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Chapter

Regenerative Medicine

Armen Haroutunian, Tennison Malcolm and Thomas Zouki

Abstract

Chronic pain is a debilitating condition that affects millions of people world-wide, leading to physical incapacitation and financial strain. Common methods for treatment include physical therapy, oral medications, injections, surgery, and neuromodulation. Injectates with steroids and local anesthetics can be a temporizing measure with intolerable side effects. The use of autologous biologic injectates (e.g., platelet rich plasma, bone marrow aspirate concentrate, tissue grafts, and stem cells) is growing in therapeutic potential and enthusiasm, giving hope to a subset of patients that have either failed conventional therapy or are not candidates for traditional steroid injections. In this chapter, we will describe different cases in which regenerative medicine can help in painful conditions as well as neuro-degenerative conditions. Regenerative medicine can be the new frontier in providing long lasting relief through changes in cell-signaling cascades, however further trials are needed to validate their use.

Keywords: platelet rich plasma (PRP), stem cell therapy, bone marrow aspirate concentrate (BMAC), adipose tissue grafts, exosomes, mesenchymal stem cells, hematopoetic stem cells (HCC's), pain management, regenerative medicine

1. Introduction

Chronic pain is a public health issue, affecting nearly a quarter of our population, and takes different forms such as neuropathic, cancer-related or inflammatory pain [1]. This condition limits patients in their daily activities leading to despair and significant loss in quality of life. The most common methods of treatment include physical therapy, oral medications, injections, surgery and neuromodulation. The injectates that are the most commonly used include local anesthetics and steroids. The use of autologous biologic injectates (e.g., platelet rich plasma, bone marrow aspirate concentrate, tissue grafts, and stem cells) is growing in therapeutic potential and enthusiasm, giving hope to a subset of patients that have either failed conventional therapy or are not candidates for traditional steroid injections. Continued clinical trials are needed to further validate their use and help expand their application in the field of medicine. The theory of using these therapies for painful conditions stems from their cytoprotective properties, as well as their regenerative potential.

2. Terminology, history, and background

The most common types of regenerative medicine therapies include platelet rich plasma (PRP), stem cell therapy from bone marrow aspirate concentrate (BMAC) and adipose tissue grafts, and exosomes. Regenerative therapies are growing worldwide

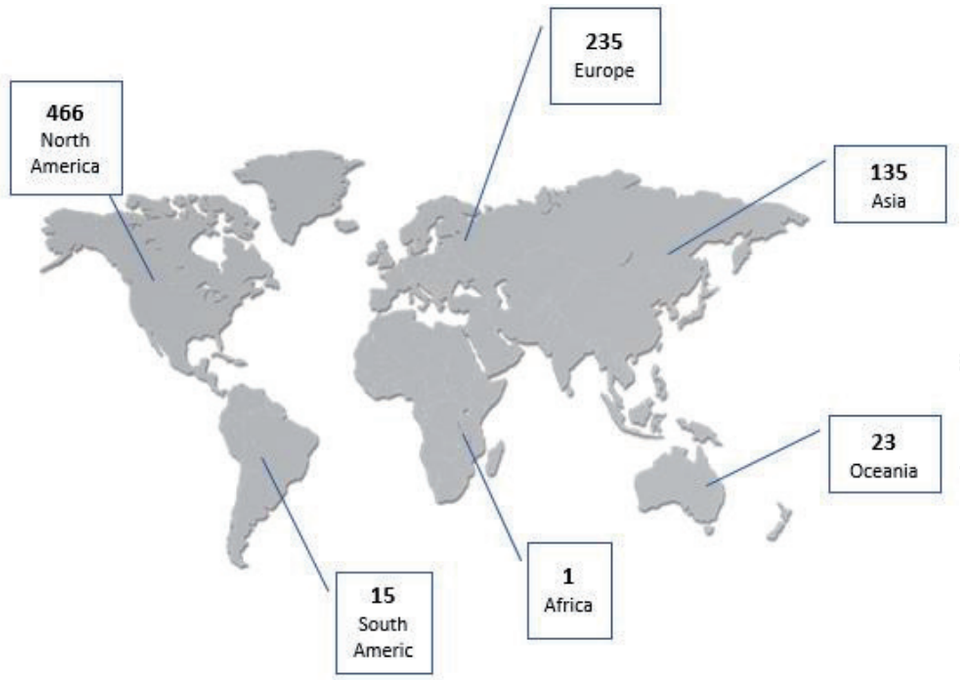

Figure 1.
An atlas of regenerative medicine therapies worldwide. Adapted from alliance for regenerative medicine.

(**Figure 1**). They are increasing from 164% in 1 year with a total of 4.1 billion dollars in total global funding [2]. These therapies can be used in conjunction or individually, and there is no set algorithm or protocol that dictates superiority [3]. Stem cell therapy in this article will refer to adult stem cells, which are multipotent and have no ethical concerns related to their use, as opposed to embryonic stem cells [4]. Typically, candidates include patients with chronic peripheral joint pain that have not responded to steroid injections, or cannot tolerate the medication due to side effects, including but not limited to hyperglycemia, hypertension, ineffective wound healing, or adrenal gland suppression. Although there is no set protocol, some studies recommend implementing a series of three injections for PRP [5]. However, some physicians may grade progress and response to the initial injection as a rationale for a repeat injection.

2.1 Platelet rich plasma

PRP is the most common and readily available treatment option. It is the plasma fraction of blood with a high platelet concentration, as well as clotting factors, growth factors, chemokines, cytokines, and other plasma proteins [6]. This therapy helps promote stem cell migration as well as healing [7]. Commonly injected into joints and tendons for repair, PRP was first coined in the 1970's and used to describe the platelet count in peripheral blood, used to transfuse patients with thrombocytopenia [6]. PRP is obtained from blood after centrifuge, which helps separate components based on density gradients (**Figure 2**). Devices used to simplify the preparation of PRP are said to amplify the concentration of PRP 2–5 times the baseline [7]. Despite the limited clinical evidence that exists, PRP has been used to initiate healing for a variety of cases, most commonly including osteoarthritis (OA), lateral epicondylitis, rotator cuff tears, ligament and tendon injuries [7]. Recent randomized control trials actually demonstrate benefit in tendinopathy [7]. It has also been suggested that PRP can play a role in elimination neuropathic pain, thought to be secondary to a cascade of inflammation followed by repair via axon and tissue regeneration [8]. PRP has also been used as an intervertebral disc injection for low

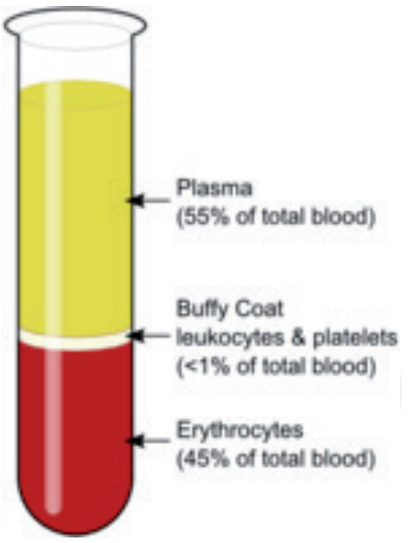

Figure 2.
Blood components after centrifugation.

back pain with promising clinical results, however more randomized controlled trials are needed [3]. Success of this therapy will ultimately depend on the preparation and composition of the injectate, location, and type and extent of injury.

2.2 Adipose tissue grafts

Stem cell therapy uses non-embryonic adult stem cells described as multipotent stem cells, and in the clinical setting refers to therapy with mesenchymal (often from adipose tissue) and hematopoietic stem cells (often from bone marrow aspirate) [3]. These cells are present in a variety of tissues (adipocytes, chondrocytes, myocytes) and are thought to play a role in immune modulation [3]. The most common source of mesenchymal stem cells (MSC) are found in adipose tissue, first discovered in 1964 by Rodell [2]. There are approximately 500 to 2500× times more MSC's when compared to bone marrow [3]. Adipose derived stem cells (ASC's) are the most promising stem cells identified in humans, since adipose tissue is easily obtained in large quantities with small donor site discomfort [4]. Sites of harvest include the abdomen, upper arm, thigh, and trochanteric fat deposits. Common mechanisms to obtain fat include liposuction or lipectomy, followed by homogenization and enzymatic digestions. Traditional cosmetic liposuction can remove large volume (>4 kg) or small volume (<4 kg) adipose tissue, however for purposes of adipose tissue grafting only 100–200 mL may be needed [9]. The resultant material is then centrifuged. Each gram of adipose tissue yields 5 × 10^3 stem cells, significantly greater than bone marrow [4]. It is important to note that stem cell harvesting is more invasive that a simple blood draw for PRP, and could thus lead to an increase risk for infection or complication for patients undergoing MSC harvesting [10]. If performed under local or tumescent anesthesia, there is minimal to no recovery time. To date, hundreds of trials are listed on the United States National Institutes of Health website (NIH) for the use of ASC's. Examples of applications include soft tissue regeneration, skeletal tissue repair, myocardial infarction, immune disorders such as lupus, multiple sclerosis, Crohn's disease, diabetes.

2.3 Bone marrow aspirate concentrate

Bone marrow aspiration is a procedure in which bone marrow is collected, usually from the pelvic iliac crest [11]. The procedure is very similar to PRP, in which the

product is centrifuged. The final product is called bone marrow aspirate concentrate, or BMAC, which contains mostly hematopoetic stem cells (HCC's), and a much smaller concentration of MSCs [3]. Like MSC's, HSC's also contain growth factors and immunomodulating enzymes [11]. Unlike adipose aspiration, the concentration of MSC's in bone marrow dramatically decreases with age. Like ASCs, BMAC is also used to treat various conditions affecting tendons, ligaments, and musculoskeletal injuries. Approximately 60 mL of aspirate can produce 10 mL of BMAC after centrifuge [11]. Again, efficacy is determined by location of injection as well as extent of tissue injury. Sites include shoulders, knees, hips, various tendons, and sometimes spinal facet joints. Current literature demonstrates benefit in utilizing BMAC as an adjunct in cartilage healing, faster time to bony union, and lower rates of tendon re-rupture [11].

2.4 Exosomes

Exosomes are endocytic vesicles released by various cells including T-cells, B-cells, reticulocytes, mast cells, platelets, tumor cells as well as MSCs [12]. They are membrane-enclosed particles surrounded by a phospholipid layer and are enriched with micro-RNAs (miRNAs) which are believed to regulate gene expression in a post-transcriptional matter and, by that matter, play a role in tissue repair and regeneration [13, 14]. They are defined as nanosized membrane vesicles with a diameter of 30–100 nm that originate from multivesicular bodies (MVB's) and are released by cells into extracellular environment (**Figure 3**) [12]. They are cholesterol-rich phospholipid vesicles. There are multiple contents that are found in exosomes including cytokines, proteins, lipids, mRNAs, miRNAs and ribosomal RNAs [15, 16]. Current recommendations for extraction of exosomes suggest ultracentrifugation at high speeds which removes cells and microvesicles. It is time consuming, labor intensive, and has therefore lead to commercially available kits, such as Exoquick ©, Invitrogen ©, and Exo-Spin ©, which reliably reduce operating time to 2 hours. Exosomes ultimately have the capacity to execute specific targeted therapy due to their ability to envelope a wide range of specific contents, including lipids, RNA's, and specific protein-signaling molecules [17]. This makes them a promising tool in nanomedicine; however, like PRP and MSC's, classification and purification needs to be standardized to ensure appropriate randomized and multicenter studies.

2.5 Mechanism of action and biology

The mechanism by which these injections treat pain is still unknown and remains mainly theoretical [15]. Platelets, also called thrombocytes, contain several secretory

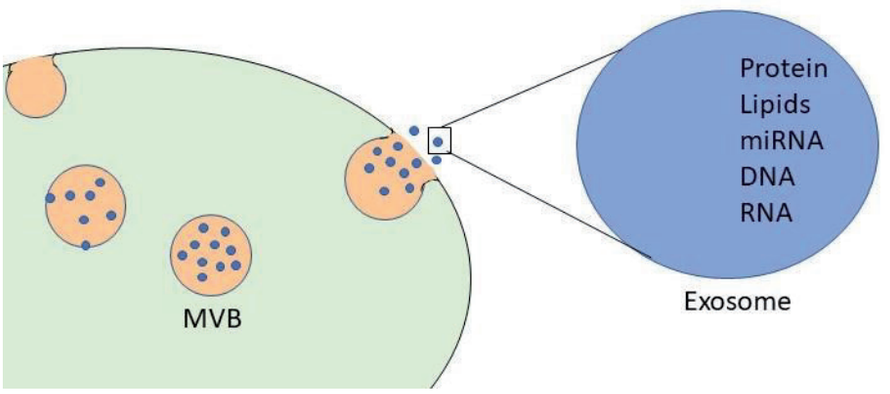

Figure 3.
Multivesicular bodies (MVB's) releasing exosomes.

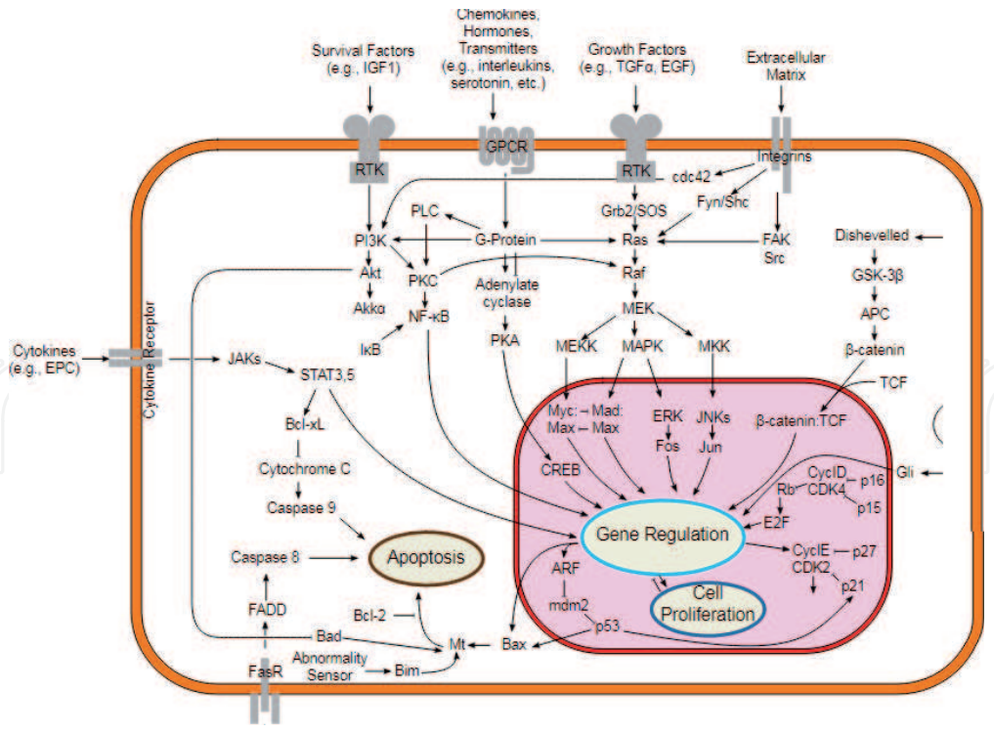

Figure 4.
Signal transduction pathways.

granules crucial to platelet function. Platelets are primarily responsible for aggregation and contribute to hemostasis through adhesion, activation, and aggregation. In recent years, research has demonstrated that platelets not only have a function in hemostasis, but also carry an abundance of growth factors and cytokines that affect inflammation, stem cell migration, and proliferation [8]. Upon activation of platelets in PRP, important growth factors, namely endothelial growth factor, fibroblast growth factor, platelet derived growth factor, epidermal growth factor, hepatocyte growth factor, matrix metalloproteinases, and interleukin 8 are released and modify the local tissue through a complex cell signaling cascade (**Figure 4**) [6].

There is increasing surfacing evidence suggesting that MSC's secrete functional paracrine factors which promote tissue regeneration, protection and repair [18–21]. Recent studies revealed that factors are released through particles known as exosomes. There is now strong belief that these exosomes secreted by MSCs are responsible for the tissue regeneration and repair rather that the ability of MSCs to trans-differentiate. They are suggested as central mediators of intercellular communication by transferring proteins, mRNAs and miRNAs to adjacent cells leading to coordinative function in organisms. Those, depending on the medium in which they are collected can halt breast cancer metastasis, regulate angiogenesis, remodel neurites and promote neurogenesis [22, 23].

Exosomes aggressively participate in the inhibition of the inflammation process. This known property of exosomes is now being considered as a novel therapeutic approach to many disease processes affecting different organ systems. Indeed, the benefits of the anti-inflammatory properties of exosomes has not only been demonstrated in various painful conditions, but also in cardiovascular and pulmonary diseases as well. MSCs-secreting exosomes lead to a reduction of white blood cell count and reduced inflammation in hearts after ischemia-reperfusion injury, which in turn decrease infarct size and enhance cardiac function. Protective properties have also been shown in the lungs for relieving symptoms of pulmonary hypertension [24, 25]. MSCs are adult multipotent cells with the ability to self-renew and differentiate into mesenchymal lineage such as osteoblasts, chondrocytes and

adipocytes [26]. MSCs were originally isolated from bone marrow, they have been isolated from other adult tissues such as adipose tissue, dental pulp, placenta, amniotic fluid, umbilical cord blood and Wharton's jelly, and even in the brain [27]. The MSCs differentiation potential for tissue repair has been studied extensively but the pattern of MSC mediated regeneration is now shifting toward secretome-based paracrine activity. The matter by which miRNAs play an essential role in physiological and pathological conditions is by regulating gene expression at the post-transcription level [28]. The pre-miRNA goes through an extensive biological process prior to maturation but an exosome can contain miRNA of different maturation stages and their release is a controlled process dependent on the source and developmental stage of derived cells rather than a random process [12]. It has been suggested that exosomes released by MSCs contain miRNA that control the microenvironment in the resident niches through a balance between proliferation and differentiation [29]. Additionally, tissue-specific responses have been described for exosomes isolated from different sources. For example, adipose tissue-derived exosomes seem to be more effective in halting the central nervous system degeneration caused by Alzheimer's disease when compared to bone marrow derived MSCs-derived exosomes [30]. But neurite outgrowth seems to be more responsive to exosomes released by menstrual fluid derived MSCs when compared to umbilical cord, chorion and bone marrow. Evidence of neurite outgrowth has also been shown in a middle cerebral artery occlusion model. MSCs exposed to ischemic cerebral extracts secreted exosomes containing mi-RNA that were transferred to neurons and astrocytes via exosomes and promoted neurite outgrowth and functional recovery. The same authors reported the use of cell free MSC-generated exosomes administered intravenously in a subject that had suffered a stroke lead to improved neurite remodeling, neurogenesis and angiogenesis which in turn significantly improved the functional recovery of the subject [31]. A similar experiment in which intravenous administration of MSCs-generated exosomes enhanced angiogenesis and neurogenesis reduced the inflammation, improved spatial learning and sensory/motor function in a traumatic brain injury model [32].

2.6 Clinical applications

At present, the use of autologous biologic injectates in the treatment of most acute and chronic conditions resulting in pain is considered investigational. There are currently 977 regenerative medicine trials worldwide, including gene therapy, cell therapy, and tissue engineering [2]. Of those, there at 51 and 66 clinical trials in the categories of musculoskeletal system and central nervous system, respectively. While a myriad of sources has reported positive results following the use of autologous biologic injectate, these reports are, overall, too heterogenous and underpowered to change the clinical practice of most. The absence of well-powered, level-1 data is demonstrating the efficacy of autologous biologic injectates may simply reflect the infancy of this field. Conditions recently studied for the use of autologous blood injectates include Complex Regional Pain syndrome (formerly called Reflex Sympathetic Dystrophy or RSD), OA, joint arthropathy including facet arthropathy and sacroiliitis, tendinopathies, degenerative disc disease, Multiple Sclerosis, headaches, migraines, and peripheral neuropathy. In this chapter we will discuss autologous biologic injectates in the treatment of OA, spondylosis, and tendon and ligament injury.

2.7 Osteoarthritis

Osteoarthritis (OA) is the most common joint disorder in the United States, and is estimated to 25% of people over 18-years old [33, 34]. OA is a progressive

disease affecting the joints and is characterized by perturbed immune responses to cellular injury resulting in cartilage degeneration, synovitis, bony remodeling, and chronic pain. Current treatment includes NSAIDs, opiate medications, topical analgesics, physical therapy, lifestyle modification, intraarticular steroid injections, intra-articular hyaluronic acid (HA) injection, and surgery. Non-steroidal anti-inflammatory drugs (NSAIDs), opiates, and intra-articular steroid injections are primarily limited negative side-effects that accompany escalations in medication dose and frequency. Exogenous HA has been used as a treatment modality given observed decreases in endogenous HA exhibited in OA joints. However, due to a lack of consistent evidence, HA is not recommended by the American Academy of Orthopedic Surgeons in treatment of patients with symptomatic OA of the knee [35]. At present, the therapeutic value of PRP in treating OA is a topic of debate and investigation. Available studies suggest its clinical benefit compared with HA in treating OA of the knee [36–40]. Several authors have reported meta-analyses demonstrating improved pain and function following intra-articular injection of PRP in the knee versus HA [36–38]. In a meta-analysis of 26 randomized controlled trials involving 2430 patients, Tan et al. found better Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total scores, WOMAC physical function, and Visual Acuity (VAS) Scores at 3, 6, and 12 months following PRP injection compared to HA [38]. Evidence supporting the use of PRP in hip OA is still lacking [39]. There is still much work to be done in understanding the therapeutic role of PRP in treating OA. It is an infrequently used treatment modality, a likely reflection of limited reimbursement. Presently, the Centers for Medicare and Medicaid Services (CMS) only cover PRP use when used for the treatment of chronic non-healing diabetic, pressure, or venous wounds in patients enrolled in clinical studies [41]. Despite growing public interest, available evidence does not support use of autologous stem cells in treatment of OA [42, 43]. In a meta-analysis of nine studies, evaluating 339 patients Huang et al. found most outcome measures similar between stem cell recipients and controls [43]. VAS was found to be statistically improved among stem cell patients; but, it is unclear whether the modest differences described were clinically relevant [43].

A new 5 year study published in 2019 demonstrates better outcomes and lower pain scores in patients who underwent knee arthroscopy for osteochondral knee injuries with and without preoperative intra-articular PRP injections. This research was the first study which used clinical data more than 5 years and demonstrates that cell therapy can promote the regeneration of articular cartilage in a lasting way [44].

2.8 Spondylosis

Cervical and lumbar spondylosis represent the constellation of degenerative changes found in the cervical and lumbar spine that progressively occur in most people with aging. 25% of people under 40 years of age, 50% of people over 40 years of age, and 85% of people over 60 years of age are estimated to have cervical spondylosis [45]. Pathologically, the same degenerative processes that characterize OA extend to the vertebral joints and result in spondylosis often characterized by disc degeneration, uncinate spurring and facet arthrosis, ligamentous thickening and infolding, and deformity. Radiculopathy, myelopathy, discogenic pain, facet pain are the clinical manifestations of vertebral joint degeneration. Regenerative techniques for the treatment of cervical and lumbar spondylosis has been previously investigated with promising results. Further studies are needed to weigh safety profiles against efficacy. In an RCT of PRP vs. contrast for discogenic pain, Tuakli-Wosornu et al., reported significant improvements in pain and function at

8-week follow-up [46]. Pettine et al. reported significant reductions in pain following BMAC use for patients with discogenic pain [47]. The principle caveat of these results is the scarcity of similar results demonstrated in the literature [48].

2.9 Tendon and ligament healing

Tendon and ligament injuries are a very common cause of pain and disability, among both the very active and the elderly. Lateral epicondylitis is significantly more common among working-age patients with physical workloads [49]. As much as 80% of patients over 80 years of age are estimated to have a rotator cuff tear [50]. The use of PRP for tendon and ligament healing has mixed reviews but is considered by many a viable treatment modality given low risks of severe associated complications and numerous positive results promulgated throughout the literature. In a meta-analysis of 21 studies comparing PRP to control (betamethasone with lignocaine, saline, corticosteroid, bupivacaine, and whole blood), Chen et al. found PRP significantly associated with short-term (2–6.5 months) improvements in VAS scores among patients with rotator cuff injuries ($p < 0.01$) and lateral epicondylitis ($p < 0.01$) and long-term pain control among patients with rotator cuff injuries ($p = 0.02$), lateral epicondylitis ($p = 0.01$), and tendinopathy ($p < 0.01$) [40]. Evidence describing the clinical utility of MSCs and BMACs a in tendon and ligament injuries is lacking and mostly limited to *in vitro* and *in vivo* studies [51, 52].

2.10 Future therapy

Many experimental trials continue to assess the role of these injectates in tissue repair of the central nervous system (CNS), cardiovascular system, hepatic, renal as well as musculoskeletal system [2]. Some studies demonstrate exosomal induced neural cell growth while others have explored with success the use of exosomes as a promising potential treatment option for Alzheimer's disease and other neurodegenerative pathologies. Others demonstrate the ability of exosomes to differentiate into bone tissue and promote skeletal regeneration [53].

Additionally, regenerative therapies such as PRP have shown a lot of promise in dermatology including prevention of hair loss, the treatment of scars and post procedure recovery, skin rejuvenation, dermal augmentation, and the treatment of striae distensae [54, 55]. Despite the lack of insurance coverage, these therapeutic modalities show much promise in the innovative world of medicine and esthetics.

3. Conclusion

These various injectates present a novel and promising treatment for many degenerative conditions including neurological and musculoskeletal diseases. Not only can biologics relieve symptoms in painful conditions, but also they can halt the degeneration of tissues, regenerate tissue and prolong their lifespan. PRP, MSC's, and exosomes have made considerable progress and will therefore undoubtedly offer new and exciting prospects for a variety of musculoskeletal and nervous system conditions. Their utility in conditions such as osteoarthritis, spondylosis, and tendon and ligamentous injuries are gaining popularity with emerging clinical reports of their efficacy.

The thought that tissue repair and regeneration was a function of the MSCs themselves is now shifting toward the thinking that, exosomes, secreted by MSCs have a more direct role in the process. These exosomes can have a different effect depending on the differentiation state of the tissue from which they are extracted.

They exert their function by communicating in a paracrine fashion with the surrounding tissue and initiate a process of cellular differentiation and proliferation, playing an important role in tissue repair. The use of exosomes shows promising results in disease processes that have no current available treatment. The use of biologic injectates for painful conditions deserves further consideration. Large, well-constructed studies are needed to better understand their applications and extents of their roles in degenerative conditions.

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References

[1] Dahlhamer J, Lucas J, Zelaya C, et al. Prevalence of chronic pain and high-impact chronic pain among adults - United States, 2016. MMWR. Morbidity and Mortality Weekly Report. 2018;**67**(36):1001-1006. DOI: 10.15585/mmwr.mm6736a2

[2] Q2 2018 Data Report - Alliance for Regenerative Medicine. Available from: https://alliancerm.org/publication/q2-2018-data-report/ [Accessed: 23 August 2020]

[3] Chen H, Purita J, Nguyen M. Regenerative medicine for pain management. In: Yong RJ, Nguyen M, Nelson E, Urman RD, editors. Pain Medicine: An Essential Review. Springer International Publishing; 2017. pp. 575-580. DOI: 10.1007/978-3-319-43133-8_153

[4] LKanth K, Sanivarapu S, Moogla S, Kutcham RS. Adipose tissue - adequate, accessible regenerative material. International Journal of Stem Cells. 2015;**8**(2):121-127. DOI: 10.15283/ijsc.2015.8.2.121

[5] Smith PA. Intra-articular autologous conditioned plasma injections provide safe and efficacious treatment for knee osteoarthritis: An FDA-sanctioned, randomized, double-blind, placebo-controlled clinical trial. The American Journal of Sports Medicine. 2016;**44**(4):884-891. DOI: 10.1177/0363546515624678

[6] Alves R, Grimalt R. A review of platelet-rich plasma: History, biology, mechanism of action, and classification. Skin Appendage Disorders. 2018;**4**(1): 18-24. DOI: 10.1159/000477353

[7] Akeda K, Yamada J, Linn ET, Sudo A, Masuda K. Platelet-rich plasma in the management of chronic low back pain: A critical review. Journal of Pain Research. 2019;**12**:753-767. DOI: 10.2147/JPR.S153085

[8] Knezevic NN, Candido KD, Desai R, Kaye AD. Is platelet-rich plasma a future therapy in pain management? The Medical Clinics of North America. 2016;**100**(1):199-217. DOI: 10.1016/j.mcna.2015.08.014

[9] Francesco S, Nicolò B, Michele PG, Edoardo R. From liposuction to adipose-derived stem cells: Indications and technique. Acta Bio Medica Atenei Parmensis. 2019;**90**(2):197-208. DOI: 10.23750/abm.v90i2.6619

[10] Cook CS, Smith PA. Clinical update: Why PRP should be your first choice for injection therapy in treating osteoarthritis of the knee. Current Reviews in Musculoskeletal Medicine. 2018;**11**(4):583-592. DOI: 10.1007/s12178-018-9524-x

[11] Gianakos AL, Sun L, Patel JN, Adams DM, Liporace FA. Clinical application of concentrated bone marrow aspirate in orthopaedics: A systematic review. World Journal of Orthopedics. 2017;**8**(6):491-506. DOI: 10.5312/wjo.v8.i6.491

[12] Huang L, Ma W, Ma Y, Feng D, Chen H, Cai B. Exosomes in mesenchymal stem cells, a new therapeutic strategy for cardiovascular diseases? International Journal of Biological Sciences. 2015;**11**(2):238-245. DOI: 10.7150/ijbs.10725

[13] Wen Z, Zheng S, Zhou C, Yuan W, Wang J, Wang T. Bone marrow mesenchymal stem cells for post-myocardial infarction cardiac repair: microRNAs as novel regulators. Journal of Cellular and Molecular Medicine. 2012;**16**(4):657-671. DOI: 10.1111/j.1582-4934.2011.01471.x

[14] Chen TS, Lai RC, Lee MM, Choo ABH, Lee CN, Lim SK. Mesenchymal stem cell secretes microparticles enriched in pre-microRNAs. Nucleic

Acids Research. 2010;**38**(1):215-224. DOI: 10.1093/nar/gkp857

[15] Lai RC, Chen TS, Lim SK. Mesenchymal stem cell exosome: A novel stem cell-based therapy for cardiovascular disease. Regenerative Medicine. 2011;**6**(4):481-492. DOI: 10.2217/rme.11.35

[16] Jenjaroenpun P, Kremenska Y, Nair VM, Kremenskoy M, Joseph B. Characterization of RNA in exosomes secreted by human breast cancer cell lines using next-generation sequencing. PeerJ. 2013;**1**:e201. DOI: 10.7717/peerj.201

[17] Zhang Y, Liu Y, Liu H, Tang WH. Exosomes: Biogenesis, biologic function and clinical potential. Cell & Bioscience. 2019;**9**. DOI: 10.1186/s13578-019-0282-2

[18] Tang YL, Zhao Q, Qin X, et al. Paracrine action enhances the effects of autologous mesenchymal stem cell transplantation on vascular regeneration in rat model of myocardial infarction. The Annals of Thoracic Surgery. 2005;**80**(1):229-236. DOI: 10.1016/j.athoracsur.2005.02.072

[19] Van Overstraeten-Schlögel N, Beguin Y, Gothot A. Role of stromal-derived factor-1 in the hematopoietic-supporting activity of human mesenchymal stem cells. European Journal of Haematology. 2006;**76**(6):488-493. DOI: 10.1111/j.1600-0609.2006.00633.x

[20] Tögel F, Hu Z, Weiss K, Isaac J, Lange C, Westenfelder C. Administered mesenchymal stem cells protect against ischemic acute renal failure through differentiation-independent mechanisms. American Journal of Physiology. Renal Physiology. 2005;**289**(1):F31-F42. DOI: 10.1152/ajprenal.00007.2005

[21] Haider HK, Jiang S, Idris NM, Ashraf M. IGF-1-overexpressing mesenchymal stem cells accelerate bone marrow stem cell mobilization via paracrine activation of SDF-1alpha/CXCR4 signaling to promote myocardial repair. Circulation Research. 2008;**103**(11):1300-1308. DOI: 10.1161/CIRCRESAHA.108.186742

[22] Wang M, Zhao C, Shi H, et al. Deregulated microRNAs in gastric cancer tissue-derived mesenchymal stem cells: Novel biomarkers and a mechanism for gastric cancer. British Journal of Cancer. 2014;**110**(5):1199-1210. DOI: 10.1038/bjc.2014.14

[23] Xin H, Li Y, Cui Y, Yang JJ, Zhang ZG, Chopp M. Systemic administration of exosomes released from mesenchymal stromal cells promote functional recovery and neurovascular plasticity after stroke in rats. Journal of Cerebral Blood Flow and Metabolism. 2013;**33**(11):1711-1715. DOI: 10.1038/jcbfm.2013.152

[24] Lee C, Mitsialis SA, Aslam M, et al. Exosomes mediate the cytoprotective action of mesenchymal stromal cells on hypoxia-induced pulmonary hypertension. Circulation. 2012;**126**(22):2601-2611. DOI: 10.1161/circulationaha.112.114173

[25] Arslan F, Lai RC, Smeets MB, et al. Mesenchymal stem cell-derived exosomes increase ATP levels, decrease oxidative stress and activate PI3K/Akt pathway to enhance myocardial viability and prevent adverse remodeling after myocardial ischemia/reperfusion injury. Stem Cell Research. 2013;**10**(3):301-312. DOI: 10.1016/j.scr.2013.01.002

[26] Pittenger MF, Mackay AM, Beck SC, et al. Multilineage potential of adult human mesenchymal stem cells. Science. 1999;**284**(5411):143-147. DOI: 10.1126/science.284.5411.143

[27] Teixeira FG, Carvalho MM, Sousa N, Salgado AJ. Mesenchymal stem cells secretome: A new paradigm for central nervous system regeneration? Cellular and Molecular Life Sciences: CMLS. 2013;**70**(20):3871-3882. DOI: 10.1007/s00018-013-1290-8

[28] Wang J, Greene SB, Bonilla-Claudio M, et al. Bmp signaling regulates myocardial differentiation from cardiac progenitors through a MicroRNA-mediated mechanism. Developmental Cell. 2010;**19**(6):903-912. DOI: 10.1016/j.devcel.2010.10.022

[29] Baglio SR, Rooijers K, Koppers-Lalic D, et al. Human bone marrow- and adipose-mesenchymal stem cells secrete exosomes enriched in distinctive miRNA and tRNA species. Stem Cell Research & Therapy. 2015;**6**:127. DOI: 10.1186/s13287-015-0116-z

[30] Katsuda T, Tsuchiya R, Kosaka N, et al. Human adipose tissue-derived mesenchymal stem cells secrete functional neprilysin-bound exosomes. Scientific Reports. 2013;**3**:1197. DOI: 10.1038/srep01197

[31] Xin H, Li Y, Buller B, et al. Exosome-mediated transfer of miR-133b from multipotent mesenchymal stromal cells to neural cells contributes to neurite outgrowth. Stem Cells. 2012;**30**(7):1556-1564. DOI: 10.1002/stem.1129

[32] Zhang B, Yin Y, Lai RC, Tan SS, Choo ABH, Lim SK. Mesenchymal stem cells secrete immunologically active exosomes. Stem Cells and Development. 2014;**23**(11):1233-1244. DOI: 10.1089/scd.2013.0479

[33] Zhang Y, Jordan JM. Epidemiology of osteoarthritis. Clinics in Geriatric Medicine. 2010;**26**(3):355-369. DOI: 10.1016/j.cger.2010.03.001

[34] Chen D, Shen J, Zhao W, et al. Osteoarthritis: Toward a comprehensive understanding of pathological mechanism. Bone Research. 2017;**5**: 16044. DOI: 10.1038/boneres.2016.44

[35] Guideline: Treatment of Osteoarthritis of the Knee (2nd edition). Available from: http://www.orthoguidelines.org/go/cpg/detail.cfm?id=1214 [Accessed: 03 August 2020]

[36] Han Y, Huang H, Pan J, et al. Meta-analysis comparing platelet-rich plasma vs. hyaluronic acid injection in patients with knee osteoarthritis. Pain Medicine. 2019;**20**(7):1418-1429. DOI: 10.1093/pm/pnz011

[37] Belk JW, Kraeutler MJ, Houck DA, Goodrich JA, Dragoo JL, McCarty EC. Platelet-rich plasma versus hyaluronic acid for knee osteoarthritis: A systematic review and meta-analysis of randomized controlled trials. The American Journal of Sports Medicine. 2020:363546520909397. DOI: 10.1177/0363546520909397

[38] Tan J, Chen H, Zhao L, Huang W. Platelet rich plasma versus hyaluronic acid in the treatment of knee osteoarthritis: A meta-analysis of 26 randomized controlled trials. Arthroscopy: The Journal of Arthroscopic & Related Surgery. 2020. DOI: 10.1016/j.arthro.2020.07.011

[39] Medina-Porqueres I, Ortega-Castillo M, Muriel-Garcia A. Effectiveness of platelet-rich plasma in the management of hip osteoarthritis: A systematic review and meta-analysis. Clinical Rheumatology. 2020. DOI: 10.1007/s10067-020-05241-x

[40] Chen X, Jones IA, Park C, Vangsness CT. The efficacy of platelet-rich plasma on tendon and ligament healing: A systematic review and meta-analysis with bias assessment. The American Journal of Sports Medicine. 2018;**46**(8):2020-2032. DOI: 10.1177/0363546517743746

[41] Autologous Platelet-rich Plasma | CMS. Available from: https://www.cms.gov/Medicare/Coverage/Coverage-with-Evidence-Development/Autologous-Platelet-rich-Plasma [Accessed: 04 August 2020]

[42] Strotman PK, Novicoff WM, Nelson SJ, Browne JA. Increasing public interest in stem cell injections for osteoarthritis of the hip and knee:

A google trends analysis. The Journal of Arthroplasty. 2019;**34**(6):1053-1057. DOI: 10.1016/j.arth.2019.03.002

[43] Huang R, Li W, Zhao Y, Yang F, Xu M. Clinical efficacy and safety of stem cell therapy for knee osteoarthritis: A meta-analysis. Medicine (Baltimore). 2020;**99**(11):e19434. DOI: 10.1097/MD.0000000000019434

[44] Monckeberg JE, Rafols C, Apablaza F, Gerhard P, Rosales J. Intra-articular administration of peripheral blood stem cells with platelet-rich plasma regenerated articular cartilage and improved clinical outcomes for knee chondral lesions. The Knee. 2019;**26**(4):824-831. DOI: 10.1016/j.knee.2019.05.008

[45] Kuo DT, Tadi P. Cervical Spondylosis. In: StatPearls. StatPearls Publishing; 2020. http://www.ncbi.nlm.nih.gov/books/NBK551557/ [Accessed: 04 August 2020]

[46] Tuakli-Wosornu YA, Terry A, Boachie-Adjei K, et al. Lumbar intradiskal platelet-rich plasma (PRP) injections: A prospective, double-blind, randomized controlled study. PM & R: The Journal of Injury, Function, and Rehabilitation. 2016;**8**(1):1-10. DOI: 10.1016/j.pmrj.2015.08.010

[47] Pettine KA, Murphy MB, Suzuki RK, Sand TT. Percutaneous injection of autologous bone marrow concentrate cells significantly reduces lumbar discogenic pain through 12 months. Stem Cells. 2015;**33**(1):146-156. DOI: 10.1002/stem.1845

[48] Valimahomed AK, Haffey PR, Urman RD, Kaye AD, Yong RJ. Regenerative techniques for neuraxial Back pain: A systematic review. Current Pain and Headache Reports. 2019;**23**(3):20. DOI: 10.1007/s11916-019-0758-0

[49] Shiri R, Viikari-Juntura E, Varonen H, Heliövaara M. Prevalence and determinants of lateral and medial epicondylitis: A population study. American Journal of Epidemiology. 2006;**164**(11):1065-1074. DOI: 10.1093/aje/kwj325

[50] Milgrom C, Schaffler M, Gilbert S, Van Holsbeeck M. Rotator-cuff changes in asymptomatic adults. The effect of age, hand dominance and gender. Journal of Bone and Joint Surgery. British Volume (London). 1995;**77**(2):296-298

[51] Pas HIMFL, Moen MH, Haisma HJ, Winters M. No evidence for the use of stem cell therapy for tendon disorders: A systematic review. British Journal of Sports Medicine. 2017;**51**(13):996-1002. DOI: 10.1136/bjsports-2016-096794

[52] Van den Boom NAC, Winters M, Haisma HJ, Moen MH. Efficacy of stem cell therapy for tendon disorders: A systematic review. Orthopaedic Journal of Sports Medicine. 2020;**8**(4). DOI: 10.1177/2325967120915857

[53] Narayanan R, Huang C-C, Ravindran S. Hijacking the cellular mail: Exosome mediated differentiation of mesenchymal stem cells. Stem Cells International. 2016;**2016**:3808674. DOI: 10.1155/2016/3808674

[54] Gentile P, Garcovich S. Autologous activated platelet-rich plasma (AA-PRP) and non-activated (A-PRP) in hair growth: A retrospective, blinded, randomized evaluation in androgenetic alopecia. Expert Opinion on Biological Therapy. 2020;**20**(3):327-337. DOI: 10.1080/14712598.2020.1724951

[55] Leo MS, Kumar AS, Kirit R, Konathan R, Sivamani RK. Systematic review of the use of platelet-rich plasma in aesthetic dermatology. Journal of Cosmetic Dermatology. 2015;**14**(4):315-323. DOI: 10.1111/jocd.12167