Bioregenerative Therapies in Osteoarthritis

Subjects: Orthopedics

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Osteoarthritis (OA) is the most common articular disease in adults, and it affects around 250 million people all over the world, with high prevalence of asymptomatic patients. In addition, pain associated with this pathology is one of the main causes of disability worldwide. OA is subcategorized into primary (idiopathic) and secondary. The most common causes of secondary OA are post-traumatic, dysplastic, infectious, and inflammatory processes. Moreover, articular cartilage injuries may lead to the early onset of OA and have a huge negative impact on patients' function and life quality.

osteoarthritis bioregenerative therapies stem cells platelet rich plasma

1. Mesenchymal Stem Cells in Osteoarthritis

The use of MSCs to treat OA has been demonstrated to be safe, and its use has increased in the last years compared to conservative treatments [1]. MSCs secrete trophic factors with regenerative functions, and they can differentiate into cartilage and bone cells, promoting cartilage regeneration [2].

The capacity of MSCs to stimulate local repair and cartilage regeneration in damaged joints has been demonstrated [3][4]. Moreover, regarding human medicine, Lendeckel et al. described the use of adipose-derived stem cells (ADSCs) combined with bone graft and fibrin glue to treat cranial critical-size bone defects in a seven-year-old girl suffering from multiple calvarial fractures. Three-month follow-up computed tomography scans revealed new bone formation and almost complete calvarial continuity [5].

In OA, MSCs therapy reduces pain and inflammation [6]. MSCs modulate the inflammatory response via the suppression of inflammatory T-cell proliferation and the inhibition of monocyte and myeloid dendritic cell maturation. Moreover, the presence of a pro-inflammatory milieu has been suggested as the key to promoting MSCs' anti-inflammatory effects [7][8]. After the IA injection of MSCs, molecules with anti-inflammatory and chondrogenic properties are expressed. These cells could help to establish a regenerative microenvironment at the site of release, which would improve the recruitment, activation, and differentiation of endogenous stem cells with potential to repair the articular cartilage [9].

Although many studies have focused on OA treatment with autologous MSCs, the safety of allogenic MSCs for treating knee OA has also been demonstrated [10][11][12][13].

There are two different types of MSCs, embryonic and adult stem cells. Adults MSCs can be obtained from different tissues such as peripheral blood, bone marrow and adipose tissue, the last two being the most commonly used sources. MSCs found in adipose tissue are called ADSCs, which have a greater proliferation capacity than the rest of the MSCs, and they are able to maintain the differentiation potential for longer periods when cultured. Additionally, their ability to proliferate is not affected by donors' age as much as in other kinds of MSCs [14], even though it has been shown that aging negatively impacts ADSCs function [15]. Moreover, ADSCs have several advantages over other kinds of MSCs: adipose tissue is abundant and easy to obtain, in vitro culture is not necessary and therefore they have a low risk of rejection [16], and it is an economical product. It has been demonstrated that the IA application of autologous ADSCs with no previous culture halted the progression of cartilage degeneration [17]. Moreover, adipose tissue contains approximately 10 times more MSCs than bone marrow, making this source of MSCs a good candidate for the treatment of OA [7]. In a recent study, the efficacy and safety of Bone Marrow Mesenchymal Stem Cells (BMMSCs) and ADSCs have been compared. Data from 19 studies including a total of 811 patients with knee OA were analyzed. At 6-month follow up, ADSCs showed significantly greater improvements in visual analog scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) than BMMSCs, compared to controls. At 12-month follow up, ADSCs outperformed BMMSCs compared to their controls in measures such as WOMAC, knee injury and osteoarthritis (KOOS), and Whole-Organ Magnetic Resonance Imaging Scores (WORMS). Similar results were observed at 24-month follow up, where ADSCs showed significantly better Lysholm scores than BMMSCs, although VAS improvement was better with BMMSCs [18].

The stromal vascular fraction (SVF) derived from adipose tissue might induce IA fatty tissue homeostasis. Moreover, it has protective and anti-inflammatory functions, inhibiting OA progression [19]. The SVF contains 500,000 to 2,000,000 cells per gram, including macrophages, monocytes, pericytes, fibroblasts and MSCs, of which approximately 1–10% are ADSCs [20][21]. The SVF and pure ADSCs have similar properties, such as anti-inflammatory, angiogenic and immunomodulatory effects, but the heterogeneity of SVF contributes to better therapeutic results [22]. Some studies have pointed out that SVF enhances new cartilage matrix formation [23] and subchondral bone regeneration better that ADSCs [24]. Furthermore, SVF is obtained more easily than pure MSCs, as it does not need special culture conditions to expand [25], which could modify the migration ability of the cells towards damaged tissue [26].

2. Mesenchymal Stem Cells Exosomes in Osteoarthritis

Exosomes are extracellular vesicles (EVs) surrounded by a phospholipid membrane, either a cell membrane- or an endosomal-derived membrane, that contains different cell-specific receptors, which are important in cell-to-cell communication [27]. MSCs-derived exosomes isolated from different tissue sources are free of cells and have shown therapeutic potential to treat many diseases [28][29]. Pre-clinical in vivo studies have demonstrated positive effects in joints and have confirmed the effectiveness of EVs injections as a minimally invasive therapy [30]. Particularly, MSCs-derived exosomes have cartilage repair properties and can delay OA progression through a variety of mechanisms; for example, stimulating ECM secretion, promoting chondrocyte proliferation, inhibiting

chondrocyte apoptosis, and maintaining chondrocyte homeostasis [31]. Recently, it has been demonstrated that IA injection of BMSCs-derived exosomes reduces inflammation and cartilage damage, and inhibits OA progression. These effects are achieved thanks to the phenotypic transformation of macrophages from M1 to M2, together with a decrease in inflammatory cytokines and the release of anti-inflammatory cytokines [32]. A research study carried out by Wang et al. reported that embryonic MSCs-derived exosomes stimulate the synthesis of type II collagen and decrease the production and expression of MMPs with thrombospondin-like motifs-5 (ADAMTS-5), providing a stable ECM in a surgically induced OA model in mice [33]. On the other hand, Tofiño-Vian et al. revealed that EVs isolated from human ADSCs promote chondroprotective functions due to a decrease in MMP activity, decrease the secretion of inflammatory mediators and stimulate anti-inflammatory cytokine IL-10 production [34]. Furthermore, Cosenza et al. reported that both exosomes and BMMSCs microparticles decrease the expression of catabolic and inflammatory markers [35]. Moreover, in a recent study in which MSCs-derived exosomes were used in cartilage repair, an increased matrix deposition and cellular proliferation and better histological scores were observed in animals treated with MSCs-derived exosomes [36].

In an in vitro study carried out by He et al. in rats with OA, significant reconstituted collagen type II and impaired MMP-13 protein expression in knee joint cartilage were observed after exosome treatment, demonstrating a significant chondrocyte proliferation and migration capacity [37]. Additionally, human articular chondrocytes and fibroblast-like synoviocytes isolated from the same OA patients were cocultured in 2D as well as in 3D conditions with fluorescently labeled ADSC-EVs, and analyzed by flow cytometry or confocal microscopy. In both 2D and 3D conditions, fibroblast-like synoviocytes were more efficient in interacting with ADSC-EVs, and 3D imaging showed a faster uptake process. The removal of the HA component from the ECM of both cell types reduced their interaction with ADSC-EVs only in the 2D system, showing that 2D and 3D conditions can yield different outcomes when investigating events wherein ECM plays a key role. These results indicate that studying EVs' binding and uptake both in 2D and 3D guarantees a more precise and complementary characterization of the molecular mechanisms involved in the process [38].

MSCs-derived exosomes are a promising new cell-free approach to treat OA and other joint conditions. However, further investigations in humans are required to assess the effectiveness and feasibility of this therapy.

Stem cell therapy could become a first-line therapy to treat OA. The efficacy of MSC-based therapies has been related to the paracrine secretion of trophic factors, and exosomes that play a fundamental role in tissue repair.

3. Platelet-Rich Plasma in Osteoarthritis

PRP is a cell-free and autologous product of fractionated plasma derived from the patient's own blood, obtained after a specific centrifugation process. The platelets contain alpha granules that are rich in several GFs with chemoattractant and mitogenic functions, which help to attract surrounding cells to injured areas. This product can also contain a high number of leukocytes, which may have a negative effect on tissue regeneration. In fact, there is a wide variation in the reported protocols for the standardization and preparation of PRP, with variable reported efficacy. PRGF could be an alternative approach; it is a 100% autologous and biocompatible preparation, with a

moderate platelet concentration and no leukocytes or erythrocytes, and it is elaborated by a single centrifugation process [39][40]. It is considered a safe product due to its autologous origin [28].

PRP regulates cartilage repair by stimulating the synthesis of proteoglycans, aggrecans or type II collagen by chondrocytes; the proliferation of synoviocytes; and the chondrogenic differentiation of MSCs. Additionally, it decreases the catabolic effects of cytokines, such as IL-1, or proteolytic enzymes, such as matrix metalloproteinases [41][42][43][44][45][46].

Despite the variability in PRP preparations, several published research and clinical studies have shown excellent outcomes. Cuervo et al. showed significant pain relief and an improvement in limb function after a single IA PRGF infiltration in canine patients with OA secondary to hip dysplasia, and this effect was maintained for more than 6 months [46]. Other studies have addressed a maximum effect 180 days after a single IA PRP injection in patients with knee OA [47]. Furthermore, in a study where patients were treated with PRP combined with HA, a significantly greater pain relief was observed in patients receiving the combination of both treatments compared with those only treated with PRP, suggesting that the association of PRP and HA could be a better long-term option [48]. Huang et al. evaluated PRP IA injections once, twice, or three times per month, and demonstrated the positive effects of PRP up to a 12-month follow-up in patients receiving one or two IA injections, whereas these effects were maintained in those patients receiving three IA injections [49]. With regard to variability in PRP preparations, a systematic review to investigate the superiority of PRP over HA concluded that it is necessary to standardize the centrifugation protocol, the activating agents, the administration frequency, and the injected total volume [50].

Scientific evidence exists regarding PRP injections in all stages of knee OA [51][52]. In a study with 214 patients with knee OA, 155 patients were classified as having Kellgren–Lawrence (KL) grade 1 OA, while 59 were grade 2 OA. Patients were treated with three PRP IA injections in knee joints with 4-weeks intervals, and the WOMAC was evaluated at the time of induction and with 6-month intervals. The mean WOMAC score before treatment was 83.05, and after 6 months, it was significantly reduced to 38.84 [53]. Patients with knee OA graded stage 1 or 2 on the KL scale showed improved WOMAC scores at 1, 2, and 6 months after PRP IA injection [54]. A significant pain relief and functional improvement was reported 3 months after PRP treatment, mainly in lower OA grades [49] compared to control groups [55]. Additionally, Cook and Smith compared PRP with traditional knee OA treatments. Patients reported good pain relief for at least 6 months, and commonly for a year or longer following the three PRP injection regimens [56]. In addition, the effect of IA PRP injection was evaluated with VAS pain scores in patients with knee OA by Taniguchi et al., and the results showed that the average VAS pain scores improved at 6-month follow-up from 71.6 to 18.5 ($p < 0.05$), with 80% of patients experiencing a 50% decrease, or higher, in VAS pain scores [57]. Similar results were obtained in a different study wherein a reduction in pain and lameness was observed in human patients treated with PRP with knee OA after 1 year follow up [58]. MRI image studies were carried out by Ornetti et al., showing no OA progression in 73% of the patients treated with PRP [59].

This therapeutic option has also reported beneficial effects in animals. In a recent study, the effects of a single PRP IA injection were evaluated in dogs with knee OA secondary to cranial cruciate ligament rupture. Improvements in kinetics were seen in dogs 3 months after treatment [41]. Another similar study was carried out by Vilar et al., where

the PRP effect was evaluated in dogs with knee OA secondary to cranial cruciate ligament rupture. Lameness and gait improvements 3 months after IA injection were observed [60]. In horses with moderate to severe forelimb OA, PRP treatment did not cause statistically significant differences in gait, although the authors suggested a possible improvement in lameness despite the lack of statistical difference [61]. Another study in 16 rats with OA induced by monoiodoacetate injection showed promising results. Rats were randomly divided into treatment group A (n = 8 rats) or non-treatment group B (n = 8 rats). The treated group (A) received a single 0.5 mL injection of activated PRP 18 days after the monoiodoacetate injection, and histological assessment of treated joints revealed a higher chondrocyte population and greater cartilage thickness than in untreated animals [62]. Moreover, a study in rabbits in which the perichondral sheaths were dissected and the costal cartilages were removed concluded that the administration of PRP is helpful in improving chondrocyte density, resulting in increased ECM [63].

A combination of IA and intraosseous (IO) PRP infiltration has also been proposed with promising results. Better outcomes at 6 and 12 months were obtained in patients when PRP was applied both IO and IA, compared to the IA application alone [64][65].

The therapeutic potential of PRP products to treat OA is not fully understood. Further studies focused on the combination of other regenerative therapies with PRP are necessary, as well as more investigations in the field of IO infiltration.

4. Future Perspectives in OA

In OA, bioregenerative therapies have been demonstrated to be a great option over other treatments due to their therapeutic potential. In recent years, OA cell therapies have been developed as an alternative or additional therapy to traditional methods, with the aim of creating a new tissue displaying the most similar characteristics to native cartilage.

The optimal OA therapy should halt disease progression through the repopulation of the injured tissue with chondrocytes able to produce a hyaline matrix, restoring cartilage structural and functional properties. Different new approaches for cartilage regeneration have been proposed, for example, anti TNF-α therapies, as TNF-α plays a considerable role in OA pathogenesis [66]. Moreover, it has been demonstrated that other biologic agents that inhibit nerve growth factor improve function and reduce pain in OA patients [67]. Future perspectives are focused on gene therapy with encoding genes for chondrogenic GFs and anti-inflammatory cytokines; particularly, this therapy exerts its effects through intracellular nucleic acid transfection and translation into protein [68]. Recently, therapeutic strategies that combine cell and gene therapy based in the production of protein platforms have been proposed as good strategies to treat OA [69][70]. The main limitation of gene therapy is its carcinogenic potential as well as the elevated costs [71].

Other important considerations include the time that the therapeutics stay in the joint tissue. Different natural and synthetic scaffolds (amphiphilic polymeric micelles and hydrogels) are being evaluated to achieve increased

articular dwelling of the drugs [72]. Moreover, several studies have reported the beneficial results of nanoparticles used for targeted drug delivery and sustained release in OA joints [73].

Nanotechnological strategies combined with cell-based therapy, biological and gene treatments could be a future perspective in the clinical management of the pathology.

References

1. Moroni, L.; Fornasari, P.M. Human mesenchymal stem cells: A bank perspective on the isolation, characterization and potential of alternative sources for the regeneration of musculoskeletal tissues. J. Cell Physiol. 2013, 228, 680–687.
2. Vinatier, C.; Guicheux, J. Cartilage tissue engineering: From biomaterials and stem cells to osteoarthritis treatments. Ann. Phys. Rehabil. Med. 2016, 59, 139–144.
3. Nomura, I.; Watanabe, K.; Matsubara, H.; Hayashi, K.; Sugimoto, N.; Tsuchiya, H. Uncultured autogenous adipose-derived regenerative cells promote bone formation during distraction osteogenesis in rats. Clin. Orthop. Relat. Res. 2014, 472, 3798–3806.
4. Dozza, B.; Salamanna, F.; Baleani, M.; Giavaresi, G.; Parrilli, A.; Zani, L.; Lucarelli, E.; Martini, L.; Fini, M.; Donati, D.M. Nonunion fracture healing: Evaluation of effectiveness of demineralized bone matrix and mesenchymal stem cells in a novel sheep bone nonunion model. J. Tissue Eng. Regen. Med. 2018, 12, 1972–1985.
5. Lendeckel, S.; Jödicke, A.; Christophis, P.; Heidinger, K.; Wolff, J.; Fraser, J.K.; Hedrick, M.H.; Berthold, L.; Howaldt, H.P. Autologous stem cells (adipose) and fibrin glue used to treat widespread traumatic calvarial defects: Case report. J. Cranio-Maxillofac. Surg. 2004, 32, 370–373.
6. Wehling, P.; Evans, C.; Wehling, J.; Maixner, W. Effectiveness of intra-articular therapies in osteoarthritis: A literature review. Adv. Musculoskelet. Dis. 2017, 9, 183–196.
7. Lopa, S.; Colombini, A.; Moretti, M.; de Girolamo, L. Injective mesenchymal stem cell-based treatments for knee osteoarthritis: From mechanisms of action to current clinical evidences. Knee Surg. Sports Traumatol. Arthrosc. 2019, 27, 2003–2020.
8. de Girolamo, L.; Kon, E.; Filardo, G.; Marmotti, A.G.; Soler, F.; Peretti, G.M.; Vannini, F.; Madry, H.; Chubinskaya, S. Regenerative approaches for the treatment of early OA. Knee Surg. Sports Traumatol. Arthrosc. 2016, 24, 1826–1835.
9. Ozeki, N.; Muneta, T.; Koga, H.; Nakagawa, Y.; Mizuno, M.; Tsuji, K.; Mabuchi, Y.; Akazawa, C.; Kobayashi, E.; Matsumoto, K.; et al. Not single but periodic injections of synovial mesenchymal

stem cells maintain viable cells in knees and inhibit osteoarthritis progression in rats. Osteoarthr. Cartil. 2016, 24, 1061–1070.

10. de Windt, T.S.; Vonk, L.A.; Slaper-Cortenbach, I.C.; van den Broek, M.P.; Nizak, R.; van Rijen, M.H.; de Weger, R.A.; Dhert, W.J.; Saris, D.B. Allogeneic Mesenchymal Stem Cells Stimulate Cartilage Regeneration and Are Safe for Single-Stage Cartilage Repair in Humans upon Mixture with Recycled Autologous Chondrons. Stem Cells 2017, 35, 256–264.
11. Vangsness, C.T., Jr.; Farr, J., II; Boyd, J.; Dellaero, D.T.; Mills, C.R.; LeRoux-Williams, M. Adult human mesenchymal stem cells delivered via intra-articular injection to the knee following partial medial meniscectomy: A randomized, double-blind, controlled study. J. Bone Jt. Surg. Am. 2014, 96, 90–98.
12. Vega, A.; Martín-Ferrero, M.A.; Del Canto, F.; Alberca, M.; García, V.; Munar, A.; Orozco, L.; Soler, R.; Fuertes, J.J.; Huguet, M.; et al. Treatment of Knee Osteoarthritis With Allogeneic Bone Marrow Mesenchymal Stem Cells: A Randomized Controlled Trial. Transplantation 2015, 99, 1681–1690.
13. de Windt, T.S.; Vonk, L.A.; Slaper-Cortenbach, I.C.M.; Nizak, R.; van Rijen, M.H.P.; Saris, D.B.F. Allogeneic MSCs and Recycled Autologous Chondrons Mixed in a One-Stage Cartilage Cell Transplantion: A First-in-Man Trial in 35 Patients. Stem Cells 2017, 35, 1984–1993.
14. Damia, E.; Chicharro, D.; Lopez, S.; Cuervo, B.; Rubio, M.; Sopena, J.J.; Vilar, J.M.; Carrillo, J.M. Adipose-Derived Mesenchymal Stem Cells: Are They a Good Therapeutic Strategy for Osteoarthritis? Int. J. Mol. Sci. 2018, 19, 1926.
15. Choudhery, M.S.; Badowski, M.; Muise, A.; Pierce, J.; Harris, D.T. Donor age negatively impacts adipose tissue-derived mesenchymal stem cell expansion and differentiation. J. Transl. Med. 2014, 12, 8.
16. McIntosh, K.R.; Frazier, T.; Rowan, B.G.; Gimble, J.M. Evolution and future prospects of adipose-derived immunomodulatory cell therapeutics. Expert Rev. Clin. Immunol. 2013, 9, 175–184.
17. Kuroda, Y.; Matsumoto, T.; Hayashi, S.; Hashimoto, S.; Takayama, K.; Kirizuki, S.; Tsubosaka, M.; Kamenaga, T.; Takashima, Y.; Matsushita, T.; et al. Intra-articular autologous uncultured adipose-derived stromal cell transplantation inhibited the progression of cartilage degeneration. J. Orthop. Res. 2019, 37, 1376–1386.
18. Jeyaraman, M.; Muthu, S.; Ganie, P.A. Does the Source of Mesenchymal Stem Cell Have an Effect in the Management of Osteoarthritis of the Knee? Meta-Analysis of Randomized Controlled Trials. Cartilage 2020.
19. Lapuente, J.P.; Dos-Anjos, S.; Blázquez-Martínez, A. Intra-articular infiltration of adipose-derived stromal vascular fraction cells slows the clinical progression of moderate-severe knee osteoarthritis: Hypothesis on the regulatory role of intra-articular adipose tissue. J. Orthop. Surg. Res. 2020, 15, 137.

20. Pak, J.; Lee, J.H.; Pak, N.; Pak, Y.; Park, K.S.; Jeon, J.H.; Jeong, B.C.; Lee, S.H. Cartilage Regeneration in Humans with Adipose Tissue-Derived Stem Cells and Adipose Stromal Vascular Fraction Cells: Updated Status. Int. J. Mol. Sci. 2018, 19, 2146.
21. Baer, P.C. Adipose-Derived Stromal/Stem Cells. Cells 2020, 9, 1997.
22. Michalek, J.; Moster, R.; Lukac, L.; Proefrock, K.; Petrasovic, M.; Rybar, J.; Capkova, M.; Chaloupka, A.; Darinskas, A.; Michalek, J.S.; et al. WITHDRAWN: Autologous adipose tissue-derived stromal vascular fraction cells application in patients with osteoarthritis. Cell Transpl. 2015, 20, 1–36.
23. Wu, L.; Prins, H.J.; Leijten, J.; Helder, M.N.; Evseenko, D.; Moroni, L.; van Blitterswijk, C.A.; Lin, Y.; Karperien, M. Chondrocytes Cocultured with Stromal Vascular Fraction of Adipose Tissue Present More Intense Chondrogenic Characteristics Than with Adipose Stem Cells. Tissue Eng. Part. A 2016, 22, 336–348.
24. Jurgens, W.J.; Kroeze, R.J.; Zandieh-Doulabi, B.; van Dijk, A.; Renders, G.A.; Smit, T.H.; van Milligen, F.J.; Ritt, M.J.; Helder, M.N. One-step surgical procedure for the treatment of osteochondral defects with adipose-derived stem cells in a caprine knee defect: A pilot study. BioResearch Open Access 2013, 2, 315–325.
25. Sohni, A.; Verfaillie, C.M. Mesenchymal stem cells migration homing and tracking. Stem Cells Int. 2013, 2013, 130763.
26. Bora, P.; Majumdar, A.S. Adipose tissue-derived stromal vascular fraction in regenerative medicine: A brief review on biology and translation. Stem Cell Res. 2017, 8, 145.
27. Schulze-Tanzil, G. Experimental Therapeutics for the Treatment of Osteoarthritis. J. Exp. Pharm. 2021, 13, 101–125.
28. Rong, Y.; Liu, W.; Wang, J.; Fan, J.; Luo, Y.; Li, L.; Kong, F.; Chen, J.; Tang, P.; Cai, W. Neural stem cell-derived small extracellular vesicles attenuate apoptosis and neuroinflammation after traumatic spinal cord injury by activating autophagy. Cell Death Dis. 2019, 10, 340.
29. Deng, S.; Zhou, X.; Ge, Z.; Song, Y.; Wang, H.; Liu, X.; Zhang, D. Exosomes from adipose-derived mesenchymal stem cells ameliorate cardiac damage after myocardial infarction by activating S1P/SK1/S1PR1 signaling and promoting macrophage M2 polarization. Int. J. Biochem. Cell Biol. 2019, 114, 105564.
30. D'Arrigo, D.; Roffi, A.; Cucchiarini, M.; Moretti, M.; Candrian, C.; Filardo, G. Secretome and Extracellular Vesicles as New Biological Therapies for Knee Osteoarthritis: A Systematic Review. J. Clin. Med. 2019, 8, 1867.
31. Tao, S.C.; Yuan, T.; Zhang, Y.L.; Yin, W.J.; Guo, S.C.; Zhang, C.Q. Exosomes derived from miR-140-5p-overexpressing human synovial mesenchymal stem cells enhance cartilage tissue

regeneration and prevent osteoarthritis of the knee in a rat model. Theranostics 2017, 7, 180–195.

32. Zhang, J.; Rong, Y.; Luo, C.; Cui, W. Bone marrow mesenchymal stem cell-derived exosomes prevent osteoarthritis by regulating synovial macrophage polarization. Aging (Albany NY) 2020, 12, 25138–25152.
33. Wang, Y.; Yu, D.; Liu, Z.; Zhou, F.; Dai, J.; Wu, B.; Zhou, J.; Heng, B.C.; Zou, X.H.; Ouyang, H.; et al. Exosomes from embryonic mesenchymal stem cells alleviate osteoarthritis through balancing synthesis and degradation of cartilage extracellular matrix. Stem Cell Res. 2017, 8, 189.
34. Tofiño-Vian, M.; Guillén, M.I.; Pérez Del Caz, M.D.; Silvestre, A.; Alcaraz, M.J. Microvesicles from Human Adipose Tissue-Derived Mesenchymal Stem Cells as a New Protective Strategy in Osteoarthritic Chondrocytes. Cell Physiol. Biochem. 2018, 47, 11–25.
35. Cosenza, S.; Toupet, K.; Maumus, M.; Luz-Crawford, P.; Blanc-Brude, O.; Jorgensen, C.; Noël, D. Mesenchymal stem cells-derived exosomes are more immunosuppressive than microparticles in inflammatory arthritis. Theranostics 2018, 8, 1399–1410.
36. Tan, S.S.H.; Tjio, C.K.E.; Wong, J.R.Y.; Wong, K.L.; Chew, J.R.J.; Hui, J.H.P.; Toh, W.S. Mesenchymal Stem Cell Exosomes for Cartilage Regeneration: A Systematic Review of Preclinical In Vivo Studies. Tissue Eng. Part. B Rev. 2021, 27, 1–13.
37. He, L.; He, T.; Xing, J.; Zhou, Q.; Fan, L.; Liu, C.; Chen, Y.; Wu, D.; Tian, Z.; Liu, B.; et al. Bone marrow mesenchymal stem cell-derived exosomes protect cartilage damage and relieve knee osteoarthritis pain in a rat model of osteoarthritis. Stem Cell Res. 2020, 11, 276.
38. Ragni, E.; Palombella, S.; Lopa, S.; Talò, G.; Perucca Orfei, C.; De Luca, P.; Moretti, M.; de Girolamo, L. Innovative Visualization and Quantification of Extracellular Vesicles Interaction with and Incorporation in Target Cells in 3D Microenvironments. Cells 2020, 9, 1180.
39. Nishiyama, K.; Okudera, T.; Watanabe, T.; Isobe, K.; Suzuki, M.; Masuki, H.; Okudera, H.; Uematsu, K.; Nakata, K.; Kawase, T. Basic characteristics of plasma rich in growth factors (PRGF): Blood cell components and biological effects. Clin. Exp. Dent. Res. 2016, 2, 96–103.
40. Wu, P.I.; Diaz, R.; Borg-Stein, J. Platelet-Rich Plasma. Phys. Med. Rehabil. Clin. N. Am. 2016, 27, 825–853.
41. Venator, K.P.; Frye, C.W.; Gamble, L.J.; Wakshlag, J.J. Assessment of a Single Intra-Articular Stifle Injection of Pure Platelet Rich Plasma on Symmetry Indices in Dogs with Unilateral or Bilateral Stifle Osteoarthritis from Long-Term Medically Managed Cranial Cruciate Ligament Disease. Vet. Med. 2020, 11, 31–38.
42. Anitua, E.; Sánchez, M.; Aguirre, J.J.; Prado, R.; Padilla, S.; Orive, G. Efficacy and safety of plasma rich in growth factors intra-articular infiltrations in the treatment of knee osteoarthritis. Arthroscopy 2014, 30, 1006–1017.

43. Garbin, L.C.; Olver, C.S. Platelet-Rich Products and Their Application to Osteoarthritis. J. Equine Vet. Sci. 2020, 86, 102820.
44. Ha, C.W.; Park, Y.B.; Jang, J.W.; Kim, M.; Kim, J.A.; Park, Y.G. Variability of the Composition of Growth Factors and Cytokines in Platelet-Rich Plasma From the Knee With Osteoarthritis. Arthroscopy 2019, 35, 2878–2884.e1.
45. Solakoglu, Ö.; Heydecke, G.; Amiri, N.; Anitua, E. The use of plasma rich in growth factors (PRGF) in guided tissue regeneration and guided bone regeneration. A review of histological, immunohistochemical, histomorphometrical, radiological and clinical results in humans. Ann. Anat. 2020, 231, 151528.
46. Cuervo, B.; Rubio, M.; Chicharro, D.; Damiá, E.; Santana, A.; Carrillo, J.M.; Romero, A.D.; Vilar, J.M.; Cerón, J.J.; Sopena, J.J. Objective Comparison between Platelet Rich Plasma Alone and in Combination with Physical Therapy in Dogs with Osteoarthritis Caused by Hip Dysplasia. Animals 2020, 10, 175.
47. Forogh, B.; Mianehsaz, E.; Shoaee, S.; Ahadi, T.; Raissi, G.R.; Sajadi, S. Effect of single injection of platelet-rich plasma in comparison with corticosteroid on knee osteoarthritis: A double-blind randomized clinical trial. J. Sports Med. Phys. Fit. 2016, 56, 901–908.
48. Zhao, J.; Huang, H.; Liang, G.; Zeng, L.F.; Yang, W.; Liu, J. Effects and safety of the combination of platelet-rich plasma (PRP) and hyaluronic acid (HA) in the treatment of knee osteoarthritis: A systematic review and meta-analysis. BMC Musculoskelet. Disord. 2020, 21, 224.
49. Huang, P.H.; Wang, C.J.; Chou, W.Y.; Wang, J.W.; Ko, J.Y. Short-term clinical results of intra-articular PRP injections for early osteoarthritis of the knee. Int. J. Surg. 2017, 42, 117–122.
50. Di, Y.; Han, C.; Zhao, L.; Ren, Y. Is local platelet-rich plasma injection clinically superior to hyaluronic acid for treatment of knee osteoarthritis? A systematic review of randomized controlled trials. Arthritis Res. 2018, 20, 128.
51. Dai, W.L.; Zhou, A.G.; Zhang, H.; Zhang, J. Efficacy of Platelet-Rich Plasma in the Treatment of Knee Osteoarthritis: A Meta-analysis of Randomized Controlled Trials. Arthroscopy 2017, 33, 659–670.e1.
52. Cole, B.J.; Karas, V.; Hussey, K.; Pilz, K.; Fortier, L.A. Hyaluronic Acid Versus Platelet-Rich Plasma: A Prospective, Double-Blind Randomized Controlled Trial Comparing Clinical Outcomes and Effects on Intra-articular Biology for the Treatment of Knee Osteoarthritis. Am. J. Sports Med. 2017, 45, 339–346.
53. Rasheed, N.; Hafeez, K.; Zaidi, I.H.; Askari, R.; Rasheed, N.; Khani, G.M.K. Role of platelet-rich plasma in early osteoarthritis of knee joint: Experience from a tertiary care center in Pakistan. J. Orthop. Surg. 2019, 27, 2309499019853953.

54. Rahimzadeh, P.; Imani, F.; Faiz, S.H.R.; Entezary, S.R.; Zamanabadi, M.N.; Alebouyeh, M.R. The effects of injecting intra-articular platelet-rich plasma or prolotherapy on pain score and function in knee osteoarthritis. Clin. Interv. Aging 2018, 13, 73–79.
55. Bennell, K.L.; Hunter, D.J.; Paterson, K.L. Platelet-Rich Plasma for the Management of Hip and Knee Osteoarthritis. Curr. Rheumatol. Rep. 2017, 19, 24.
56. Cook, C.S.; Smith, P.A. Clinical Update: Why PRP Should Be Your First Choice for Injection Therapy in Treating Osteoarthritis of the Knee. Curr. Rev. Musculoskelet. Med. 2018, 11, 583–592.
57. Taniguchi, Y.; Yoshioka, T.; Kanamori, A.; Aoto, K.; Sugaya, H.; Yamazaki, M. Intra-articular platelet-rich plasma (PRP) injections for treating knee pain associated with osteoarthritis of the knee in the Japanese population: A phase I and IIa clinical trial. Nagoya J. Med. Sci. 2018, 80, 39–51.
58. Kon, E.; Engebretsen, L.; Verdonk, P.; Nehrer, S.; Filardo, G. Clinical Outcomes of Knee Osteoarthritis Treated With an Autologous Protein Solution Injection: A 1-Year Pilot Double-Blinded Randomized Controlled Trial. Am. J. Sports Med. 2018, 46, 171–180.
59. Ornetti, P.; Nourissat, G.; Berenbaum, F.; Sellam, J.; Richette, P.; Chevalier, X. Under the aegis of the Osteoarthritis Section of the French Society for Rheumatology (Société Française de Rhumatologie, SFR) Does platelet-rich plasma have a role in the treatment of osteoarthritis? Jt. Bone Spine 2016, 83, 31–36.
60. Vilar, J.M.; Manera, M.E.; Santana, A.; Spinella, G.; Rodriguez, O.; Rubio, M.; Carrillo, J.M.; Sopena, J.; Batista, M. Effect of leukocyte-reduced platelet-rich plasma on osteoarthritis caused by cranial cruciate ligament rupture: A canine gait analysis model. PLoS ONE 2018, 13, e0194752.
61. Mirza, M.H.; Bommala, P.; Richbourg, H.A.; Rademacher, N.; Kearney, M.T.; Lopez, M.J. Gait Changes Vary among Horses with Naturally Occurring Osteoarthritis Following Intra-articular Administration of Autologous Platelet-Rich Plasma. Front. Vet. Sci. 2016, 3, 29.
62. Asjid, R.; Faisal, T.; Qamar, K.; Khan, S.A.; Khalil, A.; Zia, M.S. Platelet-rich Plasma-induced Inhibition of Chondrocyte Apoptosis Directly Affects Cartilage Thickness in Osteoarthritis. Cureus 2019, 11, e6050.
63. Sengul, A.T.; Buyukkkarabacak, Y.B.; Altunkaynak, B.Z.; Yetim, T.D.; Altun, G.Y.; Sengul, B.; Basoglu, A. Effects of platelet-rich plasma on cartilage regeneration after costal cartilage resection: A stereological and histopathological study. Acta Chir. Belg. 2017, 117, 21–28.
64. Sundaram, K.; Vargas-Hernández, J.S.; Sanchez, T.R.; Moreu, N.M.; Mont, M.A.; Higuera, C.A.; Piuzzi, N.S. Are Subchondral Intraosseous Injections Effective and Safe for the Treatment of Knee Osteoarthritis? A Systematic Review. J. Knee Surg. 2019, 32, 1046–1057.

65. Sánchez, M.; Delgado, D.; Pompei, O.; Pérez, J.C.; Sánchez, P.; Garate, A.; Bilbao, A.M.; Fiz, N.; Padilla, S. Treating Severe Knee Osteoarthritis with Combination of Intra-Osseous and Intra-Articular Infiltrations of Platelet-Rich Plasma: An Observational Study. Cartilage 2019, 10, 245–253.
66. Kim, J.R.; Yoo, J.J.; Kim, H.A. Therapeutics in Osteoarthritis Based on an Understanding of Its Molecular Pathogenesis. Int. J. Mol. Sci. 2018, 19, 674.
67. Hochberg, M.C.; Tive, L.A.; Abramson, S.B.; Vignon, E.; Verburg, K.M.; West, C.R.; Smith, M.D.; Hungerford, D.S. When Is Osteonecrosis Not Osteonecrosis?: Adjudication of Reported Serious Adverse Joint Events in the Tanezumab Clinical Development Program. Arthritis Rheumatol. 2016, 68, 382–391.
68. Toyoda, E.; Maehara, M.; Watanabe, M.; Sato, M. Candidates for Intra-Articular Administration Therapeutics and Therapies of Osteoarthritis. Int. J. Mol. Sci. 2021, 22, 3594.
69. Evans, C.H.; Ghivizzani, S.C.; Robbins, P.D. Arthritis gene therapy is becoming a reality. Nat. Rev. Rheumatol. 2018, 14, 381–382.
70. Venkatesan, J.K.; Rey-Rico, A.; Cucchiarini, M. Current Trends in Viral Gene Therapy for Human Orthopaedic Regenerative Medicine. Tissue Eng. Regen. Med. 2019, 16, 345–355.
71. Rodriguez-Merchan, E.C.; Valentino, L.A. The Role of Gene Therapy in Cartilage Repair. Arch. Bone Jt. Surg. 2019, 7, 79–90.
72. Rai, M.F.; Pham, C.T. Intra-articular drug delivery systems for joint diseases. Curr. Opin. Pharm. 2018, 40, 67–73.
73. Mohammadinejad, R.; Ashrafizadeh, M.; Pardakhty, A.; Uzieliene, I.; Denkovskij, J.; Bernotiene, E.; Janssen, L.; Lorite, G.S.; Saarakkala, S.; Mobasheri, A. Nanotechnological Strategies for Osteoarthritis Diagnosis, Monitoring, Clinical Management, and Regenerative Medicine: Recent Advances and Future Opportunities. Curr. Rheumatol. Rep. 2020, 22, 12.

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