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Articular Cartilage Injury Treatment: History and Basic Science Review

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Abstract

Cartilage injury has been a troublesome problem for a long time; nevertheless the concepts of treatment have dramatically changed over the last two decades. Currently, three surgical principles have been used for cartilage resurfacing including marrow stimulating, osteochondral transplantation, and autologous chondrocyte implantation. Microfracture based on the traditional marrow stimulating technique is recommended in small (2-4 cm^2) and well containable lesions in order to retain the marrow clot. The smaller and closer subchondral portals are necessary to concentrate the growth factors for controlling a good quality of new cartilage formation. Autologous osteochondral transplantation provides initial graft durability, and is recommended for very small lesions (< 2 cm^2) because of the donor site morbidity concern. Osteochondral allograft transplantation allows an unlimited size of reparation; however chondrocyte apoptosis and extracellular matrix breakdown secondary to the long term preservation lead to graft degradation overtime. Autologous chondrocyte implantation repairs the cartilage defect based on two potential factors; chodrocytes and periosteum-derived progenitor cells. The interaction between cells balances the growth factors at the repairing site. The suitable mechanical stimuli and cell-matrix interactions also play a crucial role in cell proliferation, differentiation, cartilage tissue formation and integration to the surrounding host tissue.

Keywords: Autologous chondrocyte implantation; Cartilage injury; Microfracture; Mosaicplasty; Osteochondral transplantation

Introduction

Articular cartilage injury treatment has been a formidable challenge because cartilage tissue was incapable of quality repair and regeneration. During the past two decades, the strategies of treatment have dramatically changed. The ultimate goal is now focused on the achievement of hyaline cartilage repair with nearly-normal physical properties. Although several surgical concepts have been described, and some under development, cartilage resurfacing currently relies on three fundamental concepts including; marrow stimulating technique (MS), osteochondral transplantation (OT), and autologous chondrocyte implantation (ACI) [1]. Each concept has distinct advantages depending on characteristics of the lesions. There have been many scientific studies and clinical milestones which support these three treatment modalities. This review provides the history of each concept, and a synoptic view of current scientific understanding. However, this review will not cover other concepts of cartilage treatment.

History of Cartilage Injury Treatment

Hunter reported from as early as the 18th century that "From Hipprocates to the present age it is universally known that ulcerated cartilage is a troublesome thing and that when once destroyed it is not repaired" [2]. In the early to mid 20th century, the problem was still similar to the one described above. The slow metabolism and physiological inactivity of cartilage tissue was confirmed by experiments which were mainly performed in animal materials at that time. A comprehensive illustration of cartilage injury and repair in humans was described by Landells in 1957 [3]. His work was on data collection in humans during operations and necropsy from three to ten years after the original injuries. He described that the normal nutrition of the articular cartilage was primarily from the synovial fluid. There is a thin sheet of bone insulating the accessible articular cartilage to underneath the cancellous bone. If granular tissue was present from traumatic causes, it was replaced by fibrous or fibrocartilage tissue. Therefore, joint debridement and free access of vascular tissue underneath the subchondral bone at the injury site were recommended in that moment.

Articular cartilage injuries were classified into three main categories by O'Donoghue in 1966 based on the mechanism of injuries and type of lesions including; shear, impaction and osteochonral avualsion [4]. In a later period, a case series of 76 patients with pure chondral lesion was reported by John-nurse in 1985 [5].Two distinct patterns of lesions were addressed; the full-thickness and the partial-thickness lesion. Operative treatment following this report was suggested in order to relieve pain and disability while preserving a useful range of motion. Full thickness cartilage lesions were treated by subchondral drilling and partial thickness lesions were treated by debridement of the flap and the removal of all loose tissue. In the meantime, a number of scientific articles exploring the knowledge of articular cartilage were reported [6], and other surgical options for restoring the cartilage defect were also studied utilizing an animal model. These contributed to an advancement of cartilage injury treatment which provided a better quality of repairing tissue in the following period.

Pridie introduced the subchondral drilling technique as an operative procedure for osteoarthritis in 1959. Subchondral bone was penetrated by using the wire. The penetration released cells in bone marrow cancellous tissue to encourage healing of articular cartilage [7]. Subchondral granulation tissue filled the defect with fibrous or fibrocartilage, or even the hyaline-like cartilage tissue [8]. Pridie drilling was subsequently performed as the primary operative procedure for full-thickness cartilage treatment. Steadman described the surgical procedure, known as microfracture based on marrow stimulating

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principle, for cartilage injury treatment in 1997. The specially designed awls were used to create multiple perforations into the subchondral bone plate. The multiple small subchondral portals and close distance between individual portals enhanced chondral resurfacing. This technique is then accepted as a small chondral defect treatment in current practice [9].

Yamashita et al. described two cases of osteochondritis dissecan treated by autologous osteochondral grafts in 1985 [10]. The graft was harvested from the normal portion of the medial femoral condyle, which in extension was in contact neither patella nor meniscus. The osteochondral grafts were fixed with AO mini-cancellous screws. In the following period, the first case of full-thickness chondral defect treated with multiple osteochondral grafts transplantation was reported by Matsusue et al. in 1993 [11]. Grafts were fitted with well suited-bone portals and the surrounding cartilage of the femoral condyle. Arthroscopic examination of two years after surgery showed that the original chondral defect was completely covered with chondral tissue, and implanted chondral fragments could not be distinguished from peripherally regenerated cartilage. Bobic reported 12 cases of chondral lesions treated by autologous osteochondral transplantation with a two year follow up in 1996 [12]. Subsequently, Hangody described the mosaicplasty, which consists of autologous osteochondral transplantation with small multiple grafts under a one-step arthroscopic technique, and reported the clinical results with five years of follow-up in 1997. Mosaicplasty technique has been increasingly performed as the potential chondral defect treatment since then [13].

Periosteum has been known to play a critical role in bone growth and fracture repair. The cambium layer of the periosteum is the source of undifferentiated mesenchymal cells which are differentiated to cartilage, and precede bone formation. The periosteal graft was preliminarily used for congenital cleft reparation by Ritsila et al. in 1972 [14]. Rubak et al. transplanted the periosteum graft to the full thickness cartilage defect in a rabbit model. The cartilage defect was completely filled with hyaline-like cartilage after 3-4 wk [15]. Meanwhile, an unfavorable result was also described due to an immobilization effect after transplantation. The cartilage defect was filled with a few chondrocytes rather than filled with hyaline-like cartilage. The following studies then further determined that the chondrogenic phenotype and durability of newly forming cartilage depended on the mechanical stimulation by continuous passive motion [16]. On the other hand, the development of cell biology research at that time suggested a possible role to maintain the chondrogenic phenotype from a primary chondroctye culture. Chondrocyte progenies were able to re-express their phenotype by reproducing collagen type II and cartilage specific proteoglycans in a monolayer culture system [17]. The role of chondrogenic regeneration from periosteum and the redifferentiation potential of chondrocyte progenies became a crucial concept for obtaining the hyaline-like cartilage repair in animal models in the later period. The first case series of autologous chondrocytes implantation was subsequently published by Brittberg et al. in 1994 [18].

The significant clinical events of three fundamental concepts were summarized and shown as a time table in Figure 1. Each concept was developing from the different clinical experiences, and supporting by different scientific backgrounds. Current scientific knowledge further helps illustration, and improving surgical and rehabilitation technique in each concept. To select the type of surgery is not only depended on character of cartilage lesion, but availability of related-technology and specific instrumentation also plays the important role in the final decision.

A number of clinical studies for chondral and osteochondral treatment have been increasingly reported. However, there is still insufficient evidence to determine a consistent guide line for management. Recommendations for surgical procedures rely on good scientific support and clinically-based evidence (Level II-III) [1]. Currently, the indication for surgical treatment is considered when the lesion consistent with full-thickness (grade-3 or 4) cartilage defect after adequate non-operative management has failed to provide acceptable pain relief. Patients who smoke, body mass index (BMI) of > 35 km/m^2, have an inflammatory condition, co-morbidility of uncorrected mechanical instability, and advanced degenerative change are not good candidates for cartilage repair [1].

Marrow Stimulating Technique

Marrow stimulating technique provides several advantages including; minimal invasiveness, technical ease, limited surgical morbidity and high cost-effectiveness [19]. This procedure is carried out by using various kinds of instruments penetrating through the subchondral bone leading to disruption of the subchondral blood vessels. The subchondral portals fill with a fibrin clot which is the source of the bone marrow mesenchymal stem cells (BM-MSCs) deposition. This technique has the potential to form fibrocartilage, or hyaline-like cartilage under a suitable environment and rehabilitation.Surgeons currently use a variety of techniques under this concept including; Pridie drilling, abrasion chondroplasty and microfracture. Each of these is different in term of subchondral-penetration technique, size and depth of the subchondral portal. Pridie drilling was originally performed by using a ¼ inch drill which created a large size of subchondral portals [7]. The smaller sizes of portals (1.5-2 mm) were rendered from later literatures and this technique is still widely used in osteoarthritis and osteochondritis dissecans [20]. Abrasion chondroplasty currently is used as the salvage operation for osteoarthritis. The technique is carried out by extended removal of the entire superficial layer of subchondral bone plate. The expanded abrasion results in fibrocartilage repair over the entire lesion [21].

Microfracture is recommended as the first line treatment for cartilage injury [19,22]. This technique concerned the portal size and distance between subchondral portals. Microfracture is carried out by the removal of calcified cartilage since it has been shown to improve the bonding of the repair tissue to the subchondral bone after operation. Subsequently, using awls creates the subchondral portals. The depth has to be achieved by observing the release of fatty droplets from the microfracture portals. Three to four-millimeter wide bone bridges are carefully maintained between individual portals to preserve the integrity and function of subchondral bone [9,22]. This technique avoids using a drill or bur creating subchondral portals in order to avoid thermal necrosis. The heat created from the electronic drill might affect the osteocyte and mesenchymal stem cell viability which would decrease the potential of forming new tissue [22]. However, the present scientific study in an animal model demonstrated a different finding about subchondral portal creation. Comparison studies between acute fracture created from awls and drilling found that an awl induced fracture which largely sealed off the adjacent bone marrow, whereas drilling cleanly removed bone debris and left channels that communicated between the portals and marrow. The well-formed marrow clot could be observed from the drilling technique rather than that using awls. Fractures created by awls also produced a higher level of osteocyte necrosis due to the mechanical pressure in contrast to the drilling which included cooled irrigation [23].

The size of the subchondral portal is one of the crucial factors for

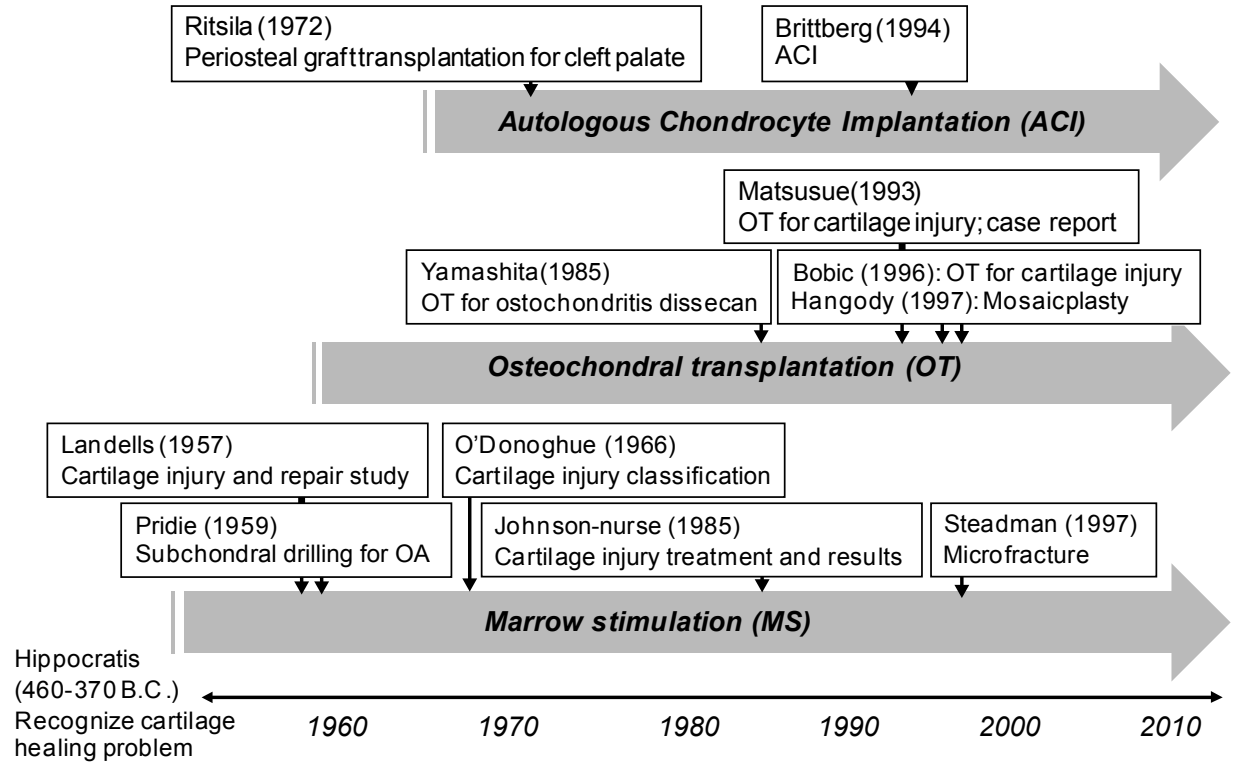

Figure 1: The historical sequence of cartilage injury treatment and emerging of new concept during the 20th century. The blog represents the signature clinical milestones.

creating hyaline cartilage repair [19,24]. A smaller size of subchondral portal (3 mm) allows better packing of undifferentiated mesenchymal cells around the portal than that in the larger portal (5 mm). Moreover, the smaller portal enhances concentrated growth factors which are required to initiate and support a chondrogenic repair in full thickness defects. From an animal model study, an endogenous FGF-2 could not reach the requirement of the growth signal in the large subchondral portal (≥ 5 mm). The repaired tissue eventually turned into a fibrous or fibrocartilage repair. The high concentration of endogenous FGF-2 was detected from the smaller portal, and provided a better quality of hyaline-like cartilage repair [24]. Currently, microfracture is recommended for a small, and well-contain chondral defect (4 cm^2; 2x2 cm). The clinical follow up reported that the small size defect treated with microfracture significantly related to a better clinical outcome than that in the large defect [25], and the best short-term outcomes are associated with a good-filled defect with new forming tissue [26]. Presumably, the small and well-contained defect would provide a better formation of a fibrin clot and greatly enhance a high concentration of growth factors which provide positive effects to the repairing process.

The patients with high BMI (> 25-30 kg/m^2) showed a significantly poor clinical outcome after being treated by microfracture [25,26]. Although there is limited scientific evidence to describe the relationship between high BMI and cartilage repair, an excessive loading across the joint would be one of the possible factors to the poor outcome [27]. An excessive loading renders an unsuitable mechanical load to the new forming tissue post-operatively. Moreover, an excessive loading across the joint exposes cartilage to the long term catabolic metabolism; an unsuitable environment would affect the differentiation process of BM-MSCs. Patient's age (>35-40) was directly related to the unfavorable treatment outcome [25,28]. According to an animal study, BM-MSCs decreased the capability of proliferation and differentiation as a function of age. The production of heat shock protein and heat shock factor-1 were reduced with the increasing of age, and the level of a core circadian protein was significantly increased in the older group [29]. Huank et al. showed that BM-MSCs derived from 0-20 years old donors demonstrated a greater ability of cellular expansion, shorter period of passage duration, and higher production of cytokine levels including IL-6, FLT-3L, and SDF-1 when compared to those from >20 years old donor [30].

Rehabilitation after microfracture creates a suitable mechanical environment for new tissue formation [31]. The critical period was the first two weeks when the defect was filled with a fibrin clot and BM-MSCs were recruited in a cartilage defect. An initial support of a fibrin-clot maintains a level of autocrine and paracrine growth factors which contributes to a better differentiation. The defect was almost filled with fibrous reparative tissue within four weeks, and subchondral bone was almost reconstituted within 8 wk [24]. A rehabilitation program primarily protects the marrow clot, giving a physical massage to the new tissue that encourages it to become cartilage. Passive range of motion helps to restore a motion, and touchdown weight bearing are promoted in this step. The progressive weight bearing is encouraged after 8 wk. The progressive muscular endurance and low impact exercises are started after 17 wk. Patients are able to return the full sport activity after 36 wk [31].

Autologous and Allogenous Osteochondral Graft Transplantation

The transplantation of osteochondral grafts provides an immediately durable surface. An immediate good outcome and early recovery is suitable for the young or high-demand patients [32]. An autologous osteochondral graft is recommended for use in a very small defect (<2 cm^2) because of the limitation of donor site morbidity. The multiple small sizes of osteochondral grafts, named mosaicplasty, permits preserving donor site integrity and allows the progressive contouring of the new surface of the defect [13]. The optimal graft size currently is suggested to be 2.7 to 8.5 mm in diameter, and a proper graft length is suggested to be 15 mm for resurfacing the pure cartilage defects and 25 mm appropriate for osteochondral defects which has been optimized from clinical experiences, and some scientific support [32].

The stiffness of an osteochondral plug is increased due to the cancellous bone healing underneath after 12 wk. Prior bone healing; the stability of grafts depends on a press-fit mechanism between the graft and recipient portal. The larger diameter of a graft provides the greater initial stability [33], nevertheless a donor morbidity from which the large graft was harvested has to be taken into consideration. The bottomed placement of a graft provides a better stability than the unbottomed placement. If an unbottomed plug needs to be performed, a longer graft would be recommended since it provides a better frictional stability than a shorter graft [34]. Incongruent replacement creates an initially abnormal biomechanical loading leading to a structural damage, loss of the viability of chondrocytes, and subsequent degeneration of the articular cartilage. Incongruent placements with either plug elevation or depression significantly increase contact pressure to local area than that of a normally congruent cartilage. The biomechanical study found that 0.5 mm plug elevation caused an increase of 48% of contact pressure. On the other hand, a 0.5 mm plug depression caused an 8% increase of contact pressure compared with the normal congruent cartilage [35]. Hangody et al. reported that the hyaline cartilage from a transplanted donor integrated with fibrocartilage ingrown from the bony base of the defect. The donor sites were filled to the surface with cancellous bone capped with fibrocartilage by 8 wk [36]. However, some studies were unable to demonstrate the histological integration between donor grafts and recipient cartilage [37,38]. Although the integration of grafts does not heal to the surrounding native cartilage, some are healed by fibrocartilage, the subchondral bone integrations are healed without a doubt. Clinically, these would be adequate to provide enough structural and mechanical integrity for transplanted tissue.

Osteochondral allograft transplantation is a suitable option for a large articular defect since the massive-graft harvest could not be acceptable for the donor morbidity. Allografts provide the completely matched surface and size with the single graft. Nevertheless, the viability of chondrocytes, quality of extracellular matrix and durability of grafts due to long-term preservation becomes the important concern. Long-term storage significantly decreases cell viability over time. The cells up-regulate genes associated with apoptosis including CD30, CD30 Ligand, Fas, Fas ligand, tumor necrosis factor, several caspases and matrix degradation enzymes when increasing the storage time [39]. Withdrawal of substantial nutrients leads to cell apoptosis. Chodrocytes from fresh allograft showed better viability when preserved in culture media rather than that in lactate ringer solution. Culture media contains the substantial nutrients for cell viability including; glucose, amino acids, inorganic salts and vitamins [40]. Losing signals from the insulin growth factor and decreasing of an integrin-mediated signal due to the ECM breakdown causes a decreasing of pro-survival signals leading to caspases activation. Subsequently, the caspases cascade renders the intranucleosomal DNA cleavage causing apoptosis of chondrocytes. Moreover, the increasing ligands (tumor necrosis factors) for death receptors also lead to a translocation of cytochrome c from the mitochondria to form apoptosome which is one activator for caspase3 [39,41].

Currently, the optimal condition for fresh allograft storage is a challenge in order to prolong the survival time of chondrocytes, maintain their metabolic activities and extracellular matrix quality. A better understanding of the apoptotic mechanism would improve the quality of allograft storage. Some chemical agents are studying to improve the preservation technique; for example ZVAD-fmk (caspase activity inhibitor) [42]. The fresh human osteochondral allograft stored in culture media at 4°C has significantly diminished the chondrocytes viability at 28 days and significant declined proteoglycan synthesis after 14 days. However, the glycosaminoglycan contents and biomechanic properties were still preserved until 28 days of an experiment [43]. These findings would encourage using allografts within 14 days after preservation, or not beyond 28 days.

Cryopreservation and fresh-frozen techniques are used for long term allograft storage. An available reserve of allografts allows improved identification of suitable recipients and more feasible scheduling of operative treatment. After transplantation, the intact structure of articular cartilage demonstrated a variable degree of degradation over time, and became totally damaged with subchondral deformation within 5-10 years [44]. Long-term storage by cooling to a low sub-zero temperature (-196°C/in liquid nitrogen) and exposing to protective chemical agents created an unfavorable effect to the chondrocytes. The low temperature slows down cellular metabolism particularly biochemical reactions meanwhile the freezing temperature causes damage to the cells by extracellular and intracellular ice formation. For fresh-frozen preservation, the freezing process causes mummification of chodrocytes in lacunae. For cryopreservation, cryoprotectants such as glycerol, dimethyl sulfoxide (DMSO) increase the viscosity of the fluid and turn it into an amorphous ice instead of crystallizing which protects cell from the freezing damage [45]. The chodrocyte viability and growth potential can be shown as long as 28 day after graft preservation in culture media and DMSO, and then controlling the freezing rate to -150°C cryopreservation [46]. Further studies are needed to determine the optimal concentrations of and new type of cryoprotectants which provide the best quality for chondrocyte preservation, as well as the freezing and thawing protocols [47,48].

Cell-based Therapy Chondrocyte Transplantation

Primary chondrocyte culture and periosteum derived progenitor cells (PDPCs) play a substantial role in cartilage defect repair [18]. Chondrocyte dedifferentiation in monolayer culture becomes a major concern in clinical practice because an adequate number of chondrocytes for transplantation depends on the number of culture passages. Chondrocyte progenies demonstrate a rapid change in the gene expression profile upon its cellular passages during cultivation. The expression of collagen type II has significantly decreased since passage II, matrix aggregan and fibromodulin significantly decreased expression since passage IV [49]. Moreover, multiple passages of chondrocytes decreased their redifferentiation capacity. The passage 3-4 has been considered as a threshold for irreversible dedifferentiation of chondrocytes in the monolayer culture system [50].

The repairing capability not only relies on the cells from

chondroctye progenies, but the regenerated-potential of new cartilage also contributed from the PDPCs as well. Periosteum contains two discrete layers: the inner cambium layer that contains PDPCs and an outer fibrous layer. Zarnet et al. proved that undifferentiated mesenchymal cells from periosteum are the source of cells in new forming-cartilage. Neo cartilage showed male karyotype in a female-recipient which had undergone repair by male-periosteal transplantation [51]. O'Driscoll et al. reported that the cells of cambium layer had potential for proliferation and differentiation to chondroid lineage. The sufficient exposure of TGF-β1 and BMP-2 in the early stage plays a role as the autocrine and paracrine regulator to enhance the cartilage growth [52]. Periosteum-derived progenitor cells of the cambium layer can express endogenous TGF-β1 and TBR-I and TBR II when they are exposed to the exogenous stimulation of TGF-β1 [53]. Although chondrocyte progenies seem to gradually dedifferentiate after the early passage, they still constantly express TGF-β upon the sixth passage of monolayer cultivation [49]. Transforming growth factor-β1 produced by chondrocytes would be the early exogenous stimulation enhancing PDPCs to continuously express endogenous TGF-β1 and their receptors [54]. Transforming growth factor-β1 plays a substantial trigger for an early phase of proliferation and chondrogenesis, whereas IGF-I alone treatment does not affect cambium cellularity or cartilage production *in vitro*. However, the long-term exposure to IGF-1, with the presence of TGF-β1 has a beneficial effect to maintain a chondrogenic phenotype by sustained expression of collagen type II until the sixth week of the culture period [55]. The interaction between chondrocyte progenies and PDPCs still presents a possible role for graft integration to host tissue. Matthias et al. studied this interaction in a co-culture model for up to 28 days. The co-culture between the periosteum and chondrocytes showed the modulating activities of MMPs family and IL-6 than that in mono-population culture which might have a possible role in the regeneration and integration of graft to host tissue [56].

The continuous passive motion has been experimentally considered to be an important enhancing factor for inducing cartilage formation. The dynamic fluid pressure (DFP) model was established for imitating an oscillating intra-synovial pressure fluctuation during continuous passive motion. The low pressure (13 kPa, at 0.3 Hz) significantly enhanced chondrogenesis, whereas the higher pressure (103 kPa, at 0.3 Hz) completely inhibited chondrogenesis. Moreover, application DFP 4 hr/day showed a significantly higher chondrogenesis than that of just 30 min/day, but not significantly less than that obtained with 24 h/day [57,58]. Juan et al. reported the effect of mechanical stimuli to the un-differentiated stem cells. The mechanical pressure up-regulated the p38MAPK which enhanced the expression of chondrogenic markers including Col2α, aggregan, Sox9 and Runx2 whereas the cells decreased their expression of chodrogenic markers when exposed top38MAPK inhibitor under compressive stimuli [59].

Although chondrocytes from monolayer cultures tend to change toward dedifferentiation over the passage, they still present the plastic potential to maintain their phenotype when cultured in a particular environment. The co-culture model showed that the older chondrocytes

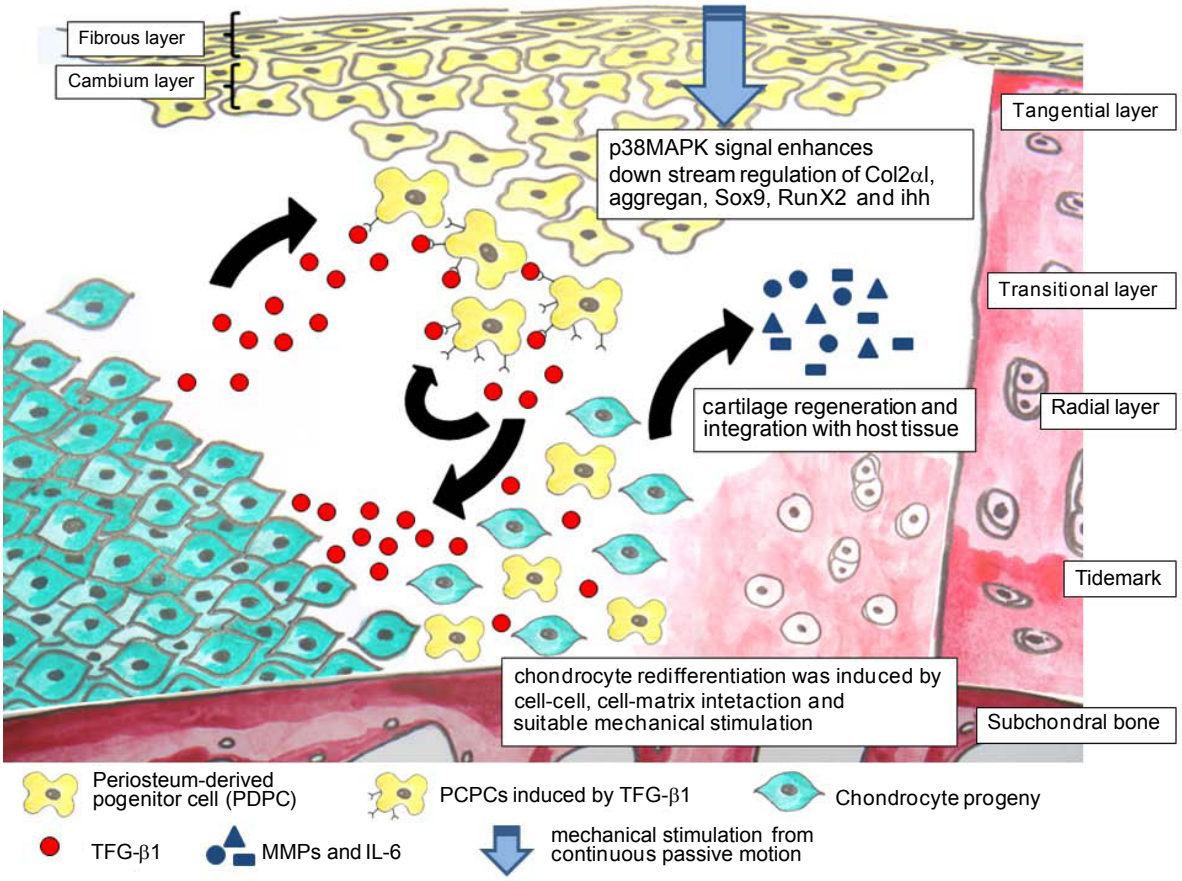

Figure 2: Hypothetical model illustrating the possible mechanism of cartilage formation due to the autologous chondrocyte implantation technique.

had potential to redifferentiate when co-cultured with the younger chondrocytes; moreover the dedifferentiated chondrocytes following the serial passage in the monolayer culture were able to redifferentiate showing the chondrogenic phenotype when co-culture with the primary chondrocytes [60]. Redifferentiated potential was also presented in chondroctye progenies from passage expansion in as described in the tissue engineering model. Presumably, the microenvironment including; cell-cell interaction, three-dimensionally culture orientation, progressive matrix deposition and matrix-cell interaction provide an enhancing effect for redifferentiation and formation of hyaline cartilage. The comprehensive illustration of cartilage repair from autologous chondroctye implantation is shown in Figure 2. Chondrocyte cultured in conventional monolayer tend to change toward dedifferentiated over the passages however they still present the plastic potential to maintain their phenotype in tissue engineering model [61,62]. Chondroctye cultured on three-dimension scaffold (tissue engineering) enhances ECM deposition to promote new tissue formation. Moreover, tissue engineering presents another clinical advantages than that conventional cell-based concept including; avoidance of periosteal harvest, increase technical ease, and a more even cell distribution and ECM production control [62]. It would be the alternative options of cell-based cartilage treatment in the future [63,64].

Conclusion

Currently, scientific studies in cartilage technology are searching for a better quality of cartilage repair meanwhile the related-researches involving non-invasive investigation including imaging and biomarkers are developing for assisting in a reliable post-operative follow-up. Those are shaping future treatment strategies. In the mean time, the clinical reports with long term follow-up and good evidence base studies are still required in order to obtain consistent guidelines of treatment. The treatment of cartilage injury is expected to continue to improve.

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