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Editorial Open Access

Osteochondral Regenerative Medicine: Classic Strategies, Current Challenges, and Future Modalities

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Editorial

Articular cartilage (AC) chondral and osteochondral injuries and defects could happen or develop due to many conditions such as advanced osteoarthritis, osteochondritis dessicans, osteochondral fractures, tumors (e.g. oneschondrosarcoma, osteosarcoma), massive trauma, gangrenous and infective ulcers, advanced osteomyelitis, chronic imbalanced weight bearing, degenerative changes, necrosis and other reasons [1,2]. These injuries may include blistering of the cartilage layers, cyst-like lesions within the bone underlying the cartilage, or fracture of the cartilage and bone layers [1]. In most cases, it is often necessary to resect and debride the diseased tissue and the resulting defect should be reconstructed [1-3]. Surgical treatment and improving the healing quality of both chondral and osteochondral lesions are technically demanding. Factors associated with repair response are mainly including depth and size of the defect, patient's age, trauma and mechanical malalignment of the joint [1]. Current options in managing cartilage defects could be divided into conservative and surgical methods. Non-surgical options in enhancing spontaneous cartilage healing include continuous passive motion (CPM), electrical stimulation (ES), lasers and pharmacological agents [1-4]. Although CPM enhances cartilage-healing, the effect is much less obvious in defects > 3 mm in diameter [1]. The role of ES in cartilage-healing is unclear and laser therapy has no beneficial role during osteochondral healing [1,2,4]. Drugs such that might enhance cartilage-healing can be administered systemically, intra-articularly, or locally. In the recent years it has well been stablished that corticosteroids are not beneficial for cartilage repair because they induce arthropathy while hyaluronic acid is effective due to its protective effects and potential modulatory roles on inflammatory mechanisms [1,5].

Bone marrow stimulation (BMS), joint debridement and drilling (JDD), spongialization (Sp), microfracture (Mf), mosaicplasty (Mp), carbon fiber implants (CFI), perichondrial grafts (PG), periosteal grafts (PG), osteotomy (Os) and autologous chondrocyte implantation (ACI) are the current surgical options. The final option is resection with or without an interposition arthroplasty [1,3,6]. Introduction of a non-absorbable material such as CFI, just deep to the subchondral bone (SB) is a concerning issue and has no acceptability these days [1,6]. While BMS, JDD, Sp, Mf, and Os through open arthrotomy or arthroscopic approaches are currently extensively used in the clinical practice, these methods are only palliative with acceptable short to midterm outcome but has no significant role on long term outcome because they only induce fibrocartilage formation in the defect area which has an inferior mechanical properties than the native hyaline articular cartilage [1,3]. Additionally, upon further mechanical loading on the joint, fibrocartilage progressively degenerates with an increase in type I collagen resulting in fibrosis development. It should be highlighted that most of these techniques may only be valuable for chondral defects and these surgical options has no significant role during osteochondral regeneration specifically at the bony part. Further attempts have suggested that ACI and autologous osteochondral transplantation (AOT; e.g. Mp) may have superior value than other classic methods mentioned above [3,6]. Promising results have been reported with both techniques, not only in the knee, but also in other joints such as the ankle. However, both procedures need to violate the integrity of healthy, intact AC at a second location to obtain the cartilage-bone cylinders to be transplanted, or the cartilage to start the cell expansion procedure. This creates the possibility for donor site morbidity, especially if another healthy joint is involved. However, because lower amount of tissue harvesting is needed in the ACI compared to the AOT, the risk of donor site morbidity is lower in the former than the latter one [3,6].

Tissue engineering and regenerative medicine (TERM) is a newer option [7-10]. In fact, ACI was the first attempts in involving the tissue engineering in orthopedic surgery and research [1,2]. The TERM approach in its new concept could be divided into three major categories including tissue scaffolds, healing promotive factors and cells [7,10]. To design a suitable, proper, scientific and effective TERM based strategies, it is necessary to consider the morphology and function of cartilage (chondral part) and subchondral bone (bony part) of osteochondral tissue. Subchondral bone is a porous structure which is mainly made up of trabecular or spongy bone containing bone marrow. The trabecular bone composed of mainly collagen type I as organic component and hydroxyapatite as inorganic component. The direction of the trabeculae is mainly in accordance to the weight bearing loads. Osteoblasts are the active cells producing osteoid tissue. Osteocytes are the mature form of osteoblasts and have less metabolic activity than the osteoblasts. The osteoclasts are the multinucleated cells produced from the aggregation of macrophages or monocytes and are responsible for bone resorption and remodeling [10]. Chondral or cartilaginous part of the osteochondral tissue is a specialized structure that has four layers including superficial, transitional, middle (radial or deep), and calcified zones. Chondroblasts are the active form of cartilage producing cells and the chondrocytes are the mature form of chondroblasts that are mainly responsible for matrix calcification of the calcified zone. Cartilaginous tissue in the AC, is a hyaline cartilage and is mainly made up of Collagen type II, glycosaminoglycans (e.g. chondroitin 4 and 6 sulfate, keratin sulphate), and proteoglycans (e.g. decorin, biglycan, fibromodulin and aggrecan) with less

concentrations of collagen types VI, IX, X, and XI. Cartilage and bone act in close to each other to provide a mechanical functional unit [1,2,11].

The main goals in osteochondral TERM is to 1) provide a native tissue- and also healing environments in the defect area, 2) provide a temporary function until the new tissue replace and/or incorporate with the TERM based grafts, and 3) induce, improve, enhance and accelerate the formation of functional tissue in the injured area with a comparable structure and function to the normal tissue. In this approach, tissue scaffolds may be a temporary house for the inflammatory- and mesenchymal cells to migrate, proliferate, differentiate and produce matrix in the injured area [7,10,12]. Recently, biphasic or multiphasic scaffolds have been placed in the focus of many studies [13,14]. The biphasic scaffolds have two distinct layers including bony- and cartilaginous parts. In the multiphasic scaffolds, more layers are designed. For example, in the simplest form of a multiphasic scaffold, an intermediate layer is designed between the cartilaginous and bony parts to separate the healing environments of the bony zone with the cartilaginous zone [13,14]. The structure of tissue scaffolds based on their biodegradation behavior could be porous or non-porous. Rapid absorbable scaffolds are normally absorbed in the recipient site after 20 to 60 days based on the materials used for their fabrication [7,10]. Long absorbable scaffolds may be degraded after 6 months. Surly, non-absorbable scaffolds would not be degraded even after many years [7,10]. In the recent years, three strategies have been developed for fabricating tissue scaffolds. In the first strategy, the synthetized polymeric materials (e.g. poly glycolic acid, polygalactin 910, poly-l-lactide acid, polydioxanone) are used to fabricate tissue scaffolds [10,15]. The scaffolds produced from these materials have excellent functional properties while having low biodegradation and to some extent, they may be non-biocompatible [7]. Due to their variable biocompatibility and low biodegradability, such scaffolds if produced from synthetic polymeric materials alone, are totally absorbed after months to years or may be rejected from the host through protrusion of the scaffolds from the injured area by the newly regenerated tissue. In such circumstances, it is often necessary to remove the rejected scaffold by a revision surgery which is a considerable limitation [10]. In the second strategy, the natural based biomaterials (e.g. collagen, gelatin, hyaluronic acid, and hydroxyapatite) are used to fabricate the tissue scaffolds [10]. The scaffolds produced from rapid natural based biomaterials are normally degraded after 20 to 60 days of implantation and have excellent bioactivity, biocompatibility, biodegradability, and incorporative properties with the regenerative tissue. However, their major limitation is that they may provide inferior short term temporary function for the treated patients [7,10]. In the third strategy, by combination of natural and synthetic polymeric materials, it is possible to provide the temporary functionality, bioactivity, optimum biocompatibility and biodegradability and healing incorporative properties for the hybrid scaffolds [10]. However, in this latter strategy, the concentration of the low or non-biodegradable synthetic materials should be as least as possible to overcome the limitations of synthetic scaffolds.

Based on the structure and function of the native osteochondral tissue, it is reasonable to design natural based scaffolds for osteochondral regenerative medicine. Acellularization and perfusion are classic TERM based strategies; in the former, the cellular components and in the latter, other antigenic components could be removed from the xeno- or allograft tissues, providing a biocompatible and effective acellularized and safe tissue matrix having all the necessary basic molecular components for the osteochondral regeneration [10,16]. The acellularized scaffolds may be the same as the tissue to be replaced (osteochondral bi-layered tissue) or may have different origin (e.g. tendon, skin, demineralized bone matrix). However, in the case of osteochondral injury, it seems the use of acellularized osteochondral bi-layered tissue matrix may be more reasonable choice than acellularized tendinous matrix because in the former, collagen type I and hydroxyapatite are present only at the bony part while the collagen type II and chondroitin sulfate are present at the cartilaginous part. In contrast, the tendinous matrix and demineralized bone matrix are mainly composed of collagen type I, which is not beneficial for chondral tissue regeneration [10]. Acellularized tissue matrices have inferior but acceptable functionality short term after implantation but because they are gradually replaced by the new tissue and some of their parts are accepted as a new part of the regenerated osteochondral tissue, they collaborate in the healing process, effectively [17,18]. Such acellular scaffolds have low porosity but because they are rapidly degraded by the host, their low porosity is not a major concern [18]. It is also possible to fabricate the natural based scaffolds that have acceptable porosity and controllable biodegradation by combination of the natural molecules. Multiphasic scaffolds may be a proper approach in this case because the major problem in osteochondral tissue engineering is that both the subchondral bone and overlying cartilage should be regenerated at the same time and therefore, their healing environment should be separated from each other [19,20]. If this matter would not be considered, then the osteochondral tissue may not be regenerated and the resulting tissue may be a fully calcified tissue (bone healing is predominant) or a cartilaginous tissue (cartilage healing is predominant). In both cases, the healing is failed [1,2]. An attractive and practical design of a multiphasic scaffold is that, the scaffold should have three layers including bone-, intermediate- and cartilage parts. The bony part could be composed of collagen type I and hydroxyapatite, the intermediate part could be a combination of collagen type I and II, hydroxyapatite and synthetic polymeric degradable nanofibers, and the cartilage part could be a combination of hyaluronic acid, chondroitin 4 and 6 sulfate and type II collagen.

Healing promotive factors (HPFs) particularly the growth factors are essential for an effective healing to occur and to differentiate the cells and matrix to a functional tissue [10,21]. By embedding the HPFs with the tissue scaffolds, a bioactive graft could be designed with more healing efficacy than a simple scaffold [7,22,23]. Although several growth factors have been shown to be effective during osteochondral tissue regeneration, transforming growth factor beta, bone morphogenetic proteins types 2, 4 and 7, and insulin like growth factor type I have the determinant roles [7,23]. The major problem is that these growth factors have roles on both bone and cartilage and in the case of osteochondral healing, because bone and cartilage are regenerating at the same time, these growth factors may not be able to differentiate the cartilage from bone [11,13,20]. For this reason we suggest the multiphasic scaffold with a designed intermediate separating layer as a possible solution for this limitation. It is reasonable to embed the mentioned growth factors in the cartilage part and to provide osteoinduction in the bony part of the scaffold, alternative HPFs such as statins, strontium, alendronate, platelet rich plasma, bioactive glass and nano-crystalline hydroxyapatite can be used [7,10,23].

Seeding, culturing and application of cells and stem cells with or without scaffolds have significant beneficial roles during osteochondral healing [24-28]. Classically, active chondrocytes harvested from non-weight bearing articular cartilage may be the only reliable option for

clinical practice these days but it should be highlighted that these cells are mature cells and may not be able to effectively synthetize the matrix required for different stages of osteochondral healing and regeneration [2,3,6,7]. In addition ACI technique only provides cells for the cartilage layer however, for osteochondral regeneration it is beneficial to provide osteoblasts for the bony part, too. Based on these information, there are a number of strategies that could be designed for osteochondral TERM. Using bi- or multiphasic scaffolds combined with necessary HPFs; active chondroblasts should be seeded and cultured on the cartilage part while the osteoblasts should be seeded on the bony part in order to close the healing environment to the native cartilage and bone, respectively. It is also possible to co-culture the active chondroblasts and osteoblasts with stem cells to reduce the number of autologous cells to be harvested from the patient's body. The valuable and widely accepted source for stem cells is mesenchymal stem cells (MSCs) which are majorly harvested from bone marrow (first priority) and adipose tissue (second priority) [16,19,27,28]. In these days, it is not acceptable to applicate undifferentiated MSCs for osteochondral regeneration because undifferentiated stem cells may be differentiate to other cells particularly the fibroblasts (responsible for fibrosis of the injured area) and adipocyte (responsible for adipose tissue formation in the injured area) [10,14,21,28]. The MSCs can be used in a differentiated or pre-differentiated manner by different methods including 1) culturing in commercially available chondrogenic (resulting in differentiating to chondroblast) or osteogenic (resulting in differentiating to osteoblast) culture mediums, 2) culturing in a costume made cell medium supplemented with different growth and differentiating factors, 3) co-culturing with chondroblasts and osteoblasts and 4) a combination of them.

For osteochondral TERM, the pre-differentiated chondrogenic and osteogenic MSCs have superiority because these cells are not aged and are in a pre-differentiating state thus they are active in the injured area [10,24,26].

The cells not only could be seeded on the scaffolds surface but also it is possible to culture them onto (two dimensional) and into (three dimensional) the scaffold [9,10,24]. Cell seeding provides lower concentration of cells in the scaffold but the cells are not aged. In contrast, cell culture onto and into the scaffold, provides adequate number of cells for tissue regeneration but because the cells are more likely going to be aged, their matrix production and effectivity decrease [24]. Using pre-osteogenic chondrocytes, together with active osteoblasts for the bony part and pre-chondrogenic chondrocytes with active chondroblasts for the cartilage part, seeded and or cultured on the multiphasic bioactive grafts may be a suitable approach for osteochondral TERM strategy.

The final solution is the scaffold free strategies in which the autologous stem cells are harvested from the patients, expanded and cultured in the chondrogenic medium for cartilage layer and osteogenic medium for bone layer, letting the cells to differentiate and produce cartilage and bone matrices, respectively. In this case, a viable graft is produced and directly transplanted in the osteochondral defect [20,27,29]. Although several strategies have been introduced and suggested in this editorial paper, most of them are still under investigation, have their limitations and are primitive. Future investigations may address which of these strategies have more reliability and effectiveness on treatment of osteochondral defects.

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