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Effect of ASC Injection in the Inflammatory Reaction in Silicone Implant Capsule: Animal Model

Cristina Pires Camargo, PhD*
Deborah Luisa de Sousa Santos, Resident†‡
Viviane Abreu Nunes Cerqueira Dantas, PhD§
Tatiane Katsue Furuya, PhD‡¶
Bruna Leticia Freitas-Marchi, PhD§
Maria José Ferreira Alves, PhD‡¶
Miyuki Uno, PhD‡¶
Rolf Gemperli, MD, PhD‖

Background: Capsular contracture is a common complication affecting about 80% of patients who receive radiotherapy after breast reconstruction with silicone prostheses. This study examines the use of adipocyte stem cells (ASCs) to treat capsular contracture.

Methods: Thirty rats were operated on to implant a minisilicone prosthesis in the dorsal region. The rats were divided into three groups: control (saline solution injection), radiotherapy (RDT), and RDT + ASC. After 3 months, the capsules were collected and submitted to histological analysis for inflammatory cell presence, vascular density, and collagen fibers, and gene expression of Tnf, *Il1rap*, *Il10*, *Cd68*, *Mmp3*, and *Mmp9* by qPCR.

Results: In macroscopic analysis, the RTGO score showed a two-point reduction in RDT + ASC compared with the RDT ($P = 0.003$). In histological analysis, ASC exhibited less than 50% of inflammatory cells compared with RDT ($P = 0.004$), which was similar to control. This study demonstrated that *Il1rap* gene expression was identical in both RDT and RTD + ASC. Compared with control, treatment with ASC reduced *Il1rap* expression by 30%. *Cd68* and *Mmp3* expression levels were similar in both the control and RTD + ASC.

Conclusion: This study suggests that ASC treatment decreases silicone prosthesis capsule inflammation. *(Plast Reconstr Surg Glob Open 2024; 12:e5977; doi: 10.1097/GOX.0000000000005977; Published online 30 July 2024.)*

INTRODUCTION

Breast reconstruction can be allogeneic (implant-based), autologous (pedicled flap, free flap). Moreover, alloplastic reconstruction is a relevant alternative considering medical team expertise and patients' preferences.[1,2]

Immediate implant-based reconstruction offers advantages such as a low-cost decrease in surgical time. However, some patients will require adjuvant therapy as radiotherapy (RDT).[3]

RDT is known to cause prosthesis complications. The most common event is capsule contracture. This fibrotic reaction around the expander or prosthesis causes pain, cosmetic deformity, reoperations, and difficulty in expander replacement by a silicone prosthesis.[3–5]

Capsular contracture is a multifactorial condition and basically consists of macrophages, lymphocytes, and fibroblasts depositing around the prosthesis.[5–7] Specifically, mast cells, a macrophage subpopulation, can be related to capsule formation. Brazin et al showed the connection between mast cells and severe capsular contracture. According to this work, the specimens from a capsule contracture material showed a higher concentration of renin, histamine and tumor growth factor β-1. Another element is the fibroblast/myofibroblast collagen production to trigger capsule formation. Histologically, thicker collagen fibers create the thicker capsule.[8,9] Moreover, RDT causes endarteritis in small diameter vessels, reducing blood supply in the irradiated area. This decrease in

*From the *Microsurgery and Plastic Surgery Laboratory, School of Medicine, Universidade de São Paulo, São Paulo, SP, Brazil; †Multiprofessional Residency Program in Oncology Care for Adults, Comissão de Residência Multiprofissional (COREMU), Hospital das Clinicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), São Paulo, SP, Brazil; ‡Center for Translational Research in Oncology (LIM24), Instituto do Cancer do Estado de Sao Paulo (ICESP), Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo (HCFMUSP), Sao Paulo, SP, Brazil; §Laboratório de Fisiologia da Pele e Bioengenharia Tecidual, Escola de Artes, Ciências e Humanidades (EACH—USP), São Paulo, SP, Brazil; ¶Comprehensive Center for Precision Oncology, Universidade de São Paulo, São Paulo, SP, Brazil; and ‖Plastic Surgery Division, School of Medicine, Universida de São Paulo, São Paulo, SP, Brazil.*

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blood supply increases the risk of wound healing complications.[3] Several animal studies aimed to analyze capsular contracture, including the action of antileukotriene,[10] corticosteroids,[11] and collagenase,[12] with unpredictable results.

On the other hand, in clinical research, a few studies analyzed the effect of fat transfer to prevent capsular contraction,[13,14] with promising results. Sutthiwanjampa et al[15] have analyzed the effect of mesenchymal stem cells as a therapy to prevent capsular contracture in an in vitro scenario. In light of these factors, our group hypothesized the use of adipocyte stem cells (ASC) as an autologous therapy to prevent capsular contracture in an in vivo model.[16] To analyze the effect of ASC in the inflammatory reactions, we analyzed the gene expression of several inflammatory markers. We selected some genes to represent different phases of surgical wound healing: *Tnf, Il1rap, Il1rap, Il10, Tnf, Cd68, Mmp3*, and *Mmp9*.

Therefore, this work aimed to investigate the effect and safety of ASC injection in capsular contracture formation in mini silicone implants in rats submitted to RDT.

Takeaways

Question: Can the injection of ASC mitigate silicone implant capsular contracture?

Findings: This study suggests that the injection of ASC surrounding the prosthesis can mitigate silicone implant contracture after radiotherapy.

Meaning: The use of autologous fat and derivates can mitigate silicone implant contracture.

METHODS

This is a pre-clinical study, with a parallel-arm design to compare the effect of ASC (intralesion injection) versus saline solution in the nontexturized silicone prosthesis pocket before RDT. We analyzed 30 Norvegius rats, whose weight ranged from 200 to 250 g.

All animals were provided and maintained in the Universidade de São Paulo *vivarium*. This study followed the national standards of good practices in animal care according to the CONCEA Brazilian National guideline for use of animals in the laboratory and ARRIVE guidelines and was approved by CEUA-FMUSP under registration 045/2017.

Adipocyte Stem Cell Harvesting and Production

Adipose tissue was collected from the inguinal region of three rats. All the animals were anesthetized by an intraperitoneal injection of the association of 100 mg per kg ketamine hydrochloride (Ketamin, Cristália, Brazil) and 5 mg per kg xylazine hydrochloride (Rompun, Bayer, Brazil). They were placed in ventral decubitus, and an area of 3 × 3 cm in the inguinal region of the animal was trichotomized. After inguinal incision, the femoral pedicle was dissected and adipose tissue was removed.

The adipose tissue was washed with phosphate-buffered saline (PBS) and then centrifuged at 430 × g for 10 minutes. The adipocytes and stromal vascular fraction were separated by centrifugation. The isolated stromal vascular fraction was filtered through a 100-µm nylon filter and then cultivated in 15 mL of prewarmed nonhematopoietic expansion medium (Miltenyi Biotec, Auburn, Calif.) at 37°C in 5% carbon dioxide with 95% humidity. After 24 hours of culture, the nonadherent cells in the flask were removed by PBS washing. The adherent adipose-derived stem cells were dissociated by 0.25% trypsin/ ethylenediaminetetraacetic acid, and the total number of adipose-derived stem cells were counted. After centrifugation of the post cultivated medium, the supernatant was collected and stored at −20°C. Before storage, 1% fetal calf serum was added to the supernatant or the corresponding nonhematopoietic expansion medium.

Flow Cytometry

Before using these cells in the animals, viability and immunophenotyping of ASC were analyzed by flow cytometry. Briefly, cells were incubated with the antibodies: anti-CD90, anti-CD31 and anti-CD45 conjugated with phycoerythrin (PE) (Abcam, Cambridge, Mass.), for 1 hour at room temperature. The analysis was performed in a Guava flow cytometer (Merck Millipore, Billerica, Mass.). Ten thousand cells per sample were evaluated. Histograms were obtained by EasyCyte Software (Merck Millipore, Billerica, Mass.). Results were expressed as the percentage of labeled cells among all analyzed events. Therefore, more than 97% of cells were positive for CD90, and negative for CD31 and CD45, as shown in Figure 1.

Surgical Procedure

All the animals were anesthetized by an intraperitoneal injection of the association of ketamine hydrochloride (Ketamin, Cristália, Brazil) 100 mg per kg and 5 mg per kg xylazine hydrochloride (Rompun, Bayer, Brazil).

They were placed in dorsal decubitus, and an area of 10 × 6 cm in the back of the animal was trichotomized. All animals were submitted to a mini-prosthesis (2 cm^3; silicone gel) implant in the dorsal region.

Antisepsis was done by topic chlorhexidine 0.5%. A horizontal incision (3 cm) was performed, and an area of 4 cm × 3 cm of subpanniculus carnosun pocket was dissected for mini silicone prosthesis (2cc, Mentor, Johnson & Johnson, New Brunswick, N.J.) inclusion. The incision was sutured (Fig. 2) with interrupted sutures using 4-0 mononylon (Ethicon, Inc., Somerville, N.J.).

Then, the animals were divided into three groups. Control group: no treatment; RDT group: culture medium injection in the prosthesis-surrounding tissues after RDT; ASC + RDT group: injection of 1×10^6 ASC in the prosthesis-surrounding tissues. After this injection, all incisions were closed with interrupted sutures using 4-0 mono nylon (Ethicon, Inc., Somerville, N.J.).

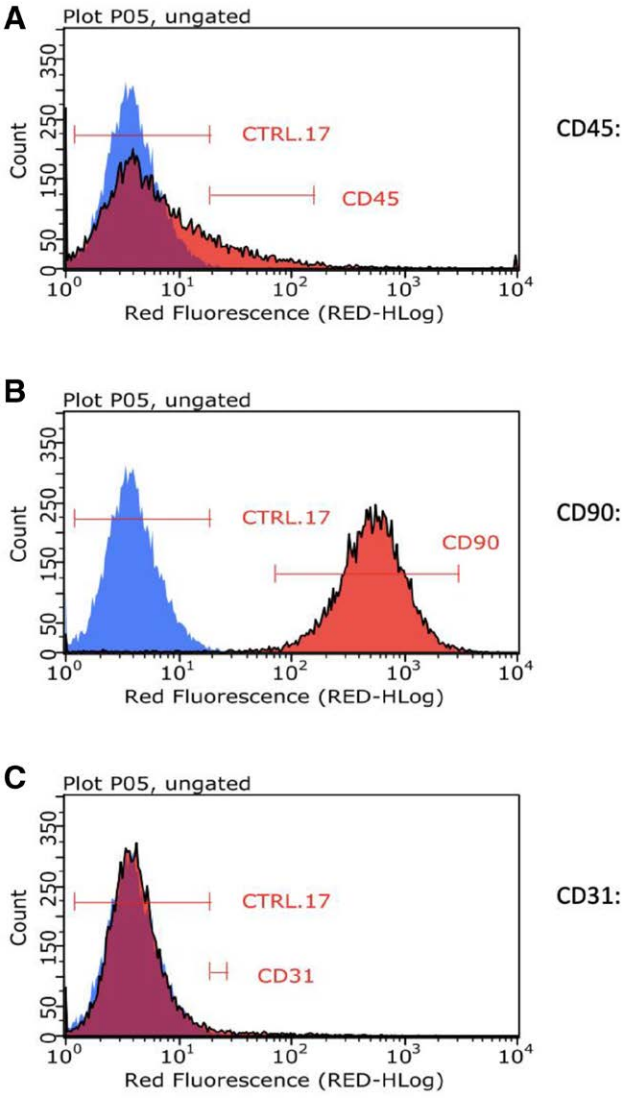

Fig. 1. ASC immunophenotyping by flow cytometry. Representative histograms displaying labeled cells with (B) anti-CD90-PE (red peak). Cells were negative for (A) anti-CD45-PE and (C) anti-CD31-PE. Negative control: cells incubated with the secondary conjugated-antibody (blue peak; 10,000 events)

Radiotherapy Procedure

Immediately after the surgical procedure, the animals allocated to RDT were submitted to one RDT session: 10 Gy dosage, 6 MeV electrons, with 10 mm "bolus" (Varian 2100 CD ou Varian Clinac iX).[8] After 3 months, all the animals were euthanized, and samples were collected from the prosthesis capsule.

Macroscopic Analysis

During the experimental study period, we analyzed if RDT caused radiodermatitis in the dorsal region. Then, the animal dorsal skin was analyzed according to RTOG scale.[17] Grade 1 = normal appearance; grade 1.5 = minimal erythema; grade 2 = moderate erythema; grade 2.5 = erythema associated with dry flaking; grade 3 = erythema associated with confluent dry desquamation; grade 3.5 = confluent dry flaking, crusts; grade 4 = moist flaking, moderate scabs; grade 4.5 = wet peeling, small ulcers; grade 5 = large ulcers; and grade 5.5 = necrosis. A five-point scale was adopted to categorize the contracture (0: no change, 1: mild deformity, 2: moderate deformity, 3: severe deformity, 4: extrusion of the prosthesis).

Microscopic Analysis

At the end of the experiment we collected the implant capsule tissue. All samples were fixed in 4% formalin for 24 hours embedded in paraffin for hematoxylin-eosin (H&E) staining and Picrius Sirius, under 20 and 40× magnification using optical microscopy (Nikon eclipse E600, Japan). Analysis and quantification of all histological structures were performed in 10 fields per slide. The endpoints analyzed by H&E staining were vascular density (angiogenesis), inflammatory cell presence (number of the polymorphonuclear cells), and fibrosis (4: point scale; 0 = no fibrosis, 1: mild fibrosis, 2: moderate fibrosis, 3: severe fibrosis). By Picrosirius staining, the collagen fiber distribution and density (graphic distribution structure) were analyzed. A blinded investigator analyzed all the samples.

Gene Expression Analysis

Tissues stabilized in RNAlater (30 mg) were used for total RNA extraction using the RNeasy Mini Kit (Qiagen).

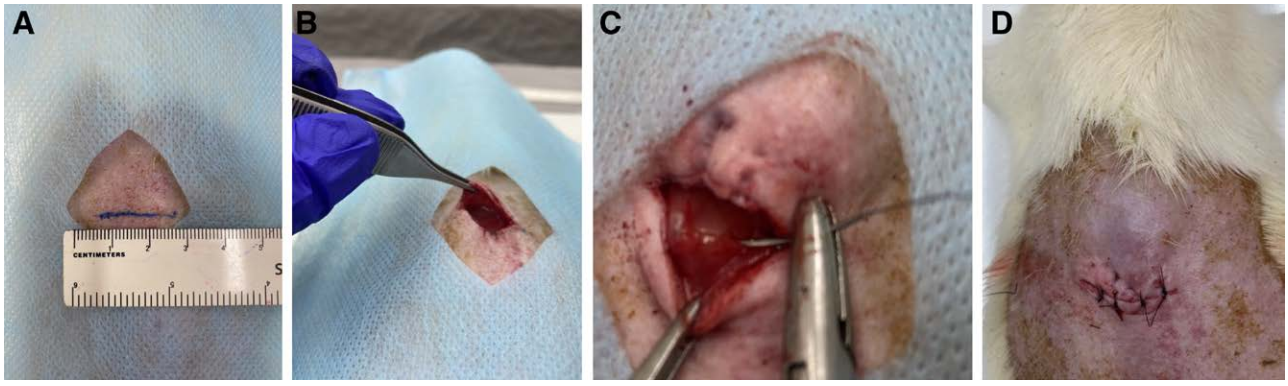

Fig. 2. Surgical procedure. A, 2-cm incision. B, Suprafascial plane to silicone implant. C, Mononylon 4-0 in each quadrant to prevent prosthesis dislocation during RDT. D, Incision in two planes to prevent prosthesis extrusion.

The tissues were disrupted using the TissueLyser LT apparatus (Qiagen). To avoid DNA contamination during the extraction, TRIzol Reagent (Thermo Fisher Scientific) was used in place of the RLT reagent from the RNeasy Mini Kit, according to the manufacturer's instructions. One milliliter of TRIzol Reagent (Thermo Fisher Scientific) and stainless-steel beads were added to the microcentrifuge tubes. Tissue disruption was carried out for 5 minutes at 50 Hz. After removing the beads, 0.2 mL of chloroform (Sigma Aldrich) was added. After homogenization in the vortex for 15 seconds, samples were incubated for 3 minutes at room temperature, followed by centrifugation at 12,000*g* for 15 minutes at 4 °C. The upper aqueous phase was transferred to a 1.5-mL tube and added a 1:1 volume of 70% ethanol, homogenized by vigorous pipetting. A volume of 0.7 mL of prepared sample, including any type of precipitate, was transferred to an RNeasy kit column. From this stage on, extraction was carried out following the kit manufacturer's recommendations. RNA purity (evaluated through the ratios 260/280 and 260/230) and integrity were determined by spectrophotometry (NanoDrop 1000 Spectrophotometer, Thermo Fisher Scientific) and gel electrophoresis, respectively. RNA samples were stored at −80 °C until use.

For the quantitative reverse transcription polymerase chain reaction (qRT-PCR), total RNA was reverse transcribed to cDNA using the High-Capacity RNA-to-cDNA Kit (Thermo Fisher Scientific) as recommended by the manufacturer. The expression levels of *Cd68* (Rn01495634_g1), *Il10* (Rn01483988_g1), *Il1rap* (Rn01404183_m1), *Mmp3* (Rn01495634_g1), *Mmp9* (Rn00579162_m1), and *Tnf* (Rn01525859_g1) genes were quantified using TaqMan methodology (Thermo Fisher Scientific) in the StepOnePlus Real-Time PCR system (Thermo Fisher Scientific), using the default cycling conditions recommended by the manufacturer. Each sample was run in duplicate, and the *Gapdh* (Rn01775763_g1) and *Actb* (Rn00667869_m1) genes were used as endogenous controls. Fold change was calculated using the comparative CT method ($2^{-\Delta\Delta CT}$).

Statistical Analysis

Because of the small sample size, the three groups' variables were compared using the Kruskal-Wallis test (parametric test). When significant, a post hoc test (Dunn test) was performed within alpha of 0.05. Statistical software STATA version 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, Tex.: StataCorp LP) was used for calculation. For the gene expression analysis, SPSS v.25 software was used. The Kruskal-Wallis test (nonparametric test) was used to analyze the differences in gene expression levels among the three groups. When the results were significant, a Bonferroni-corrected Mann-Whitney U test was performed considering *P* values less than 0.05/3 as significant.

RESULTS

Macroscopic Analysis

There were no serious adverse events (death or prosthesis extrusion). The RTOG scale of the skin over the capsule varied according to the group: four for the control group and two for the ASC+RDT group. Comparing all the groups, the ASC group showed the lesser value for RTOG scale versus the control group (2 versus 4, $P < 0.001$), and versus RDT group (2 versus 3.5, $P = 0.003$)

Table 1. Microscopic Analysis of Vascular Density, Inflammatory Cell Count, and Fibrosis by Groups

Groups	Vascular Density (Median IIQ)	Inflammatory Cells (Median IIQ)	Fibrosis (Median IIQ)
Control	17.0 (12–25)	73.5 (58–91)	+
RDT	11.5 (8–20)	182 (89–201)	++++
ASC+ RDT	16.5 (14–20)	74.5 (53–89)	++

IIQ, interquartile range.

Microscopic Analysis

Regarding vascular density, there was no difference among the groups ($P = 0.3468$).

This study showed a difference in the inflammatory cell count ($P = 0.012$). In a pairwise comparison, the ASC+RDT group showed a similar cell count to the control group. When comparing the ASC+RDT and RDT group, ASC treatment reduced the inflammatory cell count in 50%. There was a difference between the control group versus the RDT group (73.5 versus 182, $P = 0.008$, respectively), and the RDT group versus the ASC group (182 versus 74.5, $P = 0.004$, respectively; Table 1). Regarding fibrosis, the RDT group showed a higher rate of fibrosis, when compared with the control and ASC+RDT groups (Fig. 3; Table 1).

Analysis of Gene Expression

This study showed that the *Il1rap* gene expression was similar in the RDT and ASC groups. Compared with the control group, the treatment with ASC reduced 30% of *Il1rap*. We detected differences in *Il1rap* gene expression level among the three groups ($P = 0.04$), but Bonferroni correction did not show differences. This study could not find significant differences between the *Il10, Tnf, Cd68,* and *Mmp3, Mmp9* levels among the groups (Table 2).

DISCUSSION

This study aimed to analyze the mechanism of action ASC treatment in silicone implants submitted to RDT. We hypothesized that the ASC treatment could decrease the local inflammatory response induced by RDT.

Therefore, in this study, animals submitted to silicone protheses implant and RDT in the group treated with ASC showed less skin radiodermatitis than the other groups. Furthermore, the general aspect of silicone capsules was two points in the control group, four points in the RDT group, and three points in the ASC+RDT group. Similarly, Oksuz et al analyzed the effect of mesenchymal cells (bone-marrow stem cells) using a model with animals submitted to RDT. According to the Oksuz study, the skin and capsule showed less fibrosis in the RDT group without any treatment.[18]

Our microscopic assessment revealed comparable vascular density in all groups, although several other

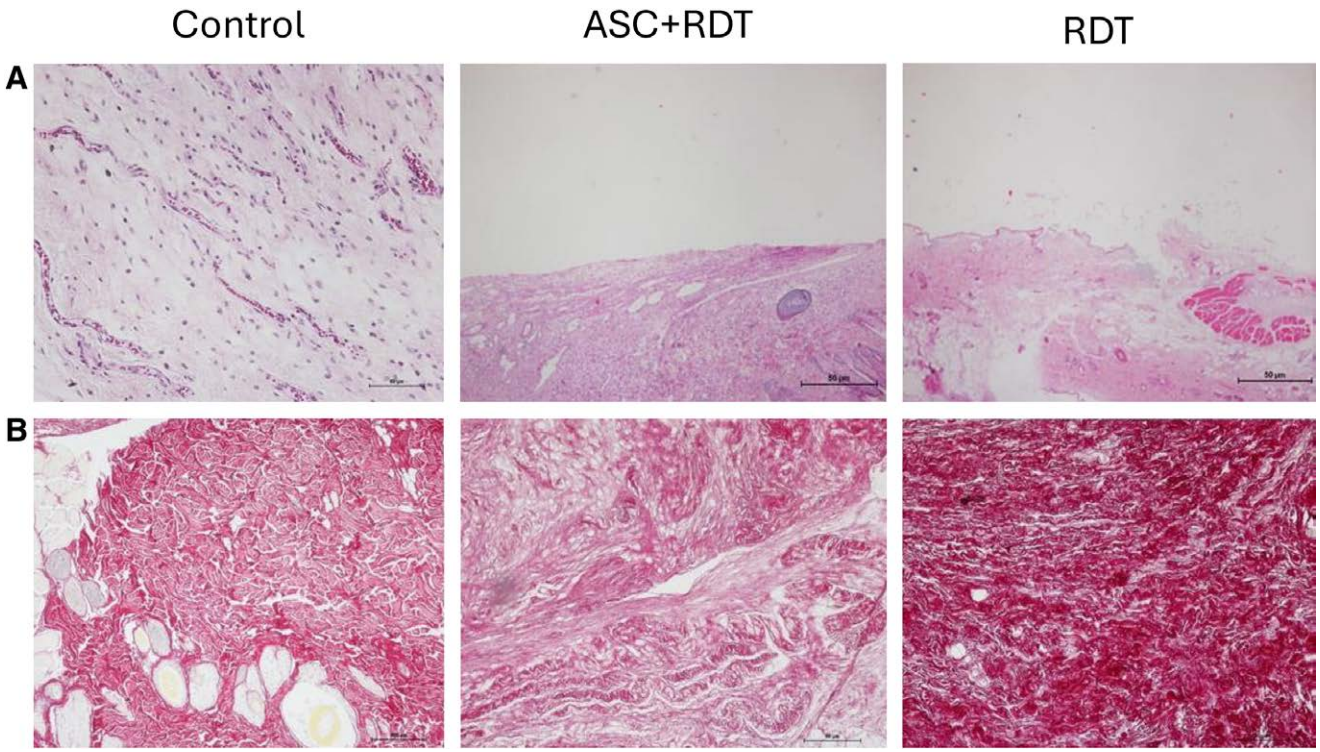

Fig. 3. Histological analysis. A, H&E staining of prosthesis capsule. Control and ASC+RDT showed an increase in neoangiogeneses; the RDT group showed a hyaline structure substantial in the extracellular matrix. B, Picrosirius staining of prosthesis capsule.

Table 2. Analysis of Gene Expression by Group (n = 4 per Group)

Gene	Control Group Mean (SD)	RDT Group Mean (SD)	ASC+RDT Group Mean (SD)	*P*
CD68	1.01 (0.15)	0.60 (0.29)	0.96 (0.59)	0.29
IL-10	1.02 (0.23)	0.85 (0.35)	0.91 (0.44)	0.78
IL-1rap	1.00 (0.08)	0.70 (0.11)	0.70 (0.11)	0.04*
TNF	1.10 (0.54)	0.60 (0.39)	0.92 (0.42)	0.35
MMP-3	1.45 (1.14)	1.14 (0.70)	1.40 (0.94)	0.79
MMP-9	1.42 (1.38)	2.15 (2.74)	2.15 (1.69)	0.74

ASC, adipocyte stem-cells; SD: standard deviation; RTD: radiotherapy. Control group was used as the reference group in this analysis.
*$P < 0.05$.

studies have reported an increase in vascular density. One possible explanation for our finding could be that ASC treatment could differentiate in endothelial cells and secrete endothelial growth factors in wound healing.[19,20]

Li et al published a literature review on the effect of ASC on breast reconstruction. The authors did not mention the time of vascular augmentation.[19] Given the differences in the biological metabolism between rats and humans, a long-term follow-up could explain the absence of increased vascularization in our study.

Our study also showed a lower inflammatory cell count in the control and ASC-treated groups. Our hypothesis is that ASC can modulate the inflammatory response to RDT in a less provocative scenario. The secretome itself could balance the inflammatory and antiinflammatory environment; therefore, ASC treatment could stimulate wound regeneration in a long-term process.[20,21]

This study showed a comparable *Il1rap* gene expression level for the RDT and ASC groups compared with the control group, the treatment of ASC reduced *Il1rap* in 30%. Janko et al[22] analyzed radiodermatitis induction in rodents and showed that the interleukin-1 (IL-1) pathway plays a significant role in the development of radiodermatitis. The decrease in IL-1 caused less inflammation and less severe pathological changes in the skin.

Although we were not able to find a significant difference, *IL-10, CD-68, TNF,* and *MMP-3* levels showed similar results in the control and ASC groups. Conversely, some studies have shown an increase in macrophage expression after RDT, but our study found a decrease in *CD68* expression in the RTD group.[7,23,24]

Aside from a few discrepancies, this study found that ASC treatment is associated with reducing the severity of radiodermatitis (macroscopic and histologic

analysis). Indeed, literature data have shown a benefit and safety profile when using stem cells in breast reconstruction.[24,25]

Based on our findings, there is a benefit to the injection of ASC in the silicone implant procedure. Although RDT can cause cell damage, this study showed the benefit of ASC therapy before RDT. According to our research, no study analyzed the effect of ASC injection in silicone implant surgery preradiotherapy.

This study had some limitations. The size of the sample was small, and the study design was based on an animal model (rodents). However, the data address a potential benefit of the biological behavior of ASC in preventing silicone encapsulation. This is the first study in our laboratory to analyze the potential mechanism of action of ASC treatment for RDT. In the next studies we will select more genes and proteins to analyze it.

In conclusion, this study suggests that ASC injection before RDT decreases silicone prosthesis capsule inflammation.

Cristina Pires Camargo, PhD
Microsurgery and plastic surgery laboratory
School of Medicine, Universidade de São Paulo
Av. Dr. Arnaldo 455, 2° floor, Room 2145—Cerqueira César.
São Paulo, SP 01246-903, Brazil
E-mail: cristinacamargo@usp.br

DISCLOSURES

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