Emerging Cartilage Repair Options

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Mario Hevesi, Bradley M. Kruckeberg, Aaron J. Krych, and Daniel B. F. Saris

24.1 Introduction

Articular cartilage defects cause pain and progression to osteoarthritis (OA), and there exists a critical need for safe and cost-effective interventions. These defects have limited healing potential secondary to the poor regenerative capacity and the avascular nature of cartilage. As a result, chondral lesions can be a source of pain and mechanical symptoms as well as a risk factor for post-traumatic osteoarthritis. Focal cartilage defects impair quality of life in a similar fashion to severe osteoarthritis, causing long-term dysfunction and deterioration of the entire joint [1].

Historical treatment strategies for articular cartilage defects have been limited in success. Whereas palliative treatment options offer limited and short-term symptom relief, articular cartilage restoration has demonstrated effectiveness in reducing pain and functional disability. A variety of surgical options are available to treat cartilage lesions, and these include microfracture, osteochondral allograft transplantation (OCA), and autologous chondrocyte implantation (ACI). Microfracture is the most commonly performed method of cartilage restoration by marrow stimulation for small defects. This technique relies on the influx of marrow products (stem cells, growth factors, and platelets) to form a fibrin clot, which is slowly remodeled into a fibrocartilage scar. This technique has limited outcomes and usefulness due to poor performance in large defects and inferior long-term outcomes compared to more advanced treatment methods. Osteochondral allograft transplantation demonstrates clinically favorable long-term outcomes, with published revision-free survival of 66–69% at 20 years of follow-up [2]. However, the use of OCA remains limited by the fact that these grafts are obtained from young deceased donors, leading to logistical scheduling challenges and lack of scalability of this efficacious resource. While efforts are underway to optimize OCA and expand graft quality availability, autologous approaches remain attractive, given the potential to restore joint biology and repair native tissues [3, 4].

Successful cartilage repair requires an abundance of cells, growth factors, and intricate modulation of the cellular regenerative process. PRP has

M. Hevesi · B. M. Kruckeberg · A. J. Krych
Orthopedics and Sports Medicine, Mayo Clinic, Rochester, MN, USA

Department of Orthopedic Surgery, Mayo Clinic, Rochester, MN, USA
e-mail: Hevesi.mario@mayo.edu; Kruckeberg.bradley@mauo.edu; Krych.aaron@mayo.edu

D. B. F. Saris (✉)
Orthopedics and Sports Medicine, Mayo Clinic, Rochester, MN, USA

Department of Orthopedic Surgery, Mayo Clinic, Rochester, MN, USA

Department of Orthopedics, University Utrecht, Utrecht, The Netherlands
e-mail: Saris.daniel@mayo.edu

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demonstrated trophic and anti-inflammatory properties utilizing in vitro models [5]. Additionally, PRP has shown favorable outcomes in the treatment of knee osteoarthritis, with the potential to be used synergistically with other surgical products to enhance the healing environment.

Cell-based strategies such as autologous chondrocyte implantation (ACI) have demonstrated better durability over microfracture, due to formation of hyaline-like cartilage over fibrocartilage [6]. However, there are disadvantages of ACI, including costly and logistically challenging need for two-stage surgery with ex vivo expansion of the chondrocytes.

Human mesenchymal stem/stromal cells (MSCs) can also be used to improve cartilage regeneration models. The use of MSCs in cartilage repair is promising, with both small and large animal models as well as pilot studies in man demonstrating safety and efficacy in cartilage regeneration [7, 8].

Finally, the combination of chondrocytes with other cell types has gained recent attention given that cells respond to their environment and can be positively influenced by the presence of other cell types [9, 10]. The combination of cells opens the door to single-stage cartilage repair as both orchestrating [stromal] cells and chondrocyte building blocks can be provided simultaneously, without the need for ex vivo expansion.

24.2 Key Concepts

- Evolving use of Platelet-Rich Plasma for Cartilage Treatment
- Emergence and growth of cell-based therapies:
  - Autologous Chondrocyte Implantation
  - Stem/Stromal Cell-Based Therapeutics
  - Single-Stage Auto/Allo Cartilage Repair

24.2.1 Platelet-Rich Plasma for Cartilage Treatment

Platelet-rich plasma (PRP) has received significant attention in recent years as a potential treatment for knee osteochondral defects and osteoarthritis. PRP contains growth factors, modulating local inflammatory responses as well as cellular proliferation and differentiation involved in healing processes [5].

The literature has demonstrated that PRP studies are quite varied with regard to their processing, composition, timing, and indications. A recent systematic review showed that only 10%, or 11/105 studies, provided a comprehensive report with clear description of preparation in composition of the PRP investigated [11]. Furthermore, PRP varies significantly with regard to its platelet, growth factor, and leukocyte composition from patient to patient [11]. Recent efforts have shown that leukocyte composition may be a key factor in the treatment efficacy of knee osteoarthritis [12]. There does appear to be a delicate balance with leukocytes and platelets, as each has important catabolic properties, but, in excess have the ability to upregulate certain proteins such as matrix metalloproteinases, leading to detrimental changes to the surrounding tissues.

Favorable outcomes of intra-articular injections of PRP when compared to saline [13], corticosteroids [14], and hyaluronic acid (HA) [15] have been reported in several blinded, randomized controlled trials (RCT). Other RCTs have demonstrated significant improvement but similar results between PRP and HA [16, 17]. In vitro studies and early clinical observations have also shown a potential synergistic interaction between PRP and HA [18, 19].

The utilization of PRP as an augmentation in the treatment of chondral defects is currently evolving. PRP as an augmentation to microfracture in the treatment of small chondral lesions may provide additional benefit at short-term follow-up, even up to 12 months [20], but did not reach the minimally clinically important difference (MCID) in a recent meta-analysis [21]. While the use of PRP for the treatment of knee cartilage defects and osteoarthritis is becoming increasing popular, its implementation and outcomes remain under scientific debate, in particular due to its heterogeneous nature and preparation. Furthermore, PRP provides a one-time dose of factors which does not have the

capacity to for long-term modulation and feedback regulation-inhibition. Given this, emerging treatment options for cartilage repair increasingly involve cell-based therapies that open the door for sustained, modulated healing and regeneration.

24.2.2 Autologous Chondrocyte Implantation

Cell-based strategies have demonstrated better durability over microfracture, due to the formation of hyaline-like cartilage over fibrocartilage [6]. Indeed, a growing body of evidence suggests that microfracture does no better than debridement alone [22, 23]. Given this, we increasingly recommend consideration of debridement for small chondral defects, to better preserve the subchondral plate, should future ACI or other biologic therapy be warranted. Furthermore, this approach has been postulated to limit the occurrence of intralesional osteophyte formation or subchondral plate fracture as well as allow for cell-based biologic intervention without having to treat the full-depth osteochondral unit, such as with OCA.

In several RCTs, we have demonstrated cell-based ACI has superior clinical outcomes and better structure repair compared to scar formation after microfracture [24–27]. Technically, ACI requires precise debridement to stable defect edges as well as close matching of defect geography to the implanted membrane. For this, we prefer to use a cookie cutter technique in order to provide efficient operative workflow, precisely cut defect edges, and a form-fitting ACI membrane [28].

It is important to note that there are several disadvantages of ACI, including the need for two-stage surgery with ex vivo expansion of the chondrocytes. This delays the final rehabilitation of the patients, and in some cases makes quadriceps atrophy and deconditioning of the affected extremity worse over time. In addition, this procedure is very costly, and is continuously challenged by payers.

24.2.3 Stem/Stromal Cell-Based Therapeutics

Stem/stromal cells represent a population of cells that demonstrate the ability for self-renewal, long-term viability, and multilinear culture [29]. Embryonically, mesenchymal stem/stromal cells (MSCs) are derived from the mesoderm and are distinguished by their capacity to divide into connective tissues including ligament, bone, and cartilage leading to evolving interest in their therapeutic use for orthopedic care [29, 30].

Stem/stromal cell preparations exist in varying formulations spanning from point-of-care aspirates to culture-expanded and characterized cell populations. Classic stem/stromal investigations in musculoskeletal repair were centered initially about bone marrow mesenchymal stem/stromal cells (BMSCs) [31]. While bone marrow is relatively enriched in MSCs as compared to other adult tissues, we caution efforts to employ bone marrow aspirate as a robust source of stem/stromal cells given that MSCs comprise only 0.01–0.001% of the harvested cell population [30, 32]. In contrast, the stromal vascular fraction (SVT) of adipose tissue contains approximately 500-fold the stem/stromal cell concentration of bone marrow [33, 34].

Adipose-derived mesenchymal stem/stromal cells (AMSCs) have also demonstrated growing interest and promise in regenerative therapeutics including cartilage repair. AMSCs differ from BMSCs in the relative ease of adipose isolation, both in clinic and in the OR, as well as the quantity of tissue that can be readily harvested in most patients depending on habitus. AMSCs have been demonstrated to differentiate into fibrocytes and tenocytes in addition to adipogenic, myogenic, and chondrogenic tissues and are therefore a natural target for tendon repair/regeneration studies [35–37]. In a recent RNA sequencing analysis of AMSCs and BMSCs obtained from the same human donors, Zhou et al. found that AMSCs demonstrated lower expression of Human Leukocyte Antigen I (HLA I) as well as higher immunosuppression capacity when compared with the BMSC population [38]. This is desirable

given that limitations in HLA effect can enable allogeneic stem cell application, easing logical preparations, especially as they relate to culture-expanded formulations [39, 40]. Furthermore, the immunomodulatory effect of stem cells may also play a key role in ligament healing given that multiple groups have proposed and reported on the positive histologic effects and recreation of native-like tendon-bone interfaces with immunosuppression and macrophage inhibition [41–43].

24.2.4 Single-Stage Auto/Allo Cartilage Repair

Finally, the combination of chondrocytes with other cell types has also gained attention as others showed that cells respond to their environment and can be positively influenced by the presence of other cell types [9, 10]. Indeed, direct contact between MSCs and dedifferentiated articular chondrocytes recently showed improvement of the cartilage phenotype of dedifferentiated articular chondrocytes [44, 45]. Therefore, combining articular chondrocytes with other cell types can help us overcome barriers and improve the traditional ACI-approach.

In their first-in-man trial, de Windt et al. demonstrated that one-stage application of allogeneic BMSCs mixed with 10–20% defect-derived autologous chondrons resulted in significant improvements in Knee Injury and Osteoarthritis Outcome Score (KOOS) as well as visual analog scale (VAS) which was durable at 18 months of follow-up [39, 46]. Furthermore, MRI demonstrated complete defect filling as well as integration with host tissue, while 32 s-look arthroscopies with tissue biopsy demonstrated that the regenerate contained only autologous DNA, supporting that MSCs provide a transient orchestrating effect whereas autologous cells are needed for defect healing.

Recently, our team has initiated an analogous trial under US Clinical trial NCT03672825. Preliminary results using allogeneic AMSCs mixed with defect-derived autologous chondrocytes demonstrate no significant adverse events and satisfactory outcomes at 3–18 months of follow-up. Formal results of this 25 patient Phase I Clinical Trial are forthcoming.

24.3 Conclusions

Cartilage defects substantially affect patient quality of life, and there remains a critical need for safe and cost-effective interventions. The recent technovolution of cartilage treatment has been rapid, with newly emerging options for repair. Methods of PRP preparation are increasingly nuanced and demonstrate promise in growth factor delivery and use as an adjuvant to advanced biologic therapies. Cell-based approaches represent the latest in emerging cartilage repair options. The latest in the evolutionary line of cell-based therapies is represented by single-stage combination autologous/allogeneic treatments which increasingly address and overcome the logistical challenges of two-stage treatments while providing the signal orchestration and autologous cells needed for defect repair.

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