ELSEVIER SAUNDERS
Clin Sports Med 27 (2008) 231–239
CLINICS IN SPORTS MEDICINE

International Olympic Committee Consensus Statement: Molecular Basis of Connective Tissue and Muscle Injuries in Sport

Arne Ljungqvist, MD, PhD[a],
Martin P. Schwellnus, MBBCh, MSc (Med), MD, FACSM, FFIMS[b,*],
Norbert Bachl, MD[a,c], Malcolm Collins, PhD[d], J. Cook, PhD[e], K.M. Khan, MD, PhD[f],
Nicola Maffulli, MD, MS, PhD, FRCS (Orth)[g], Y. Pitsiladis, MMedSci, PhD[h],
G. Riley, BSc, PhD[i], G. Golspink, PhD, ScD, CChem, FRSC[j],
D. Venter, MBChB, PhD, MBA[k], E.W. Derman, MBBCh, PhD[b],
L. Engebretsen, MD, PhD[l], P. Volpi, MD[m]

[a]International Olympic Committee Medical Commission, Lausanne, Switzerland
[b]UCT/MRC Research Unit for Exercise Science and Sports Medicine, Department of Human Biology, Faculty of Health Sciences, University of Cape Town, 3rd Floor, Sports Science Institute of South Africa, Boundary Road, Newlands, Cape Town 7700, South Africa
[c]Department of Sports and Exercise Physiology, Institute of Sports Science, University of Vienna, Auf der Schmelz 6a, A-1150 Vienna, Austria
[d]UCT/MRC Research Unit for Exercise Science and Sports Medicine, South African Medical Research Council, P.O. Box 115, Newlands, Cape Town, 7725, South Africa
[e]School of Exercise and Nutrition Sciences, Faculty of Health Medicine Nursing and Behavioural Sciences, Burwood, Melbourne, Australia
[f]Family Practice, Centre for Hip Health, University of British Columbia, 588-828 West 10th Avenue, Vancouver V5Z 1L8, Canada
[g]Department of Trauma and Orthopaedic Surgery, Keele University School of Medicine, Thornburrow Drive, Hartshill, Guy Hilton Research Centre, Stoke on Trent ST4 7QB Staffs, England
[h]Institute of Biomedical and Life Sciences, University of Glasgow, West Medical Building, Glasgow G12 8QQ, Scotland, United Kingdom
[i]School of Biological Sciences, University of East Anglia, Norwich NR4 7TJ, United Kingdom
[j]Department of Surgery, Royal Free and University College of London, Hampstead Campus, Rowland Hill, St. London NW3 2PF, United Kingdom
[k]Mater Health Services, University of Queensland, Mater Adult Hospital, Raymond Terrace, South Brisbane, Queensland 4101, Australia
[l]Orthopaedic Center, Ullevaal University Hospital, Oslo Sports Trauma Research Centre, University of Oslo, Oslo, Norway 0407
[m]IRRC-Galeazzi Orthopaedic Institute, Via R. Galeazzi 4, I-20161 Milan, Italy

More than 100 million musculoskeletal (tendon/muscle/bone) injuries occur annually worldwide. Of these, 30% to 50% are tendon and ligament injures [1], which cause significant loss of performance in sport and decreased functional capacity in the workplace and negatively affect the

*Corresponding author. UCT/MRC Research Unit for Exercise Science and Sports Medicine, Department of Human Biology, Faculty of Health Sciences, University of Cape Town, 3rd Floor, Sports Science Institute of South Africa, Boundary Road, Newlands, Cape Town 7700, South Africa. *E-mail address*: martin.schwellnus@uct.ac.za (M.P. Schwellnus).

0278-5919/08/$ – see front matter
doi:10.1016/j.csm.2007.10.007

ability of members of the general population to undertake exercise. A significant proportion of these injures remain difficult to treat, and many individuals have long-term pain and discomfort [2].

The International Olympic Committee (IOC) assembled an expert group to discuss the nature of the problem, the current state of the art, and the need for further research. Recent advances in this field relate to (1) the discovery of novel genetic markers for risk of tendon injury; (2) improved understanding of structure and composition of tendon and its response to loading; (3) increasing clinical use of growth factors to treat a variety of tendon, bone and muscle injuries; and (4) research exploring the potential of applying stem cells to benefit patients who have musculoskeletal problems. This consensus statement addresses each of these advances in more detail.

GENETIC PREDISPOSITION TO MUSCULOSKELETAL INJURY

Musculoskeletal injuries have complex causes including both genetic and nongenetic factors [3]. The search for genes that may predispose athletes to these injuries is gaining momentum but remains in its infancy. For example, variants within two genes (which produce type V collagen and tenascin C, respectively) were discovered recently to be associated with Achilles tendon pain [4,5]. Large studies in various populations using high-throughput technologies such as genomics and proteomics [6–8] will be required to advance knowledge of genetic associations with musculoskeletal injuries. This approach will allow researchers to identify further genes that may be associated with these and other specific musculoskeletal injuries. The ability to identify people at risk for these injuries will extend to the general population; injury-prevention measures will ensure that people can exercise appropriately for their inherited genetic makeup.

STRUCTURE AND COMPOSITION OF TENDON AND ITS RESPONSE TO LOADING

When athletes experience tendon pain, structural abnormalities are already present [9,10]. At light microscopy, inflammatory cells generally are absent at the site of injury [11]. Hence, the term "tendinitis" (or "tendonitis") has fallen out of favor [12]. Injured tendon has several characteristic features, such as increased or decreased cellularity and dramatic alteration in matrix structure and composition [13]. There are quantitative and qualitative changes in collagen, proteoglycan, and matrix-degrading enzymes and increased penetration of blood vessels and nerves [14,15]. A classical term to describe this overall appearance has been "tendinosis," but these features are consistent with inadequate repair–a failed healing response [16].

Although load is important to maintain the normal tendon matrix, pathology in tendons often is linked to overuse. Exercise can increase the production of collagen and other proteins in tendons and thus can be used as part of the management of tendon injuries [17]. Tendon cells respond to load by increasing protein production [17,18], but it is presently unclear what stimulus is required

to restructure a damaged matrix. Chronic end-stage tendon disease may never fully recover the normal matrix structure and composition, although adequate pain-free function is still possible [9].

INCREASING CLINICAL USE OF GROWTH FACTORS

Growth factors include a number of proteins secreted by cells [19]. Numerous experimental studies have shown that growth factors are involved in bone and cartilage formation, fracture healing, tendon and ligament repair, and skeletal muscle regeneration [20–22]. Therefore their therapeutic use is of enormous interest in the field of sports medicine and in helping treat workplace-related injuries. Growth factors of current interest include growth hormone (GH), insulin-like growth factor-1 (IGF-1), mechano growth factor (MGF), basic fibroblast growth factor (B-FGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), transforming growth factor–β (TGF-β), and bone morphogenic protein (BMP) (Table 1). Several of these growth factors are available commercially and are used in clinical settings [23].

BMPs enhance healing during different stages of fracture healing in various animal and human models. VEGF, PDGF, FGF, and TGF-β also have been shown to play an important role in ligament and tendon healing [24–37]. Although a body of research evidence exists in animal models [38], the results of late-stage, randomized, controlled clinical studies in humans are as yet unavailable (with the exception of BMPs), and the long-term local and systemic effects of these agents are unknown [39]. FGFs, TGF-β, and PDGF are important in the muscle regeneration process [22,40–47]. VEGF and PDGF increase blood flow to skeletal muscle [48–50]. The administration of B-FGF to improve blood perfusion has had limited success in other clinical studies, however [51–54]. A phase II trial of B-FGF revealed positive effects on peripheral blood flow [55].

Many fractures do not heal properly, and the bone-healing process therefore needs to be augmented. Recombinant human bone morphogenetic protein

Table 1
Growth factor expression in musculoskeletal tissues

Factor	Muscle	Cartilage	Tendon/ligament	Bone
GH	+	+	+	+
IGF-1	++	+	+	+
MGF	+++	?	+	?
B-FGF	+	+	±	+
PDGF	–	–	±	±
VEGF	+	–	±	–
TGF-β	±	+	±	+
BMP	+	+	–	–

Abbreviations: B-FGF, basic fibroblast growth factor; BMP, bone morphogenic protein; GH, growth hormone; IGF-1, insulin-like growth factor-1; MGF, mechano growth factor; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor–β; VEGF, vascular endothelial growth factor.

2 and recombinant human bone morphogenetic protein 7 or osteogenic protein 1 have been used clinically. At present, there are several published clinical studies on the effects of BMPs in bone healing or in delayed unions/non-unions, and several studies have reported the effects in fusion of the lumbar spine. This use of BMPs now constitutes a well-established practice in orthopaedic surgery.

GH, produced by the pituitary, induces the liver to produce systemic IGF-1, which forms a tripartite binding complex with IGF binding protein 3 and the acid labile subunit, to stabilize IGF-1 in the serum [56]. The levels of GH and IGF-1 reach their peak during adolescence [57]. With increasing age, however, there is a marked decline in the circulating levels of GH and a somewhat smaller decline in circulating IGF-1. Treatment of GH-deficient adults for an extended period of time results in increased muscle strength and decreased body fat [58]. These findings have encouraged the illicit use of GH and GH-like substances among athletes, even those competing at the secondary school level, in an attempt to enhance performance, an ongoing problem for anti-doping agencies. At present, there are methods for detecting GH and its isoforms, but none have been validated for IGF-1 yet. The matter is complicated by the fact that local forms of IGF-1, such as MGF, are produced after exercise by the splicing of the IGF-1 gene; its sequence differs from the regular endogenous type of IGF-1 released by the liver but also is not detectable by current anti-doping methods [59–64]. MGF is very potent for increasing muscle mass and strength [65–67]. MGF apparently acts as a separate growth factor that is involved in activating satellite cell proliferation and replenishing the pool of these muscle stem cells [68,69]. In summary, studies in animal models have highlighted some interesting candidates that await evaluation in human clinical trials.

RESEARCH EXPLORING THE POTENTIAL OF APPLYING STEM CELLS

Mesenchymal stem cells are adult tissue-producing cells that have been isolated from various parts of the body, including cartilage, bone marrow, synovium, adipose tissue, articular cartilage, muscle, and tendons [70–72]. Potentially, mesenchymal stem cells can be used for tissue-engineering strategies through implantation of scaffolds and gels, for gene delivery, and for production of growth factor to stimulate tissue repair or inhibit tissue degradation [73–75]. Most studies have been conducted in animal models. Some studies of human bone, cartilage, and tendons have produced positive results [76–78]. Further controlled clinical trials in musculoskeletal injuries in humans are warranted, however. Reasons for the lack of progress in this field include the need to find the optimal sources of and methods for the differentiation of cells and for the development of optimal surgical delivery materials and methods [79,80]. Although some studies have shown negative effects, including ectopic calcification and connective tissue overgrowth [78], further clinical trials should be undertaken to determine whether long-term complications exist.

POSSIBLE FUTURE RESEARCH DIRECTIONS IN GROWTH FACTOR THERAPY

The implementation of new biologic therapies based on the administration of growth factors and the manipulation of adult stem cells will require an improved understanding of the genetic regulatory networks affected by these agents. This understanding will be necessary for two reasons: to ensure that these therapies are optimized and to ensure the safety of patients and athletes. Knowledge of the genomic and proteomic impacts of growth factor–based therapies on the target cells and of the biomarkers reflecting stem cell differentiation status will underpin the development of tests capable of monitoring therapeutic efficacy and minimizing adverse events.

POTENTIAL FOR MISUSE OF GROWTH FACTORS AND CELL-BASED THERAPIES

The ability to manipulate existing muscle cells and muscle stem cells has the potential for use in the context of illegal performance enhancement. Knowledge of the underlying genetic and cellular events affected by growth factor administration can be used to develop tests capable of detecting the illegal use of such technologies for performance enhancement. The IOC will monitor developments in this field to ensure that such practices are discouraged, and detected if used, by working with the anti-doping agencies.

SCIENTIFIC ADVISORS

The IOC now has high-level scientific advisors who are capable of monitoring new developments in the field of growth factor– and cell-based therapies and of advising the IOC as to the use and abuse of these technologies. These advisors will help ensure that athletes and coaches receive the benefits of these developments in improving their ability to prevent injury and to enhance therapy if injured. In addition, the illegal use of these technologies for performance enhancement will be increasingly difficult as methods of detecting such use become available.

References

[1] Maffulli N, Wong J, Almekinders LC. Types and epidemiology of tendinopathy. Clin Sports Med 2003;22(4):675–92.
[2] Rompe JD, Nafe B, Furia JP, et al. Eccentric loading, shock-wave treatment, or a wait-and-see policy for tendinopathy of the main body of tendo achillis: a randomized controlled trial. Am J Sports Med 2007;35(3):374–83.
[3] September AV, Schwellnus MP, Collins M. Tendon and ligament injuries: the genetic component. Br J Sports Med 2007;41(4):241–6.
[4] Mokone GG, Schwellnus MP, Noakes TD, et al. The COL5A1 gene and Achilles tendon pathology. Scand J Med Sci Sports 2006;16(1):19–26.
[5] Mokone GG, Gajjar M, September AV, et al. The guanine-thymine dinucleotide repeat polymorphism within the tenascin-C gene is associated with Achilles tendon injuries. Am J Sports Med 2005;33(7):1016–21.
[6] Cordell HJ, Clayton DG. Genetic association studies. Lancet 2005;366(9491):1121–31.

[7] Newton-Cheh C, Hirschhorn JN. Genetic association studies of complex traits: design and analysis issues. Mutat Res 2005;573(1–2):54–69.
[8] Pearson JV, Huentelman MJ, Halperin RF, et al. Identification of the genetic basis for complex disorders by use of pooling-based genomewide single-nucleotide-polymorphism association studies. Am J Hum Genet 2007;80(1):126–39.
[9] Cook JL, Khan KM, Harcourt PR, et al. Patellar tendon ultrasonography in asymptomatic active athletes reveals hypoechoic regions: a study of 320 tendons. Victorian Institute of Sport Tendon Study Group. Clin J Sport Med 1998;8(2):73–7.
[10] Cook JL, Khan KM, Kiss ZS, et al. Asymptomatic hypoechoic regions on patellar tendon ultrasound: a 4-year clinical and ultrasound followup of 46 tendons. Scand J Med Sci Sports 2001;11(6):321–7.
[11] Maffulli N, Testa V, Capasso G, et al. Similar histopathological picture in males with Achilles and patellar tendinopathy. Med Sci Sports Exerc 2004;36(9):1470–5.
[12] Maffulli N, Khan KM, Puddu G. Overuse tendon conditions: time to change a confusing terminology. Arthroscopy 1998;14(8):840–3.
[13] Khan KM, Cook JL, Bonar F, et al. Histopathology of common tendinopathies. Update and implications for clinical management. Sports Med 1999;27(6):393–408.
[14] Riley G. The pathogenesis of tendinopathy. A molecular perspective. Rheumatology (Oxford) 2004;43(2):131–42.
[15] Riley G. Chronic tendon pathology: molecular basis and therapeutic implications. Expert Rev Mol Med 2005;7(5):1–25.
[16] Sharma P, Maffulli N. Tendon injury and tendinopathy: healing and repair. J Bone Joint Surg Am 2005;87(1):187–202.
[17] Kjaer M. Role of extracellular matrix in adaptation of tendon and skeletal muscle to mechanical loading. Physiol Rev 2004;84(2):649–98.
[18] Kjaer M, Magnusson P, Krogsgaard M, et al. Extracellular matrix adaptation of tendon and skeletal muscle to exercise. J Anat 2006;208(4):445–50.
[19] Trippel SB. Growth factors as therapeutic agents. Instr Course Lect 1997;46:473–6.
[20] Nordsletten L, Madsen JE. The effect of bone morphogenetic proteins in fracture healing. Scand J Surg 2006;95(2):91–4.
[21] Molloy T, Wang Y, Murrell G. The roles of growth factors in tendon and ligament healing. Sports Med 2003;33(5):381–94.
[22] Kasemkijwattana C, Menetrey J, Bosch P, et al. Use of growth factors to improve muscle healing after strain injury. Clin Orthop Relat Res 2000;370:272–85.
[23] Sharma P, Maffulli N. The future: rehabilitation, gene therapy, optimization of healing. Foot Ankle Clin 2005;10(2):383–97.
[24] Zhang F, Liu H, Stile F, et al. Effect of vascular endothelial growth factor on rat Achilles tendon healing. Plast Reconstr Surg 2003;112(6):1613–9.
[25] Letson AK, Dahners LE. The effect of combinations of growth factors on ligament healing. Clin Orthop Relat Res 1994;308:207–12.
[26] Hildebrand KA, Woo SL, Smith DW, et al. The effects of platelet-derived growth factor-BB on healing of the rabbit medial collateral ligament. An in vivo study. Am J Sports Med 1998;26(4):549–54.
[27] Nakamura N, Shino K, Natsuume T, et al. Early biological effect of in vivo gene transfer of platelet-derived growth factor (PDGF)-B into healing patellar ligament. Gene Ther 1998;5(9):1165–70.
[28] Weiler A, Forster C, Hunt P, et al. The influence of locally applied platelet-derived growth factor-BB on free tendon graft remodeling after anterior cruciate ligament reconstruction. Am J Sports Med 2004;32(4):881–91.
[29] Chan BP, Fu SC, Qin L, et al. Supplementation-time dependence of growth factors in promoting tendon healing. Clin Orthop Relat Res 2006;448:240–7.
[30] Anitua E, Sanchez M, Nurden AT, et al. New insights into and novel applications for platelet-rich fibrin therapies. Trends Biotechnol 2006;24(5):227–34.

[31] Chan BP, Fu S, Qin L, et al. Effects of basic fibroblast growth factor (bFGF) on early stages of tendon healing: a rat patellar tendon model. Acta Orthop Scand 2000;71(5):513–8.
[32] Fukui N, Katsuragawa Y, Sakai H, et al. Effect of local application of basic fibroblast growth factor on ligament healing in rabbits. Rev Rhum Engl Ed 1998;65(6):406–14.
[33] Kobayashi D, Kurosaka M, Yoshiya S, et al. Effect of basic fibroblast growth factor on the healing of defects in the canine anterior cruciate ligament. Knee Surg Sports Traumatol Arthrosc 1997;5(3):189–94.
[34] Hamada Y, Katoh S, Hibino N, et al. Effects of monofilament nylon coated with basic fibroblast growth factor on endogenous intrasynovial flexor tendon healing. J Hand Surg [Am] 2006;31(4):530–40.
[35] Woo SL, Smith DW, Hildebrand KA, et al. Engineering the healing of the rabbit medial collateral ligament. Med Biol Eng Comput 1998;36(3):359–64.
[36] Sakai T, Yasuda K, Tohyama H, et al. Effects of combined administration of transforming growth factor-beta1 and epidermal growth factor on properties of the in situ frozen anterior cruciate ligament in rabbits. J Orthop Res 2002;20(6):1345–51.
[37] Kondo E, Yasuda K, Yamanaka M, et al. Effects of administration of exogenous growth factors on biomechanical properties of the elongation-type anterior cruciate ligament injury with partial laceration. Am J Sports Med 2005;33(2):188–96.
[38] Angel MJ, Sgaglione NA, Grande DA. Clinical applications of bioactive factors in sports medicine: current concepts and future trends. Sports Med Arthrosc 2006;14(3): 138–45.
[39] Hsu C, Chang J. Clinical implications of growth factors in flexor tendon wound healing. J Hand Surg [Am] 2004;29(4):551–63.
[40] Lefaucheur JP, Sebille A. Basic fibroblast growth factor promotes in vivo muscle regeneration in murine muscular dystrophy. Neurosci Lett 1995;202(1–2):121–4.
[41] Mitchell CA, McGeachie JK, Grounds MD. The exogenous administration of basic fibroblast growth factor to regenerating skeletal muscle in mice does not enhance the process of regeneration. Growth Factors 1996;13(1–2):37–55.
[42] Kasemkijwattana C, Menetrey J, Somogyl G, et al. Development of approaches to improve the healing following muscle contusion. Cell Transplant 1998;7(6):585–98.
[43] Menetrey J, Kasemkijwattana C, Day CS, et al. Growth factors improve muscle healing in vivo. J Bone Joint Surg Br 2000;82(1):131–7.
[44] Iwata Y, Ozaki N, Hirata H, et al. Fibroblast growth factor-2 enhances functional recovery of reinnervated muscle. Muscle Nerve 2006;34(5):623–30.
[45] Wright-Carpenter T, Opolon P, Appell HJ, et al. Treatment of muscle injuries by local administration of autologous conditioned serum: animal experiments using a muscle contusion model. Int J Sports Med 2004;25(8):582–7.
[46] Wright-Carpenter T, Klein P, Schaferhoff P, et al. Treatment of muscle injuries by local administration of autologous conditioned serum: a pilot study on sportsmen with muscle strains. Int J Sports Med 2004;25(8):588–93.
[47] Husmann I, Soulet L, Gautron J, et al. Growth factors in skeletal muscle regeneration. Cytokine Growth Factor Rev 1996;7(3):249–58.
[48] Baumgartner I, Pieczek A, Manor O, et al. Constitutive expression of phVEGF165 after intramuscular gene transfer promotes collateral vessel development in patients with critical limb ischemia. Circulation 1998;97(12):1114–23.
[49] Cooke JP, Bhatnagar R, Szuba A, et al. Fibroblast growth factor as therapy for critical limb ischemia: a case report. Vasc Med 1999;4(2):89–91.
[50] Lazarous DF, Unger EF, Epstein SE, et al. Basic fibroblast growth factor in patients with intermittent claudication: results of a phase I trial. J Am Coll Cardiol 2000;36(4):1239–44.
[51] Rajagopalan S, Shah M, Luciano A, et al. Adenovirus-mediated gene transfer of VEGF(121) improves lower-extremity endothelial function and flow reserve. Circulation 2001;104(7): 753–5.

[52] Rajagopalan S, Trachtenberg J, Mohler E, et al. Phase I study of direct administration of a replication deficient adenovirus vector containing the vascular endothelial growth factor cDNA (CI-1023) to patients with claudication. Am J Cardiol 2002;90(5):512–6.
[53] Rajagopalan S, Mohler ER III, Lederman RJ, et al. Regional angiogenesis with vascular endothelial growth factor in peripheral arterial disease: a phase II randomized, double-blind, controlled study of adenoviral delivery of vascular endothelial growth factor 121 in patients with disabling intermittent claudication. Circulation 2003;108(16):1933–8.
[54] Kim HJ, Jang SY, Park JI, et al. Vascular endothelial growth factor-induced angiogenic gene therapy in patients with peripheral artery disease. Exp Mol Med 2004;36(4):336–44.
[55] Lederman RJ, Mendelsohn FO, Anderson RD, et al. Therapeutic angiogenesis with recombinant fibroblast growth factor-2 for intermittent claudication (the TRAFFIC study): a randomised trial. Lancet 2002;359(9323):2053–8.
[56] Boisclair YR, Rhoads RP, Ueki I, et al. The acid-labile subunit (ALS) of the 150 kDa IGF-binding protein complex: an important but forgotten component of the circulating IGF system. J Endocrinol 2001;170(1):63–70.
[57] Rudman D, Kutner MH, Rogers CM, et al. Impaired growth hormone secretion in the adult population: relation to age and adiposity. J Clin Invest 1981;67(5):1361–9.
[58] Beshyah SA, Freemantle C, Shahi M, et al. Replacement treatment with biosynthetic human growth hormone in growth hormone-deficient hypopituitary adults. Clin Endocrinol (Oxf) 1995;42(1):73–84.
[59] Goldspink G. Mechanical signals, IGF-I gene splicing, and muscle adaptation. Physiology (Bethesda) 2005;20:232–8.
[60] Greig CA, Hameed M, Young A, et al. Skeletal muscle IGF-I isoform expression in healthy women after isometric exercise. Growth Horm IGF Res 2006;16(5–6):373–6.
[61] Bamman MM, Petrella JK, Kim JS, et al. Cluster analysis tests the importance of myogenic gene expression during myofiber hypertrophy in humans. J Appl Physiol 2007;102(6): 2232–9.
[62] Yang S, Alnaqeeb M, Simpson H, et al. Cloning and characterization of an IGF-1 isoform expressed in skeletal muscle subjected to stretch. J Muscle Res Cell Motil 1996;17(4): 487–95.
[63] Haddad F, Adams GR. Selected contribution: acute cellular and molecular responses to resistance exercise. J Appl Physiol 2002;93(1):394–403.
[64] Goldspink G, Yang SY. The splicing of the IGF-1 gene to yield different muscle growth factors. Adv Genet 2004;52:23–49.
[65] Goldspink G, Yang SY. Effects of activity on growth factor expression. Int J Sport Nutr Exerc Metab 2001;11(Suppl):S21–7.
[66] Hameed M, Lange KH, Andersen JL, et al. The effect of recombinant human growth hormone and resistance training on IGF-I mRNA expression in the muscles of elderly men. J Physiol 2004;555(Pt 1):231–40.
[67] Barton ER. Viral expression of insulin-like growth factor-I isoforms promotes different responses in skeletal muscle. J Appl Physiol 2006;100(6):1778–84.
[68] Yang SY, Goldspink G. Different roles of the IGF-I Ec peptide (MGF) and mature IGF-I in myoblast proliferation and differentiation. FEBS Lett 2002;522(1–3):156–60.
[69] Ates K, Yang SY, Orrell RW, et al. The IGF-I splice variant MGF increases progenitor cells in ALS, dystrophic, and normal muscle. FEBS Lett 2007;581(14):2727–32.
[70] Giordano A, Galderisi U, Marino IR. From the laboratory bench to the patient's bedside: an update on clinical trials with mesenchymal stem cells. J Cell Physiol 2007;211(1):27–35.
[71] Hardingham TE, Oldershaw RA, Tew SR. Cartilage, SOX9 and Notch signals in chondrogenesis. J Anat 2006;209(4):469–80.
[72] Krampera M, Pizzolo G, Aprili G, et al. Mesenchymal stem cells for bone, cartilage, tendon and skeletal muscle repair. Bone 2006;39(4):678–83.
[73] Awad HA, Butler DL, Boivin GP, et al. Autologous mesenchymal stem cell-mediated repair of tendon. Tissue Eng 1999;5(3):267–77.

[74] Young RG, Butler DL, Weber W, et al. Use of mesenchymal stem cells in a collagen matrix for Achilles tendon repair. J Orthop Res 1998;16(4):406–13.
[75] Askari AT, Unzek S, Popovic ZB, et al. Effect of stromal-cell-derived factor 1 on stem-cell homing and tissue regeneration in ischaemic cardiomyopathy. Lancet 2003;362(9385): 697–703.
[76] van Beuningen HM, Glansbeek HL, van der Kraan PM, et al. Differential effects of local application of BMP-2 or TGF-beta 1 on both articular cartilage composition and osteophyte formation. Osteoarthritis Cartilage 1998;6(5):306–17.
[77] Reddi AH. Cartilage-derived morphogenetic proteins and cartilage morphogenesis. Microsc Res Tech 1998;43(2):131–6.
[78] Awad HA, Boivin GP, Dressler MR, et al. Repair of patellar tendon injuries using a cell-collagen composite. J Orthop Res 2003;21(3):420–31.
[79] Caplan AI. Review: mesenchymal stem cells: cell-based reconstructive therapy in orthopedics. Tissue Eng 2005;11(7–8):1198–211.
[80] Hui JH, Ouyang HW, Hutmacher DW, et al. Mesenchymal stem cells in musculoskeletal tissue engineering: a review of recent advances in National University of Singapore. Ann Acad Med Singapore 2005;34(2):206–12.