in contact with the implant contains fibroblasts, it makes sense that they could help mediate the foreign body response (3). Human fibroblasts would be

purchased and grown in culture medium before undergoing other treatment processes to make them ready for implantation. Before seeding, the implant would be sterilized using ethanol, washed in PBS and then dried (3). The fibroblasts would be seeded into each cell well at a high concentration, around 12,000 cells per well. The cells would be incubated before a solution was added and placed in a shaker. The implants would be the same size as the controls, which would be around 15mm in diameter. The controls would have the same procedure as the implant with fibroblasts, including the silk coating, and sample sizes. This would allow researchers to study only the effect of fibroblasts added to the new implant surface. Light and immunofluorescent microscopy would be used to example the cytoskeletal reaction of the fibroblasts (10). SEM would be used to analyze the topography. Tensile and compressive strength tests would take place while silk was electrospun and fibroblasts were added. The material would withstand all tests with significance in order to make sure it would be viable for implantation. It has been shown that the materials used are biocompatible, so no complications are expected. In order for the experiment to be considered a success, the fibroblasts would decrease the rate of capsular contracture by a statistically significant amount ($p<0.05$). If the method worked in vitro and biocompatibility was ensured, animal trials on a pig would be completed in order to mimic the human foreign body response as much as possible.

Another experiment that could be done would again use silk as a coating for the implant, but 3D imprinting would be used to create topography on the nanometer level. Electrospun silk would be used as a coating on the implant with a diameter of 15mm for both the experimental and control groups, but the control group would not undergo imprinting. ISO biocompatibility would be referenced throughout to ensure safety. SEM would be used in order to make sure that the silk was uniform before imprinting for the experimental and control groups. Sterilization would follow the same process as the first experiment. After the silk covered the implant surface, negative imprinting using 3D technology would be applied in order to create a pattern on the surface of the implant that was at the micro/nano level and that would facilitate integration of the implant into the breast. The coating would be uniform and SEM could confirm that the topography was as desired for the experiment in the test group. Tensile and compressive strength tests would take place throughout imprinting and as the silk coating was added to the implant, and if at any point the implant failed, it would be reevaluated. Statistical significance would be required for the experiment to be considered a success, with $p<0.05$. The experiment would first be done in vitro in order to ensure biocompatibility before testing on an animal model, such as a pig, and assessing the complications and foreign body response.

The experiments would be completed under similar conditions, and the foreign body response measured in order to support the hypothesis that topography and microscopic antimicrobial changes could affect the risk of lymphoma after undergoing a silicone breast implant procedure.

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