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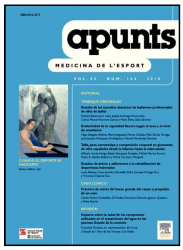

REVIEW

Current concepts in the physiopathology of tendinopathies. Tissue engineering

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Abstract
Tendinopathy is a common condition that occurs while practising sport. The unequal distribution of the work load throughout the tendon causes heterogeneous ruptures in extension and distribution. These ruptures start defective repair processes that produce a degenerated tendon with a change in structure and functional response to exercise.
In this article the different predisposing factors are study, along with the mechanisms of action of the chemical and cellular agents involved in the physiology of tendinopathies.
The basic components (support, cells and chemical substances) that are used for tissue engineering are also analysed, as well as the current possibilities of using the basic components, the inter-relationships between them and the current level of execution.

PALABRAS CLAVE
Tendinopatías;
Fisiopatología;
Ingeniería tisular;
Deporte

Conceptos actuales de la fisiopatología de las tendinopatías. Ingeniería tisular

Resumen
La tendinopatía es una afectación frecuente que produce la práctica deportiva. El reparto desigual de la carga de trabajo a lo largo del tendón produce roturas heterogéneas en extensión y distribución. Estas roturas ponen en marcha procesos de reparación defectuosos que producen un tendón degenerado con alteración estructural y de la respuesta funcional al ejercicio.

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En este trabajo se estudian y analizan los distintos factores predisponentes, mecanismos de acción de los agentes químicos y celulares implicados en la fisiopatología de las tendinopatías.
Por otra parte, se analizan los componentes básicos (soporte, células y sustancias químicas) que se usan para la ingeniería tisular. Las posibilidades actuales de uso de los componentes básicos y sus interrelaciones, y el nivel actual de desarrollo.falta

Introduction

The importance of tendon injuries in the world of sports is highlighted by the fact that tendinous involvement is a common pathology arising from sporting activity. Indeed, some authors have reported that 30-50% of all sporting injuries involve tendons[1], with up to 30% of runners, for example, having been reported to suffer from a chronic tendinopathy and 40% of racquet-sports players to suffer from tennis elbow[2]. Degenerative involvement of the Achilles tendon, which is the most common injury in long-distance runners (56.6%), is related to the number of years the sport has been practiced and most commonly occurs in the middle part of the tendon[3].

Tendinopathy of the rotator cuff is the most frequent cause of pain and dysfunction in the upper limbs and tends to appear more frequently with age[4].

Physiopathology

From an etiopathogenic and biomechanical point of view, the load which acts on the tendon during physical exercise produces a fibrillar rupture when the mechanical traction exceeds 4% of the length at rest, with a complete rupture occurring at more than 8%. An unequal distribution of the load throughout the tendon produces ruptures that are heterogeneous in terms of their length and distribution. On the other hand, due to the different proportion of cross-links between the collagen fibres in different regions of the tendon (tendinous muscle region, mid-part, osteotendinous region), the mechanical resistance and the tendon's biochemical and structural profiles also differ[5,6].

These partial or fibrillar ruptures induce tendinous repair mechanisms, which involve:

a) Various chemical substances, including growth factors.
b) Cells such as resident tenocytes, which are involved in the balance, production and destruction of the extracellular matrix, and stem cells, which differentiate into tenocytes, adipocytes or chondrogenic or osteogenic cell lines depending, amongst other factors, on the mechanical load to which they are submitted during the repair process.
c) The extracellular matrix, one of whose main components is type I collagen fibres[6,7].

These normal repair processes are considered defective when they produce a structurally altered degenerate tendon. Such defective regeneration has been linked to the hypoxia level in the lesion, the presence of ischaemic damage, unequal apoptosis mediated by cytokines and inflammatory mediators, the existence of oxidative stress, the presence of local hyperthermia and an alteration to the matrix metalloproteinase (MMP) balance.

The chemical interactions in the matrix, insoluble deposits, mechanical stress, local release of cytokines and signalling molecules will all have a direct influence on tenocyte activity, cellular gene expression and the matrix enzymes.

Tenocytes play a key role in normal homeostasis, regularisation of the matrix and the pathological change which occurs during degenerative disease. Furthermore, they also appear to play a fundamental role in the incorrect production of tissue during repair of the fibrocartilage which occurs in tendinopathies[8].

All the above processes lead to a degenerate and fibrotic tendon, thereby reducing its load-supporting ability. This therefore completes the physiopathological cycle of tendinopathies (Figure 1).

Predisposing factors

The appearance of a tendinopathy depends to a large extent on both extrinsic and intrinsic, sportsperson-related factors.

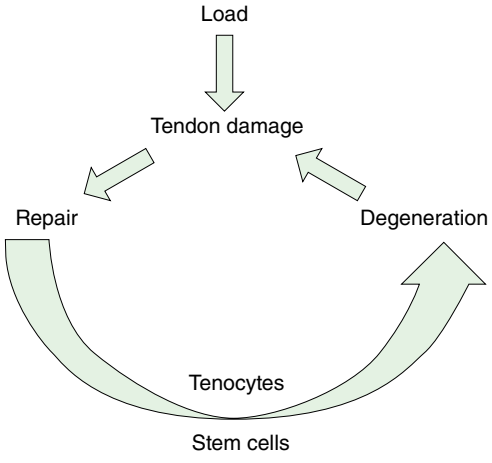

Figure 1 General scheme showing the physiopathology of tendinopathies.

Intrinsic factors: the presence of a tenascin C (TNC) gene variant and variants of the collagen V α1 (COL5A1) gene[9]; poor alignment of the lower limbs with varus/valgus or back knee; eversion of the ankle in runners favours the appearance of an Achilles tendinopathy[10,11]; changes to the normal joint biomechanics, with alteration to the tendon length, changes to the muscle thickness/power ratio when taking anabolic steroids, changes to the lever arm, which result in changes to the moment of force and thus an increase in the load at one part of the tendon, have all been reported.

The factors extrinsic to the sportsperson include the following: those parameters related with the load in terms of both intensity and frequency; training; performance of a technical movement; the time allowed for the tendon to rest and recover; certain drugs (quinolones, statins) due to their interaction with metalloproteinases (MMPs) or interference with the repair mechanisms[12,13]. MMPs themselves play a key role in tendinous degeneration[14].

The highest rate of renewal of the collagen in the extracellular matrix has been associated with an increase in the expression and activity of various members of the MMP family. Thus, MMP-3 (stromelysin) is considered to be the key regulatory enzyme involved in control of matrix renewal, and a decrease in its levels could induce a change in the normal remodelling process. A study of the tendinous synovial fluid, for example, found high expression levels for MMP-1 and -3, and a molecular study of the pathology of the Achilles tendon confirmed a lack of inflammation along with marked increases in the expression of type I and type III collagen genes and an increase in the levels of versican, biglycan, perlecan and the glycoproteins laminin, SPARC and tenascin-C. MMP-3 levels were notably lower or absent in painful tendinopathy and in the event of a ruptured tendon. Drugs such as ibuprofen increase the expression of MMP-1, -2, -8, -9 and -13 without affecting the expression of type I and III collagen[15,16], whereas fluoroquinolones can induce tendinopathies in some cases by modulating MMP activity. Likewise, corticosteroid use also increases the risk of suffering a tendinopathy[17].

Histological studies have highlighted changes to the normal distribution during healing, the lack of inflammatory cells and the existence of a poor repair response, which leads to a non-inflammatory intratendinous degeneration of the collagen fibres and thus a disorientation and thinning of these fibres, with a consequent increase in interfibrillary glucosamines, hypercellularity and disperse vascular growth. Changes to the extracellular matrix together with an increase in the expression of proteoglycans and an increase in the collagen III/I ratio have been observed in calcifying tendinopathies[18].

In tendinopathies, as regards the structure of the extracellular matrix, there is: a reduction in the total collagen content, with an abnormal morphology; a reduction in the fibrillar density and a change in the alignment[19], together with a higher proportion of randomly ordered type III collagen with respect to the more linear and organised type I collagen; an increase in the level of proteoglycans in those tendons undergoing a degenerative process; a build up of necrotic tissue and fibrin; an increase in the level of glycoproteins such as tensacin C; and a gradual decrease in tendon quality.

Likewise, measurements of the growth factors have shown that:

a) Insulin Growth Factor 1 (IGF I) promotes fibroblast proliferation and migration and increases the production of collagen.
b) Transforming Growth Factor beta (TGB beta) regulates cellular migration, cross-link proliferation and matrix remodelling[20].
c) Vascular Endothelial Growth Factor (VEGF) is a powerful angiogenesis promoter. The finding that the VEGF level increases in intrinsic tenocytes suggests a role for VEGF in the angiogenesis which occurs during tendon repair. In contrast to the situation in normal tendons, an increase in the number of type 1 and 2 VEGF receptors is observed in degenerate tendons[21,22].
d) Platelet Derived Growth Factor (PDGF) stimulates the production of other growth factors and plays a role in tendon remodelling.
e) Basic Fibroblast Growth Factor (bFGF) is a strong angiogenesis stimulator and also regulates cell proliferation and migration[23,24]. Indeed, tenocytes grow in culture when exposed to bFGF[25].

It has been shown that the pain caused by a tendinopathy doubles the intratendinous lactate concentration. An increase in the levels of glutamate, which is a neurotransmitter, and PGE2, which has been linked to the onset of calcification formation, has also been observed. The level of substance P has been linked to the level of pain in tendinopathy of the cuff and elbow[26]. Similarly, an increase in the expression of substance P and calcitonin gene related peptide (CGRP) has been observed during defective and painful tendon repair[27].

Histological evidence for neural growth inside the tendon and in the paratendon has also been reported in tendionopoathies. This growth is regulated by pro- and anti-inflammatory mediators at the periphery of the tendon during the repair process. However, this appears to depend on the repair time, sensitive and autonomic aspects and glutamate mediators as in normal tendons nerves are only observed in the paratendon, thus reflecting normal tendon homeostasis[27,28].

In summary, clinical, histological and biochemical evidence for changes to tendon homeostasis during the repair and regeneration process which occurs after a post-exercise fibrillar rupture has been reported.

Tissue engineering

From a theoretical point of view, we can consider any biological tissue consisting of:

a) A scaffold which contains the tissue support structures and is mainly composed of fibrillar substances.
b) Cells which can possess any degree of differentiation, ranging from completely undifferentiated, such as stem cells, to highly differentiated, such as mature tenocytes.

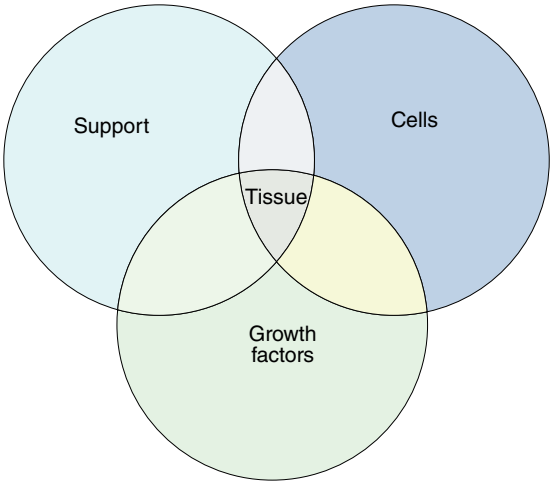

Figure 2 A graphical representation showing the components of a biological tissue.

c) Various chemical substances, including growth factors. These chemical substances act as intracellular, intercellular and autocrine messengers and mediate the different cell responses.

Tissue engineering, which is a branch of bioengineering, aims to create or produce tissues to correct tissue defects by developing or combining one, two or all three of the above-mentioned components. Thus, a scaffold can be created to act as a host for the individual's own cells, or a scaffold with cells for implantation at the site of the tissue defect, such as a collagen matrix implant containing autologous cultivated chondrocytes (MACI; Figure 2).

The present review highlights various studies currently underway in the field of tissue engineering aimed at treating tendon injuries, many of which are still at only the animal model stage or in vitro.

Current possibilities

Scaffold

Biocompatible and biodegradable biomaterials are currently being used to correct bone defects[29], and an electrospun nanofibre structure which stimulates the differentiation of tendinous stem cells has also been created[30]. Similarly, some studies have used calcium orthophosphate bioceramics to produce a support to correct tendinous insertion defects[31], and others have used double-layered planar or two-dimensional polylactic acid structures[32].

Combination of scaffold and cells

Fibroblasts have been embedded in a polymer gel to increase the production of fibrillar protein[33], and acellular human tendons have been implanted with cultivated tenocytes for subsequent implantation[34]. Similarly, mesenchymal cells have been implanted in a hydrogel support[35], and cultivated tenocytes have even been embedded in a pig gut scaffold[36].

Cells

Muscle cells subjected to a low intensity magnetic field have been implanted to regenerate tendinous muscle tissue[37], and cells which synthesise glycoproteins and lubricin have been implanted in the case of fracture and defect of the shoulder rotator cuff[38]. Likewise, a technique involving cultivated and cryopreserved tenocytes has been developed[39], and other studies have used mesenchymal cells obtained from adipose tissue[40].

Cells and growth factors

Bone marrow mesenchymal cells have been used in conjunction with growth factors to correct tendinous defects[41], whereas other studies have employed human embryonic stem cells together with foetal differentiation factor for tendon repair[42]. The possibility of implanting mesenchymal stem cells with buffered platelet-rich plasma (bPRP), which increases the proliferation and differentiation of the chondrogenic cell line, has been studied in vitro for use in the event of tendinous insertion defects[43].

Growth factors

One particular research group has developed a bioreactor to promote healing and improve the mechanical properties of tendons[44], whereas others use a soluble protein to stimulate musculoskeletal regeneration[45]. Likewise, one of the most widely studied growth factors, namely basic fibroblast growth factor (bFGF), has been used to stimulate the differentiation of mesenchymal stem cells (MSCs) in the tendon[46].

Growth factors plus scaffold

Type I collagen has been combined with chondroitin 6 sulfate to promote the release of autologous mesenchymal stem cells for tendon repair[47]. Likewise, bFGF has been incorporated into a biohybrid (nano and micro) fibrous scaffold to treat anterior cruciate ligament damage in the knee and tendon problems[48], and growth factor-enriched plasma has been used together with a synthetic scaffold to promote tendon cell proliferation and production in vitro[49]. Similarly, nanofibers with gradations in mineral content have been used to mimic the tendon insertion site[50].

Cells plus growth factors plus scaffold

Autologous and homologous tissues are currently being used to perform auto- or allografts modified using the conservation technique.

In summary, various different procedures can be used to construct a living tissue. Future studies will determine which method or procedure should be used for a particular tendon injury and will establish the indications for each therapeutic option.

Conclusions

The workload applied to a tendon produces unequally distributed damage of differing severity which activates damage-regeneration and -repair mechanisms in both the extracellular and the cellular matrix. These biochemical processes reduce the tolerance of the tendon to physical exercise.

More, and more accurate, studies are therefore required in order to be able to diagnose tendinous pathologies more precisely, define therapeutic strategies and establish therapeutic protocols to restore the tendon's normal histology.

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References

1. De Vos RJ, Weir A, van Schie HT, Bierma-Zeinstra SM, Verhaar JA, Weinans H, et al. Platelet-rich plasma injection for chronic Achilles tendinopathy: a randomized controlled trial. JAMA. 2010;303:144.
2. Sharma P, Maffulli N. Biology of tendon injury: healing, modeling and remodeling. J Musculoskelet Neuronal Interact. 2006;6:181-90.
3. Knobloch K, Yoon U, Vogt PM. Acute and overuse injuries correlated to hours of training in master running athletes. Foot Ankle Int. 2008;29:671-6.
4. Hansen P, Haraldsson BT, Aagaard P, Kovanen V, Avery NC, Qvortrup K, et al. Lower strength of the human posterior patellar tendon seems unrelated to maturecollagen cross-linking and fibril morphology. J Appl Physiol. 2010;108:47-52.
5. Hansen P, Hassenkam T, Svensson RB, Aagaard P, Trappe T, Haraldsson BT, et al. Glutaraldehyde cross-linking of tendon-mechanical effects at the level of the tendon fascicle and fibril. Connect Tissue Res. 2009;50:211-22.
6. Zhang J, Wang JH. Mechanobiological response of tendon stem cells: Implications of tendon homeostasis and pathogenesis of tendinopathy. J Orthop Res. 2010;28:639-43.
7. Abate M, Gravare-Silbernagel K, Siljeholm C, Di Iorio A, De Amicis D, Salini V, et al. Pathogenesis of tendinopathies: inflammation or degeneration? Arthritis Res Ther. 2009;11:235.
8. Clegg PD, Strassburg S, Smith RK. Cell phenotypic variation in normal and damaged tendons. Int J Exp Pathol. 2007;88: 227-35.
9. Collins M, Raleigh SM. Genetic risk factors for musculoskeletal soft tissue injuries. Med Sport Sci. 2009;54:136-49.
10. Ryan M, Grau S, Krauss I, Maiwald C, Taunton J, Horstmann T. Kinematic analysis of runners with achilles mid-portion tendinopathy. Foot Ankle Int. 2009;30:1190-5.
11. Rodas G, Bové T, Puigdellívol J, Martínez X, Pedret C, Dalmau A. Lesión de "tennis leg" asociada a rotura parcial del tendón de Aquiles. Apunts Med Esport. 2010;165:40-4.
12. Marie I, Delafenêtre H, Massy N, Thuillez C, Noblet C. Tendinous disorders attributed to statins: a study on ninety-six spontaneousreports in the period 1990-2005 and review of the literature. Arthritis Rheum. 2008;59:367-72.
13. Barge-Caballero E, Crespo-Leiro MG, Paniagua-Martín MJ, Muñiz J, Naya C, Bouzas-Mosquera A, et al. Quinolone-related Achilles tendinopathy in heart transplant patients: incidence and risk factors. J Heart Lung Transplant. 2008;27:46-51.
14. Pasternak B, Aspenberg P. Metalloproteinases and their inhibitors-diagnostic and therapeutic opportunities in orthopedics. Acta Orthop. 2009;80:693-703.
15. Hosaka YZ, Takahashi H, Uratsuji T, Tangkawattana P, Ueda H, Takehana K. Comparative study of the characteristics and properties of tendinocytes derived from three tendons in the equine forelimb. Tissue Cell. 2010;42:9-17.
16. Tsai WC, Hsu CC, Chang HN, Lin YC, Lin MS, Pang JH. Ibuprofen upregulates expressions of matrix metalloproteinase-1, -8, -9, and -13 without affecting expressions of types I and III collagen in tendon cells. J Orthop Res. 2010;28:487-91.
17. Sendzik J, Shakibaei M, Schäfer-Korting M, Lode H, Stahlmann R. Synergistic effects of dexamethasone and quinolones on human-derived tendon cells. Int J Antimicrob Agents. 2010;35:366-74.
18. Lui PP, Chan LS, Lee YW, Fu SC, Chan KM. Sustained expression of proteoglycans and collagen type III/type I ratio in a calcified tendinopathy model. Rheumatology (Oxford). 2010;49:231-9.
19. Kongsgaard M, Qvortrup K, Larsen J, Aagaard P, Doessing S, Hansen P, et al. Fibril morphology and tendon mechanical properties in patellar tendinopathy: Effects of heavy slow resistance training. Am J Sports Med. 2010;38:749-56.
20. Hou Y, Mao Z, Wei X, Lin L, Chen L, Wang H, et al. The roles of TGF-beta1 gene transfer on collagen formation during Achilles tendon healing. Biochem Biophys Res Commun. 2009;383: 235-9.
21. Petersen W, Pufe T, Zantop T, Tillmann B, Tsokos M, Mentlein R. Expression of VEGFR-1 and VEGFR-2 in degenerative Achilles tendons. Clin Orthop Relat Res. 2004;420:286-91.
22. Petersen W, Pufe T, Unterhauser F, Zantop T, Mentlein R, Weiler A. The splice variants 120 and 164 of the angiogenic peptide vascular endothelial cell growth factor (VEGF) are expressed during Achilles tendon healing. Arch Orthop Trauma Surg. 2003;123:475-80.
23. Molloy T, Wang Y, Murrell G. The roles of growth factors in tendon and ligament healing. Sports Med. 2003;33:381-94.
24. Kjaer M, Langberg H, Heinemeier K, Bayer ML, Hansen M, Holm L, et al. From mechanical loading to collagen synthesis, structural changes and function in human tendon. Scand J Med Sci Sports. 2009;19:500-10.
25. Tang JB, Xu Y, Wang XT. Tendon healing in vitro: activation of NIK, IKKalpha, IKKbeta, and NF-kappa B genes in signal pathway and proliferation of tenocytes. Plast Reconstr Surg. 2004;113:1703-11.
26. Alfredson H. The chronic painful Achilles and patellar tendon: research on basic biology and treatment. Scand J Med Sci Sports. 2005;15:252-9.
27. Lui PP, Chan LS, Fu SC, Chan KM. Expression of sensory neuropeptides in tendon is associated with failed healing and activity-related tendon pain in collagenase-induced tendon injury. Am J Sports Med. 2010;38:757-64.
28. Ackermann PW, Salo PT, Hart DA. Neuronal pathways in tendon healing. Front Biosci. 2009;14:5165-87.
29. Longo UG, Lamberti A, Maffulli N, Denaro V. Tendon augmentation grafts: a systematic review. Br Med Bull. 2010;94:165-88.
30. Yin Z, Chen X, Chen JL, Shen WL, Hieu Nguyen TM, Gao L, et al. The regulation of tendon stem cell differentiation by the alignment of nanofibers. Biomaterials. 2010;31:2163-75.
31. Dorozhkin SV. Bioceramics of calcium orthophosphates. Biomaterials. 2010;31:1465-85.
32. Inui A, Kokubu T, Makino T, Nagura I, Toyokawa N, Sakata R, et al. Potency of double-layered Poly L-lactic Acid scaffold in tissue engineering of tendon tissue. Int Orthop. 2009. [Epub ahead of print.]

33. Hunt NC, Grover LM. Cell encapsulation using biopolymer gels for regenerative medicine. Biotechnol Lett. 2010;32:733-42.
34. Thorfinn J, Saber S, Angelidis IK, Ki SH, Zhang AY, Chong AK, et al. Flexor tendon tissue engineering: temporal distribution of donor tenocytes versus recipient cells. Plast Reconstr Surg. 2009;124:2019-26.
35. Salinas CN, Anseth KS. Mesenchymal stem cells for craniofacial tissue regeneration: designing hydrogel delivery vehicles. J Dent Res. 2009;88:681-92.
36. Gumina S, Patti AM, Vulcano A, Della Rocca C, Postacchini F. Culture of human rotator cuff cells on orthobiologic support (porcine small intestinal submucosa). Chir Organi Mov. 2009; 93:S65-70.
37. Fujita H, Shimizu K, Yamamoto Y, Ito A, Kamihira M, Nagamori E. Fabrication of scaffold-free contractile skeletal muscle tissue using magnetite-incorporated myogenic C2C12 cells. J Tissue Eng Regen Med. 2010. [Epub ahead of print.]
38. Funakoshi T, Spector M. Chondrogenic differentiation and lubricin expression of caprine infraspinatus tendon cells. J Orthop Res. 2010;28:716-25.
39. Liao M, Liu C, Zhu M, Qin T. Effect of vitreous-cryopreservation on in vivo implantation of tissue engineered tendons. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi. 2009;23:1229-34.
40. Uysal AC, Mizuno H. Tendon regeneration and repair with adipose derived stem cells. Curr Stem Cell Res Ther. 2010; 5:161-7.
41. Salamon A, Toldy E. Use of mesenchymal stem cells from adult bone marrow for injured tissue repair. Orv Hetil. 2009;150:1259-65.
42. Chen X, Song XH, Yin Z, Zou XH, Wang LL, Hu H, et al. Stepwise differentiation of human embryonic stem cells promotes tendon regeneration by secreting fetal tendon matrix and differentiation factors. Stem Cells. 2009;27:1276-87.
43. Mishra A, Tummala P, King A, Lee B, Kraus M, Tse V, et al. Buffered platelet-rich plasma enhances mesenchymal stem cell proliferation and chondrogenic differentiation. Tissue Eng Part C Methods. 2009;15:431-5.
44. Saber S, Zhang AY, Ki SH, Lindsey DP, Smith L, Riboh J, et al. Flexor tendon tissue engineering: Bioreactor cyclic strain increases construct strength. Tissue Eng Part A. 2010;16:2085-90.
45. Murphy WL. Temporal and spatial control over soluble protein signaling for musculoskeletal tissue engineering. Conf Proc IEEE Eng Med Biol Soc. 2009;1:2103-5.
46. Sahoo S, Ang LT, Cho-Hong Goh J, Toh SL. Bioactive nanofibers for fibroblastic differentiation of mesenchymal precursor cells for ligament/tendon tissue engineering applications. Differentiation. 2010;79:102-10.
47. Kinneberg KR, Nirmalanandhan VS, Juncosa-Melvin N, Powell HM, Boyce ST, Shearn JT, et al. Chondroitin-6-sulfate incorporation and mechanical stimulation increase MSC-collagen sponge construct stiffness. J Orthop Res. 2010;28:1092-9.
48. Sahoo S, Toh SL, Goh JC. A bFGF-releasing silk/PLGA-based biohybrid scaffold for ligament/tendon tissue engineering using mesenchymal progenitor cells. Biomaterials. 2010;31:2990-8.
49. Visser LC, Arnoczky SP, Caballero O, Kern A, Ratcliffe A, Gardner KL. Growth factor-rich plasma increases tendon cell proliferation and matrix synthesis on a synthetic scaffold: An in vitro study. Tissue Eng Part A. 2010;16:1021-9.
50. Li X, Xie J, Lipner J, Yuan X, Thomopoulos S, Xia Y. Nanofiber scaffolds with gradations in mineral content for mimicking the tendon-to-bone insertion site. Nano Lett. 2009;7:2763-8.