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Infrapatellar fat pad may be with tendon repairing ability and closely related with the developing process of patella Baja

Yu-Ping Liu [a,b,1], Shan-Zhu Li [a,1], Feng Yuan [a], Jiang Xia [a], Xiao Yu [a], Xiaoqing Liu [c,2,*], Guang-Rong Yu [a,2,*]

[a] Department of Orthopedics, Tongji Hospital, Tongji University, Shanghai, PR China
[b] Department of Orthopedics, Tengzhou Central People's Hospital, Shandong, PR China
[c] Shanghai Tenth People's Hospital & Department of Regenerative Medicine, School of Medicine, Tongji University, No. 1239, Siping Road, Yangpu District, Shanghai 250021, PR China

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ABSTRACT

Patella Baja, as a common complication of knee trauma or knee surgery, was very difficult to deal with, and scarring and shortening of the patellar tendon were looked on as the most important reason for it. Infrapatellar fat pad, also known as Hoffa's fat pad was traditionally regarded as with only buffering and lubricating functions in knee joints, which can limit the knee's excessive activities, absorb shocks from the anterior knee and reduces friction between the patellar tendon and the tibia, it should be with direct protection function and avoid the damage of patella tendon. Recently, a large number of studies had shown that adipose tissue was an accessible and abundant source of mesenchymal stem cells for tissue engineering. Adipose derived stem cells (ADSCs) can be induced to differentiate into adipocytes, osteoblasts, nerve cells, tendon cells and so on. In addition, interestingly, infrapatellar fat pad were just located behind the patellar tendon, and SDF-1 (stromal cell-derived factor-1), as a powerful cytokine that regulates inflammatory cell recruitment and stem cell homing, was unregulated after ligament injury, so there may be a certain correlation between ADSCs from infrapatellar fat pad and injured tendons, maybe ADSCs from infrapatellar fat pad can biologically repair injured tendons when patella tendon was damaged. We hypothesized injured patella tendon repairing should include not only the self-repairing of the tendon, but also the biological repairing from ADSCs in infrapatellar fat pad. When both of the repairing failed to repair the damage of the tendon, patellar tendon may begin to shrink and scar, which will result in patella Baja. In our opinion, healthy infrapatellar fat pad was with direct protection function of patella tendon and full of rich ADSCs, which may play an important part in patella tendon repairing and the developing process of patella Baja.

Introduction

Patella Baja (the typical X-ray of patella Baja was shown in Fig. 1) was commonly encountered in knee trauma or surgery and the incidence of patella Baja after TKA had been reported in 10–65% of cases, which can alter the femoropatellar joint mechanics and result in decreased range of motion, extensor lag, anterior knee pain, polyethylene impingement and subsequent wear, and diminished outcomes. The severe patella Baja was very troublesome to deal with to every joint surgeon [1–4]. The Insall–Salvati ratio (ISR), the ratio of the greatest diagonal length of the patella to the ligament length of the patella, is one of popular parameters used to measure the patella position on images [5]. Although the pathogenesis of patella Baja still remained unclear, scarring and shortening of the patellar tendon was often the final clinical outcome, so the damage to patellar tendon was regarded as the important possible reason for patella Baja. The injury to patella tendon should include the lateral damage and longitudinal damage (Fig. 2), the lateral damage, not longitudinal damage was the major factor causing the patella Baja. The lateral damage of patella tendon must be with excellent repairing, or the scarring and shortening of patella tendon will start up and eventually result in patella Baja. We thought that the balance of patella tendon damage and repairing guaranteed the normal physiological function of it.

Infrapatellar fat pad (IFP), also known as Hoffa's fat pad was a large, deformable pad of adipose tissue occupying the space between the patella, tibia and femur, and is vascular and highly innervated [6]. The location of the IFP in knee was shown in

* Corresponding author. Address: No. 389, Xincun Road, Putuo District, Shanghai 250021, PR China. Tel./fax: +86 21 65986770.
E-mail addresses: xqliu2009@googlemail.com (X. Q. Liu), liu9534@sohu.com (G.-R. Yu).
[1] Dr. Yu-Ping Liu and Dr. Shan-Zhu Li equally contributed to this work and should be considered as co-first Authors.
[2] Dr. Xiaoqing Liu and Guang-Rong Yu equally contributed to this work and should be considered as co-corresponding Authors.

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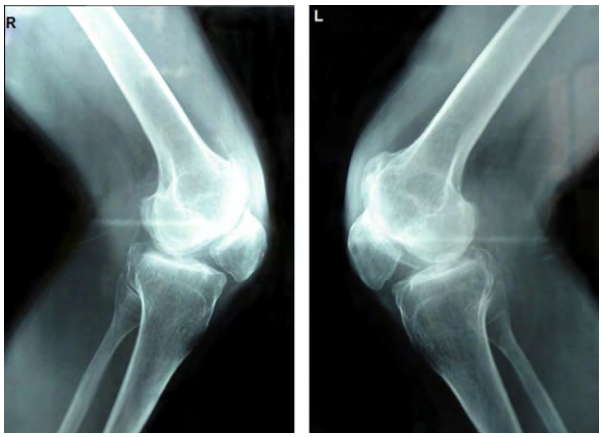

Fig. 1. The typical X-ray of patella Baja.

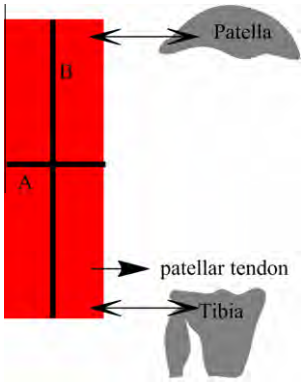

Fig. 2. The types of damage of patella tendon, (A), the lateral damage of patella tendon. (B) The longitudinal damage of patella tendon.

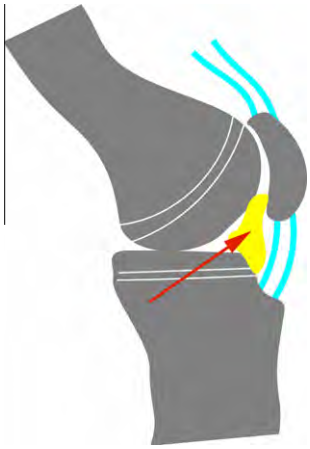

Fig. 3. The location of the infrapatellar fat pad in knee joint (red arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 3. Gallagher, J [7] found that the IFP is a constant structure in the knee joint, which may play a number of roles in knee joint function and pathology. Generically, the IFP was considered to be with buffering and lubricating functions in knee joints, which can limit the knee's excessive activities, absorb shocks from the anterior knee and reduces friction between the patellar tendon and the tibia, it should be with direct protection function and avoid the damage of patella tendon. Although the fat pad had been implicated as a common cause of anterior knee pain (Hoffa's disease), there was no sufficient evidence for this to be a definite fact. Additionally, as there are no clear clinical features, the condition was unable to be diagnosed and treated with any certainty.

Recent studies had shown that mesenchymal stem cells isolated from adipose tissue, such as infrapatellar fat pad [8], may possess significant plasticity in their multi-lineage capabilities [9]. These tissues represented attractive cell sources for tissue engineering because they are generally accessible with minimal donor site morbidity [9–11]. The mesenchymal stem cells derived from adipose tissue can be induced to differentiate into all the cell types of the human body, such as adipocytes, osteoblasts, nerve cells, tendon cells [12,13]. Moreover, interestingly, infrapatellar fat pad was located just behind the patellar tendon; the mesenchymal stem cells may immigrate to the injury location of the tendon when the patella tendon was damaged.

The hypotheses

The patella tendon damage may be the most important direct reason of patella Baja. The imbalance of patella tendon damage and repairing resulted in scarring and shortening of the patellar tendon and ultimately in patella Baja. IFP may be not only with direct protection function and avoid the damage of patella tendon for its buffering and lubricating functions, but also with powerful tendon repairing ability. The disorder or lesion of IFP may be one of the important pathogenesis and risk factors of patella Baja.

Theoretical fundamental of the hypotheses

Patella tendon was a strong, flat, ligament, which originated on the distal patellar and inserted on the tibial tubercle, and was an important component of knee extensor mechanism. As is known to all, normal healthy tendons were mostly composed of parallel arrays of collagen fibers and tendon cells closely packed together, there was a synovial tendon sheath surrounding outside of it, which can secrete synovial fluid and provide lubrication to decrease friction.

We knew that the knee was the largest and most complex joint in the human body, the patella tendon would bear the tremendous stress everyday, and the injury and repairing of tendon always presented in the life of man. Patella tendon injury should include the tendon injury and the tendon sheath injury, mostly occurred in patella tendon–patella and patella tendon–tibial tubercle connections (Fig. 4). The tendon sheath injury occurred in patella tendon–tibial tubercle connections often caused the adhesion of

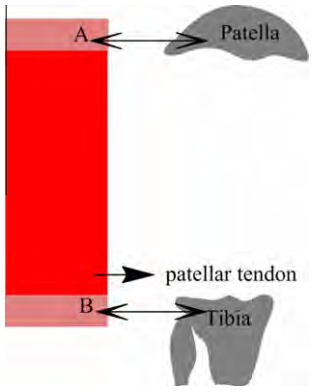

Fig. 4. The most vulnerable parts in patella tendon, (A), patella tendon–patella connections. (B) Patella tendon–tibial tubercle connections.

patellar tendon and tibial plate for the synovial tendon sheath injury, which was looked as a possible reason for patella Baja [4,14].

People thought that tendon was lack of self-healing capacity for a long time and the partial adhesion was the basic form of tendon healing. In recent years, many studies have confirmed that the process of tendon repair included not only endogenous repairing from the tendon itself, but also exogenous repairing from the outside of the tendon, two mechanisms existed together and finally completed the tendon repairing [15,16].

Many authors have demonstrated potential clinical applications of ADSCs in the field of tissue engineering and cell therapy. Mesenchymal stem cells have shown promise in their ability to augment tendon graft healing in a bone tunnel [17,18]. Atsushi Kanaya thought that intra-articularly injected mesenchymal stem cells can accelerate the healing of partially torn anterior cruciate ligament [19]. Awad [20] demonstrated that delivering mesenchymal stem cell-contracted, organized collagen implants to large tendon defects can significantly improve the biomechanics, structure, and probably the function of the tendon after injury. Recently, Gulotta [21] demonstrated that the application of mesenchymal stem cells (MSCs) transduced with adenoviral-mediated scleraxis could improve regeneration of the tendon–bone insertion site in a rat rotator cuff repair model.

SDF-1 (stromal cell-derived factor-1), as a major cytokine that regulates inflammatory cell recruitment and stem cell homing [22,23], has been reported to be with powerful function in the regeneration of various organs such as the liver, brain, heart, and kidney [24–27]. Recently, Shimode and colleagues demonstrated that the expression of SDF-1 was unregulated after ligament injury and may promote homing of bone marrow mesenchymal stem cells following systemic infusion [28], which suggested that SDF-1 may also be potential to initiate in situ regeneration by recruiting host stem cells [29]. Numerous studies showed that SDF-1 had strong induced migratory capacities to stem cells, especially CD34 positive stem cells. Recently, many studies [30–39] have shown that adipose derived stem cells were positive for the expression of CD34 molecular surface markers, which means ADSCs in infrapatellar fat Pad will be possible to reverse the concentration gradient of SDF-1 and migrate into the injury location of the patellar tendon and tendon sheath when patella tendon is injured. In addition, the microenvironment, or niche, in which stem cells reside, played an important factor in stem cells induction, differentiation and maturation [40]. The niche included not only the growth factors of cells secretion, but also the adjacent cells interactions [41]. In addition, MSCs culturing with the type of cell you want to differentiate will accelerate the rate of MSCs differentiation [42–44]. The niche of injury location of tendon or tendon sheath may respectively provide a better microenvironment for ADSCs to differentiate easily into tendon cells or synovial cells.

Moreover, excellent patella tendon repairing should include tendon repairing, and tendon sheath repairing, and the latter also can decrease the risk of scarring, shortening and adhesion of the patellar tendon.

Clinical implication of the hypotheses

We thought that the normal healthy IFP was full of mesenchymal stem cells and with the buffering and lubricating functions to avoid the patellar tendon damage. Furthermore, the expression of SDF-1 was unregulated after ligament injury, which can recruit stem cells to the injury site of the tendon or tendon–bone connections. Both of the factors mentioned above composed of the theoretical fundamental. The possible relationship of IFP, patella tendon and patella Baja was shown in Fig. 5.

We offered several possible explanations for the clinical implication of the hypotheses as follows. Firstly, the normal healthy IFP should not be extravagantly disturbed during the knee operations, such as radical excision of the fat pad and excessive burn by electrotome. Similar as to Weight loss liposuction, which decreased the ADSCs in IFP, reduce the repairing ability of IFP and lower the protection function of the IFP for the constructrue of the IFP being changed, and Lemon [45] also thought preservation of the infrapatellar fat pad may be a factor in preventing shortening of patella tendon length after total knee arthroplasty. Secondly, infrapatellar fat pad lesions such as Hoffa's disease often showed the hypertrophy and hyperplasia of adipocytes, we thought the ADSCs in IFP was more easily to differentiate into adipocytes other than

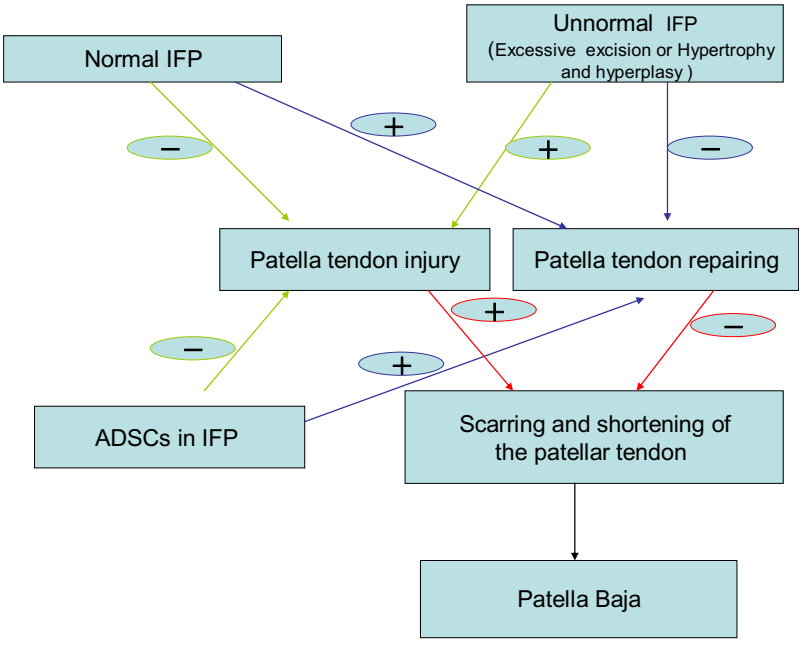

Fig. 5. The possible relationship of IFP, patella tendon and patella Baja (IFP infrapatellar fat pad, ADSCs adipose-derived stem cells).

tendon cells and more often resided in IFP other than immigrated to patella tendon for such a microenvironment in IFP. So the repairing ability of ADSCs in IFP decreased. Under such circumstances, we thought the easiest way to prevent the occurrence of patella Baja was avoiding the patella tendon being damaged. Thirdly, the hypotheses can partially explain why the incidence of patella Baja in the total knee revision was higher than in primary total knee arthroplasty, for the IFP in the latter was less disturbed.

Conclusion

In this hypothesis, we introduced the viewpoint that the normal healthy infrapatellar fat pad may be with tendon repairing ability and closely related with the developing process of patella Baja. Although there was some evidence standing up the hypothesis, the exact mechanism of IFP in patella tendon repairing still need further explore. We hope all orthopedics surgeons should pay more attention to the protection of the normal IFP when the operations involved in IFP, which may decrease the incidence of patella Baja.

Conflict of interest statement

None declare.

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References

[1] Gatha NM, Clarke HD, Fuchs R, Scuderi GR, Insall JN. Factors affecting postoperative range of motion after total knee arthroplasty. J Knee Surg 2004;17:196–202.
[2] Weale AE, Murray DW, Newman JH, Ackroyd CE. The length of the patellar tendon after unicompartmental and total knee replacement. J Bone Joint Surg Br 1999;81:790–5.
[3] Sharma V, Tsailas PG, Maheshwari AV, Ranawat AS, Ranawat CS. Does patellar eversion in total knee arthroplasty cause patella baja? Clin Orthop Relat Res 2008;466:2763–8.
[4] Chonko DJ, Lombardi Jr AV, Berend KR. Patella baja and total knee arthroplasty (TKA): etiology diagnosis and management. Surg Technol Int 2004;12:231–8.
[5] Chen HC, Lin CJ, Wu CH, Wang CK, Sun YN. Automatic Insall-Salvati ratio measurement on lateral knee X-ray images using model-guided landmark localization. Phys Med Biol 2010;55:6785–800.
[6] Brooker B, Morris H, Brukner P, Mazen F, Bunn J. The macroscopic arthroscopic anatomy of the infrapatellar fat pad. Arthroscopy 2009;25:839–45.
[7] Gallagher J, Tierney P, Murray P, O'Brien M. The infrapatellar fat pad: anatomy and clinical correlations. Knee Surg Sports Traumatol Arthrosc 2005;13: 268–72.
[8] Vinardell T, Buckley CT, Thorpe SD, Kelly DJ. Composition–function relations of cartilaginous tissues engineered from chondrocytes and mesenchymal stem cells isolated from bone marrow and infrapatellar fat pad. J Tissue Eng Regen Med 2010.
[9] Zuk PA, Zhu M, Mizuno H, Huang J, Futrell JW, Katz AJ, et al. Multilineage cells from human adipose tissue: implications for cell-based therapies. Tissue Eng 2001;7:211–28.
[10] Palpant NJ, Metzger JM. Aesthetic cardiology: adipose-derived stem cells for myocardial repair. Curr Stem Cell Res Ther 2010;5:145–52.
[11] Khan WS, Tew SR, Adesida AB, Hardingham TE. Human infrapatellar fat pad-derived stem cells express the pericyte marker 3G5 and show enhanced chondrogenesis after expansion in fibroblast growth factor-2. Arthritis Res Ther 2008;10:R74.
[12] Uysal AC, Mizuno H. Tendon regeneration and repair with adipose derived stem cells. Curr Stem Cell Res Ther 2010;5:161–7.
[13] Uysal AC, Mizuno H. Differentiation of adipose-derived stem cells for tendon repair. Methods Mol Biol 2011;702:443–51.
[14] Ranawat CS, Ranawat AS, Mehta A. Total knee arthroplasty rehabilitation protocol: what makes the difference? J Arthroplasty 2003;18:27–30.
[15] Bi Y, Ehirchiou D, Kilts TM, Inkson CA, Embree MC, Sonoyama W, et al. Identification of tendon stem/progenitor cells and the role of the extracellular matrix in their niche. Nat Med 2007;13:1219–27.
[16] Lui PP, Chan LS, Cheuk YC, Lee YW, Chan KM. Expression of bone morphogenetic protein-2 in the chondrogenic and ossifying sites of calcific tendinopathy and traumatic tendon injury rat models. J Orthop Surg Res 2009;4:27.
[17] Lim JK, Hui J, Li L, Thambyah A, Goh J, Lee EH. Enhancement of tendon graft osteointegration using mesenchymal stem cells in a rabbit model of anterior cruciate ligament reconstruction. Arthroscopy 2004;20:899–910.
[18] Ouyang HW, Goh JC, Lee EH. Use of bone marrow stromal cells for tendon graft-to-bone healing: histological and immunohistochemical studies in a rabbit model. Am J Sports Med 2004;32:321–7.
[19] Kanaya A, Deie M, Adachi N, Nishimori M, Yanada S, Ochi M. Intra-articular injection of mesenchymal stromal cells in partially torn anterior cruciate ligaments in a rat model. Arthroscopy 2007;23:610–7.
[20] Awad HA, Butler DL, Boivin GP, Smith FN, Malaviya P, Huibregtse B, et al. Autologous mesenchymal stem cell-mediated repair of tendon. Tissue Eng 1999;5:267–77.
[21] Gulotta LV, Kovacevic D, Packer JD, Deng XH, Rodeo SA. Bone marrow-derived mesenchymal stem cells transduced with scleraxis improve rotator cuff healing in a rat model. Am J Sports Med 2011.
[22] Hattori K, Heissig B, Tashiro K, Honjo T, Tateno M, Shieh JH, et al. Plasma elevation of stromal cell-derived factor-1 induces mobilization of mature and immature hematopoietic progenitor and stem cells. Blood 2001;97:3354–60.
[23] Godot V, Arock M, Garcia G, Capel F, Flys C, Dy M, et al. H4 histamine receptor mediates optimal migration of mast cell precursors to CXCL12. J Allergy Clin Immunol 2007;120:827–34.
[24] Lagasse E, Connors H, Al-Dhalimy M, Reitsma M, Dohse M, Osborne L, et al. Purified hematopoietic stem cells can differentiate into hepatocytes in vivo. Nat Med 2000;6:1229–34.
[25] Askari AT, Unzek S, Popovic ZB, Goldman CK, Forudi F, Kiedrowski M, et al. Effect of stromal-cell-derived factor 1 on stem-cell homing and tissue regeneration in ischaemic cardiomyopathy. Lancet 2003;362:697–703.
[26] Togel F, Isaac J, Hu Z, Weiss K, Westenfelder C. Renal SDF-1 signals mobilization and homing of CXCR4-positive cells to the kidney after ischemic injury. Kidney Int 2005;67:1772–84.
[27] Ji JF, He BP, Dheen ST, Tay SS. Interactions of chemokines and chemokine receptors mediate the migration of mesenchymal stem cells to the impaired site in the brain after hypoglossal nerve injury. Stem Cells 2004;22:415–27.
[28] Shimode K, Iwasaki N, Majima T, Funakoshi T, Sawaguchi N, Onodera T, et al. Local upregulation of stromal cell-derived factor-1 after ligament injuries enhances homing rate of bone marrow stromal cells in rats. Tissue Eng Part A 2009;15:2277–84.
[29] Shen W, Chen X, Chen J, Yin Z, Heng BC, Chen W, et al. The effect of incorporation of exogenous stromal cell-derived factor-1 alpha within a knitted silk-collagen sponge scaffold on tendon regeneration. Biomaterials 2010;31:7239–49.
[30] Baptista LS, do Amaral RJ, Carias RB, Aniceto M, Claudio-da-Silva C, Borojevic R. An alternative method for the isolation of mesenchymal stromal cells derived from lipoaspirate samples. Cytotherapy 2009;11:706–15.
[31] Lin CS, Xin ZC, Deng CH, Ning H, Lin G, Lue TF. Defining adipose tissue-derived stem cells in tissue and in culture. Histol Histopathol 2010;25:807–15.
[32] Yu G, Wu X, Dietrich MA, Polk P, Scott LK, Ptitsyn AA, et al. Yield and characterization of subcutaneous human adipose-derived stem cells by flow cytometric and adipogenic mRNA analyzes. Cytotherapy 2010;12:538–46.
[33] Madonna R, Renna FV, Cellini C, Cotellese R, Picardi N, Francomano F, et al. Age-dependent impairment of number and angiogenic potential of adipose tissue-derived progenitor cells. Eur J Clin Invest 2011;41:126–33.
[34] Maumus M, Peyrafitte JA, D'Angelo R, Fournier-Wirth C, Bouloumie A, Casteilla L, et al. Native human adipose stromal cells: localization morphology and phenotype. Int J Obes (Lond) 2011.
[35] De Toni F, Poglio S, Youcef AB, Cousin B, Pflumio F, Bourin P, et al. Human adipose-derived stromal cells efficiently support hematopoiesis in vitro and in vivo: a key step for therapeutic studies. Stem Cells Dev 2011.
[36] Mitchell JB, McIntosh K, Zvonic S, Garrett S, Floyd ZE, Kloster A, et al. Immunophenotype of human adipose-derived cells: temporal changes in stromal-associated and stem cell-associated markers. Stem Cells 2006;24:376–85.
[37] Traktuev DO, Merfeld-Clauss S, Li J, Kolonin M, Arap W, Pasqualini R, et al. A population of multipotent CD34-positive adipose stromal cells share pericyte and mesenchymal surface markers, reside in a periendothelial location, and stabilize endothelial networks. Circ Res 2008;102:77–85.
[38] Lin J, Lindsey ML, Zhu B, Agrawal CM, Bailey SR. Effects of surface-modified scaffolds on the growth and differentiation of mouse adipose-derived stromal cells. J Tissue Eng Regen Med 2007;1:211–7.
[39] Taha MF, Hedayati V. Isolation, identification and multipotential differentiation of mouse adipose tissue-derived stem cells. Tissue Cell 2010;42:211–6.
[40] Lemischka IR, Moore KA. Stem cells: interactive niches. Nature 2003;425: 778–9.
[41] Grassel S, Ahmed N. Influence of cellular microenvironment and paracrine signals on chondrogenic differentiation. Front Biosci 2007;12:4946–56.
[42] Lettry V, Hosoya K, Takagi S, Okumura M. Coculture of equine mesenchymal stem cells and mature equine articular chondrocytes results in improved chondrogenic differentiation of the stem cells. Jpn J Vet Res 2010;58:5–15.
[43] Hildner F, Concaro S, Peterbauer A, Wolbank S, Danzer M, Lindahl A, et al. Human adipose-derived stem cells contribute to chondrogenesis in coculture with human articular chondrocytes. Tissue Eng Part A 2009;15:3961–9.
[44] Gan L, Kandel RA. In vitro cartilage tissue formation by co-culture of primary and passaged chondrocytes. Tissue Eng 2007;13:831–42.
[45] Lemon M, Packham I, Narang K, Craig DM. Patellar tendon length after knee arthroplasty with and without preservation of the infrapatellar fat pad. J Arthroplasty 2007;22:574–80.