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Advancements in Regenerative Medicine for Articular Cartilage Repair in the Management of Osteoarthritis: A Review of Modern Treatment Methods

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ABSTRACT

Osteoarthritis (OA) is the most common form of chronic joint diseases, and its treatment still remains difficult with the current state of medicine. In this review, modern regenerative methods used in the repair of articular cartilage, both traditional techniques and innovative cellular therapies, are described. It focuses on the most updated treatment modalities, discussing, among other methods, microfracture, osteochondral grafts, autologous chondrocyte implantation (ACI), novel approaches of matrix-assisted autologous chondrocyte transplantation (MACT) and mesenchymal stem cell (MSC) treatments, with especial regard toward the use of platelet-rich plasma (PRP) in relation to other intra-articular injections, namely hyaluronic acid and ozone therapy. The regenerative treatments analyzed in this review have great potential in cartilage defect repair and possible symptom alleviation for OA; long-term efficacy, however, and limitations of cost and invasiveness do have to be more extensively considered. Another discussion concerns macrophages, modulators of the inflammatory environment of the joint, and whether they could serve as potential therapeutic targets. The need for further investigation, in order to modify the existing methods and create other effective regenerative approaches in patients suffering from OA, is presented.

Keywords: osteoarthritis, articular cartilage repair, stem cells, regenerative medicine, cartilage regeneration

INTRODUCTION

Despite all the advances in medical research, there remains a paucity of effective treatments for OA, which is the most common chronic disorder affecting joints, while no interventions have proven to halt or reduce disease progression [1]. The development of OA is driven by the complicated interaction among mechanical, cellular, and biochemical processes occurring in the joint, synovium, periosteum, and subchondral bone [2]. Age is one of the major risk factors for all joints in the case of OA. The rising prevalence and incidence of OA with advancing age likely result from prolonged exposure to risk factors and age-related biological changes, including cartilage thinning [3]. Cartilage is a dense, resilient connective tissue composed of chondrocytes and abundant extracellular matrix. Since the articular cartilage is avascular and without lymph glands, it has very limited availability of nutrients. This greatly diminishes the ability of the tissue to regenerate and its repair and restoration remain very difficult [2,4]. Different procedures have been attempted to try and stop the progression of cartilage lesions, using intra-articular injections with either hyaluronic acid or platelet-rich plasma (PRP), orthotics, and glycosaminoglycans. All these treatments have some drawbacks, especially if the defects are large or there is a significant deformity of the knee. Therefore, procedures like osteochondral transplants or bone marrow cell stimulation may be recommended in such conditions [5].

PLATELET-RICH PLASMA

PRP is a bioactive material derived from the patient's own blood, rich in a high concentration of growth factors and cytokines [6]. PRP contains a combination of pro-inflammatory and anti-inflammatory cytokines. Pro-inflammatory interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α) are of importance during cartilage catabolism; these cytokines stimulate joint cells to increase production of matrix metalloproteinases (MMPs), which contribute to the degradation of the cartilage matrix. Growth factors aid bone and soft tissue healing through hematoma formation, mesenchymal cell activity, chemotaxis, cell remodeling, angiogenesis,

and extracellular matrix production [7]. PRP can be classified into two types based on leukocyte concentration: pure PRP (P-PRP) and leukocyte PRP (L-PRP). It was demonstrated that leukocyte counts in PRP are associated with inflammatory mediators, e.g., interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α). Short-term results of a double-blind, randomized controlled clinical trial from October 2019 to October 2020 indicated that the P-PRP group, which carries a lower risk of early inflammation, had better clinical outcomes at the early postoperative rehabilitation phase and fewer adverse events when compared with the L-PRP group. However, long-term clinical efficacy of both injections was similar and decreased after 12 months [6]. Whereas several trials reported positive outcomes of PRP, recently published randomized controlled trial (RCT) raised doubts about the real benefits of this therapy and its superior efficacy compared with other intra-articular treatments [9].

PRP VERSUS OTHER INTRAARTICULAR INJECTIONS

Intra-articular injections are among the minimally invasive procedures suggested for the treatment of osteoarthritis, with a range of products including PRP, hyaluronic acid (HA), Plasma Rich in Growth Factor (PRGF), and ozone [10]. HA is a high molecular weight polysaccharide that is important for maintaining the integrity of both synovial fluid and articular cartilage. Intra-articular injections of HA increase joint lubrication, reduce cartilage wear and tear, nourish cartilage, and stimulate endogenous production of HA. These actions may delay further progression of joint diseases [8]. PRGF is a purified derivative of PRP that is leukocyte and inflammatory cytokine free. The formulation increases its efficacy while minimizing its adverse effects such as pain and swelling compared to PRP [11]. Recently, ozone therapy has drawn increasing interest in providing safe, low-cost OA treatments. With its ease of administration and affordability, intra-articular ozone injections are considered an effective approach for relieving OA symptoms [12]. The oxygen-ozone mixture improves tissue oxygenation, reduces pro-inflammatory cytokines, and limits leukocyte activation [13]. A study was conducted on 200 patients with mild to moderate knee osteoarthritis where the objective was to compare the results of different treatment groups—HA, PRP, PRGF, and ozone—using visual analog scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and Lequesne index. WOMAC, Lequesne and VAS scores significantly decreased in all groups two months after injection. The ozone group showed better improvement at two months, but its effect faded by 12 months. At six months from the injection, patients treated with HA, PRP, and PRGF had better scores compared to the ozone group, without any statistically significant differences among HA, PRP, and PRGF. Twelve

months post-injection, only patients treated with PRGF or PRP showed significantly better outcomes compared to those treated with HA or ozone [10]. Platelet concentrates demonstrate a progressive benefit that, although modest at earlier follow-ups, surpasses the placebo effect and outperforms other intraarticular treatments by 12 months, all without an elevated risk of adverse events [9].

MICROFRACTURE AND GRAFTING

Microfracture (MF), or marrow stimulation, is a surgical technique for cartilage defects smaller than 2 cm^2. It involves drilling small holes in the subchondral bone to connect the bone marrow with the cartilage [14]. Cartilage regeneration and defect area healing rely on the activity of stem cells in the bone marrow [15]. Patients undergoing MF often experience a decline in joint functionality within 24 months after surgery. Furthermore, its efficacy in delaying the progression of OA remains a subject of concern [14]. The use of osteochondral grafts to repair larger lesions (>2 cm^2) is another gold standard treatment. Autografts are osteochondral tissue segments harvested from low-load-bearing regions of a joint and transplanted into the site of the lesion [15]. In a defect, the implantation of normal tissue initiates integration and repair. A number of clinical trials demonstrate long-term effectiveness of osteochondral autografts with many outcomes reporting good results 10 years post-implantation, including rapid graft integration [16]. Osteochondral autografts are associated with some disadvantages, such as donor site morbidity and the limitation in the volume of tissue available for harvesting. Another surgical technique, mosaicplasty, was developed in order to avoid donor site morbidity; it involves harvesting small cartilage plugs from healthy tissue and transplanting them into small to medium-sized defect sites. However, using the patient's own tissue and inflicting an additional damage on the knee joint emphasize the need for alternative defect repair strategies [15]. Osteochondral allografts are another alternative to autografts and are usually harvested from young donors within 24 hours of death. These grafts have immunogenic risks and their shelf life is 28 days [17]. Though these treatments are effective in a clinical sense, tissue engineering and regenerative medicine focus on the development of new techniques of cartilage regeneration to overcome their inherent disadvantages [15].

AUTOLOGOUS CHONDROCYTE IMPLANTATION

Autologous Chondrocyte Implantation (ACI) is a two-step procedure for treating cartilage defects larger than 2 cm^2, wherein: step one is the harvest of chondrocytes from a non-load-

bearing area of the knee cartilage; and step two is the cell culture, expansion in vitro, and reintroduction of the cells into the defect site, which promotes its repair [15]. The reproducibility and durability of restored cartilage structure and function, along with the cost-effectiveness of the procedure, remain subjects of debate . In a randomized controlled trial from 2021 a costal cartilage was used as a source of graft for a repair of articular cartilage defects of the knee. Costal cartilage is also a good source of graft for rhinoplasty, laryngotracheal, canal wall, and auricular reconstruction, with low rates of complications and donor site morbidity. The study aimed to establish the efficacy and safety of costal chondrocyte-derived pellet-type autologous chondrocyte implantation (CCP-ACI), comparing it with microfracture. Cartilage defects treated with CCP-ACI showed satisfactory repair. At 24 and 48 weeks magnetic resonance imaging indicated good structural integration with native cartilage, significantly higher than those observed for microfracture treatment group [18].

MATRIX ASSISTED AUTOLOGOUS CHONDROCYTE TRANSPLANTATION

First-generation ACI improved clinical outcomes but was technically demanding, requiring periosteal patch sutures, and involved prolonged rehabilitation, often over a year before returning to sports. Matrix-assisted autologous chondrocyte transplantation (MACT) was developed to overcome limitations of first-generation ACI. [19]. Chondrocytes are harvested from patient cartilage, expanded in vitro, and subsequently seeded onto a three-dimensional matrix composed of porcine collagen membrane. This device couples a biomaterial matrix with cells in order to enhance cartilage regeneration by facilitating chondrocyte integration into native cartilage and the repair of defects [15]. MACT is superior to microfracture for defects up to 10 cm^2, showing better results in patient pain and functional scores. However, long-term results of MACT compared to microfracture remain relatively unknown. There is sparse literature comparing MACT to first-generation ACI, mosaicplasty, and mesenchymal stem cell (MSC) therapies, with no convincing differences in outcomes demonstrated [19].

STEM CELL THERAPIES

Cellular therapy involves the transplantation of human cells, such as hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), lymphocytes, dendritic cells, NK cells, and pancreatic islet cells, to repair or replace damaged tissue [20]. MSCs are of particular interest as a treatment for OA because of their immunomodulatory properties and potential for cartilage repair [21]. MSCs can be derived from various sources, including bone marrow,

adipose tissue, amniotic fluid, placenta, dental pulp, endometrium, menstrual blood, umbilical cord [20], skeletal muscle, synovium and periosteum. Of these, bone marrow and adipose tissue are the most accessible and utilized sources. Bone marrow was the first source of MSCs [21] and due to their high cell yield and robust proliferative capacity in vitro, bone marrow-derived MSCs (BM-MSCs) are a preferred choice [22]. Despite its advantages, obtaining MSCs from bone marrow for autologous use involves a highly invasive and painful procedure, often resulting in long-term donor site pain [21]. BM-MSCs are commonly harvested from the iliac crest [20]. Adipose tissue-derived mesenchymal stem cells (AMSCs) are typically harvested from the abdomen because of the high fat content. Compared with BM-MSCs, AMSCs exhibit more regenerative capacity by promoting neovascularization, resisting hypoxia-induced apoptosis, and showing higher telomerase activity. AMSCs, unlike BM-MSCs, also retain their differentiation and chondrogenic potential even with aging, and hence AMSCs are more fitting for the treatment of osteoarthritis in aged patients. AMSCs can also be isolated from the stromal vascular fraction (SVF) of adipose tissue with the advantage of a better harvest [21]. The Infrapatellar fat pad (IPFP) which is usually discarded after knee arthroscopic surgery is also an excellent source of MSCs. Using the IPFP reduces donor site damage compared to other tissues, while its MSCs have higher yield and greater differentiation potential. A study conducted at Shanghai Changzheng Hospital (April 2018–December 2019) demonstrated that knee arthroscopy combined with IPFP cell concentrates containing MSCs is safe, effectively reduces pain, and improves function in patients with knee cartilage lesions, particularly at six months post-surgery. These results provide a promising clinical strategy and will be useful information for future studies [23]. Synovial MSCs are one of the most promising sources of cells for cartilage repair and exhibit much higher chondrogenic potential compared with MSCs from other tissues. The number of MSCs in synovial fluid is elevated in osteoarthritic knees, suggesting their activity in regeneration. Arthroscopic-guided injection of primary cultured synovial mesenchymal stem cells (Sy-MSCs) in popliteal PRP combined with HA appears to have great potential for effective cartilage regeneration in the early stages of osteoarthritis. Further studies are required to evaluate long-term efficacy and durability of Sy-MSCs therapy as a new treatment for osteoarthritis [24].

MACROPHAGES

Synovial inflammation and articular inflammatory environment are pivotal drivers of chondrocyte apoptosis, hypertrophy, ectopic bone formation, and OA progression. Effective

OA treatment needs therapeutics that shift inflammation toward a pro-chondrogenic microenvironment. Macrophages in the synovial lining play here a critical role, with their polarization into pro-inflammatory (M1) or anti-inflammatory (M2) phenotypes influencing disease outcomes, as M2 macrophages are associated with wound healing. Recent evidence has shown that macrophage polarization can also be modulated by factors other than the traditional cytokines IL-4, IL-13, and IL-10. Physical exercise, for example, favors a type 2 immune response, promoting M2 polarization. In addition, exposure to oxidized low-density lipoproteins (oxLDL) has been associated with increased production of anabolic mediators such as TGF-β, which promotes tissue repair [25]. Although tissue-resident macrophages are considered pro-healing and bone marrow-derived macrophages pro-inflammatory, their role in OA pathogenesis requires further study [26].

CONCLUSION

The progress in regenerative medicine has significantly expanded the therapeutic strategies available for articular cartilage repair in osteoarthritis management. Traditional approaches such as microfracture and osteochondral grafting are still valuable, however, innovative therapies like autologous chondrocyte implantation, matrix-assisted techniques, and mesenchymal stem cell therapies hold great promise to overcome the limitations of earlier methods. Platelet-rich plasma and other intra-articular injections offer minimally invasive alternatives with variable efficacy, whereas macrophage-targeted therapies and other biologics represent emerging frontiers in modulating joint inflammation and promoting repair.

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AUTHORS'S CONTRIBUTION

Conceptualization: JD, MP, JŚ, GT, KS

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Software: JD, JW, KD, MP, JŚ

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REFERENCES:

1. Jang S, Lee K, Ju JH. Recent Updates of Diagnosis, Pathophysiology, and Treatment on Osteoarthritis of the Knee. Int J Mol Sci. 2021 Mar 5;22(5):2619. doi: 10.3390/ijms22052619. PMID: 33807695; PMCID: PMC7961389.

2. Householder NA, Raghuram A, Agyare K, Thipaphay S, Zumwalt M. A Review of Recent Innovations in Cartilage Regeneration Strategies for the Treatment of Primary Osteoarthritis of the Knee: Intra-articular Injections. Orthop J Sports Med. 2023 Apr 27;11(4):23259671231155950. doi: 10.1177/23259671231155950. PMID: 37138944; PMCID: PMC10150434.

3. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. Clin Geriatr Med. 2010 Aug;26(3):355-69. doi: 10.1016/j.cger.2010.03.001. Erratum in: Clin Geriatr Med. 2013 May;29(2):ix. PMID: 20699159; PMCID: PMC2920533.

4. Guo X, Xi L, Yu M, Fan Z, Wang W, Ju A, Liang Z, Zhou G, Ren W. Regeneration of articular cartilage defects: Therapeutic strategies and perspectives. J Tissue Eng. 2023 Mar 31;14:20417314231164765. doi: 10.1177/20417314231164765. PMID: 37025158; PMCID: PMC10071204.

5. Jarecki J, Waśko MK, Widuchowski W, Tomczyk-Warunek A, Wójciak M, Sowa I, Blicharski T. Knee Cartilage Lesion Management-Current Trends in Clinical Practice. J Clin

Med. 2023 Oct 10;12(20):6434. doi: 10.3390/jcm12206434. PMID: 37892577; PMCID: PMC10607427.
6. Zhou Y, Li H, Cao S, Han Y, Shao J, Fu Q, Wang B, Wu J, Xiang D, Liu Z, Wang H, Zhu J, Qian Q, Yang X, Wang S. Clinical Efficacy of Intra-Articular Injection with P-PRP Versus that of L-PRP in Treating Knee Cartilage Lesion: A Randomized Controlled Trial. Orthop Surg. 2023 Mar;15(3):740-749. doi: 10.1111/os.13643. Epub 2023 Jan 16. PMID: 36647244; PMCID: PMC9977604.
7. Peng J, Wang Q, Xu Y, He H. Platelet-rich plasma treatment for talar cartilage repair: a systematic review and meta-analysis. BMC Musculoskelet Disord. 2023 May 9;24(1):366. doi: 10.1186/s12891-023-06466-y. PMID: 37161527; PMCID: PMC10169378.
8. Zhao J, Huang H, Liang G, Zeng LF, 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 Apr 11;21(1):224. doi: 10.1186/s12891-020-03262-w. PMID: 32278352; PMCID: PMC7149899.
9. Filardo G, Previtali D, Napoli F, Candrian C, Zaffagnini S, Grassi A. PRP Injections for the Treatment of Knee Osteoarthritis: A Meta-Analysis of Randomized Controlled Trials. Cartilage. 2021 Dec;13(1_suppl):364S-375S. doi: 10.1177/1947603520931170. Epub 2020 Jun 19. PMID: 32551947; PMCID: PMC8808870.
10. Raeissadat SA, Ghazi Hosseini P, Bahrami MH, Salman Roghani R, Fathi M, Gharooee Ahangar A, Darvish M. The comparison effects of intra-articular injection of Platelet Rich Plasma (PRP), Plasma Rich in Growth Factor (PRGF), Hyaluronic Acid (HA), and ozone in knee osteoarthritis; a one year randomized clinical trial. BMC Musculoskelet Disord. 2021 Feb 3;22(1):134. doi: 10.1186/s12891-021-04017-x. PMID: 33536010; PMCID: PMC7860007.
11. Filardo G, Di Matteo B, Di Martino A, Merli ML, Cenacchi A, Fornasari P, Marcacci M, Kon E. Platelet-Rich Plasma Intra-articular Knee Injections Show No Superiority Versus Viscosupplementation: A Randomized Controlled Trial. Am J Sports Med. 2015 Jul;43(7):1575-82. doi: 10.1177/0363546515582027. Epub 2015 May 7. PMID: 25952818.
12. Sconza C, Respizzi S, Virelli L, Vandenbulcke F, Iacono F, Kon E, Di Matteo B. Oxygen-Ozone Therapy for the Treatment of Knee Osteoarthritis: A Systematic Review of Randomized Controlled Trials. Arthroscopy. 2020 Jan;36(1):277-286. doi: 10.1016/j.arthro.2019.05.043. Epub 2019 Oct 31. PMID: 31679646.
13. Raeissadat SA, Rayegani SM, Forogh B, Hassan Abadi P, Moridnia M, Rahimi Dehgolan S. Intra-articular ozone or hyaluronic acid injection: Which one is superior in patients with

knee osteoarthritis? A 6-month randomized clinical trial. J Pain Res. 2018 Jan 4;11:111-117. doi: 10.2147/JPR.S142755. PMID: 29379312; PMCID: PMC5757972.

14. Gou GH, Tseng FJ, Wang SH, Chen PJ, Shyu JF, Weng CF, Pan RY. Autologous Chondrocyte Implantation Versus Microfracture in the Knee: A Meta-analysis and Systematic Review. Arthroscopy. 2020 Jan;36(1):289-303. doi: 10.1016/j.arthro.2019.06.033. Epub 2019 Nov 7. PMID: 31708355.

15. Makarczyk MJ. Cell Therapy Approaches for Articular Cartilage Regeneration. Organogenesis. 2023 Dec 31;19(1):2278235. doi: 10.1080/15476278.2023.2278235. Epub 2023 Nov 14. PMID: 37963189; PMCID: PMC10898818.

16. Dekker TJ, Aman ZS, DePhillipo NN, Dickens JF, Anz AW, LaPrade RF. Chondral Lesions of the Knee: An Evidence-Based Approach. J Bone Joint Surg Am. 2021 Apr 7;103(7):629-645. doi: 10.2106/JBJS.20.01161. PMID: 33470591.

17. Elder S, Chenault H, Gloth P, Webb K, Recinos R, Wright E, Moran D, Butler J, Borazjani A, Cooley A. Effects of antigen removal on a porcine osteochondral xenograft for articular cartilage repair. J Biomed Mater Res A. 2018 Aug;106(8):2251-2260. doi: 10.1002/jbm.a.36411. Epub 2018 May 25. PMID: 29577591; PMCID: PMC6779129.

18. Yoon KH, Yoo JD, Choi CH, Lee J, Lee JY, Kim SG, Park JY. Costal Chondrocyte-Derived Pellet-Type Autologous Chondrocyte Implantation versus Microfracture for Repair of Articular Cartilage Defects: A Prospective Randomized Trial. Cartilage. 2021 Dec;13(1_suppl):1092S-1104S. doi: 10.1177/1947603520921448. Epub 2020 Jun 1. PMID: 32476445; PMCID: PMC8808917.

19. Everhart JS, Jiang EX, Poland SG, Du A, Flanigan DC. Failures, Reoperations, and Improvement in Knee Symptoms Following Matrix-Assisted Autologous Chondrocyte Transplantation: A Meta-Analysis of Prospective Comparative Trials. Cartilage. 2021 Dec;13(1_suppl):1022S-1035S. doi: 10.1177/1947603519870861. Epub 2019 Sep 11. PMID: 31508998; PMCID: PMC8808777.

20. Jeyaraman M, Muthu S, Ganie PA. 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. 2021 Dec;13(1_suppl):1532S-1547S. doi: 10.1177/1947603520951623. Epub 2020 Aug 25. PMID: 32840122; PMCID: PMC8808923.

21. Agarwal N, Mak C, Bojanic C, To K, Khan W. Meta-Analysis of Adipose Tissue Derived Cell-Based Therapy for the Treatment of Knee Osteoarthritis. Cells. 2021 Jun 1;10(6):1365. doi: 10.3390/cells10061365. PMID: 34206010; PMCID: PMC8228374.

22. Harrell CR, Markovic BS, Fellabaum C, Arsenijevic A, Volarevic V. Mesenchymal stem cell-based therapy of osteoarthritis: Current knowledge and future perspectives. Biomed Pharmacother. 2019 Jan;109:2318-2326. doi: 10.1016/j.biopha.2018.11.099. Epub 2018 Nov 29. PMID: 30551490.

23. Zhou Y, Li H, Xiang D, Shao J, Fu Q, Han Y, Zhu J, Chen Y, Qian Q. The clinical efficacy of arthroscopic therapy with knee infrapatellar fat pad cell concentrates in treating knee cartilage lesion: a prospective, randomized, and controlled study. J Orthop Surg Res. 2021 Jan 28;16(1):87. doi: 10.1186/s13018-021-02224-9. PMID: 33509248; PMCID: PMC7841893.

24. Tjandra KC, Novriansyah R, Sudiasa INS, Ar A, Rahmawati NAD, Dilogo IH. Modified Mesenchymal stem cell, platelet-rich plasma, and hyaluronic acid intervention in early stage osteoarthritis: A systematic review, meta-analysis, and meta-regression of arthroscopic-guided intra-articular approaches. PLoS One. 2024 Mar 8;19(3):e0295876. doi: 10.1371/journal.pone.0295876. PMID: 38457479; PMCID: PMC10923406.

25. Fernandes TL, Gomoll AH, Lattermann C, Hernandez AJ, Bueno DF, Amano MT. Macrophage: A Potential Target on Cartilage Regeneration. Front Immunol. 2020 Feb 11;11:111. doi: 10.3389/fimmu.2020.00111. PMID: 32117263; PMCID: PMC7026000.

26. Wu CL, Harasymowicz NS, Klimak MA, Collins KH, Guilak F. The role of macrophages in osteoarthritis and cartilage repair. Osteoarthritis Cartilage. 2020 May;28(5):544-554. doi: 10.1016/j.joca.2019.12.007. Epub 2020 Jan 8. PMID: 31926267; PMCID: PMC7214213.