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GENERAL REVIEW • SHOULDER - BIOMATERIAL

Use of stem cells and growth factors in rotator cuff tendon repair

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Abstract
The management of rotator cuff tears continues to prove challenging for orthopaedic surgeons. Such tears affect most age groups and can lead to significant morbidity in patients. The aetiology of these tears is likely to be multifactorial; however, an understanding of the mechanisms involved is still under review. Despite advancements in surgical operative techniques and the materials used, post-operative recurrence rates after surgical repair remain high. A growing area of research surrounds biological adjuncts used to improve the healing potential of the repaired tissues. This review of recent publications focuses on the strengths and limitations of using stem cells and growth factors in rotator cuff repair.

Keywords Rotator cuff tears · Mesenchymal stem cells · Growth factors

Introduction

Rotator cuff (RC) tears are among the most prevalent pathologies found in upper limb clinics and frequently cause disabling symptoms [1]. Extrinsic causative factors can be trauma, age, and a dominant arm, while intrinsic factors include degenerative processes, poor microvascular blood flow, subacromial impingement, or a combination of these factors [2]. Different strategies have been developed to improve function after an RC tear. Non-operative management consists mainly of physiotherapy and medication. Operative treatment typically consists of RC tendon repair in which a combination of suture material is attached to anchors.

Factors implicated in high failure rates are age, smoking, intrinsic tendon degeneration, fatty infiltration, muscle atrophy, the size of the tear, quality of repair, and post-operative management [3].

In recent years, an increased understanding of the biological nature of the tendon and of bone healing has resulted in the development of novel tissue engineering techniques. Numerous laboratory, animal, and human RC repair studies have focused on the use of biological adjuncts to promote RC healing which include platelet-rich plasma (PRP), stem cells, growth factors (GFs), and scaffolds [4].

The aim of this review article is to investigate the effect of the various growth factors and stem cells on rotator cuff healing process.

Materials and methods

The following terms were used in the PubMed search engine to identify relevant studies: growth factors, stem cells, biology, scaffold combined with tendon, repair, and rotator cuff. From 1208 search results, we selected 63 papers evaluating the use of growth factors and stem cells in RC repair. Review articles were also selected, and their bibliographies were scrutinised to identify any studies not captured in the search.

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Platelet-rich plasma (PRP)

Platelets contain hundreds of proteins called growth factors which are very important in the healing of injuries. PRP is plasma with many more platelets than what is typically found in blood. In laboratory studies, PRP has been shown to significantly improve biomechanical properties and the histological appearance at the rotator cuff tendon–bone interface. For moderately degenerative tendons, Cross et al. concluded that low-leucocyte concentrated PRP was better than high-leucocyte concentrated PRP in promoting normal collagen matrix synthesis and the reduced cytokine concentration associated with matrix degradation and inflammation. However, in the most severe degenerative tendons, neither of the PRP preparation types enhanced matrix synthesis [5]. In the presence of platelet-released growth factors (PRGFs), tenocytes from retracted tendons proliferate and synthesise extracellular matrix proteins that may improve the properties of the repair tissue [6]. For example, Jo et al. [7] noted that PRP promotes cellular proliferation and enhances both gene expression and the synthesis of a tendon matrix in tenocytes from degenerative human rotator cuff tendons. Beck et al.'s rat RC repair model showed that, compared to a control group, rats that underwent a repair with PRP augmentation exhibited increased fibroblastic and vascular proliferation with collagen fibres oriented in a more linear fashion towards the tendon footprint. However, augmenting RC repairs with PRP considerably reduced tendon tissue stiffness and failed to enhance tendon-to-bone healing [8].

Also using a rat RC repair model, Dolkart et al. [9] found that the immediate post-operative intra-articular injection of a single-dose autologous PRP as an adjunct to operative repair resulted in improved tendon-to-bone healing. Ersen et al. [10] compared the effect of a PRP injection into the tendon–bone interface, with or without a collagen sponge carrier, to two control groups. They found that cuffs repaired with PRP had significantly greater mean load-to-failure rates and stiffness. For the groups receiving PRP, there was no significant difference between these variables. There were no differences between any of the group on histological evaluation. Using a rabbit RC repair model, Wu et al. found that the injection of platelet-rich plasma plus a bioactive glass (PRP + BG) mixture could enhance the tendon–bone healing process in RCT repair, compared to a control and a PRP injection-only group. The maximum load-to-failure value was significantly higher after six weeks, and histologically, the tendon–bone integration was significantly sturdier in the PRP + BG group. Comparable results were found by Chung et al. [11, 12] after the local administration of autologous PRP in a similar model.

The results of randomised clinical trials (RCTs), however, have been less promising. For example, Bergeson et al. evaluated the augmentation of rotator cuff repairs with a platelet-rich fibrin matrix (PRFM). Patients were randomly enrolled into a PRFM or a control group and were matched for mean age, tear size, and median Goutallier scores. In the PRFM group, two patients became infected and re-tear rates were significantly higher (56.2% vs. 38.1%), while post-operative functional outcome scores exhibited no improvement [13]. Castricini et al. [14] made the same conclusion when comparing arthroscopic cuff repair with and without PRFM. At a 16-month follow-up, there was no significant difference in Constant score and MRI assessment of the repaired tendon.

In a RCT conducted by Zumstein et al., 35 patients receiving arthroscopic rotator cuff repair were randomised to either a control group or a group where leucocyte- and platelet-rich fibrin (L-PRF) was locally applied to the repair site. Patients were evaluated at 12 months post-operatively, radiologically by using MRI arthrography, and clinically by using a visual analogue for pain in conjunction with Simple Shoulder Test and Constant–Murley scores. All patients improved, but there were no significant differences between the groups. Furthermore, the MRI did not detect any significant structural differences regarding the mean post-operative defect size and mean post-operative tendon quality. The authors concluded that the application of L-PRF therefore had no beneficial effect on the repair in terms of clinical or radiological outcomes [15].

Finally, Hurley et al. [16] recently published a systematic review of (RCTs) comparing platelet-rich plasma (PRP) or platelet-rich fibrin (PRF) in rotator cuff repair. This meta-analysis included 18 good quality RCTs that compared PRP or PRF to a control in rotator cuff repair.

This meta-analysis showed that PRP significantly decreased rates of incomplete tendon healing for all tears combined (17.2% vs. 30.5%, respectively; $P < .05$), compared to the control. The PRP exhibited significant improvement in the Constant score (85.6 vs. 83.1, respectively; $P < .05$) and the visual analogue score for pain at both at 30 days and at final follow-up. By contrast, PRF exhibited no statistically significant benefit in terms of either improving tendon healing rates or in functional outcomes.

This review suggests that PRP can potentially improve tendon healing rates in rotator cuff repair in tears of all sizes, pain levels, and functional outcomes. Conversely, PRF has no beneficial effect on tendon healing or on clinical outcomes.

Bone morphogenic proteins (BMPs)

BMP-2 belongs to the group of bone morphogenetic proteins and plays an important role in the development of bone and cartilage.

The effects of BMP-2 have not been found to be as beneficial as BMP-7 in tendon healing. For example, Lipner et al. noted that injecting BMP-2 in an MSC-seeded scaffold for RCT led to impaired healing. They therefore suggested that this GF should not be used in tendon-to-bone repair setting [17]. Pauly et al. also found that the application of BMP-2 increased collagen type I production substantially although tenocyte cell activity decreased over time. Furthermore, the addition of both factors (BMP-2, BMP-7) resulted in decreased parameters when compared with BMP-7 alone [18]. In another study, the sustained release of BMP-7 employing a gelatin hydrogel sheet (GHS) was compared to BMP-7 injection only; BMP-7 using GHS demonstrated more favourable cartilage matrix production and tendon orientation, a higher tendon-to-bone maturing score, and ultimate force to failure to stimulate rotator cuff repair [19].

Transforming growth factor (TGF)

Transforming growth factor beta (TGF-β) is a multifunctional cytokine belonging to the transforming growth factor superfamily that includes four different isoforms (TGF-β 1–4, HGNC symbols TGFB1, TGFB2, TGFB3, TGFB4) and many other signalling proteins produced by all white blood cell lineages. Research studies have also debated for and against the use of TGF-β, whose signalling can be significantly upregulated after RC tears, as a means of biologically enhancing repair. Kim et al., for example, used a rotator cuff rat repair model to show that TGF-β isoforms play vital roles in tendon-to-bone development and healing. However, the application of exogenous TGF-β isoforms and neutralising antibodies to the subacromial space using osmotic pumps did not improve supraspinatus tendon-to-bone healing [20]. Employing a rat RC repair model, Kovasevic et al. compared the effect of TGF-β3 in an injectable calcium phosphate (Ca-P) matrix to a group with Ca-P matrix alone and a control group. The addition of TGF-β3 significantly improved the repair strength at 4 weeks post-operatively and resulted in a more favourable COLI/COLIII ratio at the tendon–bone interface [21]. Manning et al. [22] noted that, compared to controls, sustained TGF-β3 delivery at the tendon-to-bone insertion, using a heparin/fibrin-based delivery system (HBDS), produced significant improvements in structural properties at 28 days and in material properties at 56 days.

Platelet-derived growth factor (PDGF-BB)

Platelet-derived growth factor (PDGF) is one of the numerous growth factors that regulate cell growth and division. In particular, PDGF plays a significant role in blood vessel formation, the growth of blood vessels from already-existing blood vessel tissue, mitogenesis, i.e. proliferation, of mesenchymal cells such as fibroblasts, osteoblasts, tenocytes, vascular smooth muscle cells and mesenchymal stem cells as well as chemotaxis, the directed migration, of mesenchymal cells.

PDGF-BB has been tested in combination with biological scaffolds with conflicting results. In an acute ovine model of rotator cuff repair, a recombinant human PDGF-BB (rhPDGF-BB) combined with a highly porous type I bovine collagen matrix improved the biomechanical function and morphologic appearance of the repair in a dose-dependent manner, relative to a suture-only control, after 12 weeks [23]. Uggen et al. compared a suture coated with recombinant human platelet-derived growth factor BB (rhPDGF-BB) in sheep rotator cuff repairs to an uncoated suture control group. At early follow-up, rhPDGF-BB-coated sutures enhanced histological scores; however, the ultimate load-to-failure was equivalent to standard suture repairs [24].

Fibroblast growth factor (FGF)

Fibroblast growth factors are a family of cell signalling proteins that are involved in a wide variety of processes, most notably as crucial elements for normal development. FGF in animal studies has promoted the growth of tenogenic progenitor cells, resulting in biomechanical and histological improvement of the repaired rotator cuffs. Ide et al., using a rat model, compared the local application of FGF-2 in rotator cuff tendon defects reconstructed with acellular dermal matrix (ADM) grafts to a control group. The remodelling of ADM grafts was accelerated by the local administration of FGF-2 [25]. Furthermore, in a sheep rotator cuff repair model, the use of a scaffold containing F2A, a peptide mimetic of basic fibroblast growth factor (FGF), improved tendon-to-bone healing and increased the thickness of the repaired tendon at 8 weeks [26]. Zhao et al. [27] employed a basic FGF-loaded electrospun poly (lactide-co-glycolide) (PLGA) fibrous membrane to repair RC tears in a rat model. At 2, 4, and 8 weeks, bFGF-PLGA fibrous membranes significantly improved the histological and biomechanical characteristics at the repair site, in comparison with a PLGA only group and a control group.

Granulocyte-colony stimulating factor (G-CSF)

Granulocyte-colony stimulating factor (G-CSF or GCSF), also known as colony-stimulating factor 3 (CSF 3), is a glycoprotein that stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream. Two studies on G-CSF application in RCT repair have also yielded conflicting results. For example, the systemic administration of G-CSF in a rat rotator cuff repair model decreased bone density at the tendon-to-bone insertion but did not improve the biomechanical or histological characteristics of the repair [28]. However, in a chronic rat tendon

tear model, Buchmann et al. [29] found that, compared to a control, the continuous application of both isolated growth factors (G-CSF/b-FGF) improved tendon remodelling when tested for histology.

Other growth factors

Finally, in animal models of rotator cuff repair, the zinc finger transcription factor early growth response 1 (EGR1, nuclear protein and functions as a transcriptional regulator) and cartilage-derived morphogenetic protein 2 growth factor (CDMP-2, subgroup of the bone morphogenetic protein (BMP) gene family) induced a more organised form of healing in histological terms and promoted tendon repair [30, 31].

Gulotta et al. concluded that a TNF-α blockade might improve the strength of tendon–bone healing at early time points, with modest qualitative histological improvements. However, these differences were not maintained at 8 weeks [32]. Using a rat rotator cuff repair model, Cheng et al. investigated the role of TNF alpha-stimulated gene/protein 6 (TSG-6) in the treatment of rotator cuff healing with tendon-derived stem cells (TDSCs). They concluded that TSG-6 mediates the function of TDSCs, improving the structure and the attachment strength of the healing tendon–bone interface [33].

Stem cells

Laboratory studies

Stem cells are biological cells that can differentiate into other types of cells and can divide to produce more of the same type of stem cells. Several researchers have investigated the regenerating potential of specific cell populations isolated from the anatomic shoulder structures of patients with RC tears and healthy individuals [34]. Their common conclusion was that there is a significant cell depot in the shoulder joint that can be manipulated to promote or augment RC repair healing.

When injected into the supraspinatus tendons of nude rats, muscle-derived cells (MDCs) were able to differentiate into other cell lineages, such as fibroblasts [35]. In two studies, Meyer et al. examined the regenerating potential of RC muscle post-injury and subsequent repair. They found that cells from epimuscular fat in patients with degenerative tears exhibited better stem cell potential and promoted myogenesis in the neighbouring cells, compared to healthy individuals. In a separate study, the skeletal muscle progenitor (SMP) cell pool population was found to be larger in muscles from cuffs with partial tears but exhibited a reduced proliferative ability, compared with no tears or full-thickness tears. However, cells from all cuff states, when provided with the correct signals, were capable of contributing to muscle hypertrophy and regeneration regardless of tear severity [36, 37].

Three days after collagenase-induced rotator cuff injuries were applied in a rat model, Chen et al. injected adipose-derived stem cells (ADSCs) into the tendon during the healing process, while a control group was injected with saline. In the ADSC-injected group, the fibre arrangement and tendon organisation improved and the number of inflammatory cells significantly decreased. Furthermore, the load-to-failure was notably higher and the tensile strength of the supraspinatus tendon was significantly improved [38].

In another rat rotator cuff repair model, the application of ADSCs failed to improve the biomechanical properties of tendon-to-bone healing. However, the ADSCs group exhibited less of an inflammatory, possibly resulting in a more elastic repair and healing that was less scarred [39]. In a rabbit RC repair model, Kim et al. [40] noted that, compared to a control (saline injection) group, injecting ADSCs at the muscle belly near musculotendinous junction assisted the regeneration of the rotator cuff muscle by way of an insulin-like growth factor 1 (IGF-1) signalling pathway.

In another study, the injection of human umbilical cord blood (UCB)-derived MSCs (mesenchymal stem cells) under ultrasound guidance led to the regeneration of 7 out of 10 full-thickness cuff tears non-operatively [41]. Gumucio et al. injected stromal vascular fraction stem cells (SVFCs) in the supraspinatus muscle in chronic induced tears into a rat model 30 days after repair of the tendons. Rats that were treated with SVFCs injection exhibited a 40% reduction in fibrosis in the muscle, but there were no differences in lipid content or force production [42].

Cells from the subacromial bursa (BS), rotator cuff tendon [43], biceps tendon, and synovial fluid have also been isolated to histologically evaluate their regenerating potential. These cells constitute an easily accessible source of stem cells and have been found to fulfil the characteristics of mesenchymal stem cells with a high potential for application in tendon repair. Song et al. isolated cells from the BS of patients undergoing rotator cuff surgery. The cells exhibited MSC characteristics and proliferative capacity and were highly efficient in differentiating into cells of mesenchymal lineages. When properly stimulated, they formed a bone, tendon-like and fibrocartilaginous tissue [44]. Steinert et al. isolated cells from the BS of patients with degenerate rotator cuff tears and compared them with bone marrow stem cells derived from patients with osteoarthritic hips. Their aim was to assess their potential to proliferate and differentiate along chondrogenic, osteogenic, and adipogenic lineages under specific culture conditions [45]. Klatte-Schulz et al. found that the cell count and potency for self-renewal significantly decreased in tenocyte-like cells (TLCs) from donors with high muscle fatty infiltration, compared to lower

fatty infiltration groups, indicating one reason for weaker healing among this group of patients [7]. Utsunomiya et al. obtained human MSCs during arthroscopic surgery for RC tears from the synovium of the glenohumeral joint, subacromial bursa, the margin of the ruptured supraspinatus tendon, and the residual tendon stump on the greater tuberosity (enthesis) of 19 donors. They concluded that synovial cells from the BS in patients with rotator cuff tears are the best cell source in vitro, and these cells are likely to represent the optimal autologous biological adjunct in operative repairs [46]. Randelli et al. collected cultured and phenotypically characterised human tendon samples from the supraspinatus and the long head of the biceps (LHB) during rotator cuff tendon surgeries on 26 patients. The cells displayed pluripotent potential in that they could be induced to differentiate into different cell types: osteoblasts, adipocytes, and skeletal muscle cells, thus possessing high regenerative potential [47]. Tsai et al. isolated MSCs from human rotator cuffs and found that these exhibited the potential to undergo osteogenic, adipogenic, and chondrogenic differentiation. The authors concluded that these results support the application of RC-MSCs in myogenic regeneration [48].

Several studies have now suggested that the application of MSCs and other biological substitutes such as DBM [49] or periosteum [50] in the repair site is able to augment tendon-to-bone healing [51].

MSC content at the tendon–bone interface of greater tuberosity in patients with symptomatic RC tears is significantly reduced when compared to control patients without RC injury. The level of MSCs decreased as a function of several clinical factors, including time from tear onset to treatment, tear size, number of tears, and the stage of fatty infiltration [52]. Connective tissue progenitor cells can be safely and efficiently aspirated from the proximal humerus using anchor tunnels created during arthroscopic rotator cuff surgery [53]. Using a rat rotator cuff repair model, Kida et al. compared tendons repaired with or without greater tuberosity bone marrow drilling and found that in the drilled group there were more GFP-positive cells and the greater ultimate force to failure was significantly higher in the drilled versus the control group. Bone marrow-derived cells passed through holes drilled in the footprint, infiltrated the repaired rotator cuff, and contributed to post-surgical rotator cuff healing [54].

However, other studies have not been able to replicate these promising results. Levy et al. hypothesised that, in a rat RC repair model, using a cannulated humeral implant to ensure the continuous release of MSC in the repair site would improve healing when compared to a non-cannulated implant control group. Tendon thickness, all biomechanical measures, and semi-quantitative histological scores improved over time; however, humeral cannulation did not quantifiably improve tendon-to-bone healing [55].

Genetically modified stem cells may improve rotator cuff tendon healing and reduce the incidence of re-tears. The application of MSCs transduced with adenoviral-mediated scleraxis (Ad-Scx), thought to direct tendon development during embryogenesis, resulted in more fibrocartilage, higher ultimate load to failure, and higher stiffness values than a simple MSC group [56]. However, MSCs transduced with BMP-13 did not improve healing, histologically or biomechanically, in a rat model [57].

Loeffler et al. seeded cells from tendon–bone interface in sponges which were implanted in the repair site of a rat supraspinatus repair model. The treated rats displayed increased cellularity, inflammation, vascularity, and collagen organisation, compared to four differently treated groups. There was no difference in collagen organisation, compared to the healthy group, supporting the use of tendon–bone interface cells in rotator cuff healing [58].

Using a rat model, Tornero-Esteban et al. recently compared the implantation of MSCs along with a collagen I scaffold into surgically created tendon defects to a suture-only and scaffold-only group. The implantation of MSCs improved the maximum load of the tendon over time [59]. Omi et al., employing a rat rotator cuff repair model, evaluated the use of a composite of multilayer tendon slices (COMTS) seeded with bone marrow stromal cells (BMSCs) on supraspinatus tendon repair under tension versus COMTS only and no augmentation groups. Although the COMTS scaffold did not increase the initial repair strength, the BMSC-seeded scaffold increased healing strength and stiffness at 6 weeks [60].

Kim et al. explored whether a MSC-seeded three-dimensional construct into an acute rabbit rotator cuff tendon defect would promote cellular differentiation and matrix healing, compared to a cell-free scaffold group. Numerous MSCs in the scaffold survived after implantation, while the generation of type I collagen increased more significantly in the scaffold with MSCs [61].

Clinical studies

Clinical studies investigating the use of stem cells in the surgical treatment of rotator cuff tears have noted the importance of biological enhancement of the repair.

In a study conducted by Gomes et al., 14 patients with complete RC tears were fixed with transosseous stitches through, with subsequent injection of autologous bone marrow mononuclear cells (BMMC) into the tendon borders, obtained from the iliac crest, immediately prior to surgery. After a minimum 1-year follow-up period, the UCLA score increased significantly. MRI analysis at 12 months demonstrated tendon integrity in all cases, while clinical findings remained unchanged in the following year for all but one of the patients. The authors concluded that implantation

of BMMC in rotator cuff sutures appears to be a safe and promising biological approach that enhances tissue quality in affected tendons [62].

Hernigou et al. injected 45 patients with iliac crest bone marrow-derived MSCs as an adjunct to single-row rotator cuff repair at the time of arthroscopy and compared this to a non-augmented repair control group of 45 patients. The MSC injection enhanced the healing rate and improved the quality of the repair as determined by ultrasound and MRI. All the repairs with MSC augmentation had healed by six months, compared to 67% of the control group. At 10 years, intact rotator cuffs were found in 87% of the MSC-treated group and only 44% of the control group. Patients with a loss of tendon integrity at any time up to the 10-year follow-up milestone received fewer MSCs than those who had maintained successful repair during the same interval [63].

Taniguchi et al. evaluated bone marrow stimulation (BMS) at the footprint of arthroscopic RC repair. A total of 111 patients with chronic RC tears who underwent arthroscopic repair, either with BMS by the drilling of multiple holes at the footprint (67 shoulders) or without BMS (44 shoulders), were studied prospectively. The overall re-tear rate, evaluated using an MRI scan, was 23.9% in the non-BMS group and 9.1% in the BMS group. For large tears, the re-tear rate was significantly higher in the non-BMS group (28.6%) than in the BMS group (4.5%); however, the rates for medium-size tears were comparable between the two groups [64].

In a study by Jo et al., 57 out of 124 patients with a full-thickness RC tear underwent arthroscopic RC repair with multiple channelling, while 67 did not. MSCs negative for CD45 and positive for CD73, CD90, and CD105 could be isolated and cultured from bone marrow mononuclear cells of the proximal humerus. There was no statistical difference between the two groups in terms of clinical outcomes, including pain, range of motion, strength, overall satisfaction, and functional scores. Assessed using magnetic resonance imaging or computed tomography arthrography, the re-tear rate of the multiple channelling group (22.2%) was significantly lower than that of the conventional group (45.2%). Multiple channelling significantly decreased the re-tear rate after arthroscopic RC repair, most likely through the recruitment of endogenous MSCs from the proximal humerus. However, the results did not exhibit any significant differences in clinical outcomes between the two groups [7].

Discussion

To improve the biomechanical and histological properties of the repair site and thus the clinical outcomes for patients, the efficacy of augmenting rotator cuff repair by stem cells and GFs was investigated. Overall, the results are promising, but it is still not possible to draw definite conclusions [7]. Review articles have also tried to categorise and evaluate these studies to develop effective treatment strategies.

A Cochrane Review assessed the effects of platelet-rich therapies on the treatment of musculoskeletal soft tissue injuries. Selection criteria comprised randomised and quasi-randomised controlled trials (RCTs) that compared platelet-rich therapy with placebo, autologous whole blood, dry needling, or no platelet-rich therapy for people with acute or chronic musculoskeletal soft tissue injuries. Primary outcomes included functional status, pain, and adverse effects. Nineteen studies were included. The authors concluded that currently there is insufficient evidence to support the use of platelet-rich therapy in the treatment of musculoskeletal soft tissue injuries [65].

Moraes et al., also in a Cochrane Review, assessed the effects of platelet-rich therapies (PRT) in treating musculoskeletal soft tissue injuries, including rotator cuff tears. They concluded that there is currently insufficient evidence to support the use of PRT in the treatment of musculoskeletal soft tissue injuries [66].

In a very recent meta-analysis, Cai et al. reviewed the efficacy of PRP in arthroscopic repair of full-thickness rotator cuff tears. Five studies were included and used to extrapolate data. Cai et al. noted that there were no significant differences in outcome scores between PRP and non-PRP patient groups. However, for small-to-medium-sized tears, the failure-to-heal rate significantly decreased in PRP-treated patients, indicating an improvement in tendon-to-bone healing [67].

In a systematic review of the current evidence for the effects of stem cells on tendon healing in preclinical studies and human studies, Ahmad et al. concluded that stem cells can have a positive effect on tendon healing. This is because of their regeneration potential, producing tissue similar to that in a healthy state, although the results can be variable. They also noted that the use of adjuncts such as molecular signalling, mechanical stimulation, and augmentation devices can potentially enhance stem cell therapy [68].

Factor	Study	Outcome
PRFM	Castricini et al. [14]	No improvement in functional outcomes Increased re-tear rates
	Bergeson et al. [13]	Similar results to Catrinici
	Zumstein et al. [14]	No effects on the clinical and radiological evidence
PRP	Beck et al. [8]	Increased fibroblastic and vascular proliferation Failure to enhance tendon-to-bone healing in a rat model

Factor	Study	Outcome
	Jo et al. [13]	Enhances gene expression and synthesis of tendon matrix in degenerated human RC tendon
	Chung et al. [12] and Wu et al. [11]	Improved RC healing in a rabbit model
	Dolkart et al. [9]	Improved tendon healing
	Ersen et al. [10]	Greater strength to mean load-to-failure stiffness of the tendon
	Cross et al. [5]	Better results in tendon healing with low-leucocyte concentration PRP
	Cai et al. [67]	Improved results in small-size tears
	Grambart [65] and Moraes [66]	Insufficient data to support the use of PRP
	Hurley et al. [16]	PRP improved healing, no effect from PRF
PRGF	Hoppe et al. [6]	Proliferation of tenocytes
BMPs	Pauly et al. [18]	BMP 2 increases collagen type 1 activity, but tenocyte activity decreases by time
	Lipner et al. [17]	BMP 2 impaired tendon healing
	Kabuto et al. [19]	BMP 7 and GHS more favourable cortical matrix production and tendon orientation
TGF	Kim et al. [20]	Exogenous TGF β did not improve the healing of supraspinatus
	Kovacevic et al. [21]	TGF β3 and calcium phosphate matrix improved tendon repair strength in a rat model
	Manning et al. [22]	TGF β3 demonstrated significant improvement in structural properties in 28 days
PGDF$\beta\beta$	Hee et al. [23]	Improvement of the biomechanical function and morphological appearance of the repair
	Uggen et al. [24]	Enhanced histological scores at early follow-up, using a suture coated with PGDF$\beta\beta$
FGF	Ide et al. [25]	FGF 2 accelerated remodelling in a rat model RC
	Zhao et al. [27]	FGF-loaded membrane significantly improved the histological and biomechanical characteristics at the repair site
	Peterson et al. [26]	Improved tendon-to-bone healing and thickness of the repaired tendon in a sheep model
GCSF	Buchman et al. [29]	G-CSF and 6FGF improved histological results in a rat tendon tear model
	Ross et al. [28]	No biomechanical or histological improvement of the repair in a rat model
EGR1	Tao et al. [30]	Promoted tendon repair
CDMP-2	Murray et al. [31]	Promoted tendon repair
TNF-α blockade	Gullota et al. [32]	Might improve tendon-to-bone healing at early time points, but not maintained after 8/52
TSG 6	Cheng et al. [33]	Improves the structure and attachment strength of the healing tendon bone interface
Stem cells	Pelinkovic et al. [35]	MDCs in supraspinatus tendon of rats promotes differentiation into fibroblasts
	Sundar [49], Chang [50] and Durant [51]	MSCs, DBM, and periosteum augment tendon-to-bone healing
	Mazzocca et al. [53]	Connective tissue progenitor cells aspirated from anchor tunnels
	Gulotta et al. [56]	Genetically modified Stem cells improve regeneration of tendon-to-bone insertion site
	MacLean et al. [34]	MSCs promote RC healing/repair

Factor	Study	Outcome
	Gulotta et al. [32]	Genetically modified stem cells improve regeneration at tendon-to-bone insertion site
	Song et al. [44]	BS with MSCs characteristics produce bone tendon-like fibrocartilaginous tissue
	Utsunomiya et al. [46]	Human MSC is the optimal autologous biological adjunct for RC repair
	Randelli et al. [47]	Cells from cultured human tendon samples from SS and LHB demonstrate high regenerative potential
	Tsai et al. [48]	MSCs from human RC demonstrated osteogenic, adipogenic and chondrogenic potential
	Kida et al. [54]	Bone marrow-derived cells contributed to RC healing in a rat model
	Levy et al. [55]	Improved tendon thickness, biomechanical measures, and histological scores
	Loeffler et al. [58]	Increased cellularity, inflammation, vascularity, and collagen organisation in a rat model
	Kim et al. [61]	In a rabbit RC tear model, numerous MSCs survived after implantation
	Mora et al. [39]	ADSCs in a rat model, more elastic repair and less scarring
	Kim et al. [40]	In a rat model, injection of stem cells at the musculotendinous junction assisted regeneration of the RC
	Meyer et al. [36]	Two studies, MSCs contribute to muscle hypertrophy and regeneration
	Chen et al. [38]	Injection of ADSCs, higher load to failure, improved tensile strength in a rat model
	Park et al. [41]	Human MSCs injected, promoted regeneration in 7 out of 10 full-thickness tears
	Gumucio et al. [42]	SVFCS in supraspinatus rat RC resulted in 40% less fibrosis
	Steinert et al. [45]	Cells from BS demonstrated potential to differentiate into other lineages
	Hernigou et al. [52]	MSC reduced levels in patients with symptomatic RC tears
	Tornero-Esteban et al. [59]	In a rat model, MSC implantation improved the maximum load of the tendon
	Omi et al. [60]	In a rat model, the BMSC scaffold increased healing strength and stiffness in 6/52
	Gomes et al. [62]	Mononuclear autologous stem cells enhanced tissue quality of the tendon
	Ahmad et al. [68]	Stem cells can have positive effect on tendon healing
	Jo et al. [7]	Multiple channelling improves the structural integrity of the RC repair
	Hernigou et al. [63]	MSC augmentation improves healing and prevents further RC tears
	Taniguchi et al. [64]	Bone marrow stimulation at the footprint advances cuff repair integrity

Conclusion

This review study has focused on recent research evaluating the role of GFs and stem cells in the treatment of rotator cuff tendon repair. In vitro laboratory studies and animal studies suggest that the use of GFs introduced at the time of rotator cuff repair might promote more rapid healing and

correspondingly fast patient rehabilitation [31], while MSCs are thought to promote tendon healing when applied at the tendon defect [43]. Individual clinical studies, on the other hand, support the use of bone marrow-derived MSC augmentation [63] but do not encourage the use of PRP or GFs in rotator cuff repair [15]. Further laboratory and RCTs are needed until a satisfactory procedure can be established for the routine use of these cells and GFs in shoulder surgery.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

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