EXPERIMENTAL STUDY

Osteochondral tissue engineering approaches for articular cartilage and subchondral bone regeneration

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Abstract

Purpose Osteochondral defects (i.e., defects which affect both the articular cartilage and underlying subchondral bone) are often associated with mechanical instability of the joint and therefore with the risk of inducing osteoarthritic degenerative changes. This review addresses the current surgical treatments and most promising tissue engineering approaches for articular cartilage and subchondral bone regeneration.

Methods The capability to repair osteochondral or bone defects remains a challenging goal for surgeons and researchers. So far, most clinical approaches have been shown to have limited capacity to treat severe lesions. Current surgical repair strategies vary according to the nature and size of the lesion and the preference of the operating surgeon. Tissue engineering has emerged as a promising alternative strategy that essentially develops viable substitutes capable of repairing or regenerating the functions of damaged tissue.

Results An overview of novel and most promising osteochondroconductive scaffolds, osteochondroinductive signals, osteochondrogenic precursor cells, and scaffold fixation approaches are presented addressing advantages, drawbacks, and future prospectives for osteochondral regenerative medicine.

Conclusion Tissue engineering has emerged as an excellent approach for the repair and regeneration of damaged tissue, with the potential to circumvent all the limitations of autologous and allogeneic tissue repair.

Level of evidence Systematic review, Level III.

Keywords Osteochondral defect · Tissue engineering · Biomaterials · Stem cells · Growth factors · Regenerative medicine

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Introduction

Articular cartilage is a specialized tissue that plays a very important role in the natural joints [65], it increases joint congruence, it protects the subchondral bone from high stresses, and it reduces friction at the edge of long bones [91]. Cartilage response to injury does not follow the typical necrosis, inflammation, repair and scar tissue remodeling cascade of events, as it lacks vascularization. Cartilage lesions are therefore usually irretrievable, due to the avascular nature of this tissue and consequent lack of access to a pool of potential reparative cells and growth factors [94].

Osteochondral lesions, which involve both the articular cartilage and the subchondral bone, typically lead to the formation of fibrocartilage that has different biomechanical properties from the native hyaline cartilage and does not protect the subchondral bone from further degeneration [76]. This process involves both repaired and adjacent

native tissues leading to the insurgence of severe pain, joint deformity, and loss of joint motion. Osteochondral defects typically require surgical procedures [83]. A brief description of the current surgical treatments used will be made, followed by an exhaustive overview of innovative tissue engineering approaches for the regeneration of osteochondral lesions.

Current surgical treatments

Currently, for the treatment of osteochondral lesions <2.5 cm^2, mostly the techniques of Joint Debridement, Microfracture, and Mosaicplasty have been used, the choice of which to use depending on several factors, e.g., size of lesion, availability of particular treatment, the age and requirements of the patient [33, 46].

Joint Debridement eliminates debris from the joint space or joint surface only to alleviate pain [43, 87] and, in clinical, is usually associated with bone marrow stimulation technique, or microfracture. Bone marrow stimulation consists in penetration of the subchondral bone and release of progenitor cells from the bone marrow cavity into the defect. Such progenitor cells originate cells resembling morphologically the chondrocytes and that produce a fibrocartilaginous cartilage. Mosaicplasty, also called autologous osteochondral grafts, removes cylindrical plugs of hyaline cartilage with underlying subchondral bone from an unaffected area and implants them into the chondral defect, prepared with perpendicular edges of normal cartilage around, to create a "mosaic" pattern [34].

For osteochondral lesions >2.5 cm^2, cells with chondrogenic potential and osteochondral allografts have been used. Autologous Chondrocytes Implantation (ACI) consists in the isolation of chondrocytes from a small cartilage piece harvested from a low-weight-bearing area of the knee joint, their expansion in vitro for 2–3 weeks and transplantation into the chondral defect and covering with a periosteal patch usually from the upper tibia surface. The introduction of matrix-associated ACI (M-ACI) is the first ever application of tissue engineering in orthopedic surgery; it minimizes donor site morbidity associated with periosteum harvesting and prevents cell de-differentiation [4, 31, 68]. Various scaffolds are available for clinical use, but there are only a few technical reports about arthroscopic M-ACI in the literature [54, 67, 95].

Recently, 53 patients with ostheochondral defects were treated with M-ACI and after 1 year, Magnetic Resonance Imaging (MRI) revealed a completely repaired defect with slight subchondral bone abnormality in 38 cases. A 5-year follow-up revealed a complete integration with the surrounding native cartilage with no detachment or bone marrow edema in 15 out of 17 patients [97].

Osteochondral allografts are often indicated as a rescue treatment in post-traumatic situations after periarticular fracture in lesions in which there is a significant bony deficit and also after failure of other techniques [48].

Each of the above-mentioned methods has shown to have limited success in particular focusing on long-term repair, and they are usually limited to small lesions. Currently, when articular cartilage is severely damaged and it is combined with lower limb malalignment, periarticular osteotomies are the most widely used treatment methods. If varus or valgus alignment occurs, the limb is realigned to transfer joint load away from the damaged cartilage surfaces. Procedures result in long-term pain relief but overloading of the unaffected compartments implies its progressive degeneration over several years leading to complete joint failure [9]. For severe degeneration of the joint, this is replaced by a total prosthetic joint typically made up of metallic alloy combined with polyethylene liner and cup, components that suffer high wear and corrosion and at the same time are still much stiffer than cartilage, so that shock absorption, lubrication, and deformation properties are lacking in the artificial joints. Detailed limitations of the current surgical strategies for osteochondral regeneration have been recently reviewed [29].

Tissue engineering in the orthopedic field

In the last few decades, tissue engineering has emerged as a promising alternative multi-disciplinary approach for the repair and regeneration of damaged tissue. Making joint of the latest developments in materials science, engineering, chemistry, and cell biology applied to medical science, it aims at restoring both function and mechanical properties of native articular cartilage and subchondral bone. Within osteochondral tissue engineering, different approaches have been followed but the best results will probably be achieved by the combination of 1. Osteochondroconductive scaffolds, 2. Osteochondroinductive signals, 3. Osteochondrogenic precursor cells, 4. Suitable fixation. A description of the most recent approaches in osteochondral tissue engineering for each topic will be presented.

Osteochondroconductive scaffolds

Tissue engineering requires a tissue-conductive system in order to mimic the 3D environment of the extracellular matrix (ECM), provide structural support to the regenerated and surrounding tissues, and provide an increased surface area to volume ratio for cellular migration, adhesion, and differentiation [11]. Note that the cellular growth and subsequent tissue regeneration depend in part on the

characteristics and porosity of the scaffold. It must be biodegradable and biocompatible, and it must present a suitable fixation to the defect site, facilitate cell attachment, regulate cell expression, and promote the supply of nutrients and growth factors [26]. In order to control and direct cell behavior, a well-defined biomimetic environment, which surrounds the cells and promotes specific cell interactions, is necessary. Scaffold properties depend primarily on the nature of the biomaterial and the fabrication process. The nature of the biomaterial has been the subject of extensive studies including different materials such as natural, synthetic materials, ceramics or composite of these compounds.

Natural materials provide a more physiological environment for cell adhesion and proliferation and may be further divided into protein-based matrices such as collagen and fibrin, and carbohydrate-based matrices such as alginate, agarose, chitosan, and hyaluronan [75–77].

Natural materials are biocompatible, biodegradable, and they have the ability to mimic certain aspects of native ECM, thus facilitating cell adhesion, migration, differentiation, and ECM deposition. However, natural materials have several disadvantages such as immunogenecity, difficulty in processing, and a potential risk of transmitting animal-originated pathogens [57]. Moreover, despite the biocompatibility, these materials are mechanically weak and undergo rapid degradation upon implantation if not cross-linked with appropriate chemical reagents [57].

Synthetic materials have been used extensively in tissue engineering both in vitro and in vivo due to their easy molding characteristics, relatively easy production and the ability to control dissolution and degradation [11]. The most popular biodegradable synthetic polymers include poly(α-hydroxy acids), especially poly(lactic acid) (PLA), poly(glycolic acid) (PGA) and their co-polymers (PLGA), poly(ε-caprolactone) (PCL), poly(propylene fumarate) (PPF), poly(dioxanone) (PDO) [65]. Although synthetic materials are biocompatible, they do not have natural sites for cell adhesion and these often need to be added. Further, their in vivo degradation by a hydrolytic reaction causes a local reduction in pH and possible inflammation response [26].

Ceramics, such as hydroxyapatite (HA) or other calcium phosphate ceramics (including tricalcium phosphate, TCP) or bioactive glasses are known to promote, when implanted, the formation of a bone-like apatite layer on their surfaces [7, 70]. They have been investigated extensively during the last decades and are widely used for bone replacement, due to their osteoconductivity and high biocompatibility, also associated with stem cells therapy [66].

The main purpose for osteochondral tissue engineering is to recreate a more biomimetic scaffold combining synthetic materials with cell-recognition sites of naturally

derived materials [7, 69, 92]. In addition, looking to the architectures of native tissues, novel graded scaffolds represent the challenge for osteochondral defect treatment. In fact, bone and cartilage have complete different properties. For bone, mechanically stiff biomaterials with options for medium perfusion and vascularization are required to support cell expansion, as well as the production of bone matrix rich in type I collagen and HA. By contrast, native cartilage matrix consists of an avascular highly hydrated proteoglycan hydrogel embedded into a type II collagen network.

Although several studies focus on the design and optimization of a stratified osteochondral graft with biomimetic multi-tissue regions, only few show good results in experiments in vivo. Here, some encouraging examples are mentioned.

A multi-phased scaffold of agarose hydrogel and sintered microspheres of PLGA-bioactive glass composite has showed in vitro a controlled chondrocyte and osteoblast culture on each scaffold region, resulting in the formation of three distinct yet continuous regions of cartilage, calcified cartilage, and bone-like matrices [45]. Very recently, a poly vinyl alcohol/gelatin-nano-hydroxyapatite/polyamide6 (PVA-n-HA/PA6) bilayered scaffold seeded with induced bone marrow stem cells (BMSCs) showed ectopic neocartilage formation in the PVA layer and reconstitution of the subchondral bone, confined within the n-HA/PA6 layer, when implanted into the rabbit muscle pouch for up to 12 weeks [82]. A biphasic scaffold combining hyaluronic acid and atelocollagen for the chondral phase and combining HA and β-TCP for the osseous phase has proved to be effective for repairing osteochondral defects, when implanted in the knee joint of a porcine model [41]. Another biphasic scaffold based on collagen-glycosaminoglycan and nano calcium phosphate has been developed to mimic the composition and structure of articular cartilage on one side, subchondral bone on the other side and the continuous, gradual soft interface between these tissues. The different properties of the osseous and cartilaginous compartments seem promising but, as far as we know, this scaffold has not yet been tested in a biological system [36].

Very recently, a 3D biomimetic scaffold (MaioRegen, Fin-Ceramica Faenza S.p.A., Italy) was obtained by nucleating type I collagen fibrils with HA nanoparticles, in two configurations, bi- and tri-layered, to reproduce, respectively, chondral and osteochondral anatomy [52]. This scaffold has been tested in chondral defects and deep osteochondral defects made in the metacarpal bone of two adult horses and treated, respectively, with the chondral and osteochondral grafts. Results showed that the growth of trabecular bone in the osteochondral lesion was evident and newly formed fibrocartilaginous tissue was present [53]. The same scaffold has also been tested in the femoral condyles of

sheeps and 6 months after surgery, histologic and gross evaluation of specimens showed good integration of the chondral surface and significantly better bone regeneration [51]. The same scaffold has been used already in an early stability clinical trial on 13 patients with 15 large degenerative chondral lesions: four at the medial femoral condyle, two at the lateral femoral condyles, five at the patellas, and four at the trochleas. The mean size of the defects was 2.8 cm^2 and MRI evaluation at short-term follow-up has demonstrated good stability of the scaffold without any other fixation device and the histological analysis showed the formation of subchondral bone without the presence of biomaterial and the cartilage repair tissue appeared to be engaged in an ongoing maturation process [52]. Presently, an extensive clinical trial is ongoing involving eleven European centers and 150 patients (http://clinicaltrialsfeeds.org/clinical-trials/show/NCT01282034).

Osteochondroinductive signals

Induction of osteochondral tissue formation refers to the capacity of many physiological stimuli to stimulate stem cells or immature bone/cartilage cells to grow and mature, forming healthy tissue. Most of these stimuli are protein molecules (e.g., growth factors and cytokines). Much interest has centered on a group of proteins called Bone Morphogenetic Proteins (BMPs), which have a powerful effect in stimulating new bone/cartilage formation, but they are not the only option for osteochondroinduction [71, 86]. Many other growth factors are now known to have specific effects on the cell growth, migration, and development. Some of the factors that are most likely to have clinical value in the future are as follows: Epidermal Growth Factor (EGF), Platelet-Derived Growth Factor (PDGF), Fibroblast Growth Factors (FGFs), Parathyroid Hormone-Related Peptide (PTHrp), Insulin-like Growth Factors (IGFs), Transforming Growth Factor-Beta (TGF-β), and Vascular Endothelial Growth Factors (VEGFs) [26, 47, 89]. Several of these are under active investigation, though none of these works have yet advanced to the point of offering these as routine treatment options to patients. As an example, a recent study has infused a composite scaffold of PCL and HA with TGF-β_3 and transplanted into the rabbit condyle. 3–4 weeks after, all rabbits resumed weithbearing and locomotion. After 4 months, these scaffolds were fully covered with hyaline cartilage in the articular surface, with uniformly distributed chondrocytes in a matrix with collagen type II and aggrecan and recruited roughly 130% more cells into the regenerated articular cartilage than did scaffolds that had not been loaded with TGF-β_3, which instead had only isolated cartilage formation, with reduced thickness and density [56].

The method by which a growth factor is released can have a significant effect on therapeutic efficacy because the dose and spatio-temporal release of such agents at the lesion site is crucial for achieving a successful outcome. Common growth factors delivery methods involve systemic administration or direct injection into the defect site close to or in direct contact to the scaffold [57]. However, as a result of the short half-life of many inductive proteins, this method requires very high doses for therapeutic effect and still may not permit the necessary concentration of the factor to be maintained for the appropriate period of time [38].

Different strategies have been developed to create a controlled release, even if success has been restricted by problems of dosage, lack of full activity of recombinant factors and the inability to sustain the presence of the factor for an appropriate length of time [73]. Moreover, spatially controlled delivery of growth factors in the scaffold is crucial for engineering composite tissue structures, such as osteochondral constructs [98]. One of the most common methods of creating controlled growth factors and/or drug delivery is to utilize the physical properties of the scaffold material to regulate the amount of factor released. The target growth factor is mixed with the scaffold precursors during fabrication. In such systems, the properties of the scaffold, such as pore size or cross-linking density, regulate release by diffusion. For instance, BMP-2 and TGF-β_1-loaded PLGA microspheres were utilized with a gradient scaffold fabrication technology to produce microsphere-based scaffolds containing opposing gradients of these signals. This scaffold, seeded with stem cells, has shown good osteochondral tissue regeneration [19]. Hydrogel scaffolds, based on the polymer oligo(poly(ethylene glycol) fumarate), consisting of two layers: a bone-forming layer and a cartilage-forming layer loaded with TGF-β_1 encapsulated into gelatin microparticles. This approach exerts some effect on cartilage quality in the defect area in a rabbit model and demonstrates the exciting potential of these polymer-based hydrogels as carriers of bioactive agents for tissue repair [37]. In another study, BMP-2 and IGF-I were incorporated in PLGA and silk fibroin microspheres and an arginate gel was fabricated with microspheres incorporated as gradient. Silk microspheres were more efficient in delivering BMP-2, probably due to sustained release of the growth factor. This microsphere/scaffold system presents a novel opportunity for the spatial control delivery of multiple growth factors in a 3D culture environment [98].

Localized gene-therapy approaches to the delivery of inductive factors may circumvent limitations of direct protein delivery. Delivery of genes encoding the inductive factors allows sustained and localized protein production and can be used for either short-term (e.g., transient

transfection of cells) or long-term (e.g., retroviral transduction) delivery [13, 14, 63, 78]. In either case, gene delivery takes advantage of the protein synthesis machinery of the cells to produce the specific bioactive factor. However, the cell colonization of the scaffold remains a tight problem for tissue regeneration in large defect cases.

Recently, the usage of superparamagnetic nanoparticles (MNPs) for biological and medical purposes has been increasing and their biocompatibility is validated by several studies [44, 81, 90]. MNPs are unique in their reaction to magnetic force and these properties have been already used in the last decade for in vitro and in vivo applications (e.g., hyperthermia, contrast agent for MRI, magnetic drug delivery), whereas only few authors proposed approaches for tissue engineering [1, 2, 32]. Considering the employment of a magnetic field for targeted therapy, some limitations are evident in clinical application. In fact, since the magnetic gradient decreases with the distance to the target, the main limitation of magnetic drug delivery relates to the strength of the external field that can be applied to obtain the necessary magnetic gradient to control the residence time of MNPs in the desired area or which triggers the drug desorption [22, 39]. The limits inherent to the use of external magnetic fields can be circumvented by means of internal magnets located in the proximity of the target by minimally invasive surgery [79, 80]. Recently, very innovative tissue engineering approaches with pioneering magnetic scaffolds for osteochondral defect have been developed [8, 93]. Under an external magnetic field, the magnetic moment of the proposed scaffolds enables them with the fascinating possibility of being continuously controlled and reloaded from an external supervising center with tissue growth factors. The scaffolds will work like a fixed "station" that offers a long-living assistance to implanted tissue engineering constructs, providing a unique possibility to adjust the scaffold activity to the personal needs of the patient, overcoming the present difficulties of magnetic guiding. Nanomagnetic targeting represents a promising strategy to guide and accumulate growth factors, drug doses and cells in the scaffold with gradient, and reduce their loss and undesired side effects.

Osteochondrogenic precursor cells

Since only living cells can make tissue, the success of any grafting procedure is dependent on having enough tissue-forming cells in the area. In some situations, the healthy tissues around the graft site will contain a sufficient number of tissue-forming cells. However, in many clinical settings, the number of bone/cartilage-forming cells in the surrounding tissues may be limited. Areas of scarring, previous surgery or infection, tissue gaps, and areas previously treated with radiation therapy are all likely to be deficient in tissue-forming cells.

ACI and M-ACI have been successfully clinically applied to treat focal post-traumatic lesions of the knee joint (see section "Current surgical treatments"). Despite promising clinical results, the use of chondrocytes may be troublesome due to the requirement of large numbers of chondrocytes to fill large defect volumes and dedifferentiation of cultured chondrocytes in vitro. Moreover, the harvest of cartilage for a cartilage biopsy includes two separate operations and presents limitations associated with donor site morbidity [68, 99].

Enormous expectations are associated with stem cells with regard to cell therapy and tissue engineering. Mesenchymal stem cells (MSCs), defined as self-renewal, multi-potent progenitor cells with the capacity to differentiate into several distinct mesenchymal lineages, represent a promising cell source for treating osteochondral defects [3]. They are also known as marrow stromal cells or mesenchymal progenitor cells [12].

Numerous studies have been performed to investigate and improve the in vitro chondrogenesis process (by the use of various growth factors) and potential therapeutic use of MSCs [17, 59]. MSCs from bone marrow can be injected into a graft site or mixed with other components as a composite graft. However, there is limited evidence that scaffold techniques result in homogeneous distribution of cells [42]. Furthermore, the cell yield for bone marrow harvest is relatively small because only 10 to 25 ml of bone marrow can be obtained from humans [40]. A second source of autologous stem cells is the periosteum, but the harvest is invasive and moreover yields a paucity of cells [88].

MSCs derived from the Synovial Membrane (SM) are attracting considerable attention, since they apparently have great chondrogenic potential [16]. The SM is composed of a cellular lining layer adjacent to the joint cavity and a supportive layer that merges with the fibrous layer of the joint capsule. A small SM biopsy represents an easily accessible source of autologous MSCs in the context of an explorative or therapeutic arthroscopy. SM-derived cells from adult human donors of various ages can be expanded in vitro over at least 10 passages maintaining their multi-lineage differentiation potential. They may play a role in the regenerative response during arthritic diseases and are promising candidates for developing novel cell-based therapeutic approaches for post-natal skeletal tissue repair. In fact, when grown in monolayers, the synovial cells exhibited a fibroblast-like phenotype [96], but when cultured in a 3D alginate system, they underwent an immediate chondrogenic switch, even in the absence of growth factors [55]. A very recent study has shown the potential use of SM-derived cells as a cell source for cartilage tissue engineering. Cells were seeded

into clinically relevant agarose hydrogel scaffolds, and they received TGF-β_3 for the first 21 days. The constructs exhibited good mechanical and biochemical properties comparable to native tissue [85].

An alternative source of stem cells is adipose tissue. The adipose tissue contains a large number of stromal stem cells and is an abundant, easily accessible and reproducible cell source for musculo-skeletal regenerative medicine applications [27, 58]. Adipose stem cells (ASCs) have been reported to differentiate along different lineages, including bone, cartilage, fat, muscle, and nerve [84, 101]. Moreover, ASCs have been shown to be immunoprivileged [30] and appear to be more genetically stable in long-term culture compared to BMSCs [15]. Although ASCs are widely used as seeding cells for osteochondral tissue engineering studies [21, 35, 74], several challenges remain before ASCs can be used in everyday clinical practice. Indeed, at present, chondrogenesis and osteogenesis occur slower respect to adipogenesis and also the cell yields are still low, despite these differentiation protocols including several factors similar to the adipogenesis protocols [60]. Any improvement in these differentiation timeframes will make ASCs more attractive for tissue engineering purposes.

The Umbilical Cord Blood (UCB) has been used as a further alternative source of MSCs [64]. The blood remaining in the umbilical vein following birth contains a rich source of hematopoietic stem and progenitor cells and has been used successfully as an alternative allogeneic donor source to treat a variety of pediatric genetic, hematologic, immunologic, and oncologic disorders [10, 28]. Moreover, UCB-derived stem cells showed to have more chondrogenic potential in vitro than the bone marrow MSC based [6]. Cultured in a defined chondrogenic medium supplemented with TGF-β, UCB-derived stem cells present expression of genes typical of cartilage and production of cartilaginous ECM after 2–3 weeks, so that they are becoming an attractive cell source also for cartilage tissue engineering [25]. In addition, UCB-derived stem cells form cartilage and/or bone tissue when combined with different material. Human UCB cells-loaded calcium phosphate ceramic cylinders were implanted in a critical size bone defect in rats. After 12 weeks, a clear bony reconstitution was observed [50]. The same authors proved also the chondrogenic potential of UCB cells by seeding them into gelatin sponges and implanting them in nude mice; after 3 weeks, the implanted cells demonstrated strong chondrogenic differentiation [50]. In another study, UCB-derived cells were seeded onto PGA scaffolds and maintained in a rotating bioreactor with serum-free medium supplemented with TGF-β1. After 12 weeks, the constructs exhibited chondrogenic differentiation displaying histological and functional properties of native cartilage tissue [24].

Suitable fixation

Failure to regenerate the intricate tissue-to-tissue interface has been reported to compromise graft stability and long-term clinical outcome, consequently, the biological fixation or integrative repair of tissues remain a significant clinical challenge [23, 61, 62]. The limited number of publications regarding scaffold fixation is an indication of the lack of attention in this area even if this is a critical step in tissue regeneration.

A significant barrier to clinical translation is how to achieve biological fixation, functional integration, and how to prevent micromotion at the interfaces of the tissue-engineered orthopedic grafts, be it bone, ligaments or cartilage, either with each other and/or with the host environment [72].

At present, in the treatment of small osteochondral lesions, most surgeons do not use any fixation system, the stability of the scaffold being granted only by the fibrin clot and by the congruency between the prepared lesion site and the geometry of the scaffold or they use biocompatible glues (e.g., fibrin glue) as an adjuvant treatment to enhance the scaffold fixation. Recently, several studies have shown that biocompatible glues do not improve the fixation compared with the press-fit technique only [5, 20, 49]. Fibrin glue preserves the scaffold integrity compared with other more invasive fixation methods but shows less adhesion of the scaffold to the cartilage or chondral bone [5].

Suturing of cartilage grafts may cause difficulty in fixation and cartilage may shift and the operation procedure becomes longer. Multiple suture may cause fracture of the cartilage and may lead to resorption in postoperative period [18].

The pin fixation and the transosseous fixation technique have been proposed as alternatives to the conventional suture method [100]. They have been shown significantly higher ultimate failure load, yield load and stiffness than the classic suture technique for the fixation of bioabsorbable scaffolds. At the same time, the results have shown that the material properties of the scaffold have a strong influence on the biomechanical tests; therefore, the results cannot be transferred to the fixation of other matrices.

A different approach using Butyl 2-Cyanoacrylate as cartilage adhesive was proposed to facilitate matrix placement because it bonds strongly and immobilizes easily cartilage grafts [18]. Although it should be easy to apply, biodegradable and should establish a strong and flexible band, this technique is not diffused in clinical applications.

Interdisciplinary approaches that involve materials research and surgical technique development are mandatory to lead to optimal scaffold fixation with limited damage to the scaffolds.

An innovative fixation approach based on magnetic forces firmly holding the scaffold in the implanted position is coming out from a new project conception. The fascinating possibility to achieve efficient scaffold fixation via magnetic forces may provide a very elegant and simple solution to the problems of fixation that many devices present. To reach this aim, magnetic scaffolds are developed and under investigation to verify biocompatibility both in vitro and in vivo [8, 93]. These scaffolds should be enabled by a magnetization, sufficient to activate an attractive force toward selected fixating magnetic objects.

Conclusion

Tissue engineering aims to recreate the native environment to promote the appropriate cell behavior for tissue regeneration. The design of tissue engineering strategies for osteochondral lesions is in increasingly expansion but so far few of the approaches developed was effectively brought to the clinic due to the complexity of the tissue to be regenerated.

Having in mind the challenge to treat ever bigger and complex defects, it is mandatory to be able to control the 3D variable geometry of the articular surface, considering the proportions between bone and cartilage thickness and variation in the curvature radius of the articular surface but also the micro and nanoscale arrangement of cells and ECM within the tissue. In the future, multi-disciplinary osteochondral tissue engineering technology should provide the means to mimic the complex cascade of tissue regeneration in each region of the joint. The development of osteochondroconductive scaffolds, able to be fixed in order to avoid micromotion at the graft-tissue interfaces, together with osteochondroinductive signals and osteochondrogenic precursor cells are the main promising peculiarities necessary to restore function and mechanical features of the osteochondral tissue.

Conflict of interest The authors declare no conflicts of interest.

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