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EDITORIAL

Current status of regenerative medicine in osteoarthritis

STEM CELLS, EXOSOMES, AND GENES

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The high prevalence of osteoarthritis (OA), as well as the current lack of disease-modifying drugs for OA, has provided a rationale for regenerative medicine as a possible treatment modality for OA treatment. In this editorial, the current status of regenerative medicine in OA including stem cells, exosomes, and genes is summarized along with the author's perspectives. Despite a tremendous interest, so far there is very little evidence proving the efficacy of this modality for clinical application. As symptomatic relief is not sufficient to justify the high cost associated with regenerative medicine, definitive structural improvement that would last for years or decades and obviate or delay the need for joint arthroplasty is essential for regenerative medicine to retain a place among OA treatment methods.

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Osteoarthritis (OA) is a disease that can cause misery to affected patients with a deteriorated quality of life from significant pain and loss of joint function.[1] While the progression of OA takes a chronic course, unlike rheumatoid arthritis, there are currently no disease-modifying drugs on the market that can effectively alter the natural history of OA and offer structural improvements in damaged articular cartilage.[2] Although joint arthroplasties provide a final solution to end-stage disease, these procedures cannot be recommended to younger patients with early- to mid-stage OA. Further, while there are differing attitudes on artificial joints depending on cultural background, most patients prefer to have their joints treated by regenerating damaged tissue if possible. The high prevalence of OA as well as the current lack of disease-modifying drugs has provided a rationale for considering regenerative medicine as a possible treatment that can alter the course of OA through the structural modification of damaged articular cartilage.

Regenerative medicine efforts for OA can be collated with the attempts for cartilage regeneration that started in the 1980s. Cell-based cartilage tissue engineering approaches have been used to regenerate focal articular cartilage defects, with varying degrees of success. Autologous chondrocyte implantation (ACI) has been employed with varying results in younger individuals with chondral lesions of considerable size.[3] Unlike chondral defects caused by traumatic events, OA is generally associated with large, diffuse involvements of articular surfaces, and often causes generalized alterations in joint homeostasis that can interfere with chondrocyte-driven regeneration. The diffuse joint involvement and inflammatory environment in OA make ACI an unsuitable option, not to mention the biological and technical shortcomings of ACI.[4]

Adult stem cells, namely mesenchymal stem cells or mesenchymal stromal cells (both abbreviated MSCs), have been the mainstay of translational studies or clinical applications in regenerative medicine for OA. While MSCs from bone marrow have been most extensively investigated, those derived from adipose tissue or umbilical cord blood have their own distinct advantages. One of the reasons why MSCs were thought to be more suitable for OA is their anti-inflammatory and immunomodulatory properties, which may provide a local environment more suitable for the regeneration

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of damaged articular cartilage, either with transplanted MSCs or with endogenous cells mobilized by paracrine growth factors released from MSCs.[5]

The original hypothesis and expectation of cell therapy for cartilage regeneration was that the implanted cells would survive, engraft to the chondral defects, and differentiate into articular chondrocytes that would subsequently produce the extracellular matrix. The cell therapy would thus achieve structural modification of the damaged joint by regenerating articular cartilage, which might also eventually supplant conventional treatments for OA.[6] Therefore, early experimental studies for MSC-based cartilage regeneration focused on chondrogenic induction from MSCs.[7-9] Numerous studies were performed to induce chondrogenesis from MSCs by the appropriate combination of growth factors or transforming cells by the transfer of chondrogenic genes.[4,6] Other studies also investigated the application of biomechanical stimuli to enhance chondrogenic differentiation from MSCs.[10,11] As one distinctive shortcoming of MSCs as a chondrogenic cell source was early induction of hypertrophic markers such as type X collagen,[12,13] great efforts were made to devise ways to suppress hypertrophy in MSC chondrogenesis.[4,6]

The tracking of administered cells is essential for understanding the mode of action in cell therapy. While engraftment and differentiation to chondrocyte were purposed in the beginning, it became apparent that intra-articularly administered cells survived only transiently and underwent rapid cell death,[14] which was also reported from stem cell implantation in other tissues such as the myocardium. Most intra-articularly administered stem cells undergo rapid cell death, surviving from three days to several weeks depending upon the mode of administration and the local environment.[2,4] Paracrine factors that are released before undergoing apoptosis predominantly exert immunosuppressive and anti-inflammatory activity rather than chondrogenic effects. The rapid death of implanted cells is not limited to MSCs. Chondrocytes also undergo rapid clearance within two weeks when injected into joints.[14] Interestingly, stem cells survived longer when focally implanted rather than injected.[15] The rapid death of administered cells in vivo makes the efforts for chondrogenic differentiation or hypertrophy inhibition in vitro quite meaningless. Instead, the focus of research can then move to the prolongation of survival of implanted cells that could exert prolonged paracrine effects and/or engraftment with chondrogenic differentiation.[6] For example, adipose stem cells (ASCs) in spheroid form survive longer post-injection than ASCs that are injected in a free, single-cell suspension. These findings suggest that a sort of communication or interaction between the cells can promote intra-articular cell survival.[16] Also, our preliminary experiments demonstrated that ASCs immobilized on a focal chondral defect using a strong bioadhesive (mussel adhesive protein) showed longer-term survival than those fixed using a weak adhesive such as fibrin glue. These results indicate that stem cells can survive longer when forced to stay at the site of implantation. While it is not yet proven that these preliminary findings of prolonged cell survival may be translated into tangible differences in clinical application, the concept deserves further inquiry and investigation.

While not of scientific category, it is worth mentioning autologous bone marrow aspirate concentrate (BMAC) and platelet-rich plasma (PRP). Both BMAC and PRP have been used for a variety of musculoskeletal conditions including bone and tendon regeneration, fracture healing, and the treatment of tendinitis, in addition to OA treatment for cartilage regeneration. As these are classified as procedures and do not need approval from regulatory agencies, they have been used in private clinics rather than academic institutions. While various results have been reported, no scientific society including Osteoarthritis Research Society International (OARSI), American Academy of Orthopaedic Surgeons (AAOS), American College of Rheumatology (ACR), and European League Against Rheumatism (EULAR) currently recommends these for OA treatment. While the mode of action has not been well investigated, paracrine factors secreted from BMAC and PRP are attributed to their regenerative effects.[17-20]

The other field arising in regenerative medicine is the application of exosomes or extracellular vesicles (EVs). EVs are lipid bilayer-delimited particles that are naturally released from a cell and, unlike a cell, cannot replicate. They carry a cargo of proteins, nucleic acids, lipids, metabolites, and even organelles from the parent cell. As the paracrine action of MSCs is mostly explained by EVs secreted by MSCs, EVs isolated from MSCs can be used in place of MSCs per se for regenerative medicine for OA. When you expect only paracrine effects with intra-articular injection, not counting on cell survival and engraftment, the injection of isolated EVs can offer a simpler and safer alternative. Also, it may offer tremendous possible advantages in getting through the regulatory process. Nevertheless, there are very few translational studies, let alone clinical studies, that have proved the efficacy of EVs in OA treatment. In addition, isolation of large quantity is currently still a very expensive procedure. However, the above-mentioned advantages of EVs in application will draw much attention in future research.[21,22]

Finally, since first reported in the late 1990s by Pelletier et al,[23] the interest in gene therapy for treating OA has waxed and waned. There has been skepticism that gene therapy is an excessive modality of treatment in non-lethal, benign diseases such as OA. The safety of gene therapy has always been a concern, as most investigations employed viral transduction methods. Nevertheless, the transfer of anti-inflammatory genes such as interleukin-1 receptor antagonist and transforming growth factor-β has been reported in clinical trials despite these worries.[24,25] Because ex vivo gene therapy was mostly used, the

prolonged expression of the transferred genes was not realized with the death of the implanted cells.[6] This rapid cell death has rendered ex vivo gene transfer an augmentative procedure to cell therapy, where the issue of safety becomes of less concern. On the other hand, recent advancements in the efficiency of non-viral gene transfer and safer viral gene transfer including adeno-associated virus may make the direct in vivo gene transfer of chondrogenic and anabolic genes possible in the near future, which would add gene transfer to the armamentarium of regenerative medicine for OA.

In summary, while there is a tremendous interest in regenerative medicine to treat OA, there is very little evidence proving the efficacy of the modality in clinical application. Symptomatic relief is not sufficient to justify the high cost associated with regenerative medicine. Definitive structural improvement that would last for years or decades and obviate or delay the need for joint arthroplasty is essential for regenerative medicine to retain a place among OA treatment methods. Also, the focus or mainstay of regenerative medicine in OA can be fluid. The current interest in stem cell therapy can move to other items including exosomes or small molecules if well-controlled, good-quality trials show results that do not meet the high expectations due to high cost and complicated regulatory processes.

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