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Therapeutic Potential of MSCs in Musculoskeletal Diseases (Osteoarthritis)

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1. Introduction

1.1 Musculoskeletal disorders (MSDs)

The Musculoskeletal or locomotor system is defined by a complex interconnection of different body parts functionally arranged in two main sub-systems: the skeletal system, composed of the bones, and secondly the muscle system. In addition other structures such as tendons, ligaments and other connective tissue joins both sub-systems providing functional and structural support.

Musculoskeletal disorder or more generically Rheumatic disease (RD) is a term used to describe over 200 different disorders involving different connective tissue. Depending on the main target affected, RDs can be grouped into different pathologies. Joints are structures commonly affected in RDs, as it is the location where bone, tendon, ligament and muscle meet. Joint disorders are generically termed as arthropathies, and it is only when inflammation occurs, in one or more joints, that the disorder is called arthritis. However, RDs also include systemic disorders (autoimmune diseases affecting multiple organs), dorsopathies (back disorders), soft tissue disorders (involving muscles, tendons, etc.), and osteopathies/chondropathies (e.g., disorders related to bone density and structure-like osteoporosis).

The prevalence of RDs in the elderly has erroneously been associated only with ageing; however RDs may develop at any time even in childhood (Manners, 2003, Mariller, 2005). Musculoskeletal disorders constitute the most common cause of severe chronic pain and physical disability, thus they are considered a public health problem that affect millions of individuals and constitute a major burden on health care, a situation which is aggravated by an increasingly aging population (Bansback, 2005, Loza, 2008).

1.2 Aetiology of osteoarthritis

Osteoarthritis is the most prevalent type of inflammatory arthritis (Spahn, 2011). Although it has long been considered to be primarily a cartilage disorder, induced by accumulated mechanical stress, as occurs in many other arthropathies the contribution of an inflammatory component is well established; sometimes produced by an autoimmune response, leading to chronic joint inflammation, destruction and cartilage loss. Little is

known about underlying molecular mechanisms. Its initiation and progression appear to be independent processes associated with different risk factors (Worthington, 2005). In addition to biomechanical stress on articular cartilage, the involvement of other tissues of the affected joint, such as the synovium, ligaments, periarticular muscles, and nerves, have also been proposed in OA aetiology and progression (Brandt, 2006). Several studies suggest that the subchondral bone is likely to be the most important structural element in both pain generation and disease progression. At least in its generalised form, OA shows features of a systemic musculoskeletal disease with a metabolic component and a genetic predisposition leading to the formation of a defective cartilage matrix (Aspden, 2008, Zhu, 2009). Unfortunately, despite advances in research, little is known about OA's exact etiology and pathogenetic mechanisms.

Currently there is no known cure for OA, and modern treatments only manage to reduce pain and maintain joint movement as much as possible. For many years the only known options for OA treatment were disease-modifying drugs, in mild cases, and several types of surgery depending on the affectation of articular structures. Among the surgery choices, arthroscopy and joint arthroplasty are the most common. The first is used in people with moderate lesions of articular cartilage or bone, in order to alleviate pain for a short time and to allow the joints to move more easily. Although it does not seem to treat the arthritis itself, sometimes the relief can delay the use of other more aggressive surgeries (Laupattarakasem, 2008). Total or partial joint arthroplasty is the ultimate surgical treatment when joint damage can be seen on radiographs. It involves surgery to replace the ends of bones, mostly in the hip, knee and shoulder thereby creating new surfaces. However, surgery is not recommended in those cases where the patient's health is precarious, due to serious risk of infections, and because after surgery, long periods of physical rehabilitation are needed. Moreover, the prostheses have a lifespan of 10 to 20 years, after which they require substitution.

In this therapeutic context, it is easy to understand that there is a real and urgent need for new and alternative treatments to circumvent the relatively low efficiency of existing therapies. This is where the emerging potential of regenerative medicine becomes increasingly important as the most promising method to restore, maintain or improve tissue structure and joint function (Bruder, 1997, Mackay, 1998, Pittenger, 1999, Zavan, 2007).

2. Regenerative medicine in rheumatic diseases

Broadly speaking, the term "regenerative medicine" refers to a new field in biomedical research focused on the development of therapeutic approaches allowing the body to replace and regenerate damaged or diseased cells, and ultimately the function of tissues and organs. This goal is achieved by means of a combination of approaches that include the use of soluble molecules, biomaterials, tissue engineering, gene therapy, stem cell transplantation and the reprogramming of cell and tissue types.

In the context of musculoskeletal disease, and in particular the reconstruction of articular defects caused by trauma or disease, the goal is to deliver cells that become competent in the defect site, initially optimizing biomechanics, and ultimately initiating new tissue production. Sometimes, as occurs in the case of soft tissue repair, an additional implant vehicle(s), is required to transport and constrain the implanted cells in the defect site and to provide mechanical stability to the surgical site. The progressive biodegradation of the

vehicle during new tissue formation would be the optimal scenario for the repairing process. However, this seemingly straightforward schema can be complicated depending on the tissue to repair, which in turn determines not only the type of cells to use but also the number and the mode of application. Thus, current challenges in musculoskeletal regenerative medicine cover several topics under study including: (1) the better understanding of cell biology, (2) the synthesis of new biomaterials for extracellular matrices (*scaffolds*), and (3) the definition of the best combination of cells, biologically active molecules and vehicles to promote growth and differentiation.

2.1 Regenerative medicine using mature chondrocytes

Given that cells are the main building blocks of regenerative therapies, their availability and their commitment to a specific lineage are major limitations. The cells can be of autologous (host-derived) or allogeneic origin (non-host derived). Other sources, are cells of xenogeneic (from individuals of another species), syngeneic or isogeneic (isolated from genetically identical organisms or highly inbred individuals, respectively) origin are only constrained to experimental models.

Obviously, the most logical approach for the regeneration of joint degraded cartilage, consists in the direct re-establishment of its main functional component, the chondrocytes. Joint cartilage is a connective tissue with special characteristics. It consists of chondrocytes that secrete a cartilage-specific extracellular matrix (ECM) made of collagens, mainly type II collagen, and different proteoglycans. The chondrocytes do not have direct cell-to-cell contact, thus each cell acts as a functional unit responsible for the production and maintenance of the ECM in its surrounding. These characteristics, in addition to the cartilage avascularity, explain the difficulties involved in repairing this tissue, because chondroprogenitor cell access to the damaged site is very limited.

The first approach, and the gold standard for years in joint orthopaedic surgery, has been the autologous chondrocyte implantation (ACI), after harvesting, from healthy cartilage biopsies and expanded in culture. So far, thousands of ACIs have been clinically applied with encouraging results in the short- and mid-term, but their long-term efficiency needs further confirmation (Alvarez-Dolado, 2007). The effectiveness of the technique is limited by some major drawbacks, including the absence of appropriate sources of suitable hyaline cartilage and the additional damage caused at the site of biopsy. Other important issues arise during chondrocyte expansion *in vitro* and further transplantation. In culture, chondrocytes easily dedifferentiate losing their chondrogenic phenotype and their re-differentiation potential and once it occurs, about half of the ACIs show evidence of chondrocyte hypertrophy, indicating the formation of a bone-like tissue. Finally, the occurrence of poor adhesion between the new and the original tissue is common and in those cases where scaffolds are used, the biomechanical properties obtained do not achieve the expected results. These problems have raised the need for alternative cell sources with chondrogenic potential for cartilage tissue engineering, a requisite accomplished by the stem cells, and in particular by mesenchymal stem cells (MSCs).

2.2 Regenerative medicine using MSCs

Under normal conditions body tissues are subjected to a continuous process of repair and regeneration of damaged and dead cells by means of a pool of progenitor or stem cells,

which have the capacity to differentiate into the specialised cell type being replaced. 'Stem cells' is a generic term to describe a variety of cells which share two common characteristics: (1) their self-renewal potential and (2) their capacity to give rise to different tissues. However their "potency", or differentiation potential is variable and therefore there exists a hierarchy according to stem cell types. The most versatile, the totipotent embryonic stem cells (ESCs) give rise to other embryonic or extra embryonic adult stem cells (ASCs) with pluri- multi- or uni- potentiality. Pluripotent stem cells are descendants of totipotent cells and can differentiate into cells derived from the endoderm, mesoderm and ectoderm germ layers. Multipotent stem cells can produce only cells of a closely related family of cells, e.g., hematopoietic stem cells and MSCs. Finally, unipotent cells only produce one cell type, but retain their self-renewal properties, a feature that distinguishes them from other non-stem cells.

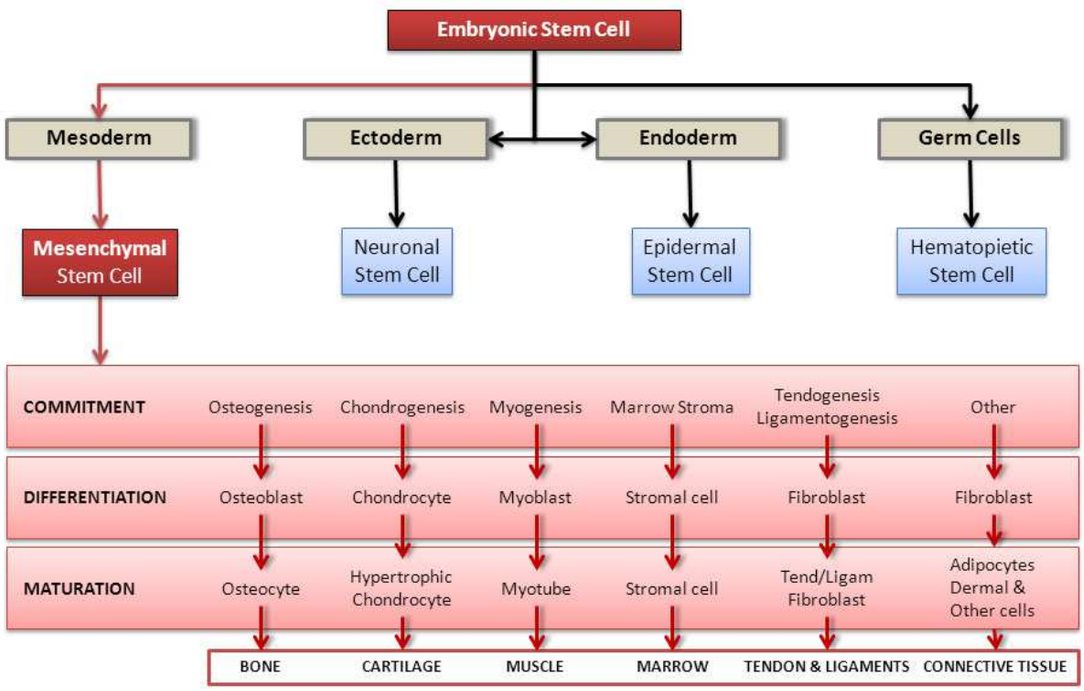

Fig. 1. Diagram of the mesenchymal stem cell lineage and its differentiation potential

MSCs have the potential to differentiate into several cell types of mesodermal origin including bone, cartilage, muscle, bone marrow stroma, tendon/ligament, fat, dermis. Thus these cells are optimal candidates in regenerative medicine strategies intended to restore these connective tissues. Adapted from (Caplan, 2007).

Although for the purposes of regenerative medicine, ESCs could be considered the optimal candidates; their clinical use in human therapies is still controversial due to ethical issues. In the context of musculoskeletal diseases, the least compromised are mesenchymal stem cells (MSCs) and are of particular interest for several reasons. First, they are the progenitors of

cells giving rise to a variety of cells which can form connective tissues such as chondrocytes, osteocytes, adipocytes and tenocytes (Pittenger, 1999), (Figure 1) and second: in contrast to most other adult stem cells, they can be isolated from a diversity of accessible tissues, such as bone marrow, fat tissues and umbilical cord blood (Chanda, 2010, Moretti, 2010, Romanov, 2005). Moreover, they can be isolated and identified through their adhesion potential in culture and by the expression of several "positive markers", represented by the transmembrane proteins CD90, CD73, CD105 and CD166. Additionally, MSCs are easily expanded *in vitro* without losing their "stemness" and/or self-renewal capacity (Bianco, 2001, Caplan, 2000, Reiser, 2005).

MSCs have been shown to differentiate *in vitro* into bone, cartilage, muscle, tendon, and fat, and possibly also into cardiomyocytes and hepatocytes (Conget, 1999, Chivu, 2009, Dennis, 1999, Pereira, 1995, Pittenger, 1999, Remy-Martin, 1999). Finally, from an immunological point of view, an important property of MSCs, especially for their use in rheumatic diseases, resides in their potent immunosuppressive and anti-inflammatory functions, the lack of induction of graft rejection and their chemotactic properties, similar to immune cells in response to injury on sites of inflammation (Le Blanc, 2004, Spaeth, 2008). As such, these cells are currently being considered for their potential use in cell and gene therapy, in a large number of human diseases, and particularly in a variety of clinical musculoskeletal conditions, including the repair of cartilage defects, tendon/ligament and bone.

2.3 MSCs and cartilage repair in OA

As occurs during embryogenesis, the generation of new cartilage (chondrogenesis) involves the MSCs progression through different stages in a tightly regulated process coordinated by multiple signalling pathways which include the Wnt, Notch or TGF (Quintana, 2009, Roelen, 2003). In particular, the Wnt/β-catenin signalling pathway plays a crucial role in cartilage reparation, since it participates in the differentiation of MSCs into osteoblasts or chondrocytes during osteogenesis and/or chondrogenesis (Day, 2005, Gaur, 2005, Hill, 2005). Markedly, alteration in any of the aforementioned pathways, as occurs in some diseases, can lead to detrimental effects during the regeneration process.

In vitro chondrogenesis is routinely performed by culturing MSCs in three dimensional scaffolds made of different biomaterials such as collagen, fibrin, agarose, alginate, chitosan or hyaluronic acid of natural or synthetic origin, or a combination of both types (Li, 2005, Lisignoli, 2005, Necas, 2010, Zhou, 2008). In addition, these scaffolds can be supplemented with soluble factors such as TGF-β, growth factors, bone morphogenetic proteins (BMPs), etc. to facilitate the chondrogenic differentiation of MSCs.

Application of engineered MSCs for cartilage regeneration has been addressed by the slight modifications of two main approaches widely tested in different OA animal models with encouraging results (Figure 2).

In the first, MSCs are seeded on 3D scaffolds with the presence or absence of soluble factors (growth factors and/or cytokines) and the resulting structure is used to repair the cartilage defect (Zscharnack, 2010). The second approach, consists of the direct administration of MSCs, (loaded or not in 3D scaffolds) without previous differentiation (Thorpe, 2010).

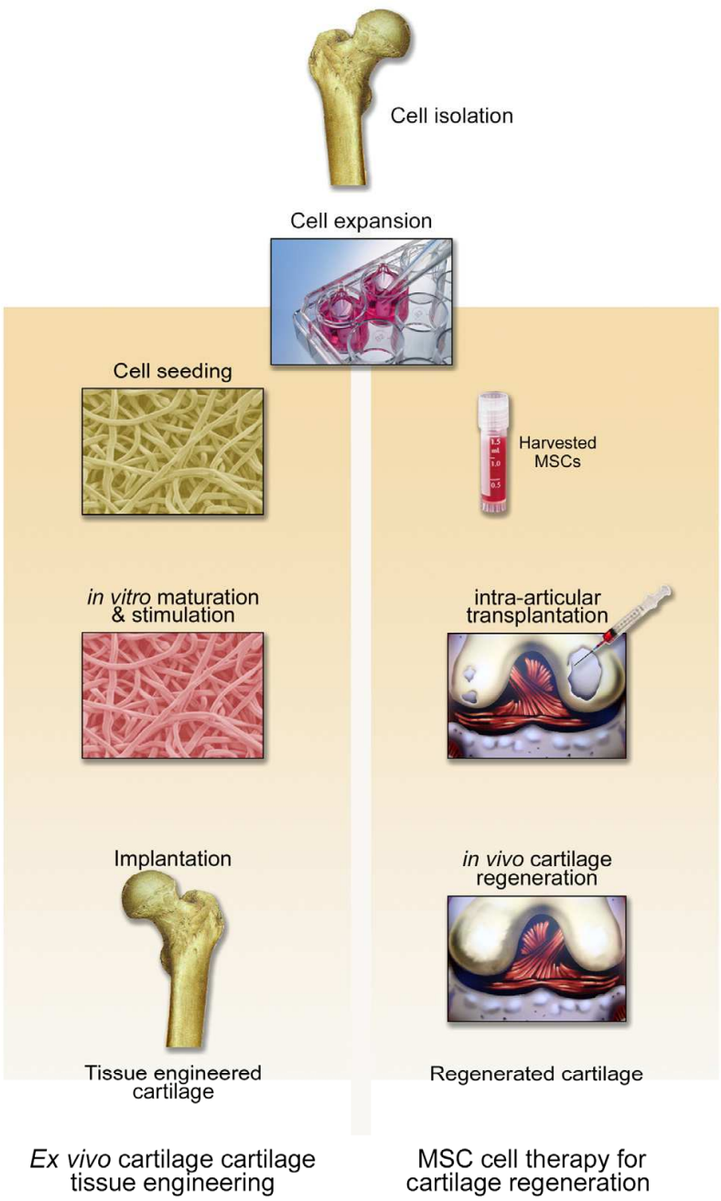

Fig. 2. MSC-based tissue engineering and cell therapy for cartilage repair and regeneration. Once MSCs are isolated and expanded, both tissue engineering and cell therapy approaches are suited for regeneration. In the *ex vivo* approach cells are loaded *in vitro* onto the scaffolds under appropriate stimuli and after a short incubation to insure attachment, the cell-scaffold composites are implanted. Another strategy is based on local injection into the affected joint. Adapted from (Caplan, 2007).

However, there are still some unanswered questions about the mechanism by which MSCs perform the repair; but several possibilities have been outlined, such as the following: (1) the secretion of cytokines to enhance repair (Chen, 2008); (2) the modulation of immune (Aggarwal, 2005, Gerdoni, 2007, Karussis, 2008, Le Blanc, 2007, Ren, 2008) and inflammatory responses (Gupta, 2007, Ortiz, 2007); (3) stimulation of the proliferation of tissue endogenous stem cells (Lee, 2006, Munoz, 2005); and (4) the rescue of damaged cells (Spees, 2006, Spees, 2003). Finally, MSCs are the subject in a controversy where their contradictory effects *in vitro* and *in vivo* on tumour cell growth have been called into question. Recent studies have shown that MSCs can increase the proliferation of tumor cells *in vitro* and promote tumor growth *in vivo* by increasing the neovascularization (Suzuki, 2011, Tian, 2011). This is a major concern that should be carefully considered, particularly in conditions where tumoral malignancies are present.

3. Studies carried out in our group

Our group has been focused for several years on the study of the biology of articular cartilage in the OA pathogenesis and the potential of MSCs in regeneration of damaged cartilage due to this disease. Some of the issues addressed include the basic research and the clinical trials to validate the translational efficacy in the clinic of MSC implantation. Much of our work in this field has been based on the use of modern techniques, that include proteomics and genomics approaches in combination with bioinformatics and genetic validation.

Proteomics is considered and emerging field with widespread potential applications to shape how rheumatic diseases are diagnosed, prognosticated, and clinically managed (Camafeita, 2009, Vanarsa, 2010). A key methodological advance in the classical two-dimensional gel electrophoresis (2-DE) has been the emergence of multiplexing two-dimensional fluorescence difference gel electrophoresis (2D-DIGE) (Unlu, 1997). The 2D-DIGE technique circumvents many of the issues associated with traditional 2-DE, providing more sensitivity, high reproducibility and a wide dynamic range of detection (Alban, 2003, Viswanathan, 2006). It consists in the labelling of lysine groups on protein extracts with fluorescent dyes with different emission spectra before isoelectric focusing (IEF). Protein samples are further labelled with Cy3 and Cy5 fluorescent dyes, while Cy2 dye is used to label the internal standard, which consists of a pooled sample comprising equal amounts of all samples to be compared. Then the three samples are electrophoresed on a single 2D gel, which allows both direct quantitative comparisons within each gel and the normalization of quantitative abundance values for each protein between gels. The combination of 2D-DIGE with matrix-assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF MS) provides a powerful tool for identifying disease-related proteins (Stults, 2005). (Figure 3). Genomic approaches have been developed through DNA microarray analysis, a proven "state of the art" technology for the simultaneous screening of expression levels in large numbers of genes (Licatalosi, 2010). (Figure 4)

Another strategy, different from the previous two, is the systemic application of MSCs, that have been shown to promote tissue repair by formation of fibrocartilage-like tissues in response to damaged subchondral bone (Chang, 2011), which is likely due to the intrinsic ability of MSCs to migrate into injured or inflamed tissues.

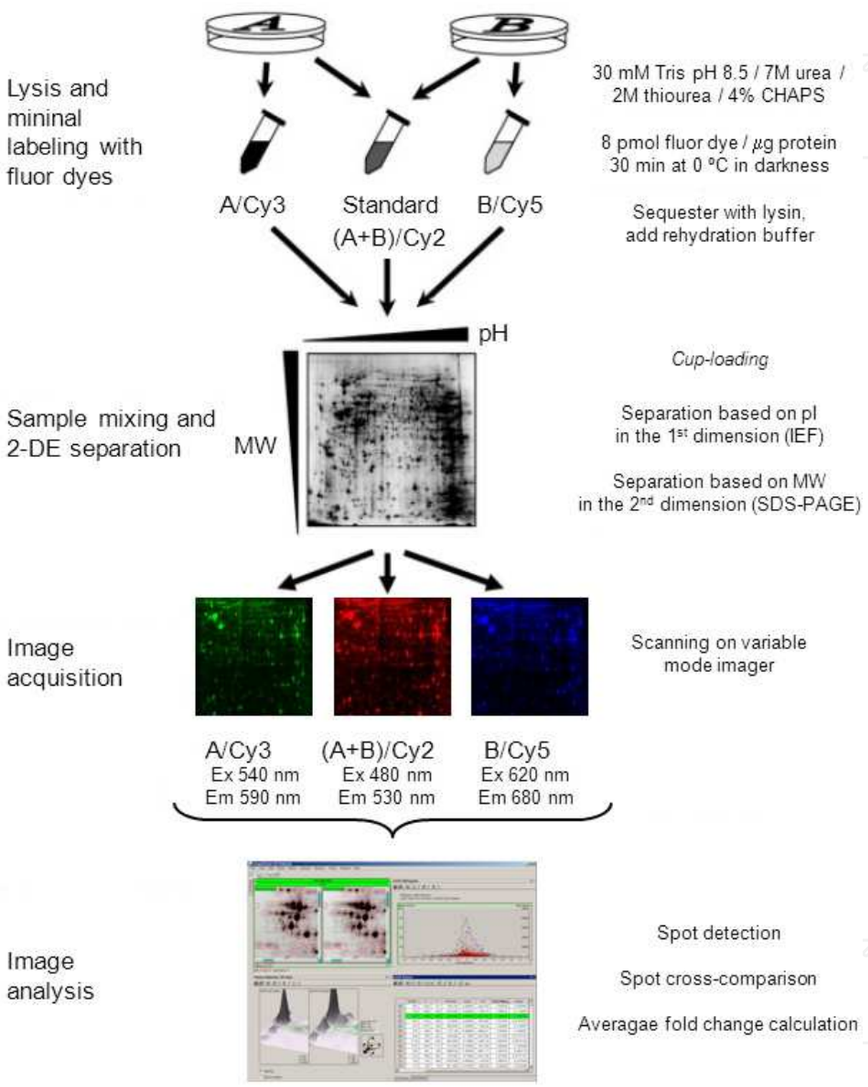

Fig. 3. Schematic representation of the 2D-DIGE methodology
2D-DIGE used for the analysis of protein differential expression in MSCs and chondrocytes of patients with osteoarthritis (sample A) compared to control subjects (sample B). CHAPS, 3-[(3-Cholamidopropyl)dimethylammonio]-1-propanesulfonate; Em, Emission; Ex, Excitation; IEF, isoelectrofocusing. MM, Molecular mass; pI, Isoelectric point; SDS PAGE, polyacrylamide gel electrophoresis in the presence of Sodium Dodecyl Sulphate.

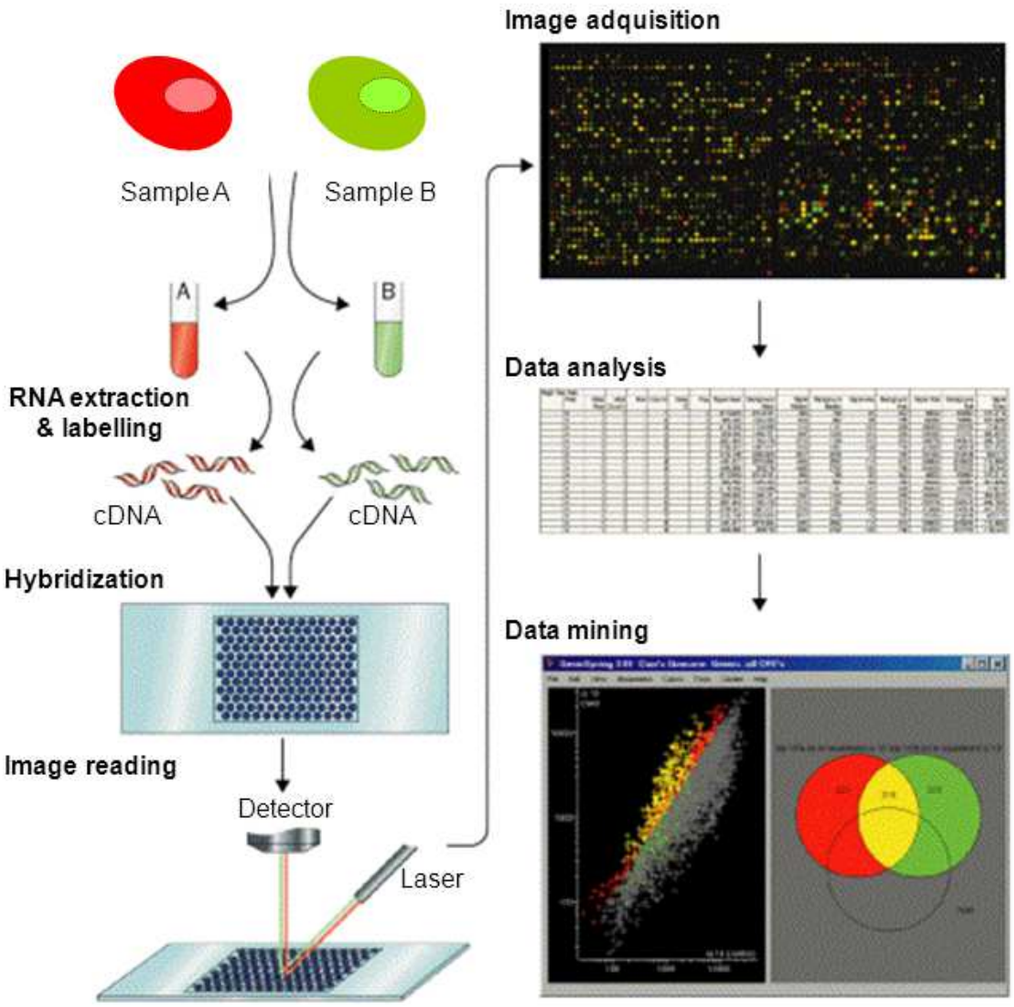

Fig. 4. Schematic representation of the DNA microarray methodology.
DNA microarrays are commonly used to detect messenger RNAs (mRNA), referred to as expression profiling. The method consists in the fluorescently labelling of RNA while the RNA is converted into complementary DNA (cDNA). Amplification of sequences by PCR is sometimes incorporated into this step. Two-color labeling allows two samples or conditions, to be hybridized to the same array and their gene expression profiles compared via the difference in the fluorescence of the two samples. Statistical post-processing of the fluorescence data is usually necessary to eliminate artifacts and false results from the data obtained.

3.1 Proteomic studies in Chondrocytes and MSCs in osteoarthritis

The breakdown of cartilage in OA involves the degradation of the extracellular matrix macromolecules and the altered expression of chondrocyte proteins necessary for normal joint function (Lane Smith, 2000). Thus the screening of proteins with altered expression in chondrocytes from patients with end stage OA compared to control subjects could expand the knowledge of the pathological processes implicated in the damage of articular cartilage in OA. Elucidation of the phenotypical alterations occurring in OA is important for the ascertainment of disease aetiology and for the development of effective treatments for OA.

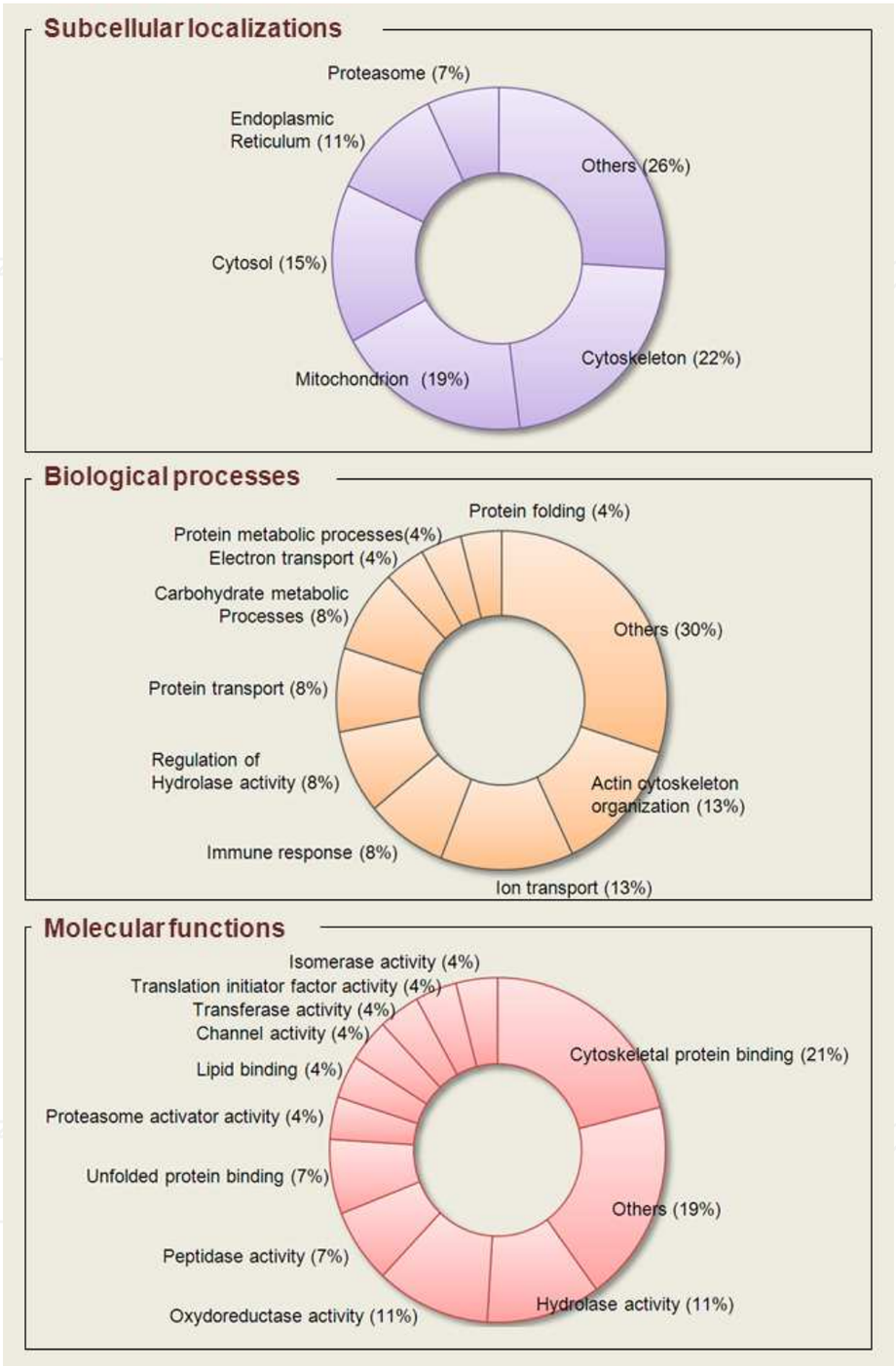

Fig. 5. Gene ontology annotation of the 27 changed proteins identified in OA chondrocytes.

Our first proteomic study dates from 2008 (Rollin, 2008c). Here human knee cartilage was obtained during total joint replacement surgery in six patients with clinical and radiological features of OA and six control samples from adult donors of similar age. Chondrocytes were isolated and cultured during 2-3 weeks at confluence in primary culture, before protein

extraction. After 2D-DIGE, differentially expressed proteins were excised from the gel, digested with trypsin and analysed by a MALDI-TOF MS mass spectrometer. Protein identification after peptide mass fingerprinting (PMF) enabled the identification of 27 proteins (14 decreased and 13 increased) in OA chondrocytes. The cellular localization, biological process and molecular functions and of the identified proteins obtained from the online FatiGO ontology database are summarized in (Figure 5).

In this study, a significant differential expression pattern was observed for 27 different chondrocyte proteins. These included an elevated number of cytoskeletal binding proteins cytoskeleton binding, protein disruption, apoptosis and glycolysis proteins displayed a significantly changed expression in OA chondrocytes. Overall, the results suggested the deregulated production in OA cartilage of proteins pertaining to key cellular processes essential for the proper functioning of the chondrocytes, which may have direct effects on OA cartilage biology.

A similar approach was also carried out to study the differential proteome of bone marrow MSCs (BM-MSCs) (Rollin, 2008b) from patients with OA *vs.* MSCs control, obtained from patients with hip fracture without OA signs. In this study we demonstrated the existence of specific alterations in the proteome content of bone marrow MSCs from patients with OA. Once classified into different groups, according to their biological function, the majority of proteins that changed at least 1.5-fold, belonged to the metabolic enzymes, cytoskeleton/motility and transport categories. Markedly, most proteins related to cytoskeleton/motility were down-regulated in MSCs from OA patients. Considering previous evidences supporting that MSCs can home to some tissues, particularly when injured or inflamed, the mechanisms underlying migratory capacity, as a key event for tissue repair by MSCs, were also studied *in vitro* using PDGF as chemoattractant. Our results demonstrated a significant increase in the motility of MSC of OA patients. Together with the differential expression of metabolic and cytoskeleton proteins we concluded that an activation of OA BM-MSCs occurs in response to chemotactic signals sent by the altered subchondral bone in an attempt to heal damaged tissues.

3.2 Gene expression alterations in bone marrow MSCs in osteoarthritis

Our previous experimental data obtained in MSCs proteomic studies indicate an increased migratory capacity of BM-MSCs to the damaged tissues, likely to initiate and/or enhance the wound repair process. In this context, it is known that transforming growth factor-β (TGF-β) plays an important role in directing the cell fate choices in mesenchymal cells (Roelen, 2003). TGF-β induces the chondrogenic differentiation of MSC in the presence of dexamethasone or 3-dimensional cell aggregates (Mackay, 1998) and may act in conjunction with other microenvironmental factors on MSC differentiation. To assess the importance of TGF-β expression in MSCs from OA we comparatively studied by quantitative real-time PCR the expression of genes encoding the total TGF-β and those of the 3 isoforms of TGF-β (1, 2, 3) and TGF-β receptors (TBR-I, TBR-II, TBR-III) in primary cultures of BM-MSCs from patients with end stage OA and healthy control subjects (Rollin, 2008a). Our results showed that only TGF-β1 isoform was significantly increased in MSCs from OA. In addition, we also described an increased expression of TBR-II and TBR-III genes, but not of TBR-I in MSCs from OA. A possible explanation for this upregulated TGF-β upregulation in MSCs could be related to an stimulatory effect on

mesenchymal cell proliferation in bone marrow allowing their expansion in response to the bone and cartilage damage characteristic of this disease.

More recently, another experimental approach was carried out by our group based on the comprehensive study of gene expression of MSCs using a DNA microarray expression analysis (Lamas, 2010). Gene expression profiles of MSCs from OA patients were compared to those of MSCs from healthy individuals. After integration of expression profiles into functional categories, by means of a gene ontology (GO)-based statistical analysis using GeneCodis 2.0 (Carmona-Saez, 2007), seventy-five genes from a list of 532 provided for comparison did not show annotations. The remaining 457 genes were grouped into different GO categories based on the subcellular location and functionality (Figure 6). Functional categories showing a major number of genes with downregulated expression in OA-MSCs

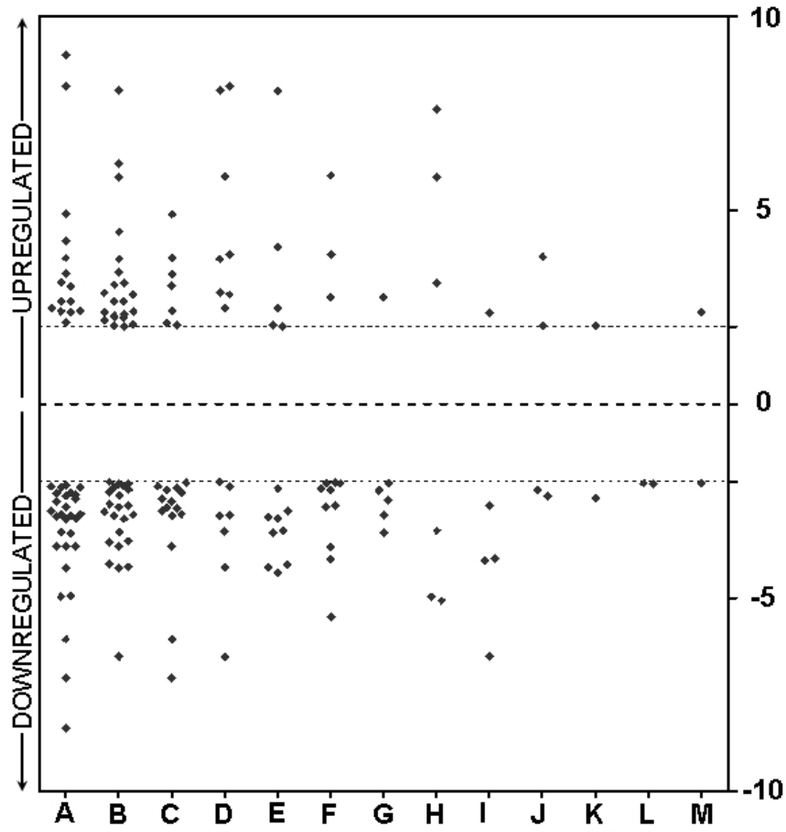

Fig. 6. Differential expression of genes in osteoarthritis mesenchymal stem cells (OA-MSCs) according to gene ontology (GO) categories.
The X-axis represents individual genes classified according to the gene ontology (GO) slim categories provided by the GeneCodis2 (Carmona-Saez, 2007) analysis. The Y-axis represents the fold variation in expression of OA-MSCs compared to control subjects ($p<0.05$). Only genes expressing at least twofold differences in expression were considered. A: Multicellular organismal development; B: Signal transduction; C: Cell differentiation; D: Cell-cell signaling; E: Cell proliferation; F: Metabolic Process; G: Carbohydrate Metabolic Process; H: Anatomical structure morphogenesis; I: Cytoskeleton organization; J: Response to stress; K: Cellular component organization; L: Response to external stimulus; M: Growth

were signal transduction, development and cell differentiation, which in turn are key functions in pluripotential cells. Based on the function of the proteins encoded by these genes, our results suggested that MSCs from patients with OA have a diminished differentiation and regenerative potentials that limit ther ability to generate a functional lineage of cells involved in musculoskeletal tissue homeostasis.

Overall, in this study we provided a reference dataset of genes related to essential functions for the normal biology of MSCs that become altered in OA (Figure 4). We also described for the first time an association between the COL10A1 gene and OA susceptibility suggesting that underlying biological changes which occur during OA disease might be related, at least in part, to defects in the ECM and the formation of subchondral bone, an essential structure for providing joint stability. Moreover, in this work we also demonstrated that the expression of multiple genes related to the wnt pathway were downregulated in OA patients.

3.3 Animal models in regenerative medicine (tendon repair)

Chronic degeneration is the most frequent cause for lesions of the rotator cuff, a set of four tendons connecting the scapula with the humeral head in shoulder. The most affected tendon of the cuff, frequently affected by tears, is the supraspinatus tendon. These lesions are increased in aged patients who frequently need reconstructive surgery. Surgical methods are often unsatisfactory due to inefficient recovery. In this context, MSC-based regenerative medicine offers a hopeful alternative for this type of treatment. In this sense, our group is performing several studies focused on the evaluation of the effectiveness of recovery after treatments consisting in surgical implantations of MSCs alone or in combination with a commercial membrane of type I collagen (Orthoadapt™). This strategy has been previously tested in in a model of acute and chronic injury in rats with promising results allowing us to conduct a clinical trial in humans that is currently under development.

4. MSCs, conventional and other experimental treatments in OA

Treatment of osteoarthritis includes a combination of pharmacological and non-pharmacological measures aimed at relieving pain and the improvement of joint function. Initial treatment is dependent on the extent of the disease, age of patients and the joints affected, in descending order of frequency: Hip, Knee, Foot and Ankle. In mild cases, treatment begins by the use of simple analgesics (eg. paracetamol), (Nonsteroidal anti-inflammatory drugs) NSAIDs (eg. ibuprofen and naproxen) or intermittent intra-articular administration (infiltration) of corticosteroids. However, although the symptoms and pain can be partially alleviated, adverse effects associated with conventional drug therapy is not recommended for long time periods. Moreover, treatment is often accompanied by non-pharmacological treatments, these include patient education and physical exercises to restore joint movement and to increase muscle strength, reduction of weight on painful joints. When joints are severely damaged treatment may require surgery. The most common surgical treatments are arthroscopic surgery, to trim damaged cartilage. Osteotomy, to change the alignment of a bone to relieve stress on the bone or joint. Arthrodesis or surgical fusion of bones, usually in the spine and the total or partial arthroplasty to replace the damaged joint with an artificial one.

Halfway between drug therapy and joint replacement surgery, several arthroscopic strategies combined with cell therapies have been developed for the treatment of cartilage injuries. The techniques used and the results obtained greatly vary depending on the size of the lesion. For smaller and medium sized cartilage defects, autologous osteochondral cylinder transfer or mosaicplasty has been widely used but its efficacy is limited by donor site morbidity and the poor integration of implants.

Techniques of cell therapy in OA were initially based on the stimulation of bone marrow by drilling, microfracture and abrasive chondroplasty to promote better access of pluripotential stem cells from subchondral vascular area, to the site of injury (Steinwachs, 2008; Chen, 2011). Although the microfracture has achieved good results in terms of functionality and reduction of pain, several limitations such as chondral defect size and age of the patient are major constraints. These methods only provide a partial filling of the defect with fibrocartilage without the characteristics of hyaline cartilage. More recently improvements of these cell therapies have been made using the implantation of cultured autologous chondrocytes in the defect site (ACI) and a variation of this technique, using collagen Type III/I scaffolds, MACI (Matrix-induced autologous chondrocyte implantation) (Strauss, 2011; Ventura, 2011). MACI was developed to enable the treatment of larger defects when cell engaged procedures such as ACI cannot be used or it is not indicated. The results of the ongoing studies in chondrocyte implantation show better results in the formation of a hyaline-like cartilage with similar characteristics and durability than normal hyaline cartilage. In any case, the major drawbacks are that the chondrocytes harvesting require additional surgery and only a small number of chondrocytes can be isolated from the explants. In addition these cells lose their phenotypic characteristics in culture, limiting their application in extensive chondral defects, such as those produced in osteoarthritis. Otherwise, allograft transplantation is limited by donor availability.

Table 1 shows a summary of the most common techniques used clinically and experimentally. However the number of combinations of treatment options with each strategy is unlimited and growing every day. A great number of studies involve animal models evaluating different scaffolds, number of cells and ambiental factors used, etc. However, given the complex variety of combinations, there are no well-conducted clinical trials in humans evaluating the efficacy of a particular method.

In summary, regarding OA, advances in research for the development of new technologies in the management of cartilage defects is currently unresolved. Actually any treatment method provides consistent and acceptable long-term clinical results, and in particular for treatment of large chondral defects. With evolving techniques, versatility, availability and differentiation potential of stem cells have become the hope to improve current treatments based on other more committed cells. Alone or in combination with different scaffold materials and environmental factors, including growth factors, signalling molecules and mechanical influence, these cells are exceptional candidates for engineer cartilage constructs *in vitro*. Several studies have shown an improvement in the quality of the new tissue formed, but its long-term efficacy and the mechanism by which it occurs are unknown. In this regard it has been postulated that the low intrinsic immunogenicity of MSCs along with its ability to reduce inflammation, are characteristics that determine the establishment of a less inflammatory environment that facilitates the repair.

Symptom	Current approach	Mode of action	Advantages	Disadvantages
Initial stages (non surgical)				
Pain and Inflammation	- Pharmacological treatment	Analgesic Anti-inflammatory	Surgery not needed	Adverse effects
	- Physical exercice	Joint structures reinforcement		Not recommended in some cases
	- Educational	Prevention		none
Structural damage of joint cartílage (surgical methods)				
Small defects <2.5cm²	- Subchondral drilling - Microfracture - Abrasive chondroplasty	Bone marrow stimulation	Relatively inexpensive surgery	Age of patients Inferior quality of neoformed tissue
Structural damage of joint cartílage (trasplantation methods)				
Medium defects 2.5 to 4 cm²	- Osteochondral allografts - Autologous periosteal grafts - Autologous mosaicplasty	Tissue trasplantation from autologous or allogeneic origin	Age of donor eligible Relatively well suited for medium cartilage defects	Availability of implants. Donor morbidity. Poor integration and maintenance of implant.
	- Autologous chondrocyte trasplantation (ACI)	Cellular therapy using committed cell lineages	Relatively well suited for medium cartilage defects Defect filling with hyaline cartilage in a short time	Two sugeries needed Small number of chondrocyte availability Poor integration Do not show improvement over other conventional techniques

Symptom	Current approach	Mode of action	Advantages	Disadvantages
	- Matrix-induced autologous chondrocyte implantation (MACI)		Better early results	Medium and long-term results not available Expensive
	Mesenchymal Stem Cells (MSCs)	Cellular therapy using stem cells	Potential	Expensive
Large defects > 4 cm^2	Total arthroplasty	Joint replacementt	Joint restoration	Infections Expiration

Table 1. Conventional and experimental treatments in OA.

5. Conclusions and future perspectives

The goal in regenerative medicine is based in a conceptually simple scheme: the development of new strategies to replace human cells or induce the regeneration of diseased or injured human tissues. Although during the last twenty years a considerable scientific progress has been done in this field, there are still many unanswered questions about key concepts concerning both tissue engineering and cell therapy.

Stem cells, in its two "flavours": embryonic and adult stem cells are the basis of regenerative medicine; however, biological differences between adult and embryonic stem cells and among adult stem cells found in different tissues is an important aspect which implication for therapeutic uses is not resolved. From the point of view of their clinical application, the source of the cells is of extreme importance. In the case of autologous cells that are not rejected by the patient's immune system their application is potentially safer than in allogeneic cells and more suitable for permanent tissue replacement. However, and for example, in cases where the recipient suffers from a genetic disorder, their application would be inappropriate. Future efforts should be done to minimise rejection, and to favour the banking and use of allogeneic adult cells. Among adult stem cells, the MSCs are of paramount importance for the treatment of several rheumatic diseases. Besides their plasticity and regenerative potential they show immunosuppressive and antiinflammatory characteristics *in vitro* and proven in preclinical and clinical studies.

Future studies will need to focus on the particular cell biology of MSCs including the biochemical signal transduction pathways involved in maintaining and enhancing chondrogenic differentiation, but also in the mechanisms implicated in immunomodulation. Other important aspects that need further research include the evaluation of safety and efficacy of local or systemic modes of admistration of MSCs; the mechanisms of cell to cell communication, such as microvesicles transporting RNAs, cytokines, etc.; the behaviour of MSCs in different niches; the design of specialised engineered scaffolds, to enable the efficient repair of a variety of tissues; and finally, the implementation and use of genetic reprogramming strategies.

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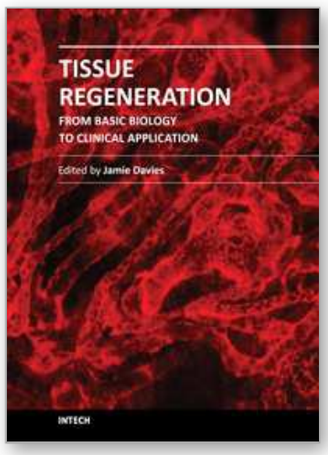

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When most types of human tissue are damaged, they repair themselves by forming a scar - a mechanically strong 'patch' that restores structural integrity to the tissue without restoring physiological function. Much better, for a patient, would be like-for-like replacement of damaged tissue with something functionally equivalent: there is currently an intense international research effort focused on this goal. This timely book addresses key topics in tissue regeneration in a sequence of linked chapters, each written by world experts; understanding normal healing; sources of, and methods of using, stem cells; construction and use of scaffolds; and modelling and assessment of regeneration. The book is intended for an audience consisting of advanced students, and research and medical professionals.

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