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Review

Management

A clinical perspective to mesenchymal stem cell-based musculoskeletal regeneration

L Labusca[1,2]*, M O'Brien[3], K Mashayekhi[2,4]

Abstract

Introduction

The global increase in number in severity of traumatic and degenerative musculoskeletal diseases affects the quality of life and increases health-care costs and resource expenditure. Facing an epidemic of orthopaedic tissue pathology in all ages and economic surroundings, modern medicine is challenged to improve strategy to deliver efficient and affordable treatments. Regenerative medicine has been identified as able to offer revolutionary solutions and to enable complete structural and functional rehabilitation of tissues, organs and bodily systems. This article reviews current regenerative medicine strategies for musculoskeletal diseases of bone, tendon and cartilage, which made their way to clinical application. Stage-related disease regenerative medicine planning and phenotypic mesenchymal stem cell biomarker characterisation are identified as potential factors accelerating the clinical applicability of mesenchymal stem cell-based therapies for musculoskeletal regeneration.

Conclusion

Cell source profiling using biomarkers for proliferation and differentiation towards the desired lineage would be the next step in improving the regenerative medicine strategy.

* Corresponding author
Email: drlluminita@yahoo.com

[1] Department of Orthopaedic Surgery, University Hospital Saint Spiridon Iasi Romania, Iasi, Romania
[2] SBIM Systems Bioinformatics and Modelling GMBH, Frankfurt, Germany
[3] NUI Galway Ireland NCBES National Centre for Biomedical Engineering Sciences, Galway, Ireland
[4] BioTalentum, Godollo, Hungary

Introduction

Regenerative medicine (RM) is sought to making possible the anatomical and functional restoration of tissues and organs impaired or lost due to disease, trauma, congenital abnormalities or advancing age[1]. RM uses advanced scientific knowledge in the field of molecular and developmental biology, nanomaterials, bioinformatics and computational biology to provide solutions for untreatable diseases till date, congenital abnormalities or age-related degeneration. Innovative, affordable RM solutions can help both developed and developing countries to address the increasing burden of disease costs and improving the global health equity[2]. In RM, cells, the ultimate 'biological executive' are manipulated or targeted for the structural, bioactive and/or immunomodulatory effect. Different cell sources are available and extensively studied for regenerative purposes. Mesenchymal stem cells (MSCs) are the adult stem cells involved in growth, maintenance and repair of connective tissues: cartilage, bone, tendon, and ligament and marrow stoma. MSCs are isolated based on their adherence to the plastic culture dish, and can be expanded *in vitro* for several passages to be used for research or clinical applications. International Society for Cell Therapy has identified the minimal criteria for the characterisation of MSCs[3]. Autologous MSCs of clinically significant volume can be obtained with minimal cell manipulation. In this article, the current MSC-based RM strategies for connective tissues are outlined, with a focus on bone, cartilage, tendons and ligaments repair.

Discussion

Bone regeneration

When damaged, the bone has a remarkable capability to rebuild completely functional tissues. Nevertheless, non-unions—failure of bone healing—are challenging to treat, requiring surgery for mechanical stabilisation and/or biological augmentation. The increasing numbers of non-unions are frequently related to the increasing cases of extensive musculoskeletal injury produced by traffic accidents, war and natural calamities[4]. Bone loss due to trauma, tumour removal or periprosthetic loosening is a clinical situation requiring tissue substitution. For mechanical stability and osteoconductivity, natural bone grafts of various origins (autografts, allografts or xenografts) are used to treat bone defects. Autologous grafts are osteoinductive, capable to locally recruit osteoprogenitors and to induce the production of *de novo* mineralised tissue, therefore, considered as the golden standard in bone replacement[5]. However, autografts are available in limited volume expose to increased surgery time and intraoperative blood loss and can result in donor site morbidity. Osseous integration at the interface of prosthetic implants, as well as bone healing at the surgically induced fusion sites for joint or spine stabilisation are increasing the demand for bone grafts. Synthetic bone substitutes are currently used as osteoconductive replacement material. However, the poor mechanical properties and the blood supply for larger implanted volumes are limiting their clinical use. MSC-based *in vivo* and *in vitro* or *ex vivo* functional tissue-engineered bone grafts are regarded as a promising solution for graft shortage[6]. Obtaining *ex vivo* bone

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grafts using MSCs seeded on scaffolds, cultivated in bioreactors with or without mechanical stimulation, proved to be less rewarding as initially thought. Some of the issues are related to the duration of the procedure, graft contamination risk, costs, scalability and product marketing approval. Moreover, large graft vascularisation remains an unsolved problem. The effort to design permeable blood vessels within the graft requires additional tissue engineering strategies, increased bioreactor time and specific implantation surgery. *In vivo* generation of stable functional bone appears to be a more simple procedure. It can be performed during one-step surgery; grafts can be prepared on the operating site, significantly reducing cell manipulation and contamination risk[7]. To date, autologous cell sources already used in clinical settings are bone marrow (BM) stromal cells and adipose-derived stem cell (ADSC). Unprocessed BM is particularly attractive as it can be easily obtained from the iliac crest with simple needle aspiration. Autologous BM aspirates, injected directly into the grafting site, have been used to treat atrophic non-union[8], lunate bone osteonecrosis[9], delayed union or non-unions of long bones[10]. BM cellularity is donor dependent, therefore, to prevent graft paucity, cells can be enriched at the site of the surgery. A device based on the principles of the affinity column, designed to populate a scaffold with BM retained nucleated cells[11], was used to concentrate the cells for spinal fusion site augmentation. The method was used in two clinical trials, BM concentrate combined with demineralised bone matrix induced up to 84% fusion rates and significantly improved clinical outcomes[7]. The use of MSCs in combination with three-dimensional scaffolds provides mechanical support for the cells and mechanical stability of the grafting site. Moreover, the scaffolds can be shaped to address the clinical needs; their stability can be further secured using conventional internal or external bone fixation. Results from a large variety of natural, synthetic or composite biomaterials (collagen, hydroxyapatite (HA), β tricalcium phosphate, polylactic glycolic acid (PLGA)) are available from preclinical or clinical studies[12]. BMSCs deposited on allogeneic bone graft were clinically used to treat large post-traumatic long bone defects[13], to stabilise posterior spinal fusion, in combination with porous bone substitute, β-tri-calcium phosphate[14]. Autologous ADSCs, fibrin glue and iliac graft, induced new bone formation after 3 months in a case of extensive paediatric calvarial bone loss[15]. There are currently several clinical trials investigating autologous BMSCs or ADSCs (Table 1). Other MSC sources (umbilical cord blood and placenta) have to prove their clinical usefulness in bone regeneration. Alternative cell sources and *in vitro* expansion could be justified in selected cases of patients with low concentration of osteoprogenitor cells in BM aspirates. Promising results from a clinical study using three-dimensional HA constructs and autologous BMMSCs reporting excellent clinical results after 6–7 years[16] are raising hopes that engineered bone could be available to the clinic in the proximate future. Preconditioning of the graft by means of dynamic bioreactor technology and methods for providing engineered bone the blood supply would be likely to accelerate this process.

Cartilage regeneration

Unlike bone, cartilage tissue has limited potential for spontaneous healing. Traumatic cartilage injuries are increasing in number and gravity of cases. Cartilage lesions as a result of sports-related injury or overuse affect mainly younger or biologically young persons who expect as complete as possible structural and functional recovery. Worldwide population ageing is also related to an increase in cartilage degenerative diseases incidence (osteoarthritis (OA) and rheumatic arthritis (RA)) and a substantial burden, in terms of quality-of-life and health expenditures. For OA and RA, joint reconstruction surgery is a successful intervention, harnessing good functional results. However, prosthetic replacement is reserved for the advanced stage of the disease, largely in the elderly. A large therapeutic gap exists in addressing the intermediary stages of degeneration and in treating younger subjects. Pharmacological and physical therapies offer limited time symptomatic improvement. RM holds the promise for biological regeneration of joint surface and sustainable function restoration. In the 1990s, a method of treating limited cartilage defects by delivery of cultivated chondrocytes, autologous cell therapy/implantation (ACT/ACI), was introduced as the first clinical application of a local cell therapy[17]. Matrix-assisted chondrocyte implantation/transplantation (MACI/MACT) addresses the problem of cell retention within the defect, in the mean time allowing for phenotype preservation in a three-dimensional (3D) environment. These technique limitations are mainly related to the biological potential of differentiated cells. Healthy cartilage biopsy can derive only limited amounts of cells; moreover, their expansion capability decreases with age and associated diseases. Cartilage donor site can become symptomatic and be the source of joint degradation. For reasons of larger availability, proliferation and differentiation potential, the use of MSCs as the cell source is sought to facilitate cartilage engineering. Three-dimensional high-density pellet or micromass-cultured MSCs exposed to specific differentiation media and growth factors (transforming growth factor (TGF)-β1, 2 and 3, bone morphogenetic protein (BMP)-2, 4 or 6, IGF-1) are used *in vitro* to obtain functional, type-I collagen and glycosaminoglycan producing chondrocytes. Similarly, MSCs seeded on various scaffolds exposed to chondrogenetic media are shown to

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Table 1. Clinical trials involving MSC of different sources for bone and cartilage repair[a,b].

Tissue	Number	Cell source	Cell culture	Method	Intention to treat	Study	Country	Study ID
Bone	1	BM	NK	Cell therapy	NU	Safety	Iran	NCT01206179
	2	BM	24 h culture	Cell therapy	NU	Safety	France	NCT01429012
	3	BM	Cultured	Cell therapy	AVN	Safety/efficacy	China	NCT00813267
	4	Bm on bone matrix	Cultured	Cell therapy	Cysts	Safety	Iran	NCT01207193
	5	BM on bone subst	Cultured	BE	Fracture	Safetyu/Eficacity	France	NCT01842477
	6	BM/DMB	Non-cultured/ Sepax/Ignite	BE	DU/NU	Safety	Israel	NCT01435434
	7	ADS	Cultured	BE	No*	Bone engineering	Switzerland	NCT01532076
	8	ADS	Cultured	Cell therapy	OP	Safety/Efficiency	Mexico	NCT01501461
	9	ADS	Cultured	Cell therapy	AVN	Efficiency	South Korea	NCT01643655
Cartilage	1	MSC	Yes	C.E.	Focal	Efficiency/NR	Sweden	NCT00885729
	2	BMMSC	Yes	ACI	Focal	Efficiency/R	Egipt	NCT00891501
	3	BMMSC	No	C.E*	Focal, OA	Safety/Efficiency	France	NCT01159899
	4	BMMSC	Yes	C.E.	Focal	Safety/Efficacy?C	Iran	NCT00850187
	5	BMMSC	Yes	Cell therapy	OA	Safety/Efficacy	Spain	NCT01227694
	6	PBMSC + HA	No?	C.E./microfx	trauma	Effects	Thailand	NCT01076673
	7	ADS/Chondro-cytes	Yes	ACI	Focal	Safety/Efficieny. rexpl Ef/R	Brazil	NCT01399749
	8	MSC	Yes	Cell therapy	OA knee	Safety/Efficnecy/C	Iran	NCT01207661
	9	BMMSc	Yes	Cell therapy	OA I/II	Efficency/R	Malaysia	NCT01459640
	10	BMMSc allogenic	Yes	Cell therapy	OA	Safety/Efficiency	Spain	NCT01586312
	11	BMMSc	Yes	Cell therapy	OA ankle	Safety/Side effects/C	Iran	NCT01436058
	12	BMMSc	Yes	Cell therapy	OA hip	Safety/C	Iran	NCT01499056
	13	UCBSC	Yes	C.E.	OA, trauma	Safety/expl Ef/R	USA	NCT01733186
	14	BMMSc	Yes	Cell therapy	OA	Safety/Efficacy	India	NCT01152125
	15	BMMSc	Yes	Cell therapy	OA, severe	Safety/eficacy/C	Iran	NCT01504464
	16	UCBSC	Yes	Cell therapy	RA	SafetyNYR	China	NCT01547091
	17	BMM/synovial MSC	Yes	CE hTERTMSC.cartilage fragments		?	China	NCT01301664
	18	ACI/AMIC	Yes	CE	Focal	RCT	Norway	NCT01458782
Tendon	19	BMMSCs	?	TE	Suture aug-mentation	Safety/efficency	Spain	NCT01687777

*No intention to treat, optimise cellular composite bone graft.
**Fresh isolated BMMSC on protein scaffold.
BE, bone engineering; CE, cartilage engineering; TE, tendon engineering; NU, non union; DU, delayed union.
[a]http://www.clinicaltrials.gov/ct2/results?term=mesenchymal+stem+cells+bone+repair&pg=2 (accessed 14 May 2013).
[b]http://www.clinicaltrials.gov/ct2/results?term=cartilage+repair+stem+cells+&Search=Search (accessed 23 May 2013); http://www.clinicaltrials.gov/ct2/show/NCT01687777?term=tendon+AND+repair+AND+stem+cells&rank=1 (accessed 25 May 2013).

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assume a chondrocyte-like phenotype, making the design of implantable grafts achievable. Reports about various strategies of grafting defects with engineered cartilage in animal models are abundant[18]. To date, the existent RM clinical application reported can be grouped into protected autologous bone marrow stimulation techniques, MSC-based engineered cartilage engineering and cell therapy. The first is based on using a method of subchondral bone stimulation (microfracture) in combination with a sealant of the cartilage defect (e.g. a glued type-I, II and III collagen membrane). For clinically limited knee cartilage defects, Autologous Matrix Induced Chondrogenesis, AMIC® is reported reducing pain and improving Lysholm score in a medium follow up[19]. Patients with patellofemoral defects way up to 8.6 cm^2 improved functional score reducing pain at a 3-year follow-up after 'biological arthroplasty' performed with BM aspirate concentrate and type-I/III collagen matrix[20]. A single-staged arthroscopic cartilage repair consisting of microdrilling protected by atelocollagen or fibrin gel under carbon dioxide insufflations was used in International Cartilage Repair Society grade III or IV knee defects. After 1 year, Lysholm and MOCART scores were improved and the defect filled with hyaline-like tissue[21]. Engineered MSC-based cartilage using autologous BMMSCs seeded on collagen scaffold was reported to heal clinical patellar cartilage defects and medial femoral condyle defects in OA patients in combination with high tibial osteotomy. Good filling of the defects was reported at 44 weeks after surgery as well as improved arthroscopic and histological grading score compared with cell-free control group[22]. Scaffold structure and geometry influence MSC chondrogenesis *in vitro* or in animal models[23]. Nanostructure scaffolds of nano-metre scale fibres, reproducing natural ECM environment size and configuration, improve MSC-based chondrogenesis and chondrocyte activity[24]. Growth factors relevant for MSC-based chondrogenesis are members of TGF-β super family, insulin growth factor, fibroblast growth factor and platelet-derived growth factor, Wnt and sox-9. TGFs isoforms activity on chondrogenesis is species dependent, TGF-β3 being more active in human MSCs than TGF-β2[25]. Wnt proteins enhance MSC chondrogenic differentiation in cross-talks with TGF-β pathway[26]. Transcription factor sox-9 is regarded as master key regulators for chondrogenesis. Co-delivery of SOX-9 genes and anti-Cbfa-1 small-interference RNA (siRNA)-coated onto PLGA nanoparticles in human MSCs enhanced chondrogenic and inhibited osteoblast gene and protein expression[27]. Some of the particular problems with the use of MSCs for cartilage engineering are phenotypic stability and graft mineralisation. Mechanical preconditioning enhances chondrogenetic commitment[28] while hypoxic culture conditions contribute to phenotype stability and improved chondrogenesis[29]. Chondrogenic TGF-β isoform precondition[30] or anti-Cbfa-1 siRNAs prevent MSCs differentiation to hypertrophic chondrocytes and trans-differentiation to osteoblasts responsive of graft mineralisation. Autologous MSC cell therapy reduces cartilage degeneration, osteophyte remodelling, subchondral bone sclerosis and meniscal regeneration was reported in a caprine model of OA[31]. Local delivery of MSCs reduced the concentration of serum TNF-α, decreased responsiveness of T lymphocytes and synovial proliferation in a mice model of collagen-induced arthritis[32]. Single intra-articular injection of autologous MSCs prevented post-traumatic arthritis in mice[33]. Several phase 1 or 2 clinical trials are investigating the use of autologous MSCs for the treatment of cartilage diseases (Table 1).

Tendon and ligament regeneration

Tendon and ligament injuries and degenerative diseases are a widespread group of connective tissue disease affecting the adult population. There are differences in the healing capabilities of different ligaments or tendons, depending on their location (intra- or extra-articular), type of injury (partial vs. complete rupture), the degree of physiological load (lower limb vs. upper limb) and patient expectation (normal physical activity or sport professionals). This leads to a diversity of clinical situations. Some ligaments, such as knee anterior cruciate ligament (ACL), are notorious for having no tendency to heal and require surgical ligament reconstruction. Others such as knee medial collateral ligament, Achilles tendon or rotator cuff RC restore continuity by means of a scar, which can be treated conservatively depending on the rupture degree. Repair tissue has higher type-III collagen content and collagen turnover, increased total glucosaminoglycans and functionally, less tensile strength and increased elasticity. As a result, tendon-muscle unit performances decrease, consequently leading to long rehabilitation time and loss of function. Surgical reconstruction uses tendon grafts of different origin; when using allogeneic grafts, the procedure exposes to contamination risk or introduces a degree of damage in a previously intact donor zone by allograft harvest. Augmentation therapy for healing tissue and provision of tendon engineered grafts are two strategies with the potential to substantially improve quality of treatment and therapeutic decision-making for tendon and ligament disease. There are different commercially available synthetic polymers and decellularised matrix scaffolds[34]; their use is controversial mainly due to graft stability over time and the presence of degradative products within the joint. Autologous MSC-based tendon engineering is regarded as an appealing perspective to producing long lasting,

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viable tendon and ligament grafts. Several ex *vivo* engineering strategies proved successful in preclinical models. Type-I collagen hydrogels with non-demineralised bone at each end seeded with human BMMSCs under mechanical preconditioning produced a construct containing elongated fibroblast-like cells and ligament-like extracellular matrix[35]. Autologous MSCs seeded on microporous silk mesh exhibit fibroblast morphology 24 weeks after implantation in a pig model with ACL defect[36]. Suture augmentation promotes functional tendon and ligament regeneration. Autologous BMMSCs cultured in collagen gel deposited on the pretensioned tendon suture site, improved rabbit Achilles tendon load-related structural and material properties[37]. BMMSCs cultured under hypoxic condition improved collagen content and ultimate failure load in rats Achilles tendon suture site[38]. Biological augmentation uses local growth factors delivery to promote one or several stages of wound healing. Autologous MSCs genetically modified by adenovirus mediated in vitro BMP-12 gene transfer in a chicken model of tendon laceration resulted in increased repair biomechanics[39]. Plasmid transfected MSC cell lines to overexpress Smad8 and BMP-2 were able to produce neo-tendon tissue when ectopically implanted in mice[40]. One phase II clinical trial investigates the safety and efficiency of autologous MSCs on a collagen membrane for augmentation of rotator cuff repair (Table 1).

Clinical applicability of musculoskeletal RM. moving forward

RM introduces new possibilities for improving existing therapies and answering unmet clinical needs in the field of musculoskeletal disease. A practical approach to advancing science and facilitating clinical application would be a more sustained effort in improving collaboration between different experts implicated in the design of regenerative approaches for a specific indication. The earlier in the basic research phase this dialogue intervenes; the future product is more likely to target a clinical situation and to obtain larger applicability and improved performances. A 'bottom-top' approach, starting the basic research effort from clinical necessities identified by panels of clinicians, biologists and bioengineers could more precisely delineate directions for RM development. Different stages of the same disease are characterised by particular normal and abnormal molecular pathways and by distinct mechanical situation at macro and ultra-structural level. Better tailored RM strategies will need to target more than a particular disease but also biological and biomechanical particularities, which characterise pre-defined pathological stages. To this end, a molecular classification of musculoskeletal diseases would be highly desirable, with the capability to discriminate the intimate structural and functional changes, offering targets for regenerative strategies. The already well-known triad cells-scaffolds-bioactive molecules could be used selectively, in part or in various combinations to better fit the clinical situation.

Conclusion

Cell source profiling using biomarkers for proliferation and differentiation toward the desired lineage would be the next step in improving the RM strategy. Algorithm-based identification of stage of the disease, profiling of donor and host biology as well as *in silico* models of cell engraftment after implantation will help in characterising RM product. Flexible, interchangeable pipelines where patient data could be incorporated in early stages of production would result in personalised and affordable regenerative therapies.

Abbreviations

ACL, anterior cruciate ligament; ADSC, adipose-derived stem cells; BMMSC, bone marrow-derived stem cell; BMP, bone morphogenetic protein; DMB, demineralised bone matrix; HA, hydroxyapatite; MOCART, Magnetic Resonance Imaging Observation of Cartilage Repair Tissue Score; PDGF, platelet-derived growth factor; PLGA, polylactic glycolic acid; siRNA, small-interference RNA; TGF-β, transforming growth factor β.

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