

# Treating Chronic Pain with Mesenchymal Stem Cells: A Therapeutic Approach Worthy of Continued Investigation

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## Abstract

Though there are various etiologies to chronic pain, one common feature is that painful states are associated with increased inflammation. This is verified by studies in both animal models and humans that have found increased expression of inflammatory proteins in muscle tissue, and increased inflammatory cytokines in cerebral spinal fluid, synovial fluid, and serum. Over the last decade we have become aware of the anti-inflammatory effects that multipotent mesenchymal stromal cells frequently referred to as mesenchymal stem cells [MSC], elicit. This ability of MSC to affect the inflammatory milieu has led researchers to consider MSC as a treatment for various painful states such as degenerative disc disease and osteoarthritis. In this article we present relevant animal and human studies, which indicate that MSC are worthy of further study as a valuable therapy in the treatment of chronic pain.

## Introduction

Pain is widespread in the United States and it has an enormous impact on society. Although the number of people suffering with pain is difficult to precisely identify, it is estimated that over 115 million people suffer from chronic pain [1]. This represents a patient population larger than the combined numbers for those suffering with diabetes, stroke, cancer, and coronary heart disease. Individuals with pain also affect the nation's productivity. The annual value of lost productivity is gauged to be between \$297 and \$333 billion. Back pain alone is estimated to cost employers over \$7 billion per year [2]. Additionally, the pain from arthritis flare-ups is calculated to cost \$7.11 billion annually in lost productive time [3]. The burden of pain to patients and society has become so extreme that the National Institute of Medicine has recommended that alleviation of pain become a national priority [1].

## Pain and inflammation

It is well recognized that inflammation plays a role in a variety of pain states at both the peripheral and central levels, and the idea that chronic pain is associated with aberrant inflammation is quickly gaining more acceptance. Numerous sources have verified an increase in pro-inflammatory cytokines such as interleukin [IL]-1, IL-2, IL-6, IL-17, and tumor necrosis factor [TNF]- $\alpha$  in various pain states [4-6]. The pro-inflammatory cytokine IL-6 has been detected in synovial fluid of patients with osteoarthritis [6], while TNF- $\alpha$  has been implicated in modifying pain perception [7]. In the synovial fluid of rheumatoid arthritis patients, IL-17 has been found to be elevated [8,9]. In contrast, IL-17 knockout mice failed to develop arthritis [10]. An additional study showed that IL-17 deficient mice had decreased neuropathic pain after peripheral nerve injury compared to those mice capable of expressing IL-17 [11]. In the central nervous system, microglia have been implicated in releasing pro-inflammatory cytokines such as IL-6, TNF- $\alpha$ , and IL-1 $\beta$ , which contribute to neuropathic pain [12]. Additionally, it has been shown that microglia play a role in chronic pain by activating astrocytes that sustain inflammation [13]. Because of the association between chronic neuropathic pain and immune responses, it has been suggested that neuropathic pain be referred to as neuro-immune pain [14].

## Current therapies for chronic pain

Many therapies have been directed towards decreasing the

inflammatory state or blocking the pain pathway with only minimal improvements in pain. Subsequently, patients are often left with few options that include chronic medication usage or invasive procedures that yield minimal results. Based on studies, lumbar decompression surgery has a suggested failure rate of approximately 35%. Despite advances in surgical techniques, the rate of failed back surgery syndrome has not decreased in the last decades [15]. An extensive 2011 review found that the use of opioids for the treatment of chronic non-cancer pain resulted in only a minor improvement in pain and function when compared to taking a placebo [16]. Moreover, opioids have unpleasant side effects that include drowsiness, dependence, constipation, nausea, and pruritus [17]. If used chronically, opioids can even lead to endocrine dysfunction [18]. Additionally, the chronic use of opioids can lead to hyperalgesia. This has been linked to *mu* opioid receptors' release of pro-inflammatory mediators, which increase the levels of IL-1 $\beta$ , IL-6, and TNF- $\alpha$  [19,20]. The use of non-steroidal anti-inflammatory drugs [NSAIDs] in patients with either symptomatic acute or chronic low back pain and no sciatica has shown to be more effective in providing short-term pain relief than narcotics, muscle relaxants, or acetaminophen. No particular NSAID appears to provide better relief than another, and the use of this class of drugs also has the risk of gastrointestinal side effects and, in specific NSAIDs, cardiovascular complications [21]. Glucocorticoids are often used in injectable form to alleviate pain at joints. These drugs inhibit a wide range of cytokines and chemokines [22]. However, their duration of action is unpredictable with a literature review revealing that there is moderate evidence for caudal epidural steroid injections providing pain relief lasting longer than 6 weeks [23]. In addition, there is the potential for adverse reactions: hyperglycemia, blood pressure

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fluctuations, Cushing's syndrome, bone demineralization, and steroid induced psychosis [24-26]. For patients enduring chronic pain from rheumatoid arthritis, disease-modifying antirheumatic drugs [DMARDs] are often prescribed. While these target inflammation, they also have systemic effects that include gastrointestinal disturbances, liver and kidney toxicity, increased risk of infection, and pancytopenia [27]. Painful diabetic peripheral neuropathy is a common complication of diabetes mellitus. Recent guidelines by the American Academy of Neurology for the treatment of painful diabetic peripheral neuropathy place only pregabalin in the level A recommendation tier [28]. This anti-epileptic medication binds to voltage gated calcium channels and attenuates the influx of calcium in neurons. The resultant effect is a decrease in the release of norepinephrine, substance P, and glutamate [29]. Substance P is known to augment the production of IL-1 $\beta$ , IL-6, and TNF- $\alpha$ , all pro-inflammatory cytokines [30]. Therefore, it is plausible that the inflammatory modifying effects of pregabalin contribute to the improvement seen in those patients receiving this medication for painful diabetic peripheral neuropathy. Side effects of pregabalin include somnolence, sedation, visual disturbances, and dry mouth [31].

### Mesenchymal stem cells and inflammation

Mesenchymal stem cells [MSC] is the conventional term used to describe the collection of poorly defined multipotent mesenchymal stromal cells [32], and as such, this misnomer will be used in this paper. In a recent article, Singer and Caplan presented a review on MSCs that outlined their effects on the immune system. Specifically, that MSCs have anti-inflammatory effects, that they inhibit dendritic cell [DC] maturation and B and T cell proliferation and differentiation, that they attenuate natural killer [NK] cell killing, and that they also support suppressive T regulatory cells [Tregs]. MSCs also decrease the amount of IL-10 and TNF- $\alpha$  secreted by DC cells, and increase the amount of the anti-inflammatory IL-4 produced by T cells [33]. MSC-based therapies have had some success in clinical trials of diseases ranging widely from graft-versus-host to joint and cartilage disorders [32,34]. MSCs are capable of attenuating the inflammatory milieu; however, the exact mechanism by which this takes place is yet to be precisely defined. Growing evidence suggests that they naturally home to sites of injury, but do not engraft in the injured tissue [32-36]. Additionally, MSC-based therapies are attractive new treatment candidates because they do not express immune co-stimulatory molecules that can elicit host rejection or immunity [32-36]. This should decrease the incidence of graft rejection even in xenotransplantation, and allow for the use of both self [autologous] or non-self [allogeneic] MSC in future therapeutics [32,34]. The above characteristics make MSC attractive as a treatment for chronic pain.

### Animal studies linking pain and inflammation

Various studies in animal models have linked increased pro-inflammatory cytokines to painful states (Table 1). Kato and colleagues investigated the effects of etanercept, a TNF antagonist, on neuropathic pain in rats. They found that in injured neurons, etanercept was able to reach the endoneurium; however, it did not do so in uninjured neurons. After local injection of etanercept into rats with sciatic nerve crush injury, behavioral assays showed improvement of pain [37]. Another study in rats revealed that in animals with injured L5 nerve roots TNF- $\alpha$  was increased [38]. Three reports in separate animal models from 2007 associated increased levels of pro-inflammatory cytokines with the development of osteoarthritis [OA] [39-41]. Maccoux and colleagues found that in the synovial fluid of dogs with OA, levels of IL-1 $\beta$ , IL-6, and IL-10 were increased [39]. The synovial fluid from the joints of horses that had OA was assayed and found to have elevated levels of IL-6 [40]. In guinea pig models of OA, Huebner and peers found that the levels of IL-6 were higher in the serum of animals with disease [41]. IL-17 is a pro-inflammatory cytokine believed to have a role in the development of inflammatory states. In studies using mice models deficient in IL-17, there was the failure of IL-17 knockout mice to develop arthritis in one of the studies; while in the other, the lack of IL-17 resulted in decreased neuropathic pain [10,11]. A recent mouse study examined spinal astrocyte activation in diabetic neuropathic pain. It concluded that the activation of the astrocytes resulted in increased IL-1 $\beta$  and was likely a contributor to the increased pain transmission found in neuropathic pain [42]. IL-21, a cytokine with pro-inflammatory properties has recently been implicated in rheumatoid arthritis. When researchers attempted to induce inflammatory arthritis in a mouse model deficient for IL-21, they were unsuccessful [43].

### Human studies linking pain and inflammation

Many human studies of diseases that cause pain have shown an increase in specific inflammatory markers (Table 2). Orita and colleagues evaluated the knee synovial fluid in 47 patients with OA. They found elevated IL-6 and TNF- $\alpha$  in knee joints of OA patients [44]. In 2011, Levinger et al. reported that greater levels of IL-6 protein and increased expression of TNF- $\alpha$  and IL-1 $\beta$  were present in the vastus lateralis muscle of patients with osteoarthritis when compared to control patients [45]. Kim and colleagues evaluated cartilage from patients with OA and compared it to normal donors. They found that in samples from both groups TNF- $\alpha$  and IL-1 $\beta$  disrupted mitochondrial function and led to the death of cartilage cells; however, the mitochondria from the OA group were more readily damaged by the pro-inflammatory cytokines than were the samples from normal

Year	Authors	Animal Model	Disease	Inflammatory Findings
2003	Nakae, et al.	Mouse	Arthritis	IL-17 deficient mice did not develop arthritis
2007	Maccoux, et al.	Dog	Osteoarthritis	Increased IL-1 $\beta$ , IL-6, IL-10 in synovial fluid
2007	Ley, et al.	Horse	Osteoarthritis	Increased IL-6 in synovial fluid
2007	Huebner, et al.	Guinea Pig	Osteoarthritis	Increased IL-6 in serum
2009	Kato, et al.	Rat	Neuropathic Pain	Decreased TNF- $\alpha$ expression correlated with less pain
2009	Sekiguchi, et al.	Rat	Neuropathic Pain	Increased TNF- $\alpha$ in L5 nerve root injury
2011	Liao, et al.	Mouse	Neuropathic Pain	Increased IL-1 $\beta$ expression in spinal cord
2011	Kim, et al.	Mouse	Neuropathic Pain	Lack of IL-17 resulted in decreased pain
2011	Yuan, et al.	Mouse	Arthritis	IL-21 deficient mice did not develop arthritis

IL=interleukin, TNF=tumor necrosis factor

Table 1: Animal studies and inflammation.

Year	Authors	Disease	Sample	Inflammatory Findings
2005	Alexander et al.	Complex Regional Pain Syndromes	Cerebral Spinal Fluid	Increased IL-6 and IL-1 $\beta$
2007	Uceyler, et al.	Complex Regional Pain Syndromes	Serum	Increased IL-2 and TNF- $\alpha$ . Decreased anti-inflammatory IL-4 and IL-10
2009	Doupis, et al.	Painful Diabetic Peripheral Neuropathy	Serum	Higher levels of TNF- $\alpha$ in painful versus painless diabetic peripheral neuropathy
2009	Lee, et al.	Degenerative Disc Disease	Intervertebral Disc	Higher levels of TNF- $\alpha$ and IL-8
2010	Kraychete, et al.	Herniated Disc	Serum	Greater levels of IL-6 and TNF- $\alpha$
2010	Cuellar, et al.	Degenerative Disc Disease	Disc Fluid	Increased IFN-gamma
2010	Kim, et al.	Osteoarthritis	Cartilage	TNF- $\alpha$ and IL-1 $\beta$ caused more damage to mitochondria of OA tissue than normal tissue
2011	Levinger, et al.	Osteoarthritis	Muscle	Higher levels of IL-6, IL-1 $\beta$ , and TNF- $\alpha$
2011	Purwata, et al.	Painful Diabetic Peripheral Neuropathy	Serum	Higher levels of TNF- $\alpha$
2011	Orita, et al.	Osteoarthritis	Synovial Fluid	Higher levels of IL-6 and TNF- $\alpha$

IL=interleukin, TNF=tumor necrosis factor

**Table 2:** Human Studies and Inflammation.

Year	Authors	Disease	Model	Therapy	Findings
2008	Alfaqeh, et al.	Osteoarthritis	Sheep	Autologous MSC injection	Articular cartilage regeneration
2008	Shibata, et al.	Diabetic Polyneuropathy	Rat	Autologous MSC injection	Improved hypoalgesia, sural nerve blood flow, and nerve conduction velocity
2008	Centeno, et al.	Osteoarthritis	Human	Autologous MSC injection	Regeneration of meniscus cartilage
2010	Yoshikawa, et al.	Degenerative Disc Disease	Human	Autologous MSC injection	Disc regeneration and decrease in back and leg pain
2011	Orozco, et al.	Degenerative Disc Disease	Human	Autologous MSC injection	Decrease in pain and disability
2011	Guo, et al.	Chronic Pain	Rat	Autologous MSC injection	Reversed mechanical hypersensitivity
2011	Waterman and Betancourt	Painful Diabetic Peripheral Neuropathy	Mouse	Human MSC2 injection	Decreased serum inflammatory cytokines, improved heat hyperalgesia and mechanical allodynia

MSC=multipotent mesenchymal stromal cells frequently referred to as mesenchymal stem cells, MSC2=anti-inflammatory mesenchymal stem cells

**Table 3:** studies of painful conditions and msc therapy.

patients [46]. A comparison study between patients with degenerative disc disease and those with a herniated nucleus pulposus evaluated disc specimens for cytokines. The patients with degenerative disc disease had greater levels of TNF- $\alpha$  and IL-8 than those patients that only had herniation. The authors posit that this increased cytokine expression could be a contributing factor for the greater pain that is experienced with degenerated discs than with herniation [47]. In a Phase 1 study of patients with symptomatic lumbar degenerative disc disease, the pro-inflammatory marker IFN-gamma was found to be elevated when disc lavage fluid was analyzed. An elevation of IFN-gamma was not found in the lavage fluid of asymptomatic controls [48]. In 23 patients with herniated lumbar intervertebral discs, levels of IL-6 and TNF- $\alpha$  were elevated when compared to 10 healthy patients [49]. There are also studies that implicate inflammation in painful diabetic peripheral neuropathy. It has been shown that patients with painful versus painless diabetic peripheral neuropathy have higher levels of TNF- $\alpha$  in their serum than those who do not suffer with the painful form of the disease [50,51]. Complex Regional Pain Syndromes [CRPS] result in severe and persistent pain and have been associated with cytokine expression that differs from those without the syndrome. In the cerebrospinal fluid of patients with CRPS, levels of IL-6 and IL-1 $\beta$  were higher than those of the controls [52]. In a study that evaluated blood from patients with CRPS, the cytokine protein and mRNA levels were higher for IL-2 and TNF- $\alpha$ , while the anti-inflammatory cytokines IL-4 and IL-10 were reduced [53].

### Use of stem cells in conditions of chronic pain

Investigators have recognized the potential for MSC to be utilized in the treatment of painful diseases (Table 3). In a pilot study, 10 patients with degenerative disc disease and low back pain received autologous MSC. The patients' pain and disability decreased to an extent comparable to those who had received spinal fusion or total disc

replacement. In addition, MSC therapy offered the advantages of being less invasive and preserving the biomechanics of the lumbar region [54]. In Japan, the autologous injection of MSC into degenerated intervertebral discs yielded disc regeneration and alleviation of back and leg pain [55]. Alfaqeh and peers surgically induced osteoarthritis in a sheep model and then injected autologous MSC into the arthritic knee joints. After six weeks, they found evidence of articular cartilage regeneration in their osteoarthritis model [56]. In 2008, Centeno and colleagues reported their novel findings that the reimplantation of autologous MSC into the knee joint of a patient with OA yielded regeneration of meniscus cartilage [57]. Subsequently, Centeno's group published on the safety of using MSC as a treatment for OA. They performed follow-up MRIs in 227 patients at various time points from 3 months to 2 years status post re-implantation with the MSCs. The MRIs did not reveal any tumor formations at the re-implantation sites [58]. MSC were evaluated as a therapy for persistent pain in a rat model. The tendons of the masseter muscles were ligated to create orofacial mechanical hypersensitivity. MSC were infused through the tail veins at 3 days, 2 months, and 4 months after tendon ligation. The infusions reversed the mechanical hypersensitivity after each injection point [59]. Shibata and peers injected MSC into rats that had streptozotocin-induced diabetes. Post injection of MSC, hypoalgesia, decreased sural nerve blood flow, and nerve conduction velocity, were all improved [60]. Our research has shown that the use of the newly described human anti-inflammatory MSC [MSC2] [61] in a streptozotocin-induced diabetic mouse model improves the behavioral assays of the mice and decreases the pro-inflammatory cytokines IL-1 $\beta$ , IL-2, IL-6, IL-17, and TNF- $\alpha$  to a greater degree than untreated MSC [62]. These findings are in agreement with the notion that MSC do not express immune co-stimulatory molecules that elicit immunity or graft rejection even in xenotransplantation [32-36].

## Summary

Pain control is an unmet medical need not only in the United States, but also in the world. The current therapies commonly used are not able to provide all patients with adequate pain control [63]. Research over the last decade has shown both in animal and human models that inflammation and painful states are intertwined. Many of the medications prescribed to patients for pain relief have some anti-inflammatory mechanisms; however, such medications often have untoward side effects or are incapable of dampening the immune system at a point where optimal anti-inflammatory effects can be elicited. Mesenchymal stem cells may provide an alternative to current therapies for pain. Their anti-inflammatory effects have been demonstrated in painful diseases ranging from degenerative disc disease to painful diabetic peripheral neuropathy. They also have the following advantages: they have not been associated with adverse events, they target the inflammation at the site of damage, they encourage growth of healthy tissue, they can be administered from either autologous or allogeneic sources, and they are showing positive effects in both neuropathic and musculoskeletal pain. The precise mechanism by which MSC decrease inflammation has yet to be completely outlined, and their long-term effects must be studied. However, because MSC have shown the potential to alleviate pain in various disease processes further investigation into their therapeutic ability is warranted.

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