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TABLE E-1 Summary of Animal Model Studies Investigating the Effects of Local Use of Osteoinductive Growth Factors to Augment Tendon-to-Bone Healing

Osteoinductive Growth Factor	Study Type*	Results*	Notes*
TGF			
Manning et al.[24]	Rat model of rotator cuff repair	Local TGF-β3 delivery at a sustained rate to the supraspinatus repair site significantly enhanced tendon-to-bone healing compared with control animals ($p \leq 0.05$).	Although TGF-β3 treatment led to improved toughness relative to repairs that received conventional treatment (i.e., surgical repair only), the biomechanical properties of TGF-β3-treated tendons were still significantly inferior to those of normal (uninjured) tendon-to-bone insertions†.
Kim et al.[22]	Rat model of rotator cuff repair	Suppression of TGF-β isoforms significantly decreased mechanical properties compared with paired control shoulders ($p < 0.05$). Application of TGF-β3 did not make any significant change.	Possible explanation given for ''lack of effect'' was the suboptimal method used in this study to deliver factors to the repair site, and the study may have been statistically underpowered.
BMP			
Ma et al.[21]	Rabbit model of ACL reconstruction	Use of recombinant human BMP-2 (rhBMP-2) significantly increased tendon-to-bone healing in a dose-dependent fashion ($p < 0.05$).	rhBMP-2 group demonstrated significantly increased stiffness at 8 wks, while there was no significant improvement in ultimate tensile load.
Seeherman et al.[26]	Sheep model of rotator cuff repair	rhBMP-12 formulations significantly increased mechanical properties ($p < 0.0001$). Histological evaluation showed accelerated healing in the rhBMP-12-treated repairs compared with the untreated repairs.	Maximum tensile load and stiffness for the rhBMP-12-collagen sponge-treated repairs were less than normal shoulders (approximately 42% and 64%, respectively, of values for normal tendon) at 8 wks ($p < 0.0001$)†.
FGF			
Ide et al.[28]	Rat model of rotator cuff repair	Local application of FGF-2 accelerated early tendon-to-bone remodeling with improved histological and biomechanical scores at two weeks ($p < 0.002$).	There was no significant difference between the FGF-2-treated groups and controls at 4 wks and 6 wks after the procedures.
G-CSF			
Sasaki et al.[23]	Canine model of ACL reconstruction	G-CSF-treated group had more vessel formation in the graft at two weeks ($p < 0.01$), smaller tibial bone tunnel ($p < 0.05$), and higher tendon ultimate load at failure ($p < 0.01$) at 4 wks compared with control group.	There was no significant difference between the groups at 2 wks in terms of tibial bone tunnel size (measured to assess bone formation in tibial tunnel) and load to failure.

*ACL = anterior cruciate ligament, TGF = transforming growth factor, BMP = bone morphogenetic protein, FGF = fibroblast growth factor, and G-CSF = granulocyte colony-stimulating factor. †When interpreting animal studies in this area, it is important to note that the strength of a healed tendon or ligament graft may never reach the strength of the native structure. However, the loads on these tissues during most activities are generally well below the ultimate failure load, and most of these tissues will function adequately despite never reaching the strength of the native tissue. Further study is required to determine the loads that occur with standard rehabilitation activities. Although an animal study may describe a significant improvement in a biomechanical property, only further clinical study will determine if such a difference is clinically important.

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TABLE E-2 Outcomes from Studies Comparing Patients Who Underwent Arthroscopic Rotator Cuff Repair and Received Local Platelet-Rich Plasma with Those Who Did Not

	Study Type and Evidence Level*	No. of Patients*	Mean Duration of Follow-up *(mo)*	Assessment Measures†	Retear Rate*	Clinical Outcomes*†
Castricini et al.[37]	RCT; Level I	88 (43 who had PRP and 45 controls)	20.2	Constant	MRI assessment: 2.5% (PRP group) versus 10.5% (control) at min. of 16 mos; not significant.	No significant difference
Randelli et al.[38]	RCT; Level I	53 (26 who had PRP and 27 controls)	24	UCLA, SST, Constant, VAS, and SER	MRI assessment: 40% (PRP group) versus 52% (control) at 23 mos; not significant	No significant difference at 6, 12, and 24 mos (final follow-up). Significantly better pain and function scores in PRP group at 3 mos.
Weber et al.[39]	RCT; Level I	60 (30 who had PRP and 30 controls)	12	ASES, UCLA, SST, and VAS	MRI assessment: 43% (PRP group) versus 29% (control) at a mean of 4.3 to 4.5 mos, respectively; not significant	No significant difference except for UCLA shoulder scores (significantly better in control group; $p < 0.046$)
Rodeo et al.[40]	RCT; Level II	79 (40 who had PRP and 39 controls)	12	ASES and L'Insalata	Ultrasound assessment: complete healing in 66.7% (PRP group) versus 80.6% (control) at 4 mos; not significant	No significant difference
Jo et al.[41]	Prospective cohort; Level II	42 (19 who had PRP and 23 controls)	19.7	ASES, UCLA, DASH, SST, SPADI, and Constant	MRI assessment: 26.7% (PRP group) versus 41.2% (control) at 9 mos; not significant	No significant difference
Barber et al.[42]	Case-control; Level III	40 (20 who had PRP and 20 controls)	31	ASES, SST, Constant, SANE, and Rowe	MRI assessment: persistent full-thickness defects 30% (PRP group) versus 60% (control) at 4 mos; significant ($p = 0.03$)	No significant difference except for Rowe scores (significantly better in the PRP group; $p = 0.03$)

*RCT = randomized controlled trial, PRP = platelet-rich plasma, and MRI = magnetic resonance imaging. †ASES = American Shoulder and Elbow Surgeons questionnaire, DASH = Disabilities of the Arm, Shoulder and Hand questionnaire, SANE = Single Assessment Numeric Evaluation, SER = Strength in External Rotation, SPADI = Shoulder Pain and Disability Index, SST = Simple Shoulder Test, UCLA = University of California, Los Angeles Shoulder Rating Scale, and VAS = visual analog scale.

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TABLE E-3 Results from Animal Model Studies Investigating the Effects of Local Mesenchymal Stem-Cell Therapy on Tendon-to-Bone Healing

	Study Type*	Therapeutic Cell*	Results	Notes
Li et al.[55]	Rat model of tendon attachment within tibial tunnel	MSCs	Max. biomechanical pullout strength significantly higher in MSC group at 4 and 8 wks ($p < 0.05$)	Labeled MSCs detected at tendon-bone interface at 2, 4, and 8 wks.
Ouyang et al.[56]	Rabbit model of tendon attachment within calcaneal tunnel	MSCs	MSC group had improved integration of tendon to bone through formation of fibrocartilaginous attachment.	Histological and immunohistochemical assessments performed at 2, 4, and 6 wks were not quantitative.
Gulotta et al.[57]	Rat model of rotator cuff repair	MSCs	No difference in histological (amount of new cartilage formation and collagen fiber organization) or biomechanical (strength, cross-sectional area, peak stress to failure, and stiffness) parameters between MSC group and control.	Assessments were performed only at 2 and 4 wks. Potential beneficial effects at later time points remained to be assessed.
Gulotta et al.[58]	Rat model of rotator cuff repair	Ad-MT1-MMP-transduced MSCs	MSCs genetically modified to overexpress the developmental gene MT1-MMP-augmented interface healing at 4 wks by the presence of more fibrocartilage at the insertion and significantly improved biomechanical strength in terms of ultimate load to failure ($p = 0.01$), ultimate stress to failure ($p = 0.005$), and stiffness ($p = 0.02$).	Comparison performed between rats that received Ad-MT1-MMP-transduced MSCs and those that received MSCs alone at 2 and 4 wks. No differences seen between groups in any outcome at 2 wks.
Lim et al.[59]	Rabbit model of ACL reconstruction	MSCs	MSC-enhanced grafts had significantly higher failure load ($p = 0.02$) and stiffness ($p = 0.005$) at 8 wks. Histologically, MSC-enhanced grafts resembled normal ACL insertions (with fibrocartilage transition zone between the graft and the bone) more than the controls.	Biomechanically, there was no significant difference between groups at 2 and 4 wks.

*ACL = anterior cruciate ligament, MSCs = mesenchymal stem cells, and Ad-MT1-MMP = adenoviral membrane type-1 matrix metalloproteinase.