

Advances in the treatment of rotator cuff lesions by cytokines

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1. ABSTRACT

Rotator cuff tear is one of the most common shoulder injuries, often requiring surgical intervention, including options such as suture repair, autografts, allografts, and synthetic prostheses. While surgery can significantly improve outcomes, an ideal therapeutic strategy has not been found. Often, injuries respond poorly and require prolonged rehabilitation. Recent attention has been focused on biologic pathways which can augment tendon healing, consequently leading to the identification of growth factors. Herein, we review growth factors and their roles in rotator cuff healing.

2. INTRODUCTION

The incidence of rotator cuff tendinopathy and degenerative tears is increasing (1). Rotator cuff lesions are found in 30 to 50 % of the population older than 50 (2, 3). Meanwhile, they also affect athletes and active individuals, regardless of age and exercise status. Rotator cuff tears result in pain and disability which usually require surgical intervention. New surgical materials and techniques have been introduced with the aim of reproducing anatomical footprints.

Although solid fixation and advanced footprint coverage are accessible, biomechanical stability is difficult to attain. In addition, the biology of tendon lesions, degeneration, and the tendon-to-bone healing process has not been completely defined. According to recent meta-analyses, surgical interventions of the rotator cuff did not result in desirable clinical and radiographic outcomes (4-8). The rate of failed healing or recurrence remains high, with rates of failed healing ranging from 13 to 94 % (9-11). Thus, current research focuses on factors that may lead to better clinical and radiographic outcomes.

Recently, the focus of research (Figure 1) has changed from improving repair techniques to improving biologic environments around footprints (12-15). These interventions include growth factors, stem cells, natural biomaterials, and genes, alone or in combination.

3. CLINICAL RELEVANCE

Primary rotator cuff disorder, usually caused by overuse or age-related degeneration, is the most common

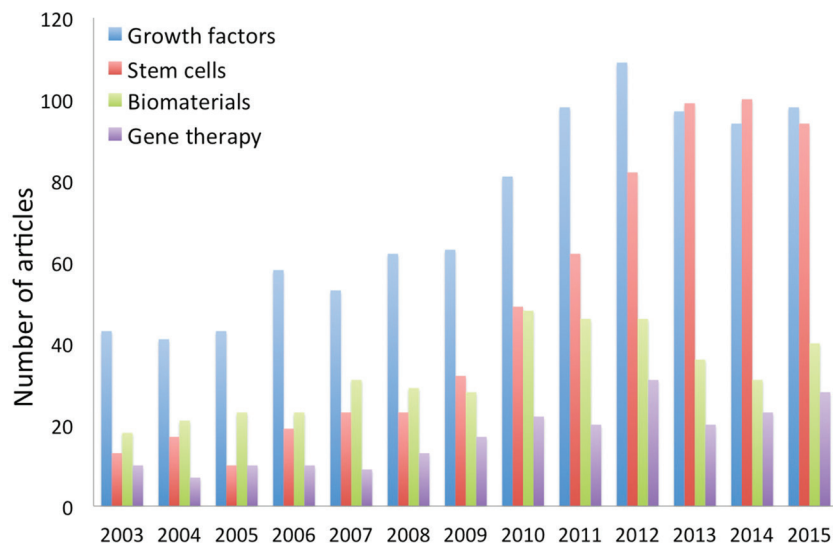


Figure 1. Studies on the use of biologics for tendon repair. The following key words were used: tendon repair/healing in combination with growth factors, stem cells, biomaterials, and gene therapy. The articles include *in vivo* and *in vitro* studies; some articles scored in more than one category. The search results demonstrate that in the last decade, the tendon research field has progressively expanded as represented by the continuous increase in the number of articles focusing on different strategies for enhancing tendon tissue healing. Such cumulative efforts may lead to the development of efficient biologics for tendon repair.

tendinopathy of the shoulder. Clinical evidence and statistical data have suggested that the incidence of rotator cuff disorders is higher than in other tendons. Although there are no accurate data specifically related to rotator cuff disorders, studies from the primary care population showed that 16 % of the general population (16) and 21% of elderly hospital and community populations (16, 17) experience rotator cuff-related shoulder pains; athletes also experience such ailments (18). A biological classification of rotator cuff disorder still does not exist, primarily due to the lack of tendon biopsy tissues in the clinic. Tendon biopsy tissues can only be collected at the end-stage of these lesions or after tendon rupture.

In general, the primary pathologic changes affecting the rotator cuff are tendinitis and tendinosis, which result in inflammation, pain, and degeneration (19). These conditions, caused by multiple factors, can ultimately lead to the primary clinical problem – loss of tissue integrity with full or partial rupture of the rotator cuff. Additionally, many factors can be attributed to the onset and progression of tendinopathies.

Factors that may cause the pathologic processes of rotator cuff lesions can be divided into intrinsic and external factors. Intrinsic factors include age, gender, anatomic variants, body weight, and systemic disease. Extrinsic factors include sporting activities, physical load, occupation, and environmental conditions (3, 20, 21). Lacking cellularity and vascularity, the natural healing ability of the rotator cuff is extremely low and inefficient (22). Rotator cuff tissues may heal spontaneously if the rupture is partial and the vascularity of the peritendinous tissues

(paratendon) is intact (21). Surgical intervention is often useless in chronic cases with recurrent disease.

Rotator cuff tears are common, affecting individuals of all ages. However, their etiology remains ambiguous, particularly when deciding which factors are more critical. Therefore, it is of great importance to identify the key molecular and cellular processes involved in the progression of tendinopathies and subsequent rupture in order to develop effective therapeutic strategies.

4. PATHOMECHANISM AND REPAIR

The rotator cuff consists of 70 % water. Type I collagen, which consists of approximately 95 % total collagen, accounts for 85 % of tendon dry weight (23). Rotator cuff cells are full of fibroblasts (90–95 %) (24). In patients with rotator cuff lesions including regeneration and injury, the healing process usually occurs by scar formation rather than regeneration of histologically normal enthesis (22). Thin and disorganized collagen fibers, the presence of granulation tissue, infiltration of glycosaminoglycans, fibrocartilaginous metaplasia, calcification, fatty degeneration, cell necrosis, and cell apoptosis, are associated with increased risk for the development of complete rotator cuff tears and recurrence (25-27). The poor healing response also relates to insufficient and disorganized expression of cytokines and the composition of enthesis (28).

Healing processes of the rotator cuff have three phases: (1) inflammatory phase; (2) repair phase; and (3) remodeling phase (29-31). In the first few days

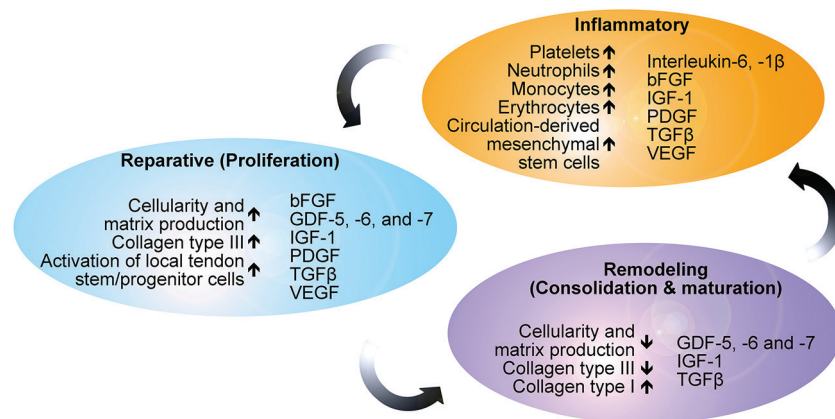


Figure 2. The critical molecular, cellular, and matrix changes occurring during the three main phases of rotator cuff repair. Each healing stage is characterized by involvement of different cytokines, activation of certain cell types, and production of essential matrix proteins.

after injury, a short inflammatory phase begins in which macrophages remove tissue debris. After inflammation, the proliferative phase, which lasts over a few weeks, results in fibroblast infiltration, type III collagen deposition, and callous formations. Prior to the final remodeling phase, collagen-rich scars become contracted (32). In the final phase, scar tissue becomes remodeled and the resultant tissues have a higher ratio of type III collagen to type I collagen, which weakens the tendon and increases the risk of rerupture (33). The final remodeling phase lasts for several months. These phases can overlap with each other and their duration is dependent on the severity of the disease.

The notion of transforming the healing process from scar formation to the regeneration of native tendon-bone insertion site is prevailing (34). Thus, the importance of the inflammatory phase has been highlighted. During the inflammatory, or so-called acute stage, vascular permeability increases and inflammatory cells flood into the lesion sites. These lesions stimulate chemotaxis of inflammatory cells such as neutrophils, macrophages, and mast cells, which produce a number of cytokines and growth factors. These factors can strengthen the process that leads to recruitment and proliferation of macrophages and resident tendon fibroblasts. Thus, the modulation of early-stage inflammation may improve the prognosis of rotator cuff lesions (35). Generally, regular inflammation is beneficial to rotator cuff repairs, whereas excessive or persistent inflammation can be damaging. Inflammatory cytokines attract fibroblasts to the lesion sites during the healing process, which may cause excessive inflammation and lead to poor clinical outcomes (36, 37).

The distinctive cellular and molecular cascades may pass through three main phases. A vascular network may start forming by secreted angiogenic factors, which reduces impairment of blood supply at the injury

sites (38). Then, the proliferation stage begins, which is characterized by increased cellularity and absorption of large amounts of water. Normally, the injury sites are healed with fibrovascular scar tissues; whereby a lack of elastic tissues results in mechanically and structurally decreased healing areas. These pathologic changes at the tendon margin causes avulsion of the edge area and a high rate of postoperative recurrence (39). Contrarily, scar tissue has been shown to be a potential reason for weakness at the tendon-bone interface, which also plays a protective role in chronic overuse injuries of tendons (40-42).

In the final stage of remodeling and maturation, cellularity and matrix production decreases. Then, collagen fibers begin to generate along the longitudinal axis, restoring stiffness and tensile strength of the rotator cuff. The maturation stage is characterized by increasing collagen fibril crosslinking and the formation of more mature tendinous tissues (43).

5. ROLE OF CYTOKINES IN ROTATOR CUFF LESION

During rotator cuff repair, cytokines play different but indispensable roles in regulating the healing process, either positively or negatively. Cytokines are involved in a complex cascade of cellular and molecular signals at the healing tendon-bone interface. Recent attention has been given towards methods of augmenting biologic responses after rotator cuff tears. Additionally, cytokines regulate cell chemotaxis, cell proliferation, matrix synthesis, and cell differentiation, all of which augment rotator cuff tendon healing processes via autocrine and paracrine signals.

The function of cytokines in rotator cuff repairs (Figure 2) are complex and orchestrated (44). Initially, certain inflammatory cytokines, such as interleukin

(IL)-6 and IL-1 β , are produced by invading inflammatory cells. After that, growth factors released by the cells at the injury sites execute repair processes in different phases with diverse molecular effects. Basic fibroblast growth factor (bFGF), bone morphogenetic protein (BMP)-12, BMP-13, and BMP-14, also known as growth and differentiation factor (GDF)-5, GDF-6, and GDF-7 respectively, transforming growth factor beta (TGF- β), insulin-like growth factor (IGF)-1, platelet-derived growth factor-b (PDGF-b), and vascular endothelial growth factor (VEGF) are all involved (31, 45, 46). During the repair process, tendon cells are activated and extracellular matrix (ECM) components are synthesized and degraded simultaneously. Therefore, tendon remodeling is a slow and continuous process (31, 45, 46).

It is now believed that fibroblasts and inflammatory cells, released from tendon peripheries, blood vessels, and the circulation, are attracted to injured sites, contributing to cell infiltration and adhesion formation. Thereafter, cells from the endotendon are activated as they migrate to and proliferate at the injury sites, reorganizing the ECM and supporting internal vascular networking (47, 48). Generally, those reconstructed tissues at the healing tendon-bone interface could not regain previous mechanical properties. This phenomenon is extraordinarily prominent in aged individuals. The primary reason for the reduced strength, compared with normal tendons, is the lack of collagen fibers, with a higher ratio of type III collagen compared with type I collagen. As a consequence, the quality and function of reconstructed tendons are inferior to those of healthy tendons (49, 50).

6. CURRENT CYTOKINE STRATEGIES TO AUGMENT ROTATOR CUFF REPAIR

The inflammatory response leads to a gene expression program and consequently results in a scar-based healing process, rather than the formation of original tissues. Thus, simply increasing cytokines can only accelerate the scar formation process, which will not predictably result in regeneration of normal tendon tissues.

Studies have shown that the rotator cuff healing process is a kind of tendon-to-bone healing, which is predicated on bony ingrowth into tendon (9, 51). Thus, it has been proposed that exogenous applications of cytokines may augment healing of the rotator cuff. Current experimental cytokine approaches for enhancing rotator cuff repairs mainly consist of applying cytokines singly or in combination, stem cells in native or genetically modified form, and biomaterials, alone or cell-loaded, at the sites of the rotator cuff lesions. In the last decade, the number of studies investigating the functionality of the above strategies has progressively increased. This section of the review will focus on these studies.

6.1. Interleukin (IL) family

The IL family is a group of cytokines which play a significant role in immunomodulation. ILs coordinate the functions of leukocytes, immune cells of lymphoid factors, and blood cell growth factors, which affect the hematopoietic system and immune system. ILs transmit cellular information to activate and regulate immune cells, playing an important role in inflammatory responses.

At lesion sites, certain inflammatory cytokines, such as IL-6 and IL-1 β , are initially produced by invading inflammatory cells (44). IL-1 β and Interferon-g (IFN-g) are responsible for degradation of the ECM. They inhibit differentiation of tendons, cartilage, and bones in injured tendon-derived progenitor cells (inTPCs) and alter glucose metabolism (35, 52). Followed by increased IL-1 β , the expression of type I collagen-related mRNA decreases together with IL-4 and IL-13, which can stimulate the proliferation of tenocytes from the torn edge of the tendon. Thus, high IL-1 β expression may slow down the rotator cuff healing process (53).

Kairui Zhang *et al.* (54) demonstrated that IL-1 β irreversibly inhibited differentiation of inTPCs into tendons. This finding indicated that inflammatory cytokines, especially IL-1 β , strongly affected the function of tendon progenitor cells in the injured rotator cuff. Thus, the inhibition of IL-1 β may be beneficial for maintaining the functions of tendon progenitor cells during the rotator cuff healing process. A recent study (55) showed that IL-1 β , which disturbed the function of tendon fibroblasts, upregulated gene expression of matrix metalloproteinase (MMP)-13 in tendon progenitor cells derived from the injured rotator cuff. Furthermore, IL-1 β reduced expression of tenogenic differentiation markers (Scx and Tnmd), the main tendon associated collagens (Col1 and Col3), and Egr-1, a transcriptional factor indispensable in rotator cuff repair. As mentioned before, IL-8 and IL-6, which increases in the early stage of rotator cuff repair, contributes to the development of acute inflammation by recruiting and activating neutrophils (56-58). Additionally, Wirtz *et al.* demonstrated that IL-6 stimulated the synthesis of other acute-phase proteins such as C-reactive protein, calcitonin gene-related peptides, and substance P, which were steps in the inflammatory response to rotator cuff tears (59).

Attention has recently been focused on IL-21 and IL-21 receptor (IL-21R), which are presented in early rotator cuff tears and can be modulated in tenocytes (60-62). According to Campbell's study, IL-21R was present in early rotator cuff tears and modulated in tenocytes by proinflammatory cytokines, promoting the concept that IL-21R acted as an inflammatory regulator in early rotator cuff lesions (60). Moreover, IL-21 also acts as an important mediator between immune and nonimmune cells, giving that it can enhance the

production of chemokines and MMPs by epithelial cells and fibroblasts (61, 62). As a result, a better understanding of IL-21R, which are involved in the pathologic cascade, may improve cell-targeted treatment of rotator cuff disorders.

6.2. G-CSF

Granulocyte-colony stimulating factor (G-CSF) is a type of growth factor synthesized in the bone marrow. G-CSF affects the inflammatory processes by direct activation of neutrophil granulocytes, and promotes chemotaxis of mesenchymal stem cells and neutrophil granulocytes. In recent studies, G-CSF peak expression was described (63, 64). Bolus application of growth factors (GFs) typically lead to clearance of the wound sites within 48 hours (65). Stefan *et al.* utilized injectable vesicular phospholipid gels to promote the continuous release of G-CSF. G-CSF improves the immunohistology and biomechanical properties of rotator cuff repairs (66). Besides, G-CSF has a significant influence on the ratio of collagen I/III, which is a marker of organization and maturation in the rotator cuff healing process (65, 67).

6.3. Growth factors

Many GFs such as PDGF, TGF- β , VEGF, and bFGF significantly influence the outcome of rotator cuff repair (68). Most of the current literature (69-71) has shown that different GFs are involved in different parts of the inflammatory, repair, and remodeling stages. Expression of certain GFs increasing cellularity and tissue volume (72) is triggered by multiple stages of the healing processes of rotator cuff lesions (44, 73). However, different from other cytokines, GFs (particularly bFGF, BMP-12, -13, -14, connective tissue growth factor, IGF-1, PDGF, TGF- β , and VEGF) (63, 64, 74) play prominent roles in the early phase of rotator cuff repairs. In the following sections, these factors are briefly introduced through *in vitro* or *in vivo* studies investigating the role of these factors in the tendon healing process. To the best of our knowledge, no human studies investigating recombinant growth factors in tendon healing have been published.

6.3.1. bFGF

Current studies have shown that bFGF is upregulated in both the inflammatory and repair phases of rotator cuff lesions. Mostly, bFGF mRNA is found in mature tenocytes, fibroblasts, and inflammatory cells surrounding lesion sites (75, 76). Due to the high ratio expression early in the healing process, bFGF is well characterized as promoting the early events of tendon healing (54).

6.3.2. BMP

The BMP family is part of the TGF- β superfamily, which is noted in embryologic studies as a group of important signaling molecules for skeletal development (77). BMP-12, -13, and -14, also known as

GDF-7, -6, and -5, respectively, stimulate mitogenesis. Furthermore, these GFs have the potential to drive differentiation, which promotes mesenchymal stem cells differentiating to heal (78, 79). Rodeo *et al.* (80) utilized BMP-2 through BMP-7, TGF- β 1 through TGF- β 3, and FGF to the bone-tendon interface acutely at the time of repair in a sheep model with a surgically created rotator cuff defect. A great volume of bone and soft tissues at the repair sites and an improved fibrocartilaginous zone at the bone-to-tendon junction was shown, though still inferior to the original enthesis. BMP-2 and BMP-7 are already used clinically to enhance bone regeneration (80). Additionally, studies have indicated that BMP-12, BMP-13, and BMP-14 have clinical benefits in rotator cuff healing (79). These cytokines are predominantly involved in the formation of fibrocartilage and tendon tissues. Some data has shown that the application of recombinant human (rh) BMP-12, rhBMP-13, and rhBMP-14 at ectopic sites constitute tendon-like tissues, enhancing the quality of the repair (79, 81, 82).

6.3.3. CTGF

CTGF, first discovered in 1991, is one of the mediators of TGF- β 1 signaling and acts as a co-factor in fibrosis (83, 84). CTGF may undergo a sustained increase in gene expression within 21 days after lesion development (74). Its primary function is to modify other GFs, such as those in the BMP family. *In vitro* studies have shown that CTGF positively promotes tenogenic effects of BMP-12 in rotator cuff lesion models (85).

6.3.4. IGF-I

IGF-1 is highly expressed in the initial inflammatory phase of the rotator cuff healing process and is associated with chemotaxis and proliferation of fibroblasts and inflammatory cells at the site of injury. Thus, IGF-1 promotes rotator cuff repair by increasing cellular proliferation, enhancing matrix synthesis, improving tendon mechanical properties, and reducing time to functional recovery in *in vivo* studies (86-88). IGF-1 is particularly important during the formation and remodeling stages of healing.

6.3.5. TGF- β

TGF- β has been shown to be integral to rotator cuff repairs, as well as to the modulation of scar tissue after wound, ligament, and tendon-to-bone healing. Except for tendon cell migration and mitogenesis, TGF β especially stimulates production of the ECM, including increases in the production of types I and III collagen by TGF β 1, TGF β 2, and TGF β 3 (89). The variable ratio between the different isoforms of TGF- β can influence the outcome of repair. Studies have shown that increased TGF- β 3 is responsible for achieving "scarless" repairs as seen in fetal wound healing, which is abundant with scar tissue (increased TGF- β 1) (90, 91). TGF- β 1 may increase during the inflammatory phase of healing and is characterized by stimulating collagen synthesis, as well

as cell proliferation and migration (91, 92). In contrast, TGF- β 3 has been shown to be associated with prenatal development of the enthesis. During the remodeling phase of healing, TGF- β 3 can reduce scar tissue formation (93-95).

In *in vivo* studies, the addition of TGF- β 3 showed a great advantage with regards to mechanical properties in rotator cuff repairs compared with TGF- β 1 (11, 93). In the exogenous application of TGF- β 1, anti-TGF β 1 antibody was used to suppress TGF- β 2 and TGF- β 3. The study resulted in an increased cross-sectional area of the repair tissues. This abundant scar formation, however, showed an inferior mechanical repair, reflecting that the scar did not necessarily correlate with a biomechanically and histologically superior enthesis. In conclusion, defining the appropriate dose and combination of isoforms may be essential for the successful application of TGF- β in tendon healing.

6.3.6. PDGF

Increased PDGF- β levels in the healing process of rotator cuff lesions have been shown to promote chemotaxis, cell proliferation, extracellular matrix production, surface integrin expression, and revascularization in fibroblasts. Thus, PDGF- β has been proposed to be a critical cytokine in the repair of tendons and ligaments (96-98).

Both *in vivo* and *in vitro* studies showed that PDGF- β had a positive effect on the healing of rotator cuff lesions. Molloy *et al.* (99) utilized a rat model of rotator cuff lesions. Compared with suture repair alone, restoration of normal crimp patterns and collagen bundle alignments occurred. Dines *et al.* (100) transduced rat tendon fibroblasts to express PDGF- β , then seeded them into a polyglycolic acid sponge. PDGF- β -transduced cells were shown to increase collagen synthesis and DNA synthesis during rotator cuff repair. Recently, Uggen *et al.* (101) proved that PDGF- β improved tendon-to bone interfaces in the rotator cuff. Despite promising early results, the exact role of PDGF- β in the enhancement of rotator cuff tendon-to-bone healing requires further elucidation and may be intimately dependent on timing, dosage, and carrier vehicles.

6.3.7. VEGF

The insertion site of the rotator cuff tendon on the bone is relatively hypovascular and correlated with degenerative rotator cuff lesions (102). VEGF is important in both tendon degeneration and regeneration (38). VEGF promotes angiogenesis in tendon healing (103) and its activity rises after the inflammatory phase, especially during the proliferative and remodeling phases.

In *in vivo* studies, topical glyceryltrinitrate, a potent vasodilator, has been utilized in patients with rotator cuff tendonitis and outlet impingement. This vasodilator

significantly improves pain, range of motion, and clinical outcomes in human studies (104). In a rat model (105) of supraspinatus tendon overuse injury, mRNA expression of VEGF and von Willebrand factor were significantly upregulated (87). Thus, it is controversial whether increased VEGF is a response to injury or is involved in the cascade of early healing. Further studies are required to fully define the role of exogenous VEGF in the augmentation of rotator cuff repair.

6.3.8. Autologous sources of cytokines

The most recent research has defined autologous cytokines, such as platelet rich plasma (PRP), (106, 107) as biologic augments in rotator cuff repairs. PRP is a cytokine treatment that has already been used clinically in patients with rotator cuff tears. PRP contains components other than growth factors, including interleukins, chemokines, proteinases, proteinase inhibitors, adhesion molecules, sphingolipids, thromboxanes, purine nucleotides, serotonin, calcium, and many other mediators. PRP is considered to have anti-inflammatory properties, but some components, such as IL-1, -6, and -8, are pyrogens (106, 108). As a result, different cytokines within PRP are important determinants of the properties of this autologous blood product. It remains controversial whether PRP can improve the healing process of the rotator cuff. However, in contrast to purified GFs, PRP has already been used clinically in patients with rotator cuff injuries.

Gosens *et al.* (109) found significant pain reduction after PRP injection. In a prospective randomized controlled study, Randelli *et al.* (110) found less postoperative pain and accelerated healing in patients with non-massive rotator cuff tears. A randomized control trial involving PRP treatment found that PRP significantly decreased the recurrence rate of tears in patients with large and massive rotator cuff tears (111). However, other investigators opposed the use of PRP. Neither Sánchez Márquez *et al.* (112) nor Ruiz-Moneo *et al.* (113) found any relevant clinical improvement with the use of PRP to augment healing of massive tears. Weber *et al.* (114) performed a prospective randomized study evaluating the effects of PRP on rotator cuff healing and found no significant differences in healing rates.

To date, it remains unclear why certain studies have performed well with augmentation but others have shown no improvement. Potential factors may include preparation mechanisms, timing of application, and technique of repair. Thus, further research is necessary to elucidate the indications and usage of PRP.

7. CONCLUSION

To achieve a better understanding of tendon-to-bone healing of the rotator cuff, the applications of specific cytokines play a significant role in treating tendinopathies

and augmenting repair. The dosage, timing, delivery vehicles used, and a multifactorial approach have critically influenced the use of cytokines. Studies have shown that specific cytokines can not only improve bone formation at the healing tendon-to bone interface, but also increase fibrocartilage formation of the healing enthesis. However, "traditional" cytokines, characterized with the overall functions of autologous cytokines, may lead to reactive scar formation rather than regenerative healing. Thus, novel signaling molecules expressed during the healing process still require further research. Also, other biologic and pharmacologic factors such as glucose control, nicotine, and nonsteroidal medications can affect healing. Further understanding of the biology of the rotator cuff in parallel with continued improvements in the technical approaches to repair will ultimately improve clinical outcomes.

8. ACKNOWLEDGEMENTS

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Abbreviation: bFGF: basic fibroblast growth factor, GDF: growth and differentiation factors, IGF: insulin-like growth factor, PDGF: platelet-derived growth factor, VEGF: vascular endothelial growth factor, TGF: transforming growth factor

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