OVERVIEW

Regenerative medicine pain management techniques aim to harness the body's innate healing mechanisms to promote and accelerate tissue regeneration. Mesenchymal stem cells (MSCs) have been the focus of many regenerative medicine treatments for musculoskeletal injuries and conditions such as osteoarthritis (OA), tendinopathy, intervertebral disc degeneration and other spinal conditions. MSCs are cells with the ability for self-renewal and can also transform into multiple specialized cell types through secretion of and interaction with growth factors and cytokines, signaling molecules found in many different physiological processes (1). The exact mechanism by which signaling molecules stimulate MSC differentiation is not completely understood, but research has demonstrated that signaling factors induce stem cells to divide, differentiate, and proliferate into specialized cell types (1). MSCs are found in many different tissues ranging from umbilical cord tissue to adipose tissue to bone marrow (2).

Treatment options for musculoskeletal injuries have previously focused on palliative care because there have been very few approved treatments that can reverse musculoskeletal damage. Articular cartilage lacks blood vessels and undifferentiated cells, so cartilage injuries often have very low spontaneous healing potential (3). In recent years, MSCs have gained the attention of many researchers and clinicians because of their immense regenerative potential for the treatment of musculoskeletal injuries. One of the primary barriers to using MSCs in the treatment of musculoskeletal injuries has been shown to be the low concentration of MSCs found in bone marrow. Researchers have explored many techniques to overcome this barrier, and the most promising solution is a novel technique called Bone Marrow Aspirate Concentrate (BMAC). BMAC can produce higher concentrations of MSCs, growth factors, and cytokines compared to bone marrow (4, 5, 6). The unique regenerative properties of BMAC provide evidence for its use in the treatment of musculoskeletal conditions such as OA, tendinopathy, and spinal conditions.

WHAT IS BMAC THERAPY

BMAC therapy is a minimally-invasive procedure that involves the harvesting of a small amount of a patient's bone marrow. Using a local anesthetic and/or light sedation, a bone marrow sample is extracted from a large bone such as the pelvis and is then processed using a centrifuge. The centrifugation process concentrates the MSCs, growth factors and cytokines in the sample. This concentrated product is then injected directly into injury sites to initiate and promote healing. BMAC therapy is an outpatient procedure with minimal downtime and the autologous nature of BMAC contents allows for minimal risk of adverse side effects (7).

REGENERATIVE PROPERTIES OF BMAC

GROWTH FACTORS

The MSCs found in BMAC may serve as a direct cell source for tissue regeneration, but BMAC MSCs also promote wound healing through the release of growth factors (6). With respect to BMAC use for musculoskeletal injury treatment, there are numerous BMAC growth factors known to reduce apoptosis, induce cell differentiation, and stimulate proliferation, all of

which are processes involved in healing pathways (6). These include platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and insulin-like growth factor (IGF-1) (6). The function of these growth factors are well-defined in cellular research literature: PDGF stimulates the proliferation of cell types that have critical roles in tissue repair, VEGF mediates changes in vascular permeability and stimulates angiogenesis, FGF induces tissue regeneration of cartilage and bone, and IGF-1 is involved in promoting cell recruitment to injured tissue (8, 9, 10, 11). As many of these growth factors are majorly involved in promoting collagen synthesis and regeneration following injury, the growth factors released by MSCs found in BMAC have immense potential in treating a wide range of musculoskeletal injuries and disorders.

CYTOKINES

In addition, MSCs found in BMAC release numerous cytokines that have defined roles in the regulation of cellular processes that lead to tissue regeneration. Cytokines are small signaling proteins that are released by cells to facilitate communication and regulate the activity of certain physiological processes (12). For example, cytokines are responsible for modulating immune responses by promoting or inhibiting inflammation, but cytokines can also alter gene expression to increase or decrease the production of proteins involved in regulating downstream signaling pathways (12, 13). Cytokines are considered to be either anti-inflammatory or pro-inflammatory (13). As the inflammatory response can be involved in the development and maintenance of pain, numerous pro-inflammatory cytokines have been shown to be associated with hyperalgesia and neuropathic pain behaviors like allodynia (14). Many studies have demonstrated that administration of anti-inflammatory cytokines can attenuate or even prevent inflammatory pain caused by pro-inflammatory cytokine action (15, 16).

MSCs found in BMAC release both pro-inflammatory and anti-inflammatory cytokines. Interleukin-1ra (IL-1RA) is a very potent anti-inflammatory cytokine that is secreted by MSCs found in BMAC (16). IL-1RA has been shown to inhibit the production of molecular mediators involved in cartilage inflammation and destruction (18, 19). Interestingly, the pro-inflammatory cytokines secreted by MSCs found in BMAC play a larger role than anti-inflammatory cytokines in driving cellular processes that result in tissue regeneration (17, 20). One of the most important pro-inflammatory cytokines released by MSCs found in BMAC is called interleukin-8 (IL-8) (17). Bone and cartilage injuries result in IL-8 release due to mechanical stress and inflammation. In these injuries, IL-8 release causes immune cells to migrate to the damaged tissue, promoting tissue regeneration and angiogenesis (17, 21). The IL-8 released by MSCs found in BMAC mirrors this innate injury response by stimulating the recruitment of additional stem cells from undamaged bone to injury sites, thus promoting tissue regeneration (17). Additionally, IL-8 released by MSCs found in BMAC contribute to tissue regeneration by stimulating the production of the growth factor VEGF, leading to increased bone cell proliferation after injury (22). Although the complex interplay between growth factors and cytokines released by MSCs found in BMAC is not fully understood, clinical and preclinical

evidence vastly supports the potential of BMAC as a therapeutic option for musculoskeletal injuries and conditions (23).

CLINICAL APPLICATIONS OF BMAC THERAPY

CARTILAGE AND BONE INJURIES

BMAC therapy has emerged as an exciting treatment option for cartilage and bone injuries such as osteoarthritis. Osteoarthritis (OA) is a progressive condition that is characterized by the deterioration of articular cartilage (24). Symptoms of OA are associated with significant functional impairment and include pain, loss of mobility and inflammation (25). Although conventional OA treatments (non-steroidal anti-inflammatory drugs and joint injections with steroids or hyaluronic acid) can provide some patients with adequate symptom relief, these options have limited success because they primarily provide symptom relief rather than addressing the physiological causes of the condition (25). Recent developments in regenerative medicine have suggested BMAC therapy as a promising alternative treatment option for OA. As BMAC contains MSCs that release growth factors and cytokines known to promote tissue regeneration and cartilage repair, BMAC therapy has immense potential to alter the trajectory of OA progression. Clinical trial outcomes have indicated that BMAC therapy can significantly improve pain and functionality in patients with knee osteoarthritis (26, 27). BMAC therapy has the capacity to positively alter the physiological changes that occur as a result of OA because the MSCs and associated growth factors and cytokines contained in BMAC coordinate and promote tissue regeneration (25, 28). Clinical and preclinical studies have demonstrated that BMAC therapy is a safe and effective therapeutic option for patients with OA (25, 28, 29, 30, 31).

TENDINOPATHIES

Tendinopathy is a broad term that describes a group of musculoskeletal disorders that involve the degeneration of tendons. Common examples of tendinopathies are Rotator cuff tears, tennis elbow, epicondylitis, plantar fasciitis, and tendonitis (32). Clinical symptoms of tendinopathies are characterized by pain, swelling, and immobility (33). Current treatment options (non-steroidal anti-inflammatory drugs, steroid injections, surgery) for tendinopathies often fail to provide patients with adequate symptom relief (33). In recent years, however, the development of novel regenerative therapeutics have revealed the potential of BMAC therapy for the treatment of tendinopathies. Tendinopathies involve mechanical and biological abnormalities that result in inflammation and degradation of tendons, so the rationale for using BMAC therapy in the treatment of tendinopathies is centered on the ability of the MSCs, growth factors, and cytokines found in BMAC to instigate tissue repair and regeneration (33). Clinical and preclinical studies have demonstrated that BMAC therapy can safely and successfully treat chronic tendinopathy and may serve as a potential alternative to more invasive interventions (33, 34, 35, 36).

BACK PAIN AND SPINE CONDITIONS

Chronic back pain is one of the most common ailments in the United States, and it can be caused by myriad musculoskeletal or nerve-related disorders (37). Chronic back pain frequently originates from either the intervertebral discs (discogenic pain) or the vertebrae (vertebrogenic pain) (38, 39). Disc degeneration is the most common cause of discogenic pain and vertebral endplate degeneration is the most common cause of vertebrogenic pain, but these conditions can be difficult to treat. Although existing therapies (i.e. non-steroidal anti-inflammatory drugs, opioids, steroid injections, surgery) may offer patients adequate symptom relief of discogenic or vertebrogenic pain, traditional treatments may not provide sufficient benefits for some patients. Recently, however, BMAC therapy has been gaining increasing interest in the search for novel therapeutics for chronic back pain.

In animal models of chronic back pain associated with intervertebral disc degeneration, BMAC therapy has been shown to successfully inhibit further disc degeneration (40). Further, in the majority of animal models, BMAC therapy has resulted in increased disc space height compared with traditional techniques (40, 41). These encouraging results served as the rationale for recent and ongoing clinical and preclinical studies. Recent clinical and preclinical studies have demonstrated that BMAC therapy can significantly reduce pain and improve functionality in patients with intervertebral disc degeneration (42, 43, 44). Further, studies suggest that the vast majority of patients with intervertebral disc degeneration who received BMAC therapy were able to avoid surgery across two- and three-year follow-up visits and took significantly less opioids for pain management (42, 43, 45, 46). Studies also indicate that MRI scans conducted on patients with intervertebral disc degeneration patients who received BMAC therapy showed considerable increases in intervertebral disc height compared to pre-procedure MRI studies (42). These results highlight the clinical benefits of BMAC therapy as a cutting-edge treatment option for intervertebral disc degeneration.

Although the exact mechanisms of how BMAC therapy mitigates symptoms of intervertebral disc degeneration are not yet fully understood, the ability of BMAC MSCs, growth factors, and cytokines to modulate biological healing processes may be in part responsible for why BMAC therapy provides significant symptom relief. As a recent meta-analysis of randomized controlled trials indicated the safety and efficacy of using MSCs in the treatment of degenerative disc disease, cell-based therapeutics are accumulating convincing evidence and may represent the future of regenerative medicine (44). BMAC therapy has remarkable potential for not only alleviating chronic back pain associated with intervertebral disc degeneration but also for addressing the physiological causes of this progressive disease.

CONCLUSION

As many symptoms of musculoskeletal injuries and conditions occur as a result of tissue degeneration, the clinical benefits of conventional treatment options are limited in the extent to which they can target the physiological processes that are responsible for the progression of these conditions. BMAC therapy offers an alternative treatment option with the potential to alter the trajectory of degenerative musculoskeletal conditions towards tissue regeneration and healing.

BMAC therapy utilizes naturally-occuring cells and cell-products to accelerate symptom relief through disease-modifying mechanisms.

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