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Original Research Paper

Anatomy

CARTILAGE REGENERATION IN OSTEOARTHRITIS – II: A REVIEW OF NEWER TECHNIQUES

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KEYWORDS :

The osteoarthritis is the common degenerative joint disease. The etiology of OA is complex and involves a variety of factors, including genetic predisposition, acute injury and chronic inflammation. The entire joint is involved in the disease process. This leads to lot of symptoms in the patient suffering from OA. The regeneration of articular cartilage remains one of the main challenges, particularly in an actively inflammatory environment. The recent strategies for osteoarthritis treatment are based on the use of different therapeutic solutions such as cell and gene therapies and tissue engineering(1).

Aging is associated with progressive loss of skeletal stem-cell (SSC) and diminished chondrogenesis in the joints. Activation of skeletal stem cell in the joint environment across the chondral surface of can be stimulated. This can lead to regenerative response. But this process also involves the microfracture surgery which leads to formation of fibrous tissues. In addition, if there is co-delivery of bone morphogenetic protein 2 and vascular endothelial growth factor leads to chondrogenesis(2).

Cartilage by nature has poor regeneration capacity. Cartilage tissue being avascular does not incite an immediate inflammatory response when there is an injury/lesion, unlike other tissues with vascular supply. As such the key players of tissue regeneration namely stem cells are not recruited to the site of lesion and hence it becomes a necessity to use stem cells isolated from other sources to aid cartilage regeneration. Stem cells are undifferentiated cells that are capable of self-renewal and differentiation towards a specific cell lineage. Stem cells have variable differentiation potential and accordingly they can be classified as pluripotent (Embryonic stem cells, ESCs, iPSCs) as these cells can give rise to almost all the tissues of the human body or multipotent (eg. adult and foetal MSCs) as these cells can be differentiated only into specific cell lineages. Stem cells are therefore an attractive choice for regenerative medicine applications and it is essential to understand the different types of stem cells that have the potential to be used for cartilage regeneration(3).

Tissue engineering and regenerative medicine is intended to facilitate the restoration of many tissues including those of the musculoskeletal system. Effective articular cartilage regeneration with the use of stem cells. Harvest of multinucleated cells from within the bone-marrow and direct injection to the cartilage defect area using the bone-marrow aspirate concentrate (BMAC) system seems to me one of the better options for the same.

Mature chondrocytes exhibit plasticity, regaining the capacity to re-enter the cell cycle and to dedifferentiate and transdifferentiate. Alterations in chondrocyte phenotypic modulation promote abnormal cartilage repair. Osteoarthritic chondrocytes may remain in an immature dedifferentiate state. Age-related factors such as senescent cells (SASP factors) may trigger tissue repair and remodelling by controlling cell reprogramming and dedifferentiation during wound healing. SASP factors, when chronically present, may negatively affect the control of redifferentiation into terminal differentiation of cells to avoid fibrosis. New disease-modifying osteoarthritis drugs that promote chondrogenic differentiation, and therefore redifferentiation, show high efficacy by promoting cartilage regeneration in animal models with osteoarthritis(4).

huCB-MSC's is a novel medicinal product composed of allogeneic human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs). Application of the allogeneic hUCB-MSCs-based novel medicinal product appears to be safe and effective for the regeneration of durable hyaline-like cartilage in osteoarthritic knees(5). Patients with Kellgren-Lawrence grade 3 osteoarthritis were enrolled in this clinical trial and composite culture of hUCB-MSCs and hyaluronic acid hydrogel was applied to the lesion site. Maturing repair tissue was observed at the 12-week arthroscopic evaluation. The histological findings at 1 year showed hyaline-like cartilage. MRI at 3 years showed persistence of the regenerated cartilage.

Intra-articular corticosteroid injections (IACI) are commonly used interventions for pain relief in patients with knee osteoarthritis (OA). Biomarkers may be helpful in further elucidating how IACI exert their effect. The aim of this study is to look at the response of biomarkers of cartilage and bone metabolism after IACI in knee OA. baseline uCTX-II values and the change in uCTX-II from baseline to 3 weeks post injection correlated with radiographic severity of joint space narrowing, but not osteophyte grade. No association between uCTX-II and pain was observed. This observational study suggests that IACI in knee OA may reduce cartilage degradation in the short term(6).

The meniscus, articular cartilage (AC), and nucleus pulposus (NP) are all significant tissues in the progression of pathologies such as osteoarthritis. What defines these three tissues as unique compared to other tissues, and subject to regenerative approaches, is their overall avascularity, inability to heal properly in vivo, and difficult clinical and translational remediation(7).

Novel biological therapies that can effectively treat joint and spine degeneration are high priorities in regenerative medicine. Mesenchymal stem cells (MSCs) isolated from bone marrow (BM-MSCs), adipose tissue (AD-MSCs) and umbilical cord (UC-MSCs) show considerable promise for use in cartilage(8).

The efficacy of MSC-based therapies which was previously predicated on the chondrogenic potential of MSC is increasingly attributed to the paracrine secretion, particularly exosomes. Exosomes are thought to function primarily as intercellular communication vehicles to transfer bioactive lipids, nucleic acids. MSC exosomes, and its mechanisms of action in cartilage repair has been reported to be immunomodulatory and regenerative potency in the cartilage injuries and osteoarthritis(9).

In cartilage regenerative medicine, growth factors are commonly used to induce chondrogenic differentiation of stem cells. A recently discovered small-molecule compound, kartogenin (KGN), has been proven to be a chondrogenic and

chondroprotective agent and is more effective in inducing cartilage regeneration when compared with growth factors(10).

Although lacking intrinsic reparative ability, articular cartilage has been shown to contain a population of stem cells or progenitor cells, similar to those found in many other adult tissues, that are thought to be involved in the maintenance of tissue homeostasis. These so-called cartilage-derived stem/progenitor cells (CSPCs) have been observed in human, equine and bovine articular cartilage(11).

Halofuginone attenuates OA progression by inhibition of subchondral bone TGF- activity and aberrant angiogenesis as a potential preventive therapy for OA. proteoglycan loss and calcification of articular cartilage were significantly decreased in halofuginone-treated ACLT rodents compared with vehicle-treated ACLT controls. Halofuginone reduced collagen X (Col X), matrix metalloproteinase-13 and A disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS 5) and increased lubricin, collagen II and aggrecan(12).

Hydrolysate Collagen (HC) consists of small peptides with a molecular weight lower than 5.000 Da. produced from gelatinization and subsequent enzymatic hydrolysis of native collagen which is found in rich collagenic animal tissues. HC ingestion therapeutical effects on some collagenic tissues as cartilage, bones and skin. HC stimulates collagenic tissue regeneration by increasing not only collagen synthesis but minor components (glycosaminoglycans and hyaluronic acid) synthesis(13).

Adipose tissue is derived from the mesoderm during embryonic development and is present in every mammalian species, located throughout the body. Adipose-derived stem cells provide a promising future in the field of tissue engineering and regenerative medicine. Due to their wide availability and ability to differentiate into other tissue types of the mesoderm-including bone, cartilage, muscle(14).

Intra-articular injection of autologous adipose tissue derived MSCs (AD-MSCs) was given to patients with knee osteoarthritis. The pain scores improved at 6 months after injection in the high-dose group. The size of cartilage defect decreased while the volume of cartilage increased in the medial femoral and tibial condyles of the high-dose group(15).

Stem cells intra-articular injection therapy showed a potential therapeutic superiority to reduce OA development. miR-140-5p was confirmed as a critical positive regulator in chondrogenesis. hUC-MSCs overexpressing miR-140-5p have better therapeutic effect on osteoarthritis. Intra-articular injection of high 140-MSCs numbers reinforces cells assembling on the impaired cartilage surface and subsequently differentiated into chondrocytes(16).

The growing need for early diagnosis and higher specificity than that which can be achieved with morphological MRI is a driving force in the application of methods capable of probing the biochemical composition of cartilage tissue, such as sodium imaging. Unlike morphological imaging, sodium MRI is sensitive to even small changes in cartilage glycosaminoglycan content, which plays a key role in cartilage homeostasis. Sodium MRI has great promise as a non-invasive tool for cartilage evaluation(17).

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