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MEDICINE

Rotator Cuff Repair Augmentation Using Osteoinductive Growth Factors

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Abstract

Rotator cuff injuries (RCIs) present a major health problem due to high incidences of degenerative tears greater than 3 cm and prevalence of re-tears following surgical procedures. Since healing and functional restoration relies upon bone ingrowth into the tendon, it is hypothesised that sustained delivery of osteoinductive factors including bone morphogenetic proteins (BMPs), specifically BMP2–7, may significantly improve RCI tendon-bone healing. Here, growth factor candidates and delivery mechanisms are reviewed, specifically for improved RCI healing through enhanced bone ingrowth. In addition to BMPs, other potentially osteogenic factors including platelet-derived growth factors (PDGF), fibroblast growth factor (FGF), transforming growth beta isoforms (TGF-β1 and TGF-3) and parathyroid hormone (PTH) are evaluated since they can induce bone formation at the healing tendon attachment site. Several challenges must be addressed prior to clinical translation. The majority of published studies utilise in vivo animal models. In general, BMP-7 demonstrates a stronger stimulating effect when compared to BMP-2; the reported effectiveness of BMP-2 is often conflicting. Alternative factors, including PDGF and PTH, also demonstrate potential for assisting bone growth in enthesis healing. The use of sustained and biomimetic delivery systems appears to have the greatest positive effects. Some studies have demonstrated a dose-dependent effect, in conjunction with varying age, indicating that stratified therapies could be a viable solution for RCI healing. To adequately resolve potential treatments for RCI, further expanded and correlated animal trials must be undertaken, and indicative human trials are required with consideration of surgical and patient-specific influences.

Keywords Rotator cuff · Osteoinductive · Bone morphogenetic proteins · Growth factors · Enthesis healing

Introduction

Rotator cuff tears are a highly prevalent musculoskeletal injury (Fig. 1); more than 200,000 repair procedures are performed annually in the USA alone, resulting in an estimated $474 million in health care costs [1]. Furthermore, there is a high prevalence of structural failures post repair, with surgically repaired tendons prone to a high rate of re-tear (between 20 and 95%) [1]. It is known that rotator cuff healing occurs in 3 stages: *inflammation, repair*, and *remodelling*. Upon completion of the healing process, the normal rotator cuff enthesis (osteotendinous unit) fails to regenerate [2]. Following repair, rotator cuff tendon healing is often limited by a deficit in tissue formation, with gap formation at the repair site being a common occurrence. Hence, the tendon is weaker than the native insertion site, which renders repairs prone to failure and, thus, repeat injuries [3].

A review of experimental studies by Gulotta and Rodeo (2009) established that bone ingrowth is vital to the healing of the repaired rotator cuff tendon and bone [3]. With this in mind, it has been hypothesised that the administration of osteoinductive agents could improve the healing of a tendon attached to the bone surface and thus strengthen the repair [3]. As a result, there have been a number of studies aimed at analysing the use of osteoinductive factors including bone morphogenetic proteins, e.g. BMP-2 through 7; for rotator cuff enthesis healing [1]. Promising results using osteoinductive factors to improve tendon healing have been reported both in vitro and in vivo, although the majority of studies are reliant upon the use of animal models [4]. However, peer-reviewed

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reports, which evaluate osteoinductive growth factors specifically for rotator cuff injuries, remain limited [5–10]; and there has yet to be a study that evaluates the effectiveness of growth factors in the treatment of rotator cuff injuries (RCIs) in humans [11].

Within the existing literature, it has become apparent that multiple factors play a role when attempting to optimise the dosage of growth factors for therapeutic applications. Determining the most effective factor or combination of factors, the optimum dose, timing, and vehicle for delivery, whilst maintaining their localisation and intended bioactivity at the injury site, is a requisite [1]. When assessing whether an intervention is successful in impacting healing in RCI, the effects of surgery and general condition of the patient, animal or human, is an important consideration. Potential factors which can affect healing have been extensively studied and reviewed [12–14] and should be listed in any report to enable true comparisons between studies (Table 1).

Identifying the most appropriate preclinical model to evaluate the strategy is also necessary as no single animal model is capable of reproducing all of the features of the human injury, and hence, this review aims to compare the current strategies that have used osteoinductive growth factors specifically for injuries of the rotator cuff, with some inference from the similar anterior cruciate ligament (ACL), to identify the most promising methods for biological augmentation. BMPs 12–14, also known as growth differentiation factors (GDFs) 5–7 are distinct from the osteoinductive BMPs (BMP-2, BMP-4, BMP-7) in the sense that they promote tendon and fibrocartilage formation [3] and not bone and, hence, will not be evaluated in this review.

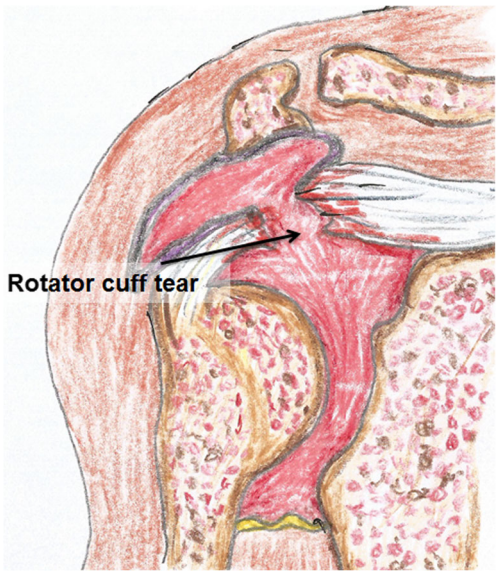

Fig. 1 Rotator cuff tear and gap formation

Comparison of Delivery Vehicles for Growth Factor Therapies

Due to their short half-life, and a low specificity in vivo [85] determining how to regulate growth factor activity is vital when developing therapeutic treatments. There are several methods that have been investigated both in vivo and in vitro with the specific aim of promoting a sustained, localised release of growth factors at the injury site.

In Vivo Models

In an early study by Rodeo (2007), an "*osteoinductive bone marrow protein extract*" comprised of proteins BMP-2 through 7, transforming growth factor beta 1 to 3 (TGF-β1–3), and basic fibroblast growth factor (b-FGF) were delivered as a growth factor mixture via a collagen sponge, in an ovine infraspinatus tendon detachment model [5]. Rodeo hypothesised that this could improve the healing of a tendon attached to the bone surface as it would induce greater bone ingrowth [5]. New bone and soft tissue formation were analysed via radiographs, magnetic resonance imaging (MRI), and histological analysis at 6 and 12 weeks. In comparison to the control groups, the specimens that had received growth factor treatment demonstrated significantly higher levels of new bone formation (not present in controls) and newly formed soft tissue in the tendon-bone gap. Tensile testing revealed that the ultimate load-to-failure was significantly greater following growth factor treatment, when compared to collagen implants alone at 6 weeks [5]. However, these failure loads were only approximately 31% of the normal tendon strength; this could be due to the disorganised reparative matrix resulting in inferior biomechanical properties. Furthermore, the authors postulated that the collagen sponge implant may have elicited a subtle immune response that was detrimental to new tissue formation. This highlights the importance of the appropriate selection and need to understand the kinetics of the delivery scaffold.

In a following study, Kovacevic and Rodeo (2008) discuss two sheep model studies, observing the effect of mixed fibroblast growth factor (FGF) and BMP-2 through 7 and BMP-12 in various delivery vehicles. Akin to the previously reported studies in ovine models (suture through bone tunnel), it was observed that scar tissue formed within the gap between tendon and bone; however, the mixture created a more robust fibrocartilaginous zone in comparison to controls. Intervention with BMP-12 resulted in increased load-to-failure ratios and stiffness (up to three times greater) after 8 weeks. From histological evaluation of the groups, re-establishment of the collagen fibre continuity between the bone and enthesis scar tissue was observed. Increased content of glycosaminoglycans (GAGs) was also present suggesting fibrocartilage formation [86].

Table 1 Factors which affect healing of rotator cuff healing

Surgical	
Repair technique	Open vs arthroscopic [15–18]
	Single or double row suture [19–22]
	Medial knots or knotless [23–25]
Suture anchor	Material, design, size, loaded suture material/numbers, location, configuration [26, 27]
Greater tuberosity preparation	Considered to be standard procedure, however positioning of shoulder may be detrimental in osteoporotic bone anchor fixation [12, 28–30]
Acrominosplasty	Removal of acromial spur in response to full thickness tear is commonplace; although optimal timing of acrominoplasty remains unclear [12, 31–34]
Augmentation	Use of patches: material, sizes vary [35–39]
	Platelet-rich plasma [40–43]
	Cell therapy (e.g. mesenchymal stem cells) [44–47]
Post-operative rehabilitation	Can be modified based on surgeon preference, tear size, location, and quality of repair [12, 48, 49]
	Removal of load [50, 51]
	Onset, number of therapy visits, duration of follow-up [49, 52, 53]
	Early vs delayed motion/immobilisation [12, 54–56]
Patient specific	
Age	Average age of unilateral tear—59 years; bilateral tears—68 years. Inferior healing environment in older patients [12, 57]
Healing environment	Presence of factors which negatively affect repair tissue (e.g. MMP-1, MMP-9, TNFα); which positively affect repair (e.g. inhibitors of aforementioned molecules, BMPs, TGF-β)
Tear characteristics	Larger size, fatty infiltration, and/or atrophy all negatively impact healing [12, 58]
	Number of tendons involved
	Recurrent vs preoperative tear size
	Normal vs degenerative/delaminated tissue; fatty infiltration and atrophy often correlates with poor functional/clinical outcome and failed repair [58–60]
	Amount of muscle-tendon unit retraction, the preoperative tendon length may act as a predictor of reparability [61, 62]
Timeline of symptoms	Surgery > 1 year vs ≤ 1 year since onset
Bone mineral density (BMD)	Normal vs osteoporosis (OP), vitamin D deficiency; reduced BMD, and OP may cause difficulties in achieving reliable fixation, reduces tendon-bone insertion strength, and detrimentally affects healing [63, 64]. Vitamin D has been linked to bone and muscle proliferation and healing [65, 66].
Pain control	Nonsteroidal anti-inflammatory drugs (NSAIDs) vs narcotics use: NSAIDs are commonly prescribed following repair; however, their effect on healing is conflicting in the literature [67–69] . Narcotics including opiates relieve post-operative pain [70] but have undesirable side effects [71] so are not recommended for long term use [72]
Diabetes	Diabetes can impair fibrocartilage formation and collagen organisation leading to post-operative wound complications [73–76]
Smoking	Smoking has been linked to increased risk and severity of rotator cuff tears [77, 78]; non-smokers have greater improvement of pain and post-operative results [79]
Hypercholesterolemia	Hypercholesterolemia has been linked to an increased likelihood of rotator cuff tears and is detrimental to healing [80–84]

As an isolated component, BMP-7 has been reported to induce cell differentiation into chondrocytes and stimulate cartilage matrix production when delivered to the shoulder joint of rats [8]. It was hypothesised that the use of a cross-linked gelatine hydrogel sheet (GHS) would maintain a sustained release and localised concentration of BMP-7, thus promoting rotator cuff repair. In comparison to controls, whereby BMP-7 was administered to the subacromial bursa via injection, GHS impregnated with BMP-7 and implanted onto tendon demonstrated significantly improved enthesis matrix production and, as a result, improved tendon-to-bone maturation scores and biomechanical properties [8]. Thus, the use of gelatine hydrogels, which are approved for clinical applications, provide an economical, customisable scaffold for the sustained release of BMP-7 for up to several weeks and a viable solution for RCI repair.

In addition to the use of hydrogel scaffolds, the use of biological patches has been investigated as an alternative delivery solution, particularly for large tears and rotator cuff repairs that have been deemed "*irreparable*" [87]. Lee et al. (2016) first reported the use of a dermal patch isolated from a human cadaver, to deliver BMP-2 [10]. In the study, a rhBMP-2-coated dermal patch (1 cm × 2 cm) was inserted in a leporine model of chronic RCI. The purpose was to evaluate the

effectiveness of the healing-inductive capacity of the biological patch. The results demonstrated that the inserted rhBMP-2-coated acellular dermal patch significantly improved new bone formation and enhanced biomechanical properties including ultimate tensile strength [10]. Although there are numerous materials available for biological patches including dermal matrices, xenogeneic intestinal submucosa or pericardium, and ceramic- or polymer-based synthetics available [88, 89], the biomechanical properties of cadaveric acellular dermal matrices appear to be a better option; potentially due to the maintenance and continuity of the inherent collagen structure. However, irrespective of the delivery mechanism or material, caution must be used with the sustained delivery of high-dosage BMPs, since BMP-7, and more frequently BMP-2, is often associated with complications including overabundant bone growth and heterotrophic ossification (HO) [35–37, 90, 91] when used to treat musculoskeletal disorders.

In developmental biology, Indian Hedgehog (Ihh) and parathyroid hormone (PTH)-related peptide (PTHrP) exist as reciprocal mediators in a feedback loop to control both chondrogenesis and mineralisation of the growth plate and enthesis [38, 39]. Taking cues from this, Hettrich et al. (2012) injected 114 Sprague-Dawley rats subcutaneously with 10 μg/kg of rhPTH on the day of surgery. From this, increased mineral content, bone volume, fibrocartilage, osteoblast presence, and blood vessels, as well as more favourable collagen fibre organisation, was observed after 56 days. Despite this, the biomechanical properties of the interface did not improve, suggesting either greater integration is needed or additional stimuli to enhance these properties [92]. A follow-up study by Duchman et al. (2016), utilising the same dosage and model in 108 rats, delayed the start of rhPTH injection until day 7 post-surgery to avoid the inflammatory phase. Two weeks postoperatively, treated rats demonstrated significantly greater load-to-failure than controls, although at 16 weeks, no significant differences were found [93].

In Vitro Models

Pauly (2012) aimed to investigate whether BMP-2 and BMP-7 could positively affect human RC tenocytes in vitro [6]. The tenocyte-like cells (TLCs) isolated from human supraspinatus and the long head of the biceps were isolated and incubated with the growth factors, alone and in combination. BMP-7 stimulated TLC activity, expression and production of collagen-I, in a dose-dependent manner. BMP-2 also stimulated collagen-I production in TLCs; however, cell activity decreased with higher dosages. The combination of BMP-2 and BMP-7 reduced all parameters in comparison to BMP-7 alone.

Klatte-Schultz (2013) postulated that inferior biological characteristics of TLCs may contribute to diminished rotator cuff healing [7]. In their study, the stimulation potential of human supraspinatus TLCs was investigated. Cell count, collagen-I expression, and protein synthesis, which are significant factors for the tendon-bone healing of the rotator cuff, were all stimulated following the application of BMP-2 and BMP-7 in 3D culture.

Critique of Growth Factor Therapies for Rotator Cuff Repair

In Vivo Strategies

Despite in vivo studies, tendon repair studies by Rodeo (2007) demonstrate that the use of a collagen sponge to deliver osteoinductive factors had the greatest biomechanical strength in comparison to the controls; it was observed that this technique consistently detached from the repair site with the gap only becoming evident following MRI analysis [5]. This is an important discovery since other investigators are using the same model for evaluation [86, 94–96]. Although they were unable to study healing of an intact tendon, the resultant model of tendon-bone gap healing is clinically relevant due to the reported high rate of gap formation between tendon-bone [97].

There are limitations to the animal model used in Rodeo's study, as the bone-forming potential of sheep is far greater than that in humans. Another limitation is that the healing of an acute repair was examined, which does not mimic the typical clinical situation. They also had a relatively small sample size, resulting in low power for clinical comparisons.

Despite the initial positive outcome from the later sheep model studies which utilised a mixture of fibroblast growth factor (FGF) and BMP-2 through 7, and BMP-12; it was suggested by Kovacevic and Rodeo (2008) that, following normalisation of failure loads to tissue volume, that the enhanced formation of fibrocartilage was actually poor-quality scar tissue rather than true regeneration.

Kabuto et al (2015) used GHS, which allows for the preservation of the biological activity of BMP-7 [8]. The different methods of growth factor application (injection vs. GHS implant) demonstrated the efficacy of delivery when comparing the GHS implant to local injection. This study also took into consideration the lengthy process of rotator cuff healing; hence, administered BMP-7 must exert a sustained effect. The GHS is a good option, as its safety is approved for clinical use and it is economically produced.

The sustained release of BMP-7 due to the GHS favourable collagen fibre orientation corresponds to the findings by Pauly (2012). The results also suggest that the GHS acted not only in the sustained release of growth factors but also by itself in tissue repair, similar to the collagen sponge in Rodeo's (2007) study. It is worth noting that Kabuto et al. did not observe any evidence of HO through microcomputed tomography (μCT) analysis. The sustained release at a reduced

dosage of BMP-7 may have reduced risk of formation, which has been reported previously as local concentrations of BMP-7 increase [36]. Kabuto et al. do, however, describe the limitations of the study in which the specific anatomy of the murine model differs from the human shoulder. Additionally, re-tear in rats has not been observed postoperatively, and as in the previous model, it does not reflect degenerative tear as in humans [50]. Despite this, the murine model is sufficiently similar enough to continue to be used in in vivo studies [98].

The work by Lee (2017) is the first study to evaluate effects of an acellular dermal patch combined with BMP-2 [10]. A chronic RCI model was used, which, in comparison to other published literature, is more representative of clinical injury. Acellular dermal matrix has shown much better mechanical support than any other ECM-based scaffolds [2]. However, the biodegradation of the GHS must be investigated further to optimise the healing and biomechanical outcomes.

Although rhBMP-2 has proven promising for tendon-bone healing, many limitations still remain for the clinical application based on safety and effectiveness; with conflicting evidence from a previous study on stromal cells which showed that rhBMP-2 led to impaired tendon-bone healing [9]. The study was also limited in that it did not demonstrate the effectiveness of various doses of rhBMP-2.

Hettrich et al. (2012) and Duchman (2016) investigated the use of Ihh and PTHrP in rats. Both these studies used a dosage based on previous literature, in which doses based in a range that may be tolerated by humans were found to be effective in enhancing fracture healing [99]. Although further optimisation of the timeline and dosage is obviously required, PTH represents a feasible augmentation to current surgical interventions in the treatment of rotator cuff repair.

In Vitro Strategies

Pauly (2012) evaluated the effect of BMP-2 and BMP-7 on human TLCs in vitro [6], unlike the aforementioned studies which only used animal models. As it compared both growth factors alone, it helped denote that overall, application of BMP-7 led to better results than with BMP-2. It also demonstrated that, the combined application of both showed decreased parameters when compared with BMP-7 alone; suggesting that BMP-2 could possibly exert a negative influence on the expression of BMP-7. Reports in this regard are conflicting; Tsai (2003) found a reduction in BMP-2 expression by 40% under BMP-7 exposure [100]. On the contrary, Nicklin (2000) reported upregulated BMP-2 expression after BMP-7 exposure [101]. One possible explanation could be that BMP-2 and BMP-7 partially bind to the same receptors, and this could have led to competitive binding [6]. Pauly also studied dose-dependent effects and found a maximum effect for BMP-7 at dosages of 1000 ng/mL. This finding is in contrast to Yeh and Tsai (2008) who observed declining effects beyond 100 ng/mL [102]. Differences in these studies could be due to different cell origin, i.e. not rotator cuff, and/or culture conditions. However, since the donor material was obtained from torn rotator cuff cells, the study is more clinically appropriate in comparison to using intact tendon.

One of the limitations of the previous study was that no TLC characteristics for sub-groups were studied, which was later investigated by Klatte-Schultz (2013), on TLCs from rotator cuff of female donors [7]. Their findings correspond to those with Pauly (2012), of a stronger stimulating effect with BMP-7 than with BMP-2 [6]. Most importantly, the results were age-specific and indicated that possibly a higher dosage of growth factors would be needed in older female donors. This study, therefore, aimed to develop more patient-specific therapy compared to uniform treatment of rotator cuff tears. However, the study failed to link female sex to inferior cuff healing; this could be due to the in vitro environment, which cannot mimic the role hormones play in the body.

Overall, BMP-7 has demonstrated a stronger stimulating effect than BMP-2, which has been agreed upon by the majority of published studies. On the contrary, the effectiveness of BMP-2 has remarkable conflicting evidence, with some studies suggesting reduction [6, 100] and some, reporting upregulation of BMP-2 with exposure to BMP-7 in ACL repair (ACL), which has very similar injury and repair mechanisms to RCI [101]. Lipner's (2015) study makes a counter-argument stating that rhBMP-2 led to impaired healing, but it can be argued that BMP-2 in their study was delivered using a gene delivery approach, leading to a sustained, but uncontrolled dosage [9]. It is possible that a different dose of BMP-2 may have been more effective in improving tendon-to-bone healing. The study by Pauly (2012) can be considered as the most demonstrative as not only did they compare the growth factors in combination as well as alone but also studied dose-dependent effect and used a clinically relevant repair model. [6]

Alternative Growth Factors to Induce Osteogenesis

Whilst not traditionally used as an osteoinductive factor, platelet-derived growth factor (PDGF) is a possible factor for future consideration. It has also been shown to inhibit osteoinduction and chondrogenesis, from demineralized bone matrix in skeletal muscle [103], but equally, in combination with BMP-2, it significantly increased osteogenic differentiation. This was demonstrated in an in vitro model of skeletal muscle [104] suggesting potential for use in other soft tissues. In addition, PDGF has been shown in vivo to increase bone formation and supplement fracture healing [105–107]. Furthermore, Caplan (2011) poses that PDGF-BB is critical for osteogenesis, in that it has been shown to free pericytes from their position, allowing an influx of mesenchymal stem cells (MSCs) to that location and facilitating vascular reorganisation and replenishment of osteoblasts following

their natural expiry during bone formation [108]. The use of PDGF to enhance bone ingrowth in tendon reattachment has yet to be studied in vivo with most studies focusing on the role of PDGF in matrix production in the tendon aspect of surgical repair [38, 109–111]. FGFs have also been implicated in bone regeneration, despite a general association with fibroblastic tissues, such as tendons. FGFs are important signalling molecules which regulate endochondral ossification and are featured heavily in fracture healing [112]. Similar to PDGF, the application of FGF, specifically FGF-2 (3 μg and 30 μg), reportedly increases the formation of dense tendon-like tissue in a rabbit model, with ectopic calcification apparent via microcomputed tomography [113]. As demonstrated above, the method of delivery is an important consideration in any healing intervention, more so when utilising a molecule which is not inherently osteoinductive.

Kim et al. (2011) investigated the use of TGF-β1 and TGF-β3 and the enthesis of a repaired rat supraspinatus tendon. Utilising an osmotic pump delivery system, Kim et al. observed an increase in type-III collagen, when compared to controls, indicative of scar-mediated healing [114]. The TGF-β3 group demonstrated no differences with paired controls; however, in a following study utilising a heparin-/fibrin-based vehicle, accelerated healing with associated cell mechanisms was observed, specifically associated with soft tissue healing [115]. In contrast, Kovacevic et al. (2011) utilised a calcium-phosphate (Ca-P) matrix to deliver 2.75 μg of TGF-β3 [116] into the supraspinatus tendon of male Sprague-Dawley rats. In groups with just Ca-P intervention, new bone, increased fibrocartilage, and matrix organisation were observed. With the addition of the TGF-β3 to the Ca-P, the strength of the tendon-bone interface was significantly improved (4 weeks after intervention) and a more favourable collagen type-I/type-III ratio, indicative of a more mature stage of healing.

A peptide consisting of 13 amino acids called Sadat-Habdan mesenchymal stimulating peptide (SHMSP) was investigated for use in ACL reconstruction [117] to enhance bone anchorage. Utilising 20 skeletally mature rabbits, 10 had an intervention of SHMSP and the remaining 10 rabbits received only a bone tunnel repair. In comparison to the control, the SHMP group showed bone formation from 4 weeks with extensive new bone growth in the tunnel by week 8. Whilst this indicates the potential for enhanced bone-tendon healing, further work is obviously required to confirm this result and is acknowledged in the discussion of the report [117].

Conclusion

From existing research, it can be concluded that BMP-7 has demonstrated the most effectiveness amongst the BMP osteoinductive growth factors, when used alone rather than in combination, with a maximum effect for BMP-7 dosage of 1000 ng/mL. Use of sustained delivery systems including GHSs and acellular matrices seem to be imperative in promoting healing as BMPs have short half-lives and require a delivery system that can maintain their effects continuously, since this is not always feasible when using local injections or systemic modes of delivery. Acellular dermal matrix grafts not only have higher suture pull-out strength in comparison to other extracellular matrix scaffolds but also minimise the problems associated with graft rejection. Studies have also explored the use of factors that are not classically associated with osteoinduction. PDGF, FGF, and TGF-β isoforms, although sometimes associated with properties detrimental to RCI healing, such as fibrosis and scarring, have shown promising results when used in combination or in place of BMPs. However, the delivery method must be carefully considered, and larger in vivo studies are still required.

A chronic injury model seems most appropriate for research, with higher relevance when human tenocytes are incorporated when compared to animal models alone. For the future outlook, growth factor delivery systems must be designed to provide an active cell-instructive environment during the therapeutic healing period. Such a strategy would especially benefit the geriatric population whose healing mechanism is detrimentally affected by senescence and degeneration.

Developmental studies using PTHrh have highlighted the importance of optimising the timing of the delivery of healing factors, especially regarding inflammatory healing responses. Further, there is a need for prolonged, in-depth analysis of the structure and organisation of the "healed" tissues, since the formation, organisation, and biomechanical properties of the tissue are paramount to the function of the tissue and avoidance of additional procedures sue to re-tear.

Compliance with Ethical Standards

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

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