Cell-Mediated Immune Responses May Play Roles in Osteochondral Allograft Transplantation Osteointegration Failures

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Abstract

Prolonged and incomplete osteochondral allograft (OCA) osteointegration is consistently cited as a major mechanism for OCA treatment failure. Subrejection immune responses may play roles in this mode of failure. Preimplantation OCA preparation techniques, including subchondral bone drilling, thorough irrigation, and autogenous bone marrow aspirate concentrate saturation, may dampen immune responses and improve OCA osteointegration. This study sought to further characterize potential immune system contributions to OCA transplantation treatment failures by analyzing donor–recipient ABO and Rh-factor mismatches and histological and immunohistochemical assessments of transplanted OCA tissues recovered from revision surgeries. Using a dedicated registry, OCA transplant recipients with documented treatment failures who met inclusion criteria ($n = 33$) as well as age-, body mass index-, and joint-matched patients with successful outcomes ($n = 70$) were analyzed to compare matched cohorts of patients with successful versus failed OCA transplantation outcomes. Tissues recovered from 18 failed OCA transplants and portions of 7 non-implanted OCA controls were further analyzed to provide contributing evidence for potential immune response mechanisms. For patients analyzed, no statistically significant differences in proportions for treatment success versus failure based on mismatches for ABO type, Rh factor, or both were noted. Further, no statistically significant differences in proportions for histological immune response presence or absence based on mismatches for ABO type, Rh factor, or both were noted. Twelve (67%) of the failed OCA tissues contained lymphocyte aggregations in the subchondral bone, which were comprised of combinations of CD3+, CD4+, CD8+, and CD20+

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lymphocytes. The mechanisms of failure for these 12 OCA transplants involved insufficient OCA osteointegration. Results of this study suggest that T- and B-cell-mediated subrejection immune responses may play roles in OCA transplant treatment failures independent of donor–recipient blood type mismatch effects.

Fresh osteochondral allograft (OCA) transplantation is a treatment option for large articular cartilage lesions, particularly in young, active patients who may not be ideal candidates for nonsurgical treatments or arthroplasty.[1] When successful, OCA transplantation can relieve pain and restore joint function in patients with symptomatic articular defects in the knee, hip, ankle, and shoulder.[2–9] Currently, most OCA transplantations are performed to treat large ($>2\,cm^2$), full-thickness symptomatic chondral or osteochondral lesions in the knee. While recent technological advances have been associated with increased OCA availability and improved clinical success, the best current evidence supports 5- to 15-year functional OCA survival rates of 68 to 75%.[2–20] As such, all components of OCA transplantation need to be further optimized to improve patient outcomes and meet the increasing clinical demand for this important treatment option for the growing number of patients affected by these complex joint problems.

Recognized factors contributing to functional graft survival after OCA transplantation include OCA-related factors (storage time, preservation methods, chondrocyte viability at the time of implantation, and preimplantation preparation and surgical techniques) and recipient-related variables (age, sex, body mass index [BMI], nicotine use, joint pathology, and patient adherence with prescribed postoperative restrictions and rehabilitation protocols) that influence cartilage integrity, rate and extent of allograft osteointegration, and joint health.[2–20] With recent advances in tissue preservation, transplantation techniques, and patient management tools and strategies that have reportedly mitigated related modes of failure, prolonged and incomplete OCA osteointegration has become a primary mechanism for OCA treatment failure.[18–22] Preimplantation OCA preparation techniques, including subchondral bone drilling, thorough irrigation, and autogenous bone marrow aspirate concentrate saturation, may dampen immune responses and improve OCA osteointegration.[11,14,18,19] Still, insufficient OCA osteointegration remains a significant cause of treatment failure, and studies suggest that recipient immunological responses may influence the process of creeping substitution and contribute to undesirable outcomes.[21–36]

Unlike other forms of allogeneic transplantation, fresh OCAs are considered "immunoprivileged" such that human leukocyte antigen or ABO blood group donor–recipient matching is not required for transplantation.[22–36] Further, OCA transplant patients receive no immunosuppressive medications. This approach has proven safe and effective based on the lack of immediate graft rejection responses and the documented functional graft survival rates. However, short-term treatment failures still occur, which suggests that immune system processes other than those associated with rejection, or "subrejection responses," may directly or indirectly influence OCA transplantation outcomes.[22] These responses and their impacts on OCA transplantation treatment failures have not been fully characterized. This gap in knowledge poses a limitation to further optimization of OCA transplantation outcomes. Therefore, the objective of this study was to further characterize the potential immune system contributions to OCA transplantation treatment failures by analyzing donor–recipient ABO and Rh-factor mismatches as well as histological and immunohistochemical assessments of transplanted OCA tissues recovered from revision surgeries. The study was designed to test the hypothesis that treatment failures would be associated with lymphocyte phenotype profiles, potentially associated with cell-mediated subrejection immune responses independent from donor–recipient blood type mismatches.

Methods

With institutional review board (IRB) approval and documented informed consent, a defined subset of age-, BMI-, and joint-matched OCA transplant recipients enrolled in our institution's lifelong OCA patient outcomes registry such that there was a 2:1 ratio of successful versus failed outcomes was analyzed. Cases performed by one of four surgeons were included based on the following criteria:

- Complete donor and recipient ABO and Rh factor data were available. (Donor blood type data were obtained from American Association of Tissue Banks [AATB]-accredited tissue banks [MTF Biologics, Joint Restoration Foundation, RTI Donor Services], and recipient blood type data were retrieved from the patient's electronic medical records.)
- OCA transplantation was performed according to our institution's standard of care for preimplantation preparation, transplantation techniques, and prescribed postoperative management, as previously described.[18,19]
- Treatment failure data were documented. (Patients who required OCA revision surgery or artificial arthroplasty at any time point were defined as treatment failures. A successful outcome was defined as the documented absence of any revision or arthroplasty surgery for a minimum of 2 years following the index OCA transplantation surgery.)

Cases not fulfilling all of the inclusion criteria for this analysis were excluded.

Osteochondral Allograft Tissue Recovery

With IRB approval and documented informed consent, resected osteochondral tissues that would otherwise be discarded after standard-of-care revision surgeries to treat OCA treatment failures in the knee were recovered from patients. For controls, osteochondral tissues from unused portions of allografts that would otherwise be discarded after standard-of-care OCA transplantation surgeries were recovered, processed, and analyzed in the same ways as resected tissues.

Histological Assessments

Sections of OCA tissues were fixed in 10% neutral-buffered formalin for 1 week and then placed in 10% ethylenediaminetetraacetic decalcifying solution until the bone was suitable for sectioning (~3 weeks). After decalcification, specimens were routinely processed, sectioned (5 µm), and stained with hematoxylin and eosin (H&E). Subjective histological assessments were performed on H&E-stained, and toluidine blue-stained sections by a pathologist blinded to patient demographics, outcomes data, and tissue source. Histological immune response was defined by the aggregation of lymphocytes and plasma cells surrounding small blood vessels in the OCA subchondral bone and neighboring soft tissues. OCA tissues with evidence for this immune response were then processed for immunohistochemical assessments.

Immunohistochemistry

Antigen markers CD3, CD4, CD8, and CD20 were chosen to characterize lymphocytes (T-cell marker, cytotoxic T-lymphocytes, and B-cell marker, respectively) to provide a broad view of immune cell populations and allow for subjective assessment of relevant immune cell mechanisms. Paraffin-embedded specimens were deparaffinized, rehydrated, and quenched of endogenous peroxidase. Antigen retrieval was performed with Diva Decloaker 10X (CD3, CD4, and CD8) or Borg Decloaker 1X (CD20). Background Sniper was applied, and primary antibodies were incubated: CD3 (Dako rabbit polyclonal; 1:150 dilution) for 45 minutes, CD4 (Abcam rabbit monoclonal; 1:750 dilution) for 30 minutes, CD8 (Life-Span BioSciences mouse monoclonal; 1:1000 dilution) for 30 minutes, and CD20 (Laboratory Vision rabbit polyclonal; 1:300 dilution) for 40 minutes, all at room temperature. To confirm cross-reactivity, appropriate positive controls were included in each immunostaining protocol with human lymph node and tonsil tissue. Conjugated goat anti-mouse secondary antibody (MACH 2 Universal HRP-Polymer Detection; CD8) or conjugated goat anti-rabbit secondary antibody (Dako EnVision+ System- HRP; CD3, CD4, and CD20) and Romulin AEC Red Chromogen were used for detection of primary antibodies, and sections were counterstained with CT hematoxylin. Immunohistochemistry staining for NCR-1/NKP46 (natural killer cells) was attempted with multiple different primary antibodies. Either no to minimal staining or nonspecific staining was detected in control and experimental tissues; therefore, the results were excluded from this study.

Statistical Analysis

A subset of age-, BMI-, and joint-matched OCA transplant recipients were defined from the registry enrollees such that there was a 2:1 ratio of documented successful versus failed outcomes for analyses based on the case–control-matched experimental design. R for Statistical Computing software was used for all statistical analyses. Descriptive statistics were calculated to determine means, medians, ranges, and percentages. All case–control comparisons were made using the Fisher's exact tests to assess for significant differences in proportions. When significant differences in proportions were noted, odds ratios were calculated. A p-value of ≤ 0.05 was used to define statistical significance.

Results

Study Population and Osteochondral Allograft Tissue Recovery

A subset of registry patients meeting all inclusion criteria was selected from 414 OCA transplant recipients enrolled at the time of study initiation (►**Fig. 1**; ►**Table 1**). All treatment failures meeting inclusion criteria were first identified, which yielded 33 patients (15 female; mean age = 38.1, range = 16–60 years; mean BMI = 28.8, range = 18–37 kg/m^2; 30 knees, 2 hips, 1 ankle). Then, an age-, BMI-, and joint-matched cohort with documented successful outcomes and meeting inclusion criteria were identified, which yielded 70 patients, for a total of 103 patients (45 female; mean age = 36.9, range = 16–60 years; mean BMI = 27.5, range = 17–37 kg/m^2; 96 knees, 4 hips, 3 ankles) included for analyses. Of the 33 treatment failures, adequate OCA tissues were recovered from 18 patients for immune response assessments. Portions of seven OCAs not used during standard-of-care transplant surgeries were recovered as controls.

Treatment failure mechanisms were attributed to allograft bone necrosis and/or collapse ($n = 14$, 42.4%), damage to new nontransplanted areas in the knee ($n = 10$, 30.3%), meniscus tear and/or extrusion ($n = 8$, 24.2%), or unknown reasons ($n = 1$, 3.0%). Treatment failures occurred at a mean and median of 26.2 and 23 months after primary OCA transplantation, respectively, with a range of 7 to 56 months.

Blood Type Matching

No statistically significant differences in proportions for treatment success ($n = 70$) versus failure ($n = 33$) based on mismatches for ABO type ($n = 73$), Rh factor ($n = 30$), or both ($n = 85$) were noted (►**Table 2**). No statistically significant differences in proportions for histological immune response presence or absence based on mismatches for ABO type ($n = 10$), Rh factor ($n = 2$), or both ($n = 10$) were noted (►**Table 3**).

Histological Assessments

No control OCA tissues were noted to include lymphocyte aggregations in the subchondral bone or neighboring soft tissues (►**Fig. 2A**), whereas 12 (67%) of the failed OCA tissues contained lymphocyte aggregations in the subchondral bone, suggestive of a cell-mediated immune response

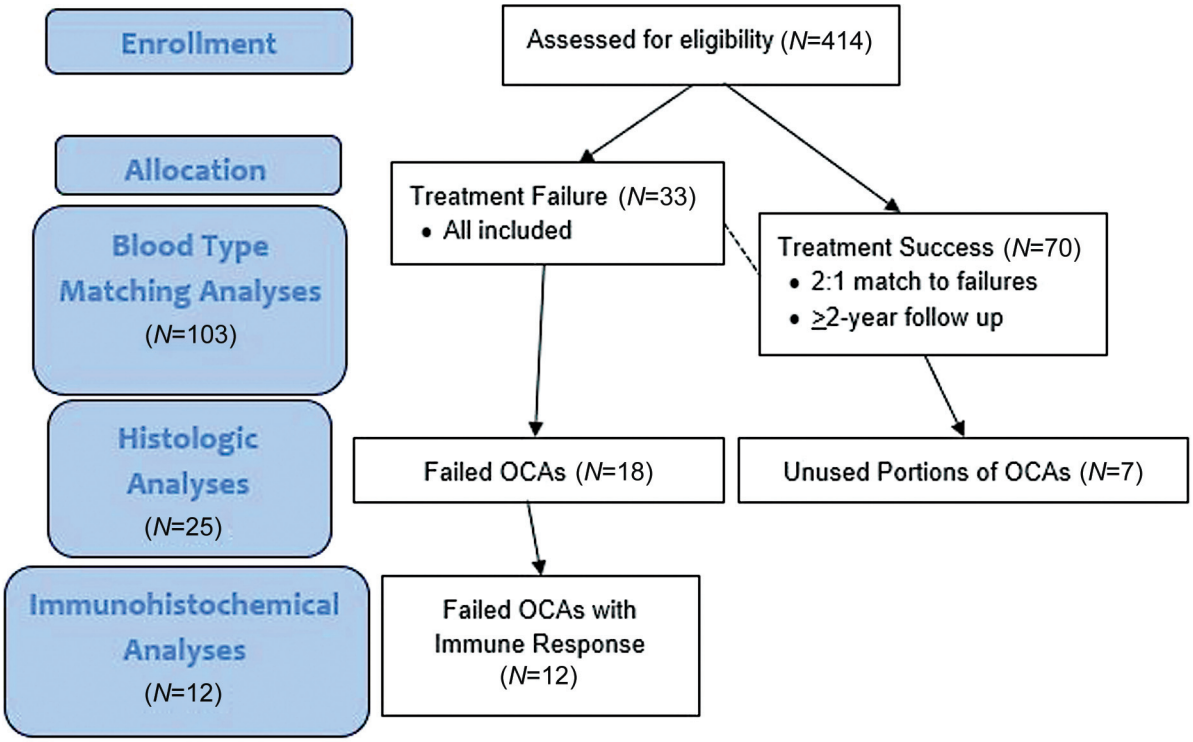

Fig. 1 CONSORT flow chart for study population and tissue recovery allocation and analyses. OCA, osteochondral allograft.

(►**Fig. 2B**). Interestingly, the mechanisms of failure for each of these 12 tissues involved insufficient OCA osteointegration, characterized by subchondral bone fracture, collapse, subsidence, and/or necrosis, whereas only 2 of the "no immune response" OCAs failed by these mechanisms.

Immunohistochemical Assessments

For the 12 OCA tissues histologically defined to have a cell-mediated immune response and further characterized immunohistochemically, combinations of CD3+, CD4+, CD8+, and CD20+ lymphocytes comprised the perivascular aggregations in each case (►**Fig. 3**).

Discussion

The results of this study suggest that cell-mediated subrejection immune responses may play roles in some mechanisms of treatment failure after OCA transplant surgeries.

Table 1 Key variables assessed for osteochondral allograft transplantation cases in treatment success and treatment failure matched cohorts

Variable	Treatment success ($N = 70$)	Treatment failure ($N = 33$)
Age, y, mean, range	36.9, 18–58	38.1, 16–60
Sex, *N* (%), female	30 (42.9)	15 (45.5)
BMI, kg/m^2, mean, range	27.5, 17–35	28.8, 18–37
Previous surgeries, mean, range	2.8, 1–11	2.9, 1–9
OCAT type, N-joint, technique	66 knees (27 plug, 39 shell) 2 hips (1 plug, 1 shell) 2 ankles (2 shell)	30 knees (13 plug, 17 shell) 2 hips (1 plug, 1 shell) 1 ankle (1 shell)
Concomitant procedures, N-type	5 ligament recon 18 osteotomy	4 ligament recon 8 osteotomy
Follow-up duration, mo, mean, range	49.1, 24–70	26.2, 7–56

Abbreviations: BMI, body mass index; OCAT, osteochondral allograft transplantation.
Notes: plug = cylindrical osteochondral allografts press-fit into sockets; shell = patient-specific custom-cut osteochondral allografts stabilized in custom-cut recipient beds using screws, pins, or nails; concomitant procedures = autograft or allograft ligament reconstruction(s) for ligament-related instability in the affected knee and/or distal femoral osteotomy, high tibial osteotomy, or tibial tuberosity osteotomy in ipsilateral lower extremity for malalignment or maltracking; follow-up duration = the time point for which functional graft survival or nonsurvival was documented for each included case.

Table 2 Proportions of treatment successes and failures for osteochondral allograft transplant patients based on Rh-factor and ABO blood type matching

Rh Fisher's exact—failure			
Rh	Success	Failure	*p*-Value = 0.352
Same	52	21	
Opposite	18	12	
ABO Fisher's exact—failure			
ABO	Success	Failure	*p*-Value = 0.821
Same	21	9	
Different	49	24	
ABO and Rh Fisher's exact—failure			
ABO and Rh	Success	Failure	*p*-Value = 0.412
Same	14	4	
Different	56	29	

Table 3 Proportions of histologic immune responses for failed osteochondral allograft transplants based on Rh-factor and ABO blood type matching

Rh Fisher's exact—immune response			
Rh	Success	Failure	*p*-Value = 1
Same	5	11	
Opposite	1	1	
ABO Fisher's exact—immune response			
ABO	Success	Failure	*p*-Value = 0.312
Same	4	4	
Different	2	8	
ABO and Rh Fisher's exact—immune response			
ABO and Rh	Success	Failure	*p*-Value = 0.312
Same	4	4	
Different	2	8	

Interestingly, OCA transplant treatment failures and cell-mediated immune responses in failed OCAs could not be attributed to ABO blood type or Rh-factor mismatches. Immune responses in OCA subchondral bone recovered from failed transplants were consistently characterized by perivascular lymphocyte aggregations comprised of CD3+, CD4+, CD8+, and CD20+ phenotypes. Interestingly, the mechanisms of failure for OCA transplants with these cell-mediated immune responses involved insufficient osteointegration, characterized by subchondral bone fracture, collapse, subsidence, and/or necrosis. Considering the results, these data support the possibility that mixed-aggregate T- and B-cell infiltrates directly or indirectly prohibit timely and complete OCA osteointegration, posing a threat to the functional survival of the transplanted tissues. Based on the lack of association with blood type mismatches and the nature and location of the lymphocyte aggregates, remaining donor bone marrow elements are the most likely culprits for initiating this subrejection immune response.

Previous studies have also suggested the potential for subrejection immune responses contributing to OCA failures.[24–32] Humoral and cell-mediated immune responses to osteochondral, cortical, and corticocancellous allograft bone have been documented in preclinical and clinical studies. These responses and related outcomes have been attributed to graft type and volume, blood type mismatches, and sex mismatches.[22,24–34] In the present study, only fresh OCAs were considered, humoral immune responses were not assessed, and graft volume and donor–recipient sex were not analyzed as variables. Therefore, these initial results are limited to characterizing localized cell-mediated immune responses in failed OCAs. Based on these data, blood type mismatching was not considered a primary culprit for inciting subrejection immune responses associated with treatment failures. While intact hyaline cartilage is well documented to be immunoprivileged and OCA bone is not expected to contain viable cells, donor cell debris and proteins are immunogenic.[23–36] As such, the study results point to residual donor bone marrow elements as a potential stimulus for mixed T- and B-cell aggregations in the subchondral bone of OCAs recovered from revision and arthroplasty surgeries for failed transplants (see ►**Tables 1**–**3** and ►**Figs. 1**–**3**).

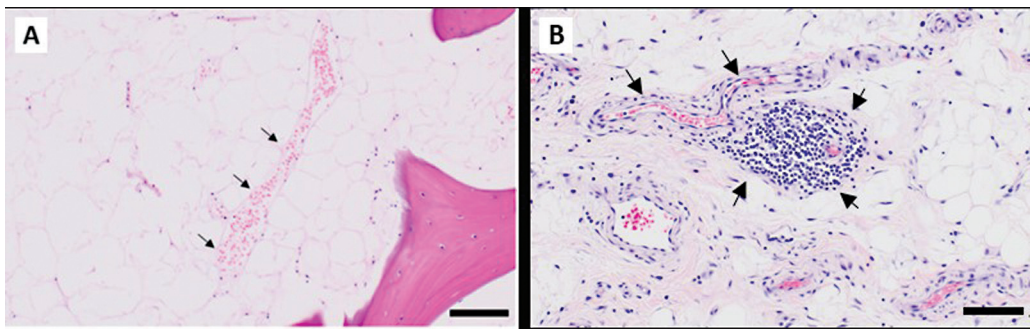

Fig. 2 Tissues from osteochondral allograft (OCA) revision surgeries were stained with hematoxylin and eosin (H&E) to identify immune reactions of interest. (**A**) Healthy tibial plateau OCA used as a negative control. (**B**) Failed tibial plateau OCA (inclusion criteria): lymphocyte aggregation around blood vessels. (Black arrows indicate blood vessel, scale = 100 µm).

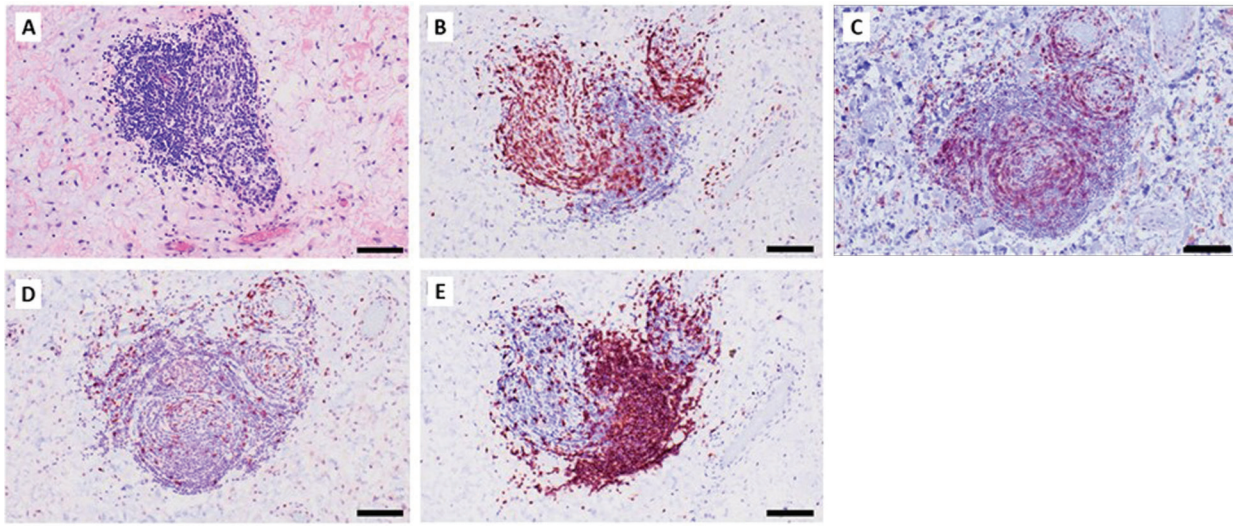

Fig. 3 Observed aggregation of lymphocytes around small blood vessels in a failed hip osteochondral allograft. (**A**) Hematoxylin and eosin (H&E) [aggregate of blue cells: lymphocytes], (**B**) CD3+ [red: positive staining; blue: counterstain], (**C**) CD4+ [red: positive staining; blue: counterstain], (**D**) CD8+ [red: positive staining; blue: counterstain], and (**E**) CD20+ [red: positive staining; blue: counterstain] stained lymphocytes. [scale = 100 µm].

In this study, mechanisms of failure for the OCAs noted to be associated with cell-mediated immune responses involved insufficient OCA osteointegration, whereas the majority of the unsuccessful OCAs with no noted immune responses failed by other mechanisms. Insufficient OCA osteointegration is characterized by subchondral bone fracture, collapse, subsidence, and/or necrosis, all of which can be influenced by cell-mediated immune responses. Successful OCA integration requires an intricate balance between degradative and regenerative immune responses during the process of creeping substitution. The immunogenic potential of OCA bone marrow elements may trigger responses that favor degradative mechanisms, regulated by cytotoxic T-cells, weakening the subchondral bone of the graft and subjugating the OCA to biomechanical failure. Cycles of continuous exposure to OCA marrow elements during bone turnover may stimulate prolonged proinflammatory responses capable of deterring adequate responses for regeneration.

Limitations of this study should be considered when interpreting and applying the data. The study population comprised a relatively small number of patients selected from a single institution's OCA transplantation registry to include all documented treatment failures with complete blood type and outcomes data matched 1:2 with patients documented to have successful outcomes. As such, selection bias is likely, type II statistical errors are possible, and the results are not generalizable. Further selection bias is likely with respect to the limited number of adequate OCA tissues available for assessment. In addition, immune response characterizations were subjective, and only nonimplanted OCA controls could be included based on ethical considerations for human subjects research that makes recovery of transplanted OCAs from patients with successful outcomes unfeasible. Finally, only short-term outcomes were evaluated, and patient, surgical, and biomechanical mechanisms for failure were not considered in this study. From these data, only potential associations and possible mechanisms related to localized cell-mediated subrejection immune responses can be used for further research aimed at preventing OCA osteointegration failure toward optimizing outcomes for patients undergoing OCA transplantation.

Conclusion

The results of this study suggest that T- and B-cell-mediated subrejection immune responses may play roles in OCA transplant treatment failures independent of donor–recipient blood type mismatch effects. Residual donor bone marrow elements are a potential stimulus for these immune responses, which were associated with OCAs that failed due to insufficient osteointegration.

Author Contributions

J.P.S. and J.L.C.: formal analysis; A.M.S., E.T., and J.L.C.; investigation: J.L., C.C.B., J.W., A.M.S., and E.T.; methodology: E.T. and J.L.C.; project administration: C.C.B. and A.M.S.; resources: A.M.S.; supervision: A.M.S. and J.L.C.; writing—original draft: J.L., C.C.B., J.W., A.M.S., J.P.S., E.T., and J.L.C.; writing—review and editing: J.L.C. All authors have read and approved the final submitted manuscript.

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Conflict of Interest

A.M.S. receives IP royalties from Musculoskeletal Transplant Foundation.

J.P.S. is a paid consultant and receives research support from Arthrex, Inc; is a paid consultant for DePuy, A

Johnson & Johnson Company; is on the editorial or governing board for the Journal of Knee Surgery; receives research support from National Institutes of Health (NIAMS & NICHD); is a paid consultant for Orthopedic Designs North America; is a paid consultant for Smith & Nephew; receives publishing royalties, financial or material support from Thieme; and receives research support from the U.S. Department of Defense.

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