Editorial Commentary: Subacromial Bursa—Friend or Foe Within The Shoulder? An Old Debate With New Insights

Andre F. Steinert, M.D., M.H.B.A., and Frank Gohlke, M.D.

Abstract: There is an ongoing debate about whether to resect or preserve the subacromial bursa during surgical treatment of rotator cuff tears. Neer was the first to systematically describe bursitis as a component of subacromial impingement syndrome that may extend to rotator cuff disease, often discussed as a point of controversy with Uhthoff who first identified the bursa as a contributor to rotator cuff healing, both experimentally and clinically. Because the subacromial bursa provides the gliding mechanism of the shoulder and regenerates itself after surgical removal, interest evolved on the role of the bursa in the healing of rotator cuff tears for evolution of regenerative therapies as a support of arthroscopic repair techniques. In vitro work could identify human subacromial bursa as a source of mesenchymal stem cells, which revealed lineage-specific differentiation capacity, including the tendon and a marker profile that was highly similar to, although in some aspects distinct from, marrow-derived mesenchymal stem cells. Only recently, this knowledge was used in controlled experimental work in vivo to demonstrate superior engraftment of bursal cells within tendon tissue. These findings shed new light on the biology of the subacromial space and provides novel prospects for the clinical use of local stem cells in rotator cuff repair.

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We appreciate very much that the authors of the well-designed experimental study, "Examining the Potency of Subacromial Bursal Cells as a Potential Augment for Rotator Cuff Healing: An In Vitro Study," Morikawa, Johnson, Kia, McCarthy, Macken, Bellas, Baldino, Cote, and Mazzocca,[1] confirm previous results that reflect the cellular base of old surgical principles known since Uhthoff et al.,[2] who demonstrated that the natural intrinsic healing mechanism of the rotator cuff starts from the bursal-side epithenon: "The vascularized connective tissue covering the area of rupture and the proliferating cells in the fragmented tendons reflected more of the features of repair than of degeneration and necrosis. The main source of this fibrovascular tissue was the wall of the subacromial bursa." This was later confirmed by Hirose et al.,[3] who described the great potential for spontaneous healing in animals after artificial rotator cuff defects from the bursal side layer of the rotator cuff and Iwata et al.,[4] who demonstrated in an experimental rat model the migration of autogenous host stem cells in tendon grafts mainly from the bursal side of the tendon stumps. Already Codman, who, after his fellowship to Europe was familiar with the ideas of Jarjavay and Duply that acute and chronic bursitis are the source of inflammation and adhesions to the rotator cuff, stated in chapter 3 of his famous book, *The Shoulder*, that "I have come to believe that the bursa, like the peritoneum, possesses the function of rapidly forming protective adhesions to confine inflammation, and also the ability to absorb them and thus restore, in whole or in part, the mobility of the adjacent tissues."[5,6]

In their work, Morikawa and colleagues[1] compared subacromial bursa cells isolated by collagenase digestion from the bursa tissue of individuals on arthroscopic rotator cuff repair compared with concentrated bone marrow aspirate cells isolated by adherent culture from aspirates of the proximal humerus from the same individuals. Bursal cells (BC) were further distinguished by whether they were retrieved from either over the rotator cuff tendon (BC-T) or the rotator cuff muscle

Bad Neustadt/Saale, Germany

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(BC-M). The bone marrow aspirate and BC cells were compared in vitro using standard assays for their ability to proliferate, to form colonies on cell culture dishes, and to differentiate into the mesenchymal lineages bone, cartilage, or fat on protein and gene expression level. Because of the fact that all cell types were retrieved from the same individual, patient-related factors that account for donor variability, such as age, sex, inflammation, cytokine expression, and medication, were alleviated, and patients with potential marrow alterations were excluded from the study, providing a reasonable base for a fair comparison of the different cell types.

In summary, the authors found superior cell proliferation and colony formation capacity of both types of BCs compared with bone marrow cells (BMCs) over an examined time period of 10 days. Colony formation capacity was highest in the BC-T cultures, compared with BC-M cultures, which was again higher than the BMC cultures, with differences being significant among all groups. For all of the mesenchymal differentiation assays including chondrogenesis, osteogenesis, and adipogenesis, a significantly superior differentiation capacity was seen in both types of BCs compared with BMCs, but no clear-cut differences were seen between BC-T and BC-M cultures.[1]

The reasons for the differences observed are manifold and were adequately addressed in the Discussion. We and others observed, to some extent, differences in the comparative proliferation and differentiation capacity of BCs with BMCs, and the fact that no patient matching was performed in these studies, different sources, isolation and cultivation techniques of BMCs were used, likely account for these differences.[7-9] Furthermore, BMCs are per se a mixed population of cells derived from marrow cavities, which are very sensitive to cell cycle turnover and expansion conditions needing sometimes specialized stem cell media and other factors compared with highly plastic adherent cultures of fibroblastic cells derived from connective tissues such as subacromial bursa, that are highly prone to rapid growth in clusters.

Therefore further in-depth characterization of the different cell types used, including cell surface marker determination and genomic screening using array technologies is mandatory to shed light into the distinct cellular entities that were finally used. Although donor variability could not be excluded in previous work, such types of analyses revealed that alkaline phosphatase and cluster of differentiation 34 and 106 expression could further distinguish between BCs and BMCs, and that certain aspects such neurogenic, gland, and vascular development were more present in BCs on array screening for whole genome expression.[9] This is supported by the work of Aydın and coworkers,[10] who found higher levels of neurotrophic factors in BCs compared with BMCs, which might be harnessed for any approach toward restoration of the neuromuscular unit and the neurogenic control of cell turnover of the soft tissues in the subacromial space.

However, all of these works share the finding that bursa tissue is a rich source of mesenchymal stem cells adjacent to the rotator cuff, and therefore we believe that BCs are a good biologic augmentation to the otherwise vulnerable repair site of the torn rotator cuff. This is supported on the one hand by recent in vivo works by the same group of this study that could demonstrate that BCs can be readily engrafted into tendon tissue after transplantation in a mouse model.[11] Furthermore, recently arthroscopic rotator cuff repair has evolved new techniques that correspond to the principle of open transosseous repair, which covered the tendon with bursa tissue and therefore obtained excellent long-term results.[12] This also corresponds to our clinical experience, because we always tried to preserve the bursa as much as possible or to perform a bursa plasty onto the repair site during mini-open or arthroscopic rotator cuff repair. We believe that this additional layer provides the repair site with a biologically potent source for the continuous delivery with cells and cytokines. However, it remains to be seen whether the bursa alone or further stimulating biologics such as platelet-rich plasma combined with a scaffold, patch, or biceps tendon graft or bone marrow preparations might be additionally harnessed to support the rotator cuff repair site.

Unfortunately, there are many parameters that we do not know yet. First, we need to clarify the appropriate patient and the defect site. Do smokers, rheumatic patients, and inactive patients advanced in years need different treatments than otherwise healthy and active individuals? Can outcomes be even predicted according to the preoperative condition of the patient? Apart from defect size of the rotator cuff tear and Goutallier stage of fatty infiltration and atrophy of the rotator cuff muscles, we have no clear picture of the biologic potency of the tissue remnants after rupture regarding cellularity, vascularity, cytokine expression, and inflammatory status—these are critical factors currently often neglected. Is there a difference regarding mechanical or biological aspects regardless of whether an additional acromioplasty is performed? With more insights into the biologic milieu at the repair site, we might be able to resolve which defects need augmentation and which probably do not.

Second, we need to clarify the properties of our graft. The consistency of the bursa tissue is very variable in thickness and cellularity depending on the patient, tear size, location (adjacent to the tuberosity, delta muscle, tendon, or rotator cuff muscle), among other factors. Actually, in this study, it would have been very interesting to see the variability of the harvested tissues

between donors and to compare the cellular potency of different phenotypes. Are inflamed bursae equally or even more suitable for engraftment purposes compared with noninflamed ones? Are the cells from inflamed bursa tissues exclusively local cells, or have they been partly recruited as a response to injury via circulation or the synovial fluid?

Third, we need to know what happens to our transplanted bursa tissue once engrafted. How is the turnover of our bursa graft, and how is it regulated? To what extent can incorporation in the repair site be expected, and what are the factors involved? Can a scaffold or additional BMCs help, when the intrinsic capacity of the BCs seems insufficient? To answer these and other questions, more basic and translational science is mandatory, and clarification of at least some of these open questions is necessary, before meaningful clinical approaches can be formulated.

Nevertheless, the clinical implications to us are clear: First, do not waste the subacromial bursa and preserve as much tissue as possible along with the epitenon of the rotator cuff tendon. Even when you work exclusively arthroscopic, rather push the bursa aside and spread it over the repair site or at the end of the repair, than resecting it. Second, drugs such as corticosteroids are anti-inflammatory; however, they may have an adverse effect on tendon healing and should rather be avoided at repair sites if possible. Third, the bursa provides BCs that produce all kinds of cytokines, which are needed for tendon healing and also hold promise to augment restoration of the insertion site, including potential for lubrication, tendon neogenesis, and enthesis formation via chondrogenic and osteogenic pathways. It remains to be seen whether the different aspects of healing can be further supported by blood or bone-marrow preparations and might be considered in cases where these agents are not naturally present anyway.

We can conclude that, although many issues in the healing of the rotator cuff remain unresolved, the work by Morikawa and colleagues[1] confirms that the subacromial bursa tissue and cells provide a rich population of highly potent mesenchymal stem cells that should be taken into consideration as an augment to rotator cuff repair, especially in cases where the repair site appears vulnerable. Uhthoff's old principle that rotator cuff degeneration is mostly located at the articular side but that its regeneration starts from the bursal side epitenon is not forgotten.

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