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Editorial

Cartilage Repair and Regeneration: Focus on Multi-Disciplinary Strategies—Highlight on Magneto-Responsive Techniques

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Abstract: This editorial focuses on the interesting studies published within the present *Special Issue* and dealing with the innovative multi-disciplinary therapeutic approaches for musculoskeletal diseases. Moreover, it highlights the noteworthy magneto-responsive technique for a cartilage regeneration scope and reports some interesting studies and their outcomes in this specific field.

Keywords: tissue engineering; 3D bioprinting; ChondroMimetic; cartilage regeneration; osteochondral repair; mosaicplasty; matrix-assisted autologous chondrocyte transplantation; magneto-responsive techniques; biomechanical stimuli; multi-disciplinary approach

1. Introduction

The articular cartilage represents an incredibly complex multi-layered tissue, characterized by avascular and aneural structure, which limits its regenerative properties. Once injured, cartilage leads to its progressive degeneration with severe consequences such as the onset of chronic degenerative disorders like osteoarthritis (OA). The latter determines articular pain and stiffness, until the total disability of the joint in advanced stages [1]. Until now, no therapeutic strategy exists for this complex disease and the necessity to find the optimal approach for the cartilage regeneration still represents a big challenge.

Recently, a lot is known concerning the onset and the triggering factors of OA, as well as the main events at the base of its progression. It is well known that this severe disorder represents a multifactorial, progressively degenerating pathologic event that, principally, affects the cartilage tissue, but that expands to all the tissues of the joint [2]. It appears evident that the most promising therapeutic strategy for this complex disorder, is represented by a multi-disciplinary and multi-targeted approach.

2. Highlights on the Studies Published in the Present Special Issue: Emerging Therapies for Osteochondral Regeneration

The most promising approach for osteochondral repair is certainly represented by the tissue engineering, which aim is to create a cartilage and bone tissues able to replace the injured ones. This technique seems very encouraging, if it were not for the fact that the articular cartilage tissue has a multilayered complex structure, where every layer possesses its own spatial heterogeneity, different cell distribution and different mechanical properties [1]. With the advancement of the 3D bioprinting, the engineered grafts and the fabrication of the gradient scaffolds, enhanced their biomimicry and, consequently, their functionality and efficacy. In an interesting study by Dimaraki et al. [3] the authors bioprinted a scaffold with different zonal cell densities to mimic the organization of the complex three-layered articular cartilage structure. They observed a successful formation of a new cartilage-like tissue with a cell-density dependent zonal gradient. In another study by Berta et al. [4] a cell-free biphasic scaffold (ChondroMimetic) was evaluated for long-term outcomes in the treatment of osteochondral defects. The authors observed a cartilage-like repair tissue formation and clinical improvement at 7.9 years post-implantation. Zaffagnini et al. [5]

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compared the clinical outcomes of mosaicplasty and matrix-assisted autologous chondrocyte transplantation (MACT) at long-term follow-up (12 years post-surgery), concluding that both of these surgical procedures give satisfactory clinical results. Moreover, the authors suggest that MACT is the most suitable approach for the treatment of larger lesions. Indeed, many factors have to be considered when considering different strategies for the osteochondral defect treatment. The studies conducted in the field of histopathological aspects of musculoskeletal diseases, represent a pilot studies for the development of successful regenerative medicine approaches. In the study carried out by Desando et al. [6], which compared the histopathological features of osteochondral units, obtained from patients with both non-traumatic femoral head and with post-traumatic femoral head osteonecrosis. The authors reported substantial differences among them and suggested a multi-disciplinary and multi-targeted approach for osteonecrosis treatment based on its etiology.

Moreover, developing satisfactory strategies for cartilage regeneration requires deeper knowledge on biological systems. When considering the cartilage engineering strategy based on the use of mesenchymal stem cells (MSCs), the environment in which these cells are destined to promote chondrogenesis, has to be well-thought-out. The mechanical stimuli experienced by chondrocytes within the joint play a pivotal role in chondrogenesis and the development of bioreactors able to mimic the biomechanical load on cells in vitro, becomes of fundamental importance in developing new, multi-disciplinary strategies for cartilage regeneration approaches as suggested by Ravalli et al. [7].

3. Magneto-Responsive Techniques for Cartilage Regeneration

With the development of biotechnology, other promising techniques have been developed such as magnetic cell manipulation, achieved by the synergy between magnetic objects and magnetic field [8,9]. In general, there are four techniques based on the magnetic cell manipulation for the tissue engineering approaches. The first one includes the magnetic field-based guiding of the cells to the targeted site, which permits to the relatively small number of cells (i.e., magnetic mesenchymal stem cells) to accumulate at the level of the defect site and promote cartilage regeneration [10,11]. The second one is based on the enhancement of the seeding ability of cells within the scaffold, which permits the cells to migrate symmetrically and to promote the cell condensation, providing a suitable environment for cell proliferation and differentiation [12]. The third technique regards the formation of magnetic scaffolds, where the magnetic force is used to assemble the 3D structure to mimic the native tissue [13,14]. This technique based on magnetic patterning, works across a range of materials (e.g., hydrogels) and diamagnetic objects (e.g., living cells, drug delivering microspheres, etc.), characterized by differential magnetic susceptibility, with the potential to predictably position these objects in 3D materials, in response to brief magnetic field application. It confers several advantages, including remote control ability, sufficient cell density and cell adhesion enhancement, permitting one to achieve a very good grade of engineered tissue biomimicry [8,9]. Zlotnik et al. [15], demonstrated that a naturally diamagnetic objects, comprising living cells, can be predictably positioned throughout the 3D hydrogel. In this study, the magnetic susceptibility of the latter was enhanced by the addition of magnetic contrast agent (gadodiamide). After the cells achieved the required position, by the brief exposure to magnetic field, they were 'locked in' by a photo-crosslinking method. Afterwards, the magnetic contrast agent was washed out of the hydrogel to not interfere with the long-term cell viability. In the study, the authors applied this method to engineer cartilage constructs with a depth-dependent cellularity, mirroring that of the native tissue. The fourth strategy is based on guiding cell assembly into sheet-like structures to stack layer-by-layer, used for the formation of scaffold-free 3D cell culture. In this way, magnetic-labeled cells can be guided to a targeted location and form 3D arrangements in a convenient microenvironment to mimic tissue properties without the use of scaffolds [16,17].

In addition, it has been widely demonstrated that mechanical forces acting as an additional tool to mimic the in vivo environment are also applied to improve cartilage reconstruction as suggested above [7,18]. Magnetic nanoparticles represent the excellent candidates to apply remote magnetic-induced mechanical stimulation. Luciani et al. [19] used magnetic MSCs to enhance their seeding density and condensation into the scaffolds subjected to dynamic bioreactor. The results showed that MSC differentiation was markedly improved. Son et al. [20] exposed magnetic nanoparticle-labeled MSCs to static magnetic field and magnet-derived shear stress, demonstrating higher chondrogenic differentiation efficiency and no hypertrophic effects. Further, Hou et al., [21] demonstrated that the multifunctional hyaluronic acid-graft-amphiphilic gelatin microcapsules, loaded with the superparamagnetic iron oxide nanoparticles and chondrocytes, subjected to static magnetic field and magnet-derived shear stress, were able to stimulate chondrogenesis and fabricate cartilage tissue-mimetic pellets.

4. Conclusions

Several approaches have been evaluated for the cartilage regenerative outcomes including 3D bioprinting, cell-free biphasic scaffolds, mosaicplasty, MACT, and stem cell therapy [3–5,19,22]. Many of them giving encouraging results. However, the innovative multi-functional approaches in this field are still needed to overcome the existing limits. The most promising strategy for the cartilage regeneration seems to be represented by a multi-disciplinary approach based on tissue engineering combining innovative techniques such as formation of magneto-guided zonal cell gradient 3D structures to mimic the native tissue, application of biomechanical stimulation to reproduce the native environment of the joints, and the use of exogenous biomolecules (i.e., drug delivery scaffolds) able to stimulate cell differentiation and counteract the pathologic milieu of the affected joints.

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