

Editorial Commentary: Stem Cell Exosomes Can Promote Healing and Muscle Function After Rotator Cuff Repair



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Abstract: Stem cell–based therapies are a growing area of interest within regenerative musculoskeletal medicine. Exosomes represent an attractive emergent clinical strategy for the delivery of stem cell–derived growth factors and small molecules to a regenerating tissue environment. Stem cells themselves may not engraft into host tissue but more likely promote a pro-regenerative state through the release of autocrine and paracrine factors. Exosomes, a type of small membrane–bound extracellular vesicle secreted by cells, are of interest as an emergent clinical strategy because they have several key factors that could provide the elusive goal of stem cell therapies in a more practical manner. Exosomes from stem cells appear to have much of the machinery that could promote regenerative capabilities, including growth factors, micro-RNAs (miRNAs), and other signaling molecules that can induce the necessary growth signaling and transcriptional changes to induce a phenotypic change in the local delivery environment. It is important to note that they also have a limited host immune response and can be stored in a freezer, as opposed to many stem cell products that need specialized storage systems to maintain viability. For these reasons, exosome-based therapeutic solutions for rotator cuff repair offer a potential treatment strategy. Recent research provides a highly translational application of exosomes to a chronic rotator cuff repair model and shows efficacy in improving the biomechanical strength of tendon healing at the tendon-bone interface, in addition to partially ameliorating the development of fatty infiltration. Further work is needed to characterize the components of exosomes that result in their bioactivity in addition to considering their cost-effectiveness as a regenerative musculoskeletal treatment.

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For the past 20 years, stem cell therapies have been touted as the future, the answer, and the obvious next step for a multitude of musculoskeletal processes. However, despite the growing interest in the use of “biologics” and other stem cell–based therapies, there remain few data in clinical studies that suggest we are ready as an orthopaedic community to embrace these therapies as commonplace. Barriers exist in terms of cost, the demonstration of efficacy, and the need to determine which patient population will benefit most from the use of these emerging strategies.¹⁻³ Rotator cuff repair appears to be a promising early candidate because recapitulation of the biology of tendon-to-bone attachments and improved muscle quality remain a challenge that has not yet been solved with traditional repair and biologic augmentation strategies. Current

stem cell therapy options, which involve either donor harvest or allograft use of stem cells, have not been shown to add considerably to the outcomes of rotator cuff repair.^{2,3} The use of whole stem cell products remains in relative exile—a treatment strategy that has promise but not practicality.

Over the past decade, there has been a growing strategy to leverage the mechanisms by which stem cells may actually affect surrounding tissue. It is known that stem cells themselves may not engraft into host tissue but more likely promote a pro-regenerative state through the release of autocrine and paracrine factors. Exosomes, a type of small membrane–bound extracellular vesicle secreted by cells, are of particular interest as an emergent clinical strategy because they have several key factors that could provide the

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elusive goal of stem cell therapies in a more practical manner. Exosomes from stem cells appear to have much of the machinery that could promote regenerative capabilities, including growth factors, micro-RNAs (miRNAs), and other signaling molecules that can induce the necessary growth signaling and transcriptional changes to induce a phenotypic change in the local delivery environment.^{4,5} It is important to note that they also have a limited host immune response and can be stored in a freezer, as opposed to many stem cell products that need specialized storage systems to maintain viability. For these reasons, exosome-based therapeutic solutions for rotator cuff repair offer a potential treatment strategy.

Kim, Shim, Choi, Lee, Lee, Jeon, and Koh⁶ have done a commendable job in their report, “Extracellular Vesicles Delivered by Injectable Collagen Promote Bone-Tendon Interface Healing and Prevent Fatty Degeneration of Rotator Cuff Muscle,” showing the effects of stem cell exosome-based treatment on healing rates and the healing quality of the rotator cuff in a rabbit model. The choice of a delayed healing model is important because it allows for a more chronic condition to develop, with the development of scar tissue at the bone-tendon junction, and allows for muscle degeneration to occur. This is a much more rigorous and clinically applicable model. The groups are appropriately controlled, and the authors are to be commended on the judicious use of animals while still maintaining thorough outcome measures. Showing that the exosomes are retained in tissue at 4 weeks after injection suggests a durable effect even after a single injection and suggests that the exosomes are not rapidly degraded after injection.

A key finding of the study by Kim et al.⁶ is the improved bone-tendon healing that exosome-mediated therapy appears to result in, yielding improved healing of the chronic rotator cuff injury in this model, consistent with other prior studies.⁷⁻⁹ Kim et al. show that there is not only improved histologic scoring of the bone-tendon interface (Table III) but also improved biomechanical strength of the repair. A second important finding of this study is that fatty infiltration is improved but not eliminated in the setting of a delayed rotator cuff repair in small animals. The authors found that repair alone decreased fatty infiltration by about 50% in the repair groups, but the addition of exosomes improved the muscle quality with a decrease in fatty infiltration. This finding is consistent with findings in other studies^{9,10} and, importantly, is consistent with what is seen clinically, when even successful repair does not ameliorate muscle deterioration nor does it lead to perfect function in many patients.¹¹ Fortunately, treatments that appear to improve bone-tendon healing also appear to have the ability to indirectly improve the muscle

quality; however, whether these are direct or indirect effects remains to be seen.

Although there are many strengths to this study, as with many translational studies, it often brings up more questions than answers. A critical question is, “What is actually in these exosomes that provides a boost to tendon-bone healing?” Answering this question is important in that it can guide potential modifications within the stem cell lines used to produce more efficient and effective exosome-based therapies in the future. A second key question is how the exosome-based treatment improves muscle quality: Is it due to an indirect effect of tendon-bone healing being improved, with more mechanical strength through the tendon-muscle interface, or is there a direct effect of the exosome therapy on the muscle-tendon junction that is not appreciated? Additionally, although Kim et al.⁶ used a collagen-based delivery method for exosomes, there was not a comparison to exosome injection alone, thus limiting the conclusions that can be drawn regarding the efficacy of the injectable collagen in promoting the stability and durability of the exosomes within the tissue. Finally, one must question the overall cost and compare exosome-based therapies with other treatment strategies. How would this compare (cost- and efficacy-wise) with the use of other recently developed treatment options such as nanofiber scaffolds¹² or with the use of other more standard grafts¹³?

So, are we there yet? Does this study provide the logical next step to bring stem cell-based therapies to the clinical arena? Although the study clearly shows the promise and practicality that have often been lacking in other translational studies using stem cell-guided therapies to improve rotator cuff repair, well-performed clinical trials with the appropriate suite of outcomes (imaging, patient-reported outcomes, and shoulder function), mechanistic studies, and evaluations of the actual cost-effectiveness of these treatments will be required to determine whether we are approaching the end of our journey to bring stem cell science to the bedside.

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