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EDITORIAL

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Custom tailoring of Cell therapies to address cartilage damages efficiently

Among the reported regenerative approaches to address cartilage damage such as injection of different growth factors, molecules, cell-based therapies, and concurrent surgical maneuvers to aid regeneration, each one has its merits and limitations. Bone marrow stimulation by microfracture and mosaicplasty/osteochondral grafting are the common surgical approaches to aid regeneration, while growth factor/molecule-based therapies include injection of platelet-rich plasma (PRP), hyaluronic acid (HA), bio-active growth factors and MicroRNA-based therapeutics. Established cell therapy procedures like the Autologous Chondrocyte Implantation (ACI) use chondrocytes alone, while Matrix Associated Chondrocyte Implantation (MACI) is an umbrella term that combines chondrocytes and other cells/stem cells with different scaffolds[1].

In case of bone marrow stimulation, microfracture is not very successful as it does not reach the large vessels in the bone marrow, which is the richest source of cells to repair the defect[2]. Further, the repair process produces a fibrocartilage to fill the defect. Autologous osteochondral grafts have been reported to have better durability than microfracture, as it tends to address the underlying bone defect as well[1]. PRP-based trials have mostly reported improvement in subjective scores such as pain relief, and functional improvement whereas, only few studies have shown objective improvement. Nevertheless, the efficacy of PRP is unpredictable due to the highly heterogeneous nature of the reported studies, especially severity of damage, demographics, and varying composition of PRP preparations[1]. When looking into other bio-active agents, while miRNA has not entered the phase of human clinical studies[3], HA-based therapeutics have shown inconsistency of results in clinical studies with many, reporting effects akin to Placebo[4].

While coming to cell therapies, they have evolved over a period with four generations of approaches. In the first generation, chondrocytes as suspension are injected under the periosteal membrane; in the second generation, chondrocyte suspension is injected under a collagen membrane. The third generation approach employs *in vitro* cultured chondrocytes implanted along with porous matrix/scaffold and the fourth generation being the latest array, wherein chondrocytes or other types of stem cells are implanted using different maneuverers combined with biomaterials and scaffolds as one stage procedure, though the categorization of fourth generation does not have clarity yet[1]. The first and second generation approaches without the matrix can be considered to come under ACI while third is MACI and fourth can be either ACI or MACI. In comparative clinical trials, ACI and MACI have been established to have significantly better outcome in terms of primary endpoints and functional improvement than microfracture[5,6].

With the above plethora of studies reporting varying outcomes based on each approach to cartilage injury, in the current issue of JSRM, Dykstra *et al* report on stromal vascular fraction (SVF), that this heterogeneous cell population enriched with mesenchymal stem cells (MSCs) exert its therapeutic effects of amelioration of symptoms of cartilage injury more by paracrine mechanisms without any signs of cell engraftment[7], thus probably cautioning on the efficacy when cells alone are applied for cartilage repair. Another review by Vasiliadis & Galanis report that intra-articular injections of adipose-derived mesenchymal stem cells (AD-MSCs) are clinically more effective in patients with mild to moderate knee OA but not in severe OA[8]. This study grades the outcome of therapies based on severity of cartilage defect based on only one specific approach, i.e injection of AD-MSCs.

Given the above information, considering the need for a wholesome approach to cartilage damage, the article by Brittberg[1] on various therapeutic options is worth a mention, which provides an algorithm for choosing the right option of treatment for cartilage defect in which cell-based therapies such as ACI and MACI are mentioned as a components. But we would like to emphasize that cell-based therapies themselves have to be further categorized based on several parameters among which, the nature and extent of the severity of the disease should be the first priority. In mild to moderate cartilage defects while ACI alone may suffice, for larger and severe defects, scaffold-based approaches especially bio-printed ones seemingly work better[10-12]. In diseases with underlying bone defect, apart from fixing the osteochondral bone defect using bone graft or combining high tibial osteotomy, hybrid implants incorporating biomaterials, cells and bioactive cues could also be considered on a case to case basis[13]. An important limitation of clinical trials on cell therapies for cartilage damage is that they have concentrated only on younger patients with sports injuries[14]. However, a recent study has reported the capability of an appropriate scaffold-based environment to help culture good quality chondrocytes from osteoarthritic knees of elderly patients in the lab[15]. Though it is an *in vitro* study needing further validation, the necessity for creation of an environment though not the same as what is physiological, at least closer to it, using appropriate scaffolds for cartilage repair when cells are used as a component, cannot be ignored.

Cartilage tissue with its unique cell-extracellular matrix composition of 2% chondrocytes, 65~ 80% extracellular matrix[16], remaining being water, with a cell-doubling time of 3 to 6 days[17] when gets damaged, and if the damage extends into the underlying bone, the innate healing process, including inflammatory response of two physiologically different tissues in terms of composition, growth pattern and remodelling dynamics, comes into

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play, leading to a complex healing process[18]. Therefore, when a solution to resolve the pathophysiology across different tissue paradigms, having a symbiotic relationship physiologically in spite of other differences is considered, in which cell therapy is a component, factors such as (i) the source of the cells, (ii) culture environment and method, (iii) cell secreted factors, (iv) biomaterials or scaffolds for implantation either mixed or encapsulated (v) Appropriate materials to protect the cell-scaffold implant until their engraftment and (vi) concurrent surgical procedures that will directly or indirectly aid the regeneration and/or a smooth engraftment, should be given a balanced importance based on their merits of contribution. While cell is the prima facie, biomaterials that may yield a temporary support until engraftment or that provide a long term support by way of a protection to the cell transplant site must be considered, based on the optimal physical activity expected as an outcome relevant to the general health of the patient, to yield a justifiable quality of life especially in terms of pain relief and functional recovery.

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