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The effect of augmenting suture material with magnesium and platelet-rich plasma on the *in vitro* adhesion and proliferation potential of subacromial bursa-derived progenitor cells

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Background: Connective tissue subacromial bursa-derived progenitor cells (SBDCs) have been suggested as a potent biologic augment to promote healing of the repaired rotator cuff tendon. Maximizing the amount of retained progenitor cells at the tendon repair site is essential for ensuring an optimal healing environment, warranting a search for proadhesive and proliferative adjuvants. The purpose was to evaluate the effect of magnesium (Mg), platelet-rich plasma (PRP), and a combination of both adjuvants on the *in vitro* cellular adhesion and proliferation potential of SBDCs on suture material commonly used in rotator cuff surgery.

Methods: SBDCs were isolated from subacromial bursa samples harvested during rotator cuff repair and cultured in growth media. Commercially available collagen-coated nonabsorbable flat-braided suture was cut into 1-inch pieces, placed into 48-well culture dishes, and sterilized under ultraviolet light. Either a one-time dose of 5 mM sterile Mg, 0.2 mL of PRP, or a combination of both adjuvants was added, while a group without treatment served as a negative control. Cellular proliferation and adhesion assays on suture material were performed for each treatment condition.

Results: Augmenting the suture with Mg resulted in a significantly increased cellular adhesion (total number of attached cells) of SBDCs compared to PRP alone (31,527 ± 19,884 vs. 13,619 ± 8808; $P < .001$), no treatment (31,527 ± 19,884 vs. 21,643 ± 8194; $P = .016$), and combination of both adjuvants (31,527 ± 19,884 vs. 17,121 ± 11,935; $P < .001$). Further, augmentation with Mg achieved a significant increase in cellular proliferation (absorbance) of SBDCs on suture material when compared to the PRP (0.516 ± 0.207 vs. 0.424 ± 0.131; $P = .001$) and no treatment (0.516 ± 0.207 vs. 0.383 ± 0.094; $P < .001$) group. The combination of Mg and PRP showed a significantly higher proliferation potential compared to PRP alone (0.512 ± 0.194 vs. 0.424 ± 0.131; $P = .001$) and no treatment (0.512 ± 0.194 vs. 0.383 ± 0.094; $P < .001$). There were no significant differences in the remaining intergroup comparisons ($P > .05$, respectively).

Conclusion: Augmenting suture material with Mg resulted in a significantly increased cellular adhesion of SBDCs compared to untreated suture material, as well as augmentation with PRP alone or a combination of both adjuvants. Further, Mg with or without PRP augmentation achieved a significant increase in the cellular proliferation of SBDCs on suture material compared to untreated sutures and augmentation with PRP alone. Application of Mg may be a clinically feasible approach to optimizing the use of SBDCs as a biological augment in rotator cuff repair, while combined augmentation with PRP may harness the full potential for optimized tissue recovery due to the high concentration of PRP-derived growth factors.

Investigation performed at the Department of Orthopaedic Surgery, University of Connecticut, Farmington, CT, USA.
Institutional review board approval was not required for this basic science study.

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Given the high retear rates following rotator cuff repair,[5,16,37] efforts to improve the biological healing potential via biologic augmentation techniques have become increasingly popular.[4,43,44] Recently, connective tissue progenitor cells derived from subacromial bursa-derived progenitor cells (SBDCs) have been suggested to be an easily accessible, inexpensive, and highly potent biologic augment to promote the endogenous healing potential of the repaired rotator cuff tendon, with promising preliminary clinical outcomes reported in the literature.[3,9,22,24,26,27,35,36,39]

However, maximizing the amount of retained progenitor cells at the targeted zone of repaired tissue still remains essential for ensuring an optimal healing environment.[28,29] Interestingly, SBDCs were found to have the *in vitro* ability to adhere and proliferate on suture material commonly used in rotator cuff repair.[28] More importantly, augmenting the surface of the suture with magnesium resulted in a significant increase in the cellular adhesion of SBDCs when compared to nonaugmented sutures while not impairing their proliferative capacity.[28] Although maximizing the amount of SBCDs retained at the repair site can be expected to further promote tissue recovery, suitable adjuvants targeted at enhancing the proliferation potential of SBDCs are yet to be investigated.

A promising approach to promoting healing is the use of platelet-rich plasma (PRP), as it contains a high concentration of growth factors within the alpha-granules of the platelets.[18] Although clinical outcomes following PRP application in the setting of rotator cuff repair have been inconsistent, recent meta-analyses consistently found significantly lower retear rates when augmenting the repair with PRP.[1,10,12,15,41,42] As such, augmentation of sutures with PRP has been shown to significantly increase the *in vitro* cellular proliferation of osteoblasts and ligamentocytes.[31] While this previous work suggests a favorable impact of PRP on the proliferative capacity of various cell sources, the effect of PRP application on the biologic activity of SBDCs remains unknown.

Thus, the purpose of the study was to evaluate the effect of Mg, PRP, and a combination of both adjuvants on the *in vitro* cellular adhesion and proliferation potential of SBDCs on suture material commonly used in rotator cuff surgery. It was hypothesized that augmenting the suture with Mg would significantly increase the cellular adhesion of SBDCs, while the application of PRP would additionally result in a significantly higher proliferative capacity.

Materials and methods

SBDCs were isolated from human subacromial bursa samples, which were obtained from four consecutive patients during arthroscopic rotator cuff repair at the University of Connecticut Health Center (Institutional Review Board no. 10-204-2). Cellular proliferation and adhesion assays on flat braided suture material treated with a one-time dose of Mg, PRP, or a combination of both adjuvants were performed. SBDCs without treatment served as a control group. Consequently, 6 pieces of suture per treatment group (control, Mg, PRP, and Mg + PRP) were evaluated for each assay, resulting in a total of 24 suture pieces per assay in each patient.

Cell isolation and culture

SBDC of four consecutive patients (mean age: 49.3 ± 5.6 years) was collected from over the rotator cuff tendon using an arthroscopic grasper device and placed into sterile 3 mL syringes, according to a previously published technique.[3,14,22,24,25] Each sample was immediately transported from the operating room to a laminar flow hood for processing. A 200 mg sample of each bursa specimen was carefully weighed for plating. The sample was placed in a culture dish and mechanically digested for 60 seconds using scissors sterilized in 100% ethanol. When the tissue sample resembled a finely minced, liquified particulate, it was re-suspended in 10 mL complete Dulbecco's Modified Eagle's Medium (DMEM (1X), Gibco, Life Technologies, Grand Island, NY, USA), containing 10% fetal bovine serum (FBS, Gibco, Life Technologies, Grand Island, NY, USA) and 1% penicillin/streptomycin (Pen Strep Glutamine (100X), Gibco, Life Technologies). Cells were then cultured in growth media at 37 °C with 5% CO_2 until reaching confluence.[22,23,28,29]

Preparation of platelet-rich plasma

Sixty mL of venous peripheral whole blood were drawn using a 60-mL syringe prefilled with 8 mL anticoagulant citrate dextrose solution A from a healthy 28-year-old male.[40] The blood was processed using a fully automated three-sensor technology system based on flow cytometry and light absorption (Angel System; Arthrex Inc., Naples, FL, USA). In a single-spin centrifugation process set at 7% hematocrit, approximately 3 mL of leukocyte-rich PRP was obtained.[40]

Preparation of suture material

Commercially available collagen-coated nonabsorbable flat braided suture material (FiberTape; Arthrex Inc., Naples, FL, USA) was used. Sutures were cut into 1-inch pieces and placed into Primaria 48-well culture dishes (Fisher Scientific, Agawam, MA, USA). The sutures were held in place at the bottom of each well with a sterile, inert aluminum metal mesh (1 cm × 1 cm) and were sterilized under ultraviolet light for 30 min prior to cell plating.[19,28,31] A one-time dose of either 1.0 mL 5 millimolar sterile Mg chloride, 0.2 mL of PRP, or a combination of both adjuvants was added to each piece of suture and was allowed to absorb and dry onto the suture material at room temperature for 30 minutes under the laminar flow hood.[28,31,34]

Cell plating

To define and ensure correct plating density, SBDCs were trypsinized with 0.5 mL of 0.01% trypsin-0.04% ethylenediaminetetraacetic acid for 15 minutes at 37 °C and counted using a nucleated-cell counter (Coulter Electronics, Hialeah, FL, USA). Subsequently, cells were plated at a density of 20,000 cells/cm^2 into 48-well Falcon plates containing the suture material. SBDCs were then cultured according to the required time for each assay.[19,28,31]

Cellular adhesion assay

To measure the ability of SBDCs to adhere to the different substrates, adhesion assays were performed according to a previously published method.[13,19,28,31] All sutures were subjected to the same adhesion protocol for analysis, where cells were added to the suture material for 24 hours prior to counting. At the end of this incubation period, the mesh was discarded, and the sutures were transferred into empty, clean 48-well plates. Sutures were then rinsed three times with 1X phosphate buffered saline to remove nonadherent cells. This step was critical to ensuring that only cells that actually adhered to the suture material were assayed. Cells attached to the suture were then released with 0.5 mL of 0.01% trypsin-0.04% ethylenediaminetetraacetic acid for 15 minutes at 37 °C and counted in 9.5 mL of 0.9% saline solution using a nucleated cell counter (Coulter Electronics, Hialeah, FL, USA). Counting was performed three times for each sample to account for accuracy. Suture pieces without any cells added were used as controls.[13,19,28]

Proliferation assay

The ability of SBDCs to proliferate on the suture material was determined by an Cell Proliferation Kit II (XTT) (2,3-bis (2-methoxy-4-nitro-5-sulfophenyl)-5- [(phenylamino) carbonyl]-2H-tetrazolium hydroxide) assay (Roche Diagnostics, Mannheim, Germany) as previously described.[22,28,29,31,33] All sutures were subjected to the same proliferation protocol for analysis, where cells were added to the suture material for 48 hours prior to performing the proliferation assay. After 40 hours in culture, wells were aspirated, the mesh was discarded, and the suture was transferred into clean 48-well plates. Each new well was supplemented with 300 μL growth media and 150 μL (0.3mg/mL) XTT labeling mixture (0.1 mL electron coupling reagent/5 mL XTT labeling reagent), followed by incubation incubated at 37 °C for 8 hours. At the end of the incubation period, a 100 μL aliquot was removed from each well, and absorbance was measured using an automated plate reader (BIO Tek, Bad Friedrichshall, Germany) at 450 nm with a reference wavelength of 650 nm. This assay is based on the cleavage of the tetrazolium salt XTT to a soluble formazan salt by mitochondrial dehydrogenases, which are only active in metabolically intact cells. As the increase in formazan formed is measured by the absorbance, this directly correlates to the number of viable cells within the sample. Suture pieces without any cells added were used as controls.[19,28,29,31]

Statistical analysis

Data were summarized with the mean and standard deviation (SD) as well as the median and interquartile range (IQR). Differences in adhesion and proliferation potential between treatment groups (no treatment, PRP, mMg, and PRP and mMg) were assessed using mixed effects linear regression. The distributions of the model residuals were examined to ensure large deviations from normality were not present. Pairwise comparisons of marginal mean values were carried out with adjustment for multiple comparisons using Bonferroni's method. An alpha level of 0.05 was set for all comparisons. All statistical analyses were performed using Stata 15.1 (StataCorp. 2017. Stata Statistical Software: Release 15; StataCorp LP, College Station, TX, USA).

Results

Cellular adhesion

Augmenting the suture with Mg resulted in a significantly increased cellular adhesion of SBDCs compared to the PRP group ($P < .001$), no treatment group ($P = .016$), and Mg plus PRP group ($P < .001$) (Table I). The remaining comparisons revealed no significant differences between treatment groups (Table II).

Cellular proliferation

Augmentation with Mg achieved a significant increase in the cellular proliferation of SBDCs on suture material when compared to the PRP ($P = .001$) and no treatment ($P < .001$) group (Table I). Further, the combination of Mg and PRP showed a significantly higher proliferation potential compared to the PRP ($P = .001$) and no treatment ($P < .001$) group, while the remaining comparisons revealed no significant differences between treatment groups (Table III).

Discussion

The most important finding of the present study was that augmenting the suture material with Mg resulted in a significantly increased cellular adhesion of SBDCs compared to untreated suture material, augmentation with PRP alone, or a combination of both adjuvants. Further, augmentation with Mg and Mg with PRP achieved a significant increase in the cellular proliferation of SBDCs on suture material compared to untreated sutures or augmentation with PRP alone. These findings expand the understanding of the biologic potential of Mg, an endogenous, ubiquitously available trace element, for optimizing the use of SBDCs in the setting of biologic augmentation of rotator cuff repair.[28] As the present study found no additional benefit of PRP alone in directly stimulating the proliferative capacity of SBDCs in this specific *in vitro* setting, yet the application of PRP may hold other important constituents to promote tissue recovery following repair.

Recently, the use of connective tissue progenitor cells derived from SBDCs has come to the fore as an easily accessible, inexpensive, and highly potent biologic augment in the setting of arthroscopic rotator cuff repair.[3,9,17,22,24,26,35,36,39] More specifically, Morikawa et al found that SBDCs had superior differentiation and proliferation potential compared to concentrated bone marrow aspirate and proposed a feasible method for isolating SBDCs for clinical use.[22,24] Interestingly, SBDCs were shown to have a high cellular proliferation potential regardless of patient demographics, rotator cuff tear characteristics, or severity of glenohumeral joint degeneration, alleviating concerns that SBDCs may lose biologic activity in the setting of massive and degenerated rotator cuff tears.[25] Further, Tamburini et al recently reported a significant upregulation of gene expression when torn tendon was cocultured with SBDC compared to culturing alone.[38]

These promising *in vitro* findings have led to the development of multiple surgical techniques regarding the use of SBDCs for biologic augmentation of rotator cuff repair.[6,11,30,32] While clinical evidence pertaining to postoperative functional improvement and repair integrity is yet to be provided, efforts to maximize the amount of SBDCs retained directly at the tear site may be critical to creating a sufficient healing environment regardless of the surgical augmentation technique performed. Recently, SBDCs were found to have the *in vitro* ability to adhere and proliferate on suture material commonly used in rotator cuff repair.[28] More importantly, augmenting the surface of the suture with Mg resulted in a significant increase in the cellular adhesion of SBDCs when compared to nonaugmented sutures.[28] Consistently, the present study also found a significantly increased adhesive potential of SBDCs when

Table I
Cellular adhesion and proliferation of SBDCs on suture material augmented with Mg, PRP, or combination of both adjuvants.

	Adhesion (total no. of attached cells)	Proliferation (corrected absorbance)
No treatment		
Mean ± SD	21,643 ± 8194	0.383 ± 0.094
Median	20,800	0.346
IQR	7800	0.054
Mg		
Mean ± SD	31,527 ± 19,884	0.516 ± 0.207
Median	27,200	0.404
IQR	23,600	0.311
PRP		
Mean ± SD	13,619 ± 8808	0.424 ± 0.131
Median	11,800	0.365
IQR	9400	0.223
Mg + PRP		
Mean ± SD	17,121 ± 11,935	0.512 ± 0.194
Median	14,600	0.431
IQR	17,600	0.309

Mg, magnesium; *SBDCs*, subacromial bursa derived progenitor cells; *PRP*, platelet-rich plasma; *SD*, standard deviation; *IQR*, interquartile range.

Table II
Statistical intergroup comparisons for cellular adhesion of SBDCs on suture material.

Comparison	Difference	*P* value
Mg vs. Mg + PRP	14,720	**<.001***
Mg vs. PRP	17,656	**<.001***
Mg vs. No treatment	9761	**.016***
PRP vs. No treatment	−7895	.097
PRP vs. Mg + PRP	−2936	>.999
No treatment vs. Mg + PRP	4959	.733

Mg, magnesium; *SBDCs*, subacromial bursa derived progenitor cells; *PRP*, platelet-rich plasma.
Presented *P* values are adjusted for multiple comparisons using Bonferroni's method.
*Indicates statistical significance.

Table III
Statistical intergroup comparisons for cellular proliferation of SBDCs on suture material.

Comparison	Difference	*P* value
Mg vs. Mg + PRP	0.005	>.999
Mg vs. PRP	0.093	**.001***
Mg vs. No treatment	0.135	**<.001***
PRP vs. No treatment	0.041	.528
PRP vs. Mg + PRP	−0.088	**.001***
No treatment vs. Mg + PRP	−0.130	**<.001***

Mg, magnesium; *SBDCs*, subacromial bursa derived progenitor cells; *PRP*, platelet-rich plasma.
Presented *P* values are adjusted for multiple comparisons using Bonferroni's method.
*Indicates statistical significance.

the suture was augmented with Mg. In contrast to this previous work, augmentation with Mg also resulted in a significant increase in cellular proliferation. These observations expand the understanding of the biologic activity of SBDCs, which is subject to substantial interindividual variability and may be influenced by the vascularity and fatty infiltration of the bursal tissue as well as the size of the rotator cuff tear.[3,21] Of note, similar to the findings of the present study, Mg has been shown to promote the proliferation of bone marrow-derived mesenchymal stem cells.[7]

Interestingly, this study demonstrated no additional benefit of PRP for the in vitro cellular adhesion and proliferation of SBDCs. Especially the inability to demonstrate proliferative effects of PRP on SBDCs is of interest, considering its previously reported proliferative effect otn other cell types.[2,8,31] Recently, Otto et al observed a significant increase in the cellular proliferation of human osteoblasts and tenocytes on flat braided suture material when a biological augmentation with PRP was performed.[31] The positive proliferative effect of PRP has also been shown for chondrocytes and mesenchymal stem cells.[8] The observation that the Mg + PRP group presented less attachment of SBDCs to suture material when compared to the Mg group may be explained by the fact that SBDCs were hindered from attaching to the Mg-soaked suture at places that were covered with PRP. Thus, PRP may clinically be applied directly to the repair site, rather than the suture, to utilize its biologic activity.

Although this study found no proliferative effect of PRP on SBDCs in this specific in vitro setting, either due to the molecular characteristics of SBDCs or due to the *ex vivo* testing conditions, these previous investigations indicate the favorable impact of PRP on other cell types involved in the rotator cuff tendon healing process.[31] Both osteoblasts and tenocytes have been reported to be important for sufficient bone-enthesis healing.[19,43] As osteoblasts and tenocytes have been shown to adhere and proliferate on suture material used in rotator cuff surgery, maximizing these cells directly at the tear size by stimulating their proliferation with PRP may aid in the tendon-to-bone incorporation process critical for rotator cuff healing.[19,20,28,31] Further, PRP contains a high concentration of growth factors critical for the enhancement of tissue recovery.[18] These promising *in vitro* findings are also reflected in recent meta-analyses of clinical studies, which found that PRP significantly reduced retear rates, while evidence pertaining to significantly improved functional outcomes remains rather inconsistent.[1,10,12,15,41,42]

Interpreting the findings of the present study in the context of these previous investigations, a combination of Mg and PRP may most efficiently maximize the number of SBDCs, osteoblasts, and tenocytes retained at the targeted zone of repaired tissue while also improving the biologic acceptance of the suture and creating a milieu rich in growth factors. More importantly, the findings of this study, underscoring the favorable biologic effect of an application of Mg to suture material, are of particular clinical relevance given the low barriers for clinical translation, as Mg is Food and Drug Administation-approved for human use, inexpensive, and easily available. As such, augmenting suture material with Mg may be a feasible approach to optimizing the use of SBDCs as a biological augment in rotator cuff repair.

There were several limitations to the study. As an *in vitro* study, these findings may not reflect the cellular adhesion and proliferation potential of SBDCs in an *in vivo* shoulder environment. Thus, definitive conclusions regarding the impact of these *in vitro* findings on rotator cuff tendon healing cannot be drawn. In addition, it is unknown to what extent a constant exposure to a wet environment during arthroscopic rotator cuff repair may have influenced the results. Lastly, the generalizability of the present findings may be limited due to the fact that adhesion and proliferation were only tested on flat braided sutures from 1 manufacturer.

Conclusion

Augmenting suture material with Mg resulted in significantly increased cellular adhesion of SBDCs compared to untreated suture material, as well as augmentation with PRP alone or a combination of both adjuvants. Further, Mg with or without PRP augmentation achieved a significant increase in the cellular proliferation of SBDCs on suture material compared to untreated sutures and augmentation with PRP alone. Application of Mg may be a clinically feasible approach to optimizing the use of SBDCs as a biological augment in rotator cuff repair, while combined augmentation with PRP may harness the full potential for optimized tissue recovery due to the high concentration of PRP-derived growth factors.

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