CiSE
Clinics in Shoulder and Elbow

Rotator cuff degeneration and healing after rotator cuff repair

Stefano Gumina[1,*], Hyungsuk Kim[2,*], Younsung Jung[2], Hyun Seok Song[2]

[1]Department of Anatomy, Histology, Legal Medicine, and Orthopaedics, Sapienza University of Rome, Rome, Italy
[2]Department of Orthopedic Surgery, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Rotator cuff tear is a common shoulder injury that compromises both function and quality of life. Despite the prevalence of the injury and advancements in repair techniques, a significant percentage of these repairs fail. This review aims to explore the multifactorial reasons behind this failure, including the degenerative nature of the rotator cuff tendon, inherent and extrinsic factors, and the role of hypoxia in tissue degeneration. Additionally, it elucidates potential strategies for improving healing outcomes.

Keywords: Rotator cuff tear; Degeneration; Treatment failure

INTRODUCTION

The rotator cuff (RC), a crucial part of our musculoskeletal system, shows wear over time, often resulting in damage that significantly impacts mobility and quality of life [1,2]. These tears, both distressing and prevalent, have given rise to a burgeoning area of clinical and scientific research. The mechanisms of rotator cuff tear (RCT) healing, the intricate balance of collagen synthesis and degradation, and the influence of various risk factors on the outcome of healing are now more deeply understood, albeit still evolving areas of study [3].

Comprised predominantly of water (70%) and a dry mass of proteins (30%), the RC tendon primarily consists of collagen fibers, with type 1 collagen contributing to over 95% of the total. The other minor players, collagen types 3 and 5, account for the residual composition. Within this framework, tenocytes and tenoblasts emerge as the key cellular elements, constituting about 95% of the total cellular type. Intriguingly, a decrease in type 1

collagen is the signature feature of tendinopathy, a pathological condition affecting the tendon. The pivotal role of type I collagen in maintaining structural integrity is thus indicated [4].

However, even with the sophisticated understanding of the tendon composition and advanced surgical techniques, the likelihood of a retear post-repair remains high, and is reported to be anywhere from 13% to 94% [5-7]. Such a wide range of variability could be attributed to multiple factors, such as the inadequacy of diagnostic imaging, differing follow-up time points, and variable patient selection criteria. Furthermore, it is worth noting that retears are most common within the initial 6 to 26 weeks following arthroscopic rotator cuff repair, pointing to the crucial need for diligent postoperative management and ongoing research to further refine treatment protocols [8].

Therefore, exploring the complexity of RCT healing and strategies to enhance postoperative outcomes is a dynamic and imperative field of study. The intricate balance between collagen types, the role of cellular elements, and factors influencing retear

rates need more thorough investigation for improved patient care and prognosis.

The complexity of RC degeneration necessitates a multifaceted approach for successful healing. There is a strong belief in the inherent ability of tendons to heal, even when moderately degenerated, irrespective of the suturing process. Yet, patient age and the size of the cuff tear play significant roles in the prognosis of healing. The need for institutional review board approval was waived because this is a review article.

TENDON DEGENERATION

Understanding the pathology and process of degeneration is crucial to unraveling the complex puzzle that is RC healing. In tendon degeneration, there is a marked shift in the collagen concentration, specifically to a higher prevalence of type III collagen. This type III collagen forms thin, reticular fibers, which are unfortunately more vulnerable to lesions, particularly when compared to the more robust type I collagen [9]. Intriguingly, these shifts in the tendon's composition and structural arrangement transpire in the absence of inflammation, leading to the condition recognized as a degenerated cuff [3].

Degenerated cuff can be characterized as a multifaceted landscape of chondroid metaplasia, fatty infiltration, and myxoid change. It is not uncommon to spot regions of dystrophic calcification, adding to the complexity of the pathology [10]. This degenerative process of the RC tendon is conceptualized in three distinct stages in a review article by Lewis [11]. The initial stage is denoted by reactive tendinopathy. Here, there is a transformation in the tenocytes, as they assume a more chondroid shape owing to the deposition of glycosaminoglycans. However, collagen integrity is, for the most part, preserved, although there may be some evidence of longitudinal separation. As the pathology progresses, the second stage of tendon disrepair is defined by extensive areas of swelling, evident tendon degeneration, and hypoechoic regions visible on ultrasound imaging that correlate with disorganization of the extracellular matrix. This stage is also characterized by an increase in the number of chondrocytes, as well as some myofibroblasts. This myofibroblast population surge results in a marked boost in proteoglycan synthesis, leading to separation of collagen fibers. The third and final stage manifests as degenerative tendinopathy, where tendon degeneration is paramount. In this stage, regions of apoptosis are identifiable, and the capacity for reversibility of pathological changes is significantly reduced. This stage witnesses notable heterogeneity of the matrix. For the RC, this stage is associated with significant structural failure, making this the most concerning phase in terms of

potential recovery and healing.

Movin score, a semiquantitative histologic score, is used to diagnose degenerative tendons and assess their severity. It is derived from parameters like fiber structure, rounding of the nuclei, fiber arrangement, regional variations in cellularity, increased vascularity, decreased collagen stainability, and glycosaminoglycans content, without implying its decrease. This score has a range from 0 representing a normal tendon to 24 signifying a severe abnormality [12]. Similarly, the Bonar score is also used and considers variables such as tenocytes, ground substance, collagen, and vascularity. It ranges from 0 to 12, where 0 symbolizes a normal tendon, and 12 a severe abnormality [12]. A study by Sethi et al. [13] showcased pictures of a normal RC with a low Bonar score of about 3 and a degenerated cuff with a score of 12. The degenerated tissue exhibited increased vascularity, a marked separation of collagen fibers, and rounded, large tenocytes. However the degree of tendinopathy with Bonar score did not correlate with the gross appearance of the RC tendon, patient outcome, or RC healing in medium sized full-thickness RCTs. The extent of tendon degeneration can vary considerably based on degradation location and the state of the tendon, and is generally found to be more prominent in the supraspinatus tendon. Interestingly, in terms of cellularity, fiber organization, and nuclei shape, similar degrees of degeneration were noted in both intact and torn tendons [14].

The question therefore arises: why does healthy tissue degenerate? Tendon degeneration is, to some extent, a physiological aging process linked to the individual's age. It's important to emphasize that the discussion around pathological tendon degeneration primarily concerns degeneration that occurs in young or middle-aged patients, and not just the aging population [15]. Increasing age has been associated with higher rates of retears [16]. A systematic review and meta-analysis study by Longo et al. [17] found a retear rate of 14.4% in individuals under 60 years, which escalated to 24.3% in those over 60 years. Age has been linked with retears because of its association with fatty infiltration, a critical point of consideration in the ongoing research on RCT healing.

EXTRINSIC FACTORS

Understanding the intricacies of RCT healing necessitates an in-depth exploration of all relevant factors that influence this process. Both intrinsic and extrinsic factors, as well as the debatable concept of overuse, play significant roles in the progression and healing of these injuries (Table 1). Starting with the controversial topic of overuse, the traditional paradigm suggests that excessive

Table 1. Extrinsic factors and intrinsic factors of rotator cuff tendon degeneration

Extrinsic factor	Intrinsic factor
overuse	Tight posterior joint capsule
	Aberrant scapular muscle activity
	Scapular dyskinesis
	Thoracic hyperkyphosis
	AC joint arthritis
Intra-articular high temperatures	Smoking
	High body mass index
	Alcohol consumption
Subacromial space impingement	Uncontrolled high blood pressure
	Diabetes mellitus
	Hyperlipidemia
	Tissue hypoxia

AC: acromioclavicular.

use of the RC might lead to degeneration and subsequent tearing [18,19]. However, a work of research conducted on amputees who did not use prostheses provides an intriguing counterpoint [20]. In individuals with unilateral upper limb amputation, the healthy limb naturally incurs an increased workload during daily activity. Both shoulders of these patients were evaluated using magnetic resonance imaging, and the condition of the cuff was classified based on the Sugaya method [21]. Remarkably, the prevalence of RC degeneration or tearing was higher in the amputee side. This intriguing finding suggests that non-use, rather than overuse, might be a more substantial risk factor in the development of these injuries [20]. As early as 1970, Rathbun and Macnab [22] postulated that the muscle-tendon vascularity of the superoposterior cuff is "squeezed" when the arm is held in a position of neutral rotation and adduction. It is the position most commonly assumed by the amputee shoulder. Consequently, the RC on the amputee side might be poorly vascularized. This limited blood flow could play a critical role in tendon degeneration.

This brings us to another intriguing area of exploration, the possible effusion of synovial fluid into the RC during shoulder movement. Although it remains relatively unexplored, this phenomenon, if it occurs, could be profoundly affected by the limited mobility of the amputee limb, inhibiting the effusion of synovial fluid and possibly contributing to degeneration. Transitioning to the study of intra-articular high temperatures, it has been found that elevated temperatures within the joint can inflict serious damage to the collagen fibers of the extracellular matrix [23]. Experimental evidence has shown that at 37 °C, the stability of type I collagen derived from rat tail tendons is significantly diminished. As such, intra-articular high temperatures may well contribute to the progression of tear size, affecting the healing outcomes of RC injuries.

Finally, there is the once widely accepted notion that pathological narrowness of the subacromial space could be the principal cause of impingement, leading to tendon degeneration and tearing [24]. Bigliani and Levine [25] attributed the responsibility of impingement, degeneration, and tearing to the hooked shape of the acromion. Subsequent research has further investigated the shape, slope, and index of the acromion, along with its coverage, to consider their potential effects on RC degeneration [26-28].

INTRINSIC FACTORS

The intricacies of RCT healing span a myriad of factors, both intrinsic and extrinsic, that together orchestrate this multifaceted process. In the absence of RCT, the subacromial space may be compromised by several factors, such as a tight posterior glenohumeral capsule, aberrant scapular muscle activity, scapular dyskinesis, thoracic hyperkyphosis, and acromioclavicular joint arthritis. In a study of 50 pairs of elderly twins aged between 50 to 75 years, it was determined that anatomical features that influence the width of the subacromial space are predominantly genetically determined, with minimal influence from external factors. These genetic factors also play a critical role in determining the acromiohumeral distance [29]. In addition, arthroscopic findings often reveal that degeneration and tear of the cuff begin on the joint side, significantly undermining the potential role of subacromial influences. Moreover, lifestyle choices and habits, such as smoking, high body mass index, uncontrolled high blood pressure, and alcohol consumption, further compound these intrinsic influences [30-33].

Regarding the implications of hyperlipidemia and diabetes, studies have shown that elevated cholesterol levels significantly impact the RC healing process. A rat model study revealed that hyperlipidemia's effects persist despite surgical repair, likely affecting the tendon's healing potential [34]. Patients with hyperlipidemia are 6.5 times more likely to experience retears than those with normal lipid levels [35]. The combination of an anteroposterior tear size of over 40 mm, hyperlipidemia, and critical shoulder angle exceeding 37° dramatically increases the prediction probability for retear to 86.2% [36]. Moreover, the failure rate of RCT healing was found to be significantly higher in diabetic patients compared to non-diabetic ones [37].

All these intrinsic factors have tissue hypoxia in common, induced by alterations of the peripheral microcirculation, which appears to be a critical link. The cuff draws its vascular supply from the myotendinous junction, supplemented by osteo-tendon vascularization and bursal side vascularization. Without this blood supply, the cuff degenerates and fails to heal. Hypoxia is an

essential factor in tendon degeneration as it triggers the formation of reactive oxygen species (ROS), leading to apoptosis and a shift in cellular metabolism towards glycolysis [38]. These changes result in the production of intermediates such as lactic acid and succinate, which in turn enhance the secretion of interleukin (IL)-6, IL-23, and IL-1β. Hypoxia also causes a downregulation of type I collagen genes and an increase in type III collagen genes in tenocytes, disrupting collagen I homeostasis. Conditions such as hypercholesterolemia, diabetes, and obesity exacerbate these processes, thereby accelerating tendon senescence [39]. An accumulation of ROS induces tenocyte apoptosis through the action of mediators like metalloproteinases, cytokines, and Jun N-kinase, which, when phosphorylated, lead to cell death. Over time, apoptosis results in matrix degeneration, reduced collagen synthesis, decreased mechanical tendon resistance, and consequently, tissue degeneration and rupture.

To further comprehend these processes, patients with RCTs were subjected to capillaroscopic examination to analyze the peripheral microcirculation of the upper limbs. The study's focus was particularly on the presence of dilated capillaries, capillary morphology, hemosiderin deposits, visibility of the subpapillary venous plexus, pericapillary edema, capillary blood flow, ectasias, microaneurysms, and neoangiogenesis. The findings revealed a significant association between these variables and the presence of a RCT, supporting the hypothesis that microcirculation disorder plays a vital role in cuff degeneration and subsequent tendon rupture [40].

Despite the plethora of intrinsic and extrinsic factors contributing to RC degeneration and tear, it's noteworthy that a study conducted on monozygotic and dizygotic twins over 60 years of age revealed that only 18% of the genesis of the cuff degeneration and tear could be attributed to genetic factors. Shared environmental factors and unique environmental factors, such as working, sports activity, comorbidities and poor habits, play a more significant role in influencing RC degeneration than genetic factors. Collectively, these factors account for more than 80% of the total heritability index. [41].

TENDON HEALING AFTER REPAIR

The journey through RCT healing is complex, involving a remarkable interplay of proteins, cells, and healing techniques that bring together intricate biological processes. Exploring this topic, the role of periostin, a matricellular protein highly implicated in fracture healing, is being considered in the process of tendon repair. Correlations have been demonstrated between periostin synthesis and the healing process of flexor digitorum longus ten-

don graft in a mouse model, suggesting its importance in tissue repair. Specifically, the splice variant of periostin interacts with the extracellular matrix, inciting myofibroblast migration. Myofibroblast cells have a critical role in type I collagen production during tissue repair [42]. Interestingly, in the context of a RCT, there is a high level of immunohistochemical expression of periostin at the tear margins, while it's scarcely expressed in healthy tendons [43]. This discrepancy indicates a potential role of periostin in RC degeneration and tear, and, in broader terms, in tendon healing mechanisms.

Moreover, the role of nuclear factor-kB (NF-kB), a key transcription factor in the immune system, cannot be overlooked in the evolution of RCT and the healing mechanism of cuff tendons. This regulatory protein modulates the expression of crucial biomolecules like inducible nitric oxide synthase, cytokines, cyclooxygenase, growth factors, and effector enzymes. Interestingly, NF-kB activation is observed in RCTs but is relatively low in healthy tendons. This activation might result from tissue apoptosis or hypoxia, further highlighting the complex interplay of factors during the tendon healing process [44].

Understanding tendon healing after repair necessitates a deeper look into surgical techniques, particularly those that might induce further ischemia, such as the double-row or suture bridge technique [45]. This highlights the need for refining and developing surgical interventions that can minimize further damage and promote optimal healing environments for torn tendons.

Nuclear lamin A, an anti-apoptotic and cell mechanostat factor located in the nuclear envelope, is a crucial player in maintaining cellular stability. Lamin A, which provides an anchoring site for nuclear pore complexes, is believed to offer protection against apoptosis and mechanical insults, thereby preserving nuclear integrity. Immunohistochemical investigations reveal its functionality in cells of healthy tissues or cells near the margins of either small or large lesions. However, lamin A's protective action appears to be lost in the cells of massive tears, emphasizing the importance of early repair of small RCTs. The high retear rate in massive cuff repairs might be attributable to cellular apoptosis and nuclear modifications instigated by a lack of lamin A [46].

As the intricacies of RC repair are traversed, a vital question confronts us: can we tilt the scales to favor healing? The path to avoiding repair failure must lie in a technique that ensures robust fixation but primarily hinges on facilitating the natural healing process. Several methods, such as platelet-rich plasma therapy, microfracture, acromioplasty, and the use of autologous microfragmented lipoaspirate tissue, are showing promise in this respect [47-49].

In research on the origin of tendon healing cells, multiple ani-

mal studies point to an unexpected source: the paratenon. Traditionally, the belief was that tendon healing cells originate from the bone or the tendon, but this view is shifting. It is now proposed that the so-called 'bursa' is, in fact, the paratenon of the RC, and that this bursa contains the cells necessary for healing [50]. This hypothesis underscores a critical shift in understanding RC healing, paving the way for new strategies in promoting optimal tendon recovery and minimizing the risk of retear.

CONCLUSIONS

Biological factors may contribute positively to the healing process, irrespective of the size of the tear. However, a word of caution is expressed against certain repair techniques that potentially favor ischemia, as they are assessed not to facilitate healing. As the exploration into this subject of RC tear healing continues, the aim should be to fine-tune understanding and strategies to optimize patient outcomes. It is the hopeful expectation of the authors that this review will stimulate further investigation into the complex dynamics of RC degeneration and healing.

NOTES

ORCID
Stefano Gumina   https://orcid.org/0000-0002-6097-4136
Hyungsuk Kim   https://orcid.org/0000-0003-3400-0263
Younsung Jung   https://orcid.org/0009-0008-3493-203X
Hyun Seok Song   https://orcid.org/0000-0002-7844-2293

Author contributions
Conceptualization: SG, HK, HSS. Data curation: SG, HK, YJ. Formal analysis: HK, YJ. Investigation: HK, YJ. Methodology: SG, HK, YJ, HSS. Resources: SG. Writing – original draft: HK. Writing – review & editing: SG, HSS.

Conflict of interest
None.

Data availability
None.

REFERENCES

1. Wang PW, Jo CH. Prognostic factors affecting structural integrity after arthroscopic rotator cuff repair: a clinical and histological study. Clin Shoulder Elb 2023;26:10–9.

2. Kim H, Byun CH, Han SB, Song HS. Surgical treatment outcomes for everted bursal flap of delaminated supraspinatus tear. Orthop J Sports Med 2021;9:2325967121990423.

3. Sharma P, Maffulli N. Tendon injury and tendinopathy: healing and repair. J Bone Joint Surg Am 2005;87:187–202.

4. Thankam FG, Dilisio MF, Gross RM, Agrawal DK. Collagen I: a kingpin for rotator cuff tendon pathology. Am J Transl Res 2018;10:3291–309.

5. Huijsmans PE, Pritchard MP, Berghs BM, van Rooyen KS, Wallace AL, de Beer JF. Arthroscopic rotator cuff repair with double-row fixation. J Bone Joint Surg Am 2007;89:1248–57.

6. Tashjian RZ, Hollins AM, Kim HM, et al. Factors affecting healing rates after arthroscopic double-row rotator cuff repair. Am J Sports Med 2010;38:2435–42.

7. Joo MS, Kim JW. Significant radiologic factors related to clinical outcomes after arthroscopic rotator cuff retear repair. Clin Shoulder Elb 2022;25:173–81.

8. Iannotti JP, Deutsch A, Green A, et al. Time to failure after rotator cuff repair: a prospective imaging study. J Bone Joint Surg Am 2013;95:965–71.

9. Riley GP, Harrall RL, Constant CR, Chard MD, Cawston TE, Hazleman BL. Tendon degeneration and chronic shoulder pain: changes in the collagen composition of the human rotator cuff tendons in rotator cuff tendinitis. Ann Rheum Dis 1994;53:359–66.

10. Gumina S, Di Giorgio G, Bertino A, Della Rocca C, Sardella B, Postacchini F. Inflammatory infiltrate of the edges of a torn rotator cuff. Int Orthop 2006;30:371–4.

11. Lewis JS. Rotator cuff tendinopathy: a model for the continuum of pathology and related management. Br J Sports Med 2010;44:918–23.

12. Maffulli N, Longo UG, Franceschi F, Rabitti C, Denaro V. Movin and Bonar scores assess the same characteristics of tendon histology. Clin Orthop Relat Res 2008;466:1605–11.

13. Sethi PM, Sheth CD, Pauzenberger L, et al. Macroscopic rotator cuff tendinopathy and histopathology do not predict repair outcomes of rotator cuff tears. Am J Sports Med 2018;46:779–85.

14. Ferrer GA, Miller RM, Yoshida M, Wang JH, Musahl V, Debski RE. Localized rotator cuff tendon degeneration for cadaveric shoulders with and without tears isolated to the supraspinatus tendon. Clin Anat 2020;33:1007–13.

15. Gumina S, Carbone S, Campagna V, Candela V, Sacchetti FM,

Giannicola G. The impact of aging on rotator cuff tear size. Musculoskelet Surg 2013;97 Suppl 1:69–72.

16. Diebold G, Lam P, Walton J, Murrell GA. Relationship between age and rotator cuff retear: a study of 1,600 consecutive rotator cuff repairs. J Bone Joint Surg Am 2017;99:1198–205.

17. Longo UG, Carnevale A, Piergentili I, et al. Retear rates after rotator cuff surgery: a systematic review and meta-analysis. BMC Musculoskelet Disord 2021;22:749.

18. Yamamoto A, Takagishi K, Osawa T, et al. Prevalence and risk factors of a rotator cuff tear in the general population. J Shoulder Elbow Surg 2010;19:116–20.

19. Jeong J, Shin DC, Kim TH, Kim K. Prevalence of asymptomatic rotator cuff tear and their related factors in the Korean population. J Shoulder Elbow Surg 2017;26:30–5.

20. Gumina S, Candela V, Mariani L, et al. Rotator cuff degeneration of the healthy shoulder in patients with unilateral arm amputation is not worsened by overuse. Knee Surg Sports Traumatol Arthrosc 2018;26:182–7.

21. Sugaya H, Maeda K, Matsuki K, Moriishi J. Repair integrity and functional outcome after arthroscopic double-row rotator cuff repair: a prospective outcome study. J Bone Joint Surg Am 2007;89:953–60.

22. Rathbun JB, Macnab I. The microvascular pattern of the rotator cuff. J Bone Joint Surg Br 1970;52:540–53.

23. Leikina E, Mertts MV, Kuznetsova N, Leikin S. Type I collagen is thermally unstable at body temperature. Proc Natl Acad Sci U S A 2002;99:1314–8.

24. Neer CS 2nd. Anterior acromioplasty for the chronic impingement syndrome in the shoulder: a preliminary report. J Bone Joint Surg Am 1972;54:41–50.

25. Bigliani LU, Levine WN. Subacromial impingement syndrome. J Bone Joint Surg Am 1997;79:1854–68.

26. Oh JH, Kim JY, Lee HK, Choi JA. Classification and clinical significance of acromial spur in rotator cuff tear: heel-type spur and rotator cuff tear. Clin Orthop Relat Res 2010;468:1542–50.

27. Ogawa K, Yoshida A, Inokuchi W, Naniwa T. Acromial spur: relationship to aging and morphologic changes in the rotator cuff. J Shoulder Elbow Surg 2005;14:591–8.

28. Tucker TJ, Snyder SJ. The keeled acromion: an aggressive acromial variant: a series of 20 patients with associated rotator cuff tears. Arthroscopy 2004;20:744–53.

29. Gumina S, Arceri V, Fagnani C, et al. Subacromial space width: does overuse or genetics play a greater role in determining it?: an MRI study on elderly twins. J Bone Joint Surg Am 2015; 97:1647–52.

30. Carbone S, Gumina S, Arceri V, Campagna V, Fagnani C, Postacchini F. The impact of preoperative smoking habit on ro-

tator cuff tear: cigarette smoking influences rotator cuff tear sizes. J Shoulder Elbow Surg 2012;21:56–60.

31. Gumina S, Candela V, Passaretti D, et al. The association between body fat and rotator cuff tear: the influence on rotator cuff tear sizes. J Shoulder Elbow Surg 2014;23:1669–74.

32. Gumina S, Arceri V, Carbone S, et al. The association between arterial hypertension and rotator cuff tear: the influence on rotator cuff tear sizes. J Shoulder Elbow Surg 2013;22:229–32.

33. Passaretti D, Candela V, Venditto T, Giannicola G, Gumina S. Association between alcohol consumption and rotator cuff tear. Acta Orthop 2016;87:165–8.

34. Chung SW, Park H, Kwon J, Choe GY, Kim SH, Oh JH. Effect of hypercholesterolemia on fatty infiltration and quality of tendon-to-bone healing in a rabbit model of a chronic rotator cuff tear: electrophysiological, biomechanical, and histological analyses. Am J Sports Med 2016;44:1153–64.

35. Garcia GH, Liu JN, Wong A, et al. Hyperlipidemia increases the risk of retear after arthroscopic rotator cuff repair. J Shoulder Elbow Surg 2017;26:2086–90.

36. Harada N, Gotoh M, Ishitani E, et al. Combination of risk factors affecting retear after arthroscopic rotator cuff repair: a decision tree analysis. J Shoulder Elbow Surg 2021;30:9–15.

37. Lu X, Sun H, Xu Y, Cao X. The influence of diabetes mellitus on rotator cuff repair: a systematic review and meta-analysis. Comb Chem High Throughput Screen 2021;24:908–20.

38. McGarry T, Biniecka M, Veale DJ, Fearon U. Hypoxia, oxidative stress and inflammation. Free Radic Biol Med 2018;125:15–24.

39. Thankam FG, Agrawal DK. Hypoxia-driven secretion of extracellular matrix proteins in the exosomes reflects the asymptomatic pathology of rotator cuff tendinopathies. Can J Physiol Pharmacol 2021;99:224–30.

40. Gumina S, Proietti R, Caccavale R, et al. Peripheral microcirculation alteration as cause of posterosuperior rotator cuff tear: the possible indirect contribution of nailfold capillaroscopy. J Shoulder Elbow Surg 2023;32:604–9.

41. Gumina S, Villani C, Arceri V, et al. Rotator cuff degeneration: the role of genetics. J Bone Joint Surg Am 2019;101:600–5.

42. Idolazzi L, Ridolo E, Fassio A, et al. Periostin: the bone and beyond. Eur J Intern Med 2017;38:12–6.

43. Gumina S, Leopizzi M, Carnovale M, et al. The attempt of spontaneous repair of rotator cuff tear: the role of periostin. J Orthop 2019;16:400–4.

44. Gumina S, Natalizi S, Melaragni F, et al. The possible role of the transcription factor nuclear factor-κB on evolution of rotator cuff tear and on mechanisms of cuff tendon healing. J Shoulder Elbow Surg 2013;22:673–80.

45. Kim H, Park SB, Song HS. A propensity score-matched com-

parison between knotless layer-by-layer and en masse suture bridge techniques for delaminated rotator cuff tears. Am J Sports Med 2022;50:2219–26.

46. Gumina S, Peruzzi B, Leopizzi M, et al. Nuclear lamin A in rotator cuff tear margin tenocytes: an antiapoptotic and cell mechanostat factor. J Orthop Surg Res 2021;16:413.

47. Gumina S, Campagna V, Ferrazza G, et al. Use of platelet-leukocyte membrane in arthroscopic repair of large rotator cuff tears: a prospective randomized study. J Bone Joint Surg Am 2012; 94:1345–52.

48. Jo CH, Shin JS, Park IW, Kim H, Lee SY. Multiple channeling improves the structural integrity of rotator cuff repair. Am J Sports Med 2013;41:2650–7.

49. Jo CH, Chai JW, Jeong EC, Oh S, Yoon KS. Intratendinous injection of mesenchymal stem cells for the treatment of rotator cuff disease: a 2-year follow-up study. Arthroscopy 2020;36:971–80.

50. Lebaschi A, Kriscenski DE, Tamburini LM, et al. Subacromial bursa increases the failure force in a mouse model of supraspinatus detachment and repair. J Shoulder Elbow Surg 2022; 31:e519–33.