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Stem cells and pain

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Abstract

Pain can be defined as an unpleasant sensory and emotional experience caused by either actual or potential tissue damage or even resemble that unpleasant experience. For years, science has sought to find treatment alternatives, with minimal side effects, to relieve pain. However, the currently available pharmacological options on the market show significant adverse events. Therefore, the search for a safer and highly efficient analgesic treatment has become a priority. Stem cells (SCs) are non-specialized cells with a high capacity for replication, self-renewal, and a wide range of differentiation possibilities. In this review, we provide evidence that the immune and neuromodulatory properties of SCs can be a valuable tool in the search for ideal treatment strategies for different types of pain. With the advantage of multiple administration routes and dosages, therapies based on SCs for pain relief have demonstrated meaningful results with few downsides. Nonetheless, there are still more questions than answers when it comes to the mechanisms and pathways of pain targeted by SCs. Thus, this is an evolving field that merits further investigation towards the development of SC-based analgesic therapies, and this review will approach all of these aspects.

Key Words: Inflammation; Neuropathy; Nociceptive; Pain; Pain treatment; Stem cells

Core Tip: Since the discovery of stem cells (SCs), they have emerged from a distant dream into a routine therapeutic approach depending on the field. Nowadays, the use of SCs in pain management is mainly based on their anti-inflammatory capacities, releasing neurotrophic factors and providing cellular support to replace damaged neural cells. Evidence supports that SCs can influence nociceptor neuron sensitization building a foundation for the application of these versatile cells in the treatment of neuropathic and inflammatory pain.

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INTRODUCTION

Pain is a major cause of suffering and disability, and can be characterized as a distressing experience that usually signals the presence of injury or disease, generating complex physiologic and emotional responses[1]. According to the Global Pain Index Study by GlaxoSmithKline released in 2020, interviews with 19000 individuals around the world indicate that 34% of the globe's population is in pain every day[2]. Consistently, United States's National Center of Health and Statistics revealed that 20.4% of adults suffered from chronic pain in 2019, and indicated the three major consequences of the condition were: Decreased quality of life, opioid dependence, and poor mental health[3]. This alarming scenario highlights the urgency to pinpoint the physiopathological mechanisms underlying pain and how they interconnect with other systems, which are essential to developing and improving the availability of therapeutic approaches. In this review, we highlight the stem cell (SC)-based therapies aiming to reduce pain. Despite the existence of review articles on SCs and specific types of pain, we observed that there is a gap in the literature regarding comprehensive review articles in this topic approaching various types of pain, the mechanisms of action of SC-based analgesic therapies, and pre-clinical and clinical articles. Therefore, the present review article aims to fill this gap. Data supports that SC-based approaches will revolutionize the field of pain treatment of varied etiologies as we will discuss.

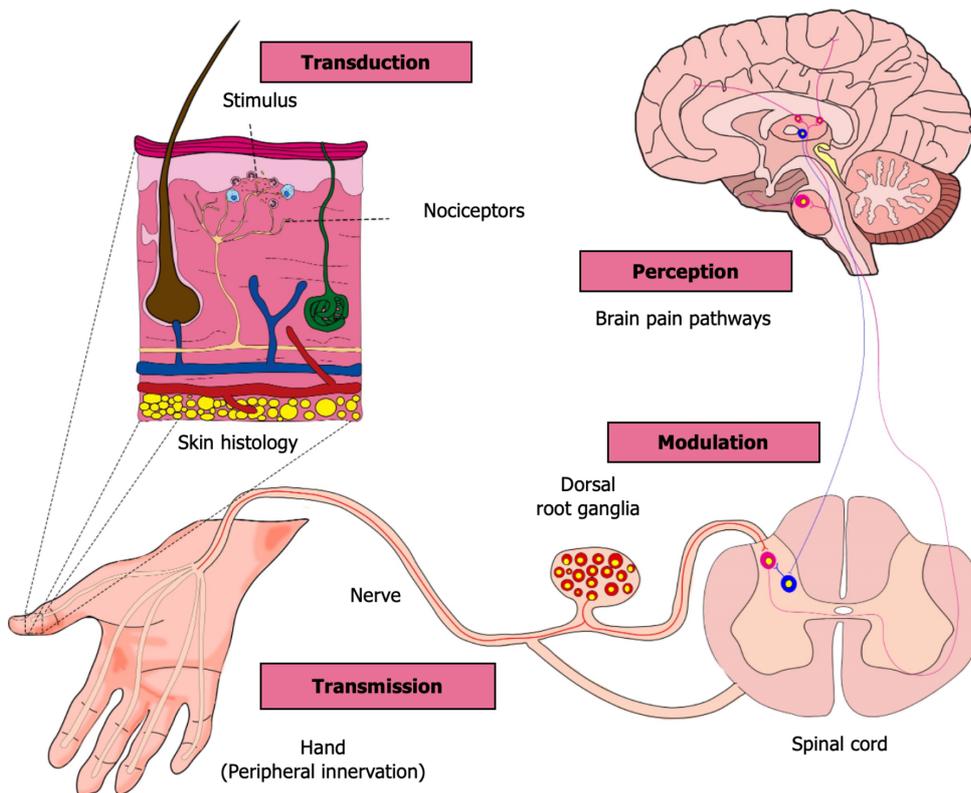
GENERAL VIEW OF PAIN MECHANISMS AND DEFINITIONS

According to the International Association for the Study of Pain (IASP), pain can be defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage"[4]. The mechanisms underlying the physiology of pain are extremely complex, involving at least two types of neurons; one whose cellular bodies are in the dorsal root ganglia (DRG) and axons projecting to peripheral tissues and the spinal cord, which are specialized in the perception of potentially harmful stimuli, and then neurons which are present in the spinal cord and in the cortex of the brain, responsible for interpreting the harmful stimuli[5] (Figure 1).

To fully comprehend the pain-related states that can affect the human body, it is imperative to define their source or the causal initiators. The present review will divide pain scenarios as: (1) Inflammatory pain, which involves the presence of inflammation as the primary cause of pain and is responsible for nociceptor neuron activation and plasticity to induce chronic pain[4]; (2) Pathogen-induced pain, a painful state caused by microbial pathogens that directly activate pain-related receptors, which also involves inflammation, but with the presence of a microorganism initiating the process[6]; and (3) Neuropathic pain (NP), a consequence of damage to the nervous system and extensive tissue repair, leading to residual nerve-healing pain[7].

Usually, pain begins with the recognition of possible damage or potentially harmful molecules. When facing a noxious stimulus, our body is able to respond, at cellular and molecular levels, through the immune and nervous system in an attempt to neutralize and repair the damage caused by such stimulus[8]. The immune system and nervous system are responsible for mediating the inflammatory process, generating edema, heat, redness, pain, and loss of function depending on the intensity of those cardinal signs of inflammation[9,10].

For an inflammatory response to occur, the harmful agent must cause tissue damage in the host, or possess molecules that are recognized by immune cells or neurons to trigger either a pro-inflammatory cascade or neurogenic inflammation, respectively[9]. After recognition, a complex cell signaling process begins, inducing vascular alterations to recruit leukocytes that will reach the primary inflammatory foci by diapedesis[10]. Several molecules secreted by immune cells (e.g., cytokines, chemokines, prostanoids) as well as receptors present in their cell membranes and molecules expressed by the pathogen itself are capable of activating nociceptors[9,11]. Nociceptors consist of a subset of sensory neurons, which innervate peripheral tissues (e.g., joints, skin, respiratory and gastrointestinal tract) and have a role in sensing nociceptive stimuli that will be interpreted in the cortex as pain with all its affective and cultural aspects[12].



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Figure 1 Pain mechanism. Representative diagram of anatomical levels involved in the steps of pain from detection of stimulus up to its interpretation and modulation. Starting from the left to the right sides of the figure. The initiation of pain processing starts with the sensing of a noxious stimulus on the skin. This stimulus is detected by nociceptors (whose cellular bodies are in dorsal root ganglia and axons that project to the peripheral tissues and spinal cord) and then relayed to the spinal cord before ultimately reaching the brain (depicted by the ascending pathways in pink). In the brain, the stimulus is interpreted and converted into the sensation of pain. Subsequently, descending pathways (represented in blue) become active, limiting nociceptive input at the spinal cord level. It is crucial to emphasize that glial cells play a significant role in the transmission and modulation of pain. They are activated by neuropeptides released by neurons as well as inflammatory molecules released by immune cells. The recognition of these molecules, whether they are pro-nociceptive or anti-nociceptive, can stimulate glial cells to alter their behavior and contribute to the persistence of the stimulus by releasing nociceptive molecules. Nociceptive neurons can also interact with immune cells that release molecules capable of activating and sensitizing these neurons as well as cause neurogenic inflammation. Varied pathogens (e.g., bacteria, parasites, virus) present virulence factors that can activate nociceptor neurons. For a further in-depth understanding of pain mechanisms in varied conditions we recommend the following review articles[125,174-177].

These stimuli (e.g., inflammatory molecules, pathogen virulence factors) can activate receptors present in nociceptors triggering the phosphorylation of ion channels controlled by ligands [transient receptor potential (TRP) channels] or modify sodium channels controlled by voltage [Voltage-gated sodium (Nav) channels]. Those stimuli, therefore, cause changes in the ion channels facilitating and/or inducing nociceptive neuron depolarization resulting in their sensitization to mechanical and thermal stimulation as well as neuronal firing to transduce the nociceptive information, respectively[9, 13]. It is important to stress that the expression of these channels can also be increased due to chronic stimulus, so that neurons that initially express low levels of an ion channel or cytokine receptor start to express them at higher levels[14].

Another important fact, as touched on above, is that the receptor/ion channel activation and pattern of expression can lead to pain sensitization. According to IASP, pain sensitization is defined as increased responsiveness of nociceptors to their normal or subthreshold afferent, and can be divided as hyperalgesia, characterized by increased pain due to a noxious stimulus, or allodynia, a painful response to normally innocuous mechanical or thermal stimuli[15]. Thus, the modifications of what is expressed by nociceptive neurons, and modulating their activation state and responsiveness to stimuli are plastic changes potentially leading to chronic pain.

The functions of the TRP ion channels are related to thermal and mechanical perception[16]. For example the TRP cation channel subfamily V member 1 (TRPV1), involved in heat hypersensitivity and activated by capsaicin; TRP melastatin 8 (TRPM8), involved in cold hypersensitivity; and TRP ankyrin 1 (TRPA1), involved in hypersensitivity to chemical and mechanical stimulation[17]. Furthermore, Nav channels (Nav1.7, Nav1.8 and Nav1.9) are directly responsible for neuronal depolarization, and their expression and activation state can also be modulated during inflammation, infection, and nerve lesions leading to acute and chronic pain[18].

HOW CAN PAIN BE QUANTIFIED IN ANIMAL MODELS?

As this review will approach in great part pre-clinical data using animals, it is important to briefly discuss how “pain” is quantified in animal models. The usage of the term pain to define the quantification of nociceptive behavior in animal models is not widely accepted, because pain assessment involves an emotional component that is often lost in the evaluation of animal responses in most tests. On the other hand, simplifying the terminology by using the word pain, facilitates the understanding by the non-specialized reader about what is under discussion. As an essential physiological mechanism that helps to guarantee the integrity of the organism, pain triggers behavioral responses, for example, moving the hand or paw from a noxious stimulus that can cause tissue damage[19]. In fact, there are subjective components associated with the painful sensation that can only be assessed in humans, since there are variations in the quality and intensity of pain experienced by different individuals for similar injuries, influenced by culture, sex, age, personal experiences, comorbidities and genetic factors[20].

There are different methods to analyze the presence of pain, as well as methods to quantitate it. Most laboratory studies use experimental rodent models, thus, the methodologies are focused on the evaluation of behaviors that can be quantified, such as paw withdraw, paw flinching, paw licking, and abdominal contortions[21], with or without the combination of other methodologies (*i.e.*, place preferences to temperatures or even self-administration of treatment).

Nociceptive assessment methods can be divided into stimulus-evoked and non-stimulus-evoked (spontaneous) behaviors. Spontaneous pain occurs regardless of the presence of an additional evoking stimulus and can be assessed using grimace scales, burrowing assays, gait analysis and weight-bearing methods[21]. Pain evoked by a stimulus can be described as hyperalgesia or allodynia[22]. This parameter is evaluated according to the type of stimulus, being subdivided into mechanical, heat and cold stimuli. Methods that assess pain evoked by mechanical stimuli seek to assess nociceptive sensitivity to a mechanical stimulus (*i.e.*, mechanical pressure on the paw), normally using the von Frey filament method (allodynia indicator), electronic pressure meter test (hyperalgesia indicator), and Randall & Sellito tests (which use increasing pressure or constant pressure over time, assessing hyperalgesia). The analysis of pain evoked by temperature stimuli seeks to assess thermal nociception, either by a heat source (*i.e.*, hot plate, Hargreaves test, tail flick), cold (*i.e.*, cold plate, cold plantar assay and acetone application/evaporation test) or both (*i.e.*, temperature place preference)[21].

Furthermore, behavioral tests are usually analyzed in conjunction with data obtained from cellular and molecular experimental approaches. For instance, neuronal function, activity, and phenotype can be assessed *in vivo* and *in vitro* using electrophysiology studies, intracellular calcium levels, immune staining of neuronal populations and their markers of activation and/or function, release of neuropeptides, cytokines and neurotransmitters, patterns of mRNA, protein and lipid profiles, and optogenetics. Additionally, it is also possible to study the contribution of non-neuronal cells in the nociceptive processes by staining glial immune and parenchymal cells, phenotype markers, and quantitating their production of mediators and functions. Thus, behavioral assays can be accompanied by a great variety of non-behavioral methods to demonstrate a specific hypothesis[23,24].

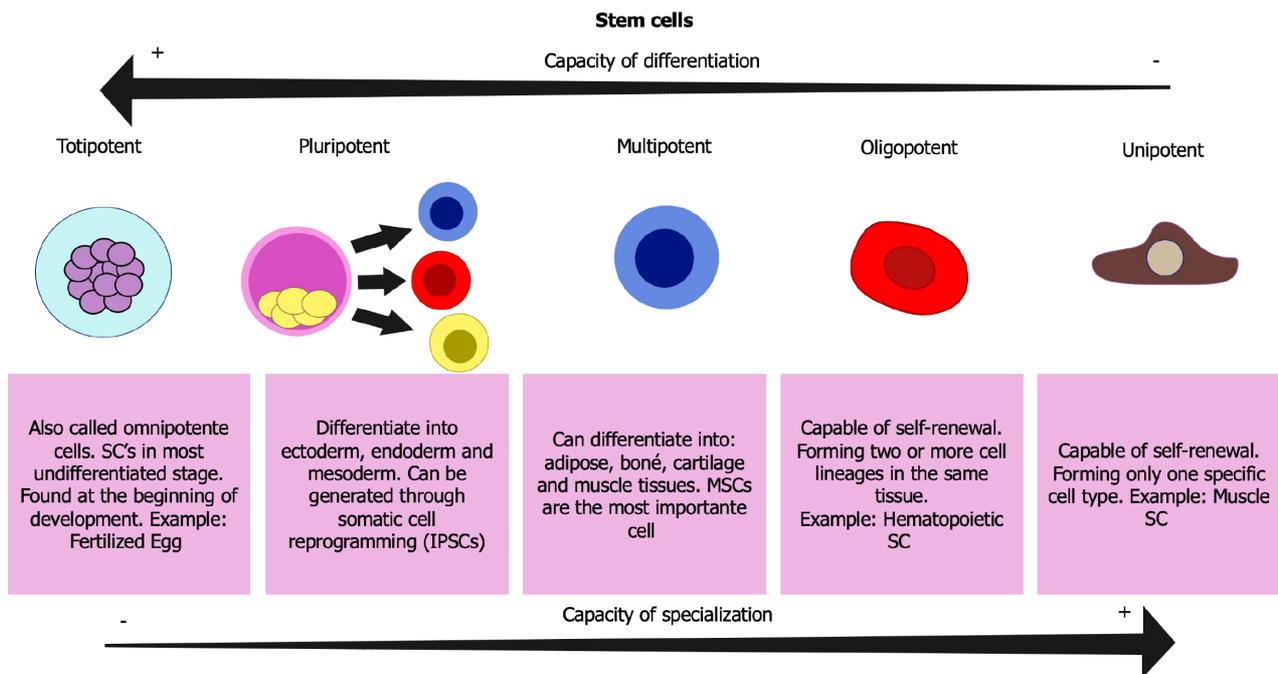
SCS: TYPES AND SOURCES

SCs are non-specialized cells with a high capacity for replication and self-renewal that have a wide range of differentiation possibilities[25]. These cells are present in all stages of life (embryonic, fetal, and adult), they give rise to differentiated cells in organs[26] and are involved in the development, maintenance, repair and renewal of tissues[27].

SC can be categorically divided into five distinct groups (totipotent, pluripotent, multipotent, oligopotent, and unipotent) according to their ability to differentiate, which varies according to the origin and derivation of the cell[26]. Totipotent SC, also called omnipotent, are the cells in the most undifferentiated stage and are found at the beginning of development (*i.e.*, fertilized oocyte)[28]. Pluripotent SC are cells that differentiate from the three germ layers (ectoderm, endoderm and mesoderm)[29]. These cells can be generated through somatic cell reprogramming and are called induced pluripotent SC (iPSC)[26]. Multipotent SC are found in most tissues and have the ability to differentiate into varied tissues, such as adipose, bone, cartilage, and muscle[30]. Within this group, mesenchymal SC (MSC) are the most important cells as will be discussed[26]. Oligopotent SC (*i.e.*, hematopoietic SC) are cells capable of self-renewal, forming two or more cell lineages in the same tissue[31]. Finally, unipotent SC are cells capable of self-renewal and differentiation into only one specific cell type[26] (Figure 2).

Although it might seem that specialization could mean restriction in some tissue types, totipotent SC have virtually no boundaries for differentiation, whereas pluripotent SC demonstrate some degree of specialization. As for the multipotent subgroup, MSC have the advantage of originating in different tissues. MSC have a differentiation rate compatible with the potential application as a pain treatment, particularly for inflammatory and autoimmune diseases[25,32,33].

In addition to classification according to their ability to differentiate, SC can also be classified according to their origin, forming four distinct groups (embryonic, fetal, adult and induced). Embryonic SC (ESC) are pluripotent SC derived from the blastocyst after fertilization (5 to 6 d)[34]. Similar to pluripotent SC, ESC differentiate into the three germ layers or remain in an undifferentiated stage[29,35]. Fetal SC are cells that remain in tissues in a quiescent state until local stimulus induces their proliferation and differentiation into specific cells of the tissues in which they are located[26]. Adult SC are cells derived from the three germ layers and the placenta[26] and depend on specific signals to enter cell division[36]. These cells are important resources in the cell repair and healing processes, as they help to maintain tissue homeostasis by replacing senescent or damaged cells[36]. Finally, iPSC are pluripotent SC produced from the genetic reprogramming of adult somatic cells[26], developing a state similar to ESC, both in morphology, proliferation and gene expression[37].



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Figure 2 Types of stem cells: Different types and characteristics. Representative scheme of the different subtypes of stem cells and their main characteristics. SC: Stem cells; MSC: Mesenchymal stem cell; iPSC: Induced pluripotent stem cell.

Currently, MSC are the main subset of SC used in therapeutic approaches, as they can be isolated from any source of human tissue and reprogrammed. MSC have the advantage of being derived from the patient and, therefore, are adequate for the donor/patient, minimizing the possible ethical issues that could arise from the use of cells from a third-party donor[38,39].

In this review, we discuss recent studies that illustrate the advantages and disadvantages of SC technology to treat painful conditions. Although SC studies have become a popular field of research, there are still a lot of unanswered questions regarding the possible application of SC in pain treatment as well as data supporting their therapeutic benefit.

HOW CAN SC TREATMENT BE USED IN PAIN MANAGEMENT?

Currently, analgesic treatment strategies include acetaminophen, nonsteroidal anti-inflammatory drugs, antidepressants, antiepileptics, local anesthetics, and opioids; and their use is closely linked to significant side effects such as: High renal and hepatic toxicity, headaches, mood swings, constipation, nausea, weight gain and even dependence[40]. Furthermore, these drugs have limited efficacy (Table 1). The statistical measurement for this effectiveness is the number needed to treat (NNT), which is the number of people who must be treated with a given drug for the desired effect to be observed in one person. Thus, the closer the NNT is to 1 the higher the treatment efficacy is[41]. Along with concerning adverse effects, the present scenario highlights the need of additional options to control and treat painful conditions[40].

In this context, the use of SC as a therapeutic approach for pain treatment has great potential due to their unique properties. In general, the use of SC for pain treatment is based on their ability to: (1) Modulate the inflammatory process, switching the pro-inflammatory profile into a pro-resolving state; (2) Interacting directly on the peripheral nervous system, promoting changes on neuronal excitability of primary afferent nociceptor neurons; and (3) Acting on the central nervous system (CNS), *via* alteration of neuronal excitability in the spinal cord and brain (Figure 3). These mechanisms will be discussed in detail throughout the following paragraphs.

The first mechanism of action of SC to control pain is to modulate the inflammatory process. SC can shape the activity of neutrophils, macrophages, B cells, T cells, natural killer (NK) cells and dendritic cells[42] (Figure 3). In innate immunity, SC regulatory action is based on their ability to produce soluble human leukocyte antigen G5 [capable of inhibiting NK cell-mediated cytotoxicity and interferon-gamma (IFN- γ) secretion][43]. Another important point is that SC are able to increase the production of interleukin-10 (IL-10), an important cytokine involved in the polarization of M2 macrophages, inducing tissue repair effects[44]. In adaptive immunity, the effects of SC actions involve increased nitric oxide (NO) production (suppressing T cell activity)[45], reduced prostaglandin E₂ (PGE₂) levels[46] and increased indoleamine 2,3-dioxygenase (IDO) activity[47]. Furthermore, it has also been described that treatment with SC increase the expression of IL-4 (by type 2 helper cells)[46] and IL-10[44].

On the other hand, SC can also produce soluble mediators to shape the inflammatory response. SC can be stimulated by inflammatory cytokines such as IFN- γ , IL-1 α , IL-1 β and tumor necrosis factor alpha (TNF- α)[45,48]. However, in response to those inflammatory cytokines, SC produce transforming growth factor-beta (TGF- β) and IL-10, which are

Table 1 Painkillers and numbers needed to treat

Drug	Drug class	NNT	Ref.
Acetaminophen 650 mg + oxycodone 10 mg	NSAID + opioid	2.7	Gaskell <i>et al</i> [178], 2009
Acetaminophen 500 mg + ibuprofen 200 mg	NSAID combination	1.6	Moore and Hersh[179], 2013
Aspirin 1200 mg	NSAID	2.4	Bandolier Extra[180], 2003
Codeine 60 mg	Opioid	16.7	Maxwell and Bateman[181], 2007
Diclofenac 100 mg	NSAID	1.8	Gaskell <i>et al</i> [178], 2009
Ibuprofen 400 mg	NSAID	2.5	Lyngstad <i>et al</i> [182], 2021
Morphine 10 mg (intramuscular)	Opioid	2.9	Bandolier Extra[180], 2003
Naproxen 500 mg	NSAID	2.7	Derry <i>et al</i> [183], 2009
Oxycodone 15 mg	Opioid	4.6	Gaskell <i>et al</i> [178], 2009

NSAIDs: Nonsteroidal anti-inflammatory drugs; NNT: Number needed to treat.

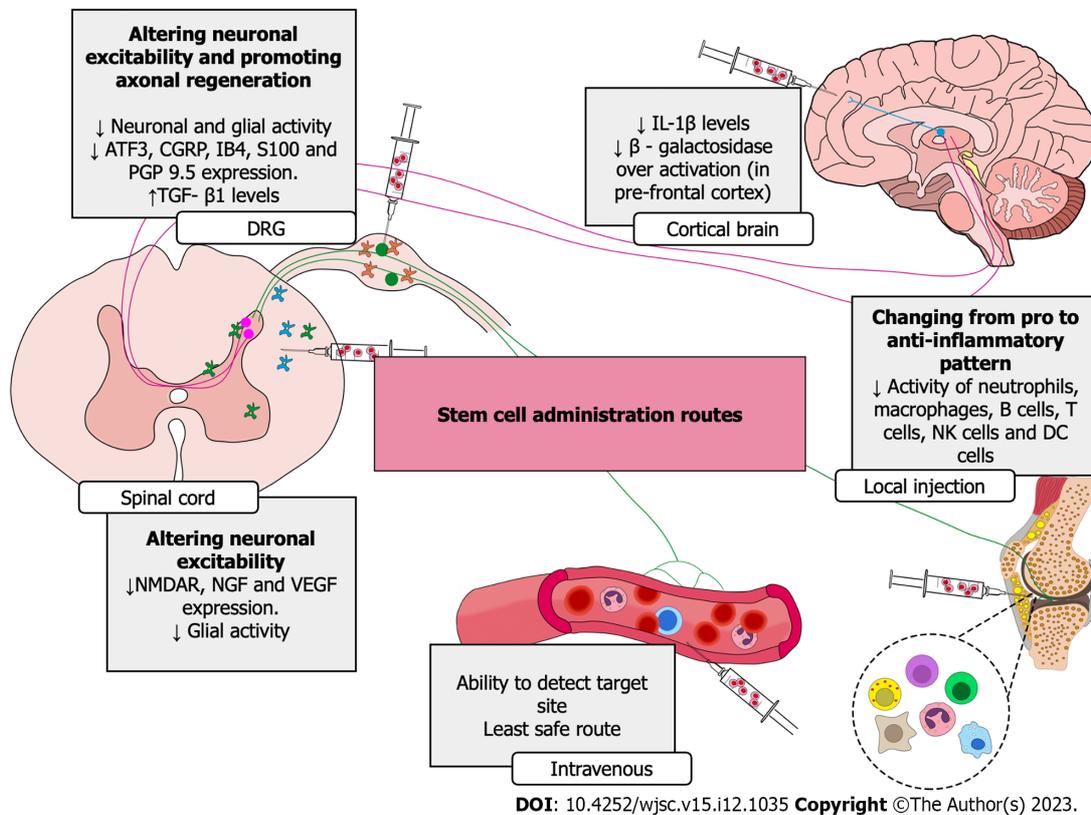


Figure 3 Analgesic mechanisms of stem cells depending on the route of administration and targets/tissues. This scheme summarizes the mechanistic changes caused by stem cell (SC) treatment that resulted in analgesia. The explanation of analgesic mechanisms of SC treatments in the cerebral cortex, spinal cord, dorsal root ganglia, intravenous and local treatment (intra articular) (indicated by the syringes) can be observed by up and down arrows plus the changed parameter. ATF3: Activating transcription factor 3; CGRP: Calcitonin gene-related peptide; IB4: Isolectin B4; NMDAR: N-methyl-D-aspartate receptor; NGF: Nerve growth factor; PGP9.5: Protein gene product 9.5; VEGF: Vascular endothelial growth factor; TGF: Transforming growth factor; IL: Interleukin.

anti-inflammatory and analgesic cytokines[49,50].

Added to their anti-inflammatory capabilities, SC become promising potential candidates to reduce peripheral sensitization of afferent sensory neurons[51] (Figure 3). SC can decrease the production of cytokines (IFN- γ [46], IL-2[46], IL-17[52] and TNF- α [46]) capable of sensitizing nociceptors and leading to hyperalgesia. SC can also increase the level of cytokines capable of decreasing nociception such as IL-4[46] and IL-10[53,54]. On the other hand, treatment with SC can increase the level of molecules indirectly linked to the promotion of hyperalgesia, such as NO (has a dual role in pain)[45, 55], PGE₂[46,56] and IDO[47,57].

These data provide evidence that the applicability of treatment in inflammatory conditions directly depends on the inflammatory microenvironment, which can be positively influenced by SC both by decreasing molecules linked to nociceptive sensitization and by increasing molecules indirectly linked to reducing pain (Figure 3). However, specific cellular targets and the source of soluble mediators were not fully investigated in the experimental settings. We envisage that the field would present a huge evolution if the studies focused not only in quantitating the modulation of soluble mediators, but also investigating the cellular targets and interactions explaining the activity of SC.

In addition to their action on the neuroimmune axis (DRGs and the immune system), an interesting fact that has not been explored much is that SC have a key structural similarity with primary afferent nociceptive sensory neurons. Primary afferent nociceptive sensory neurons and bone marrow-derived mesenchymal stromal cells express the TRPM8 receptor. Recent studies demonstrate that the influence of this receptor on neurons involves the detection of cold temperatures (18-23 °C), and that TRPM8 inhibition reduces pain[58]. In addition, this channel is also capable of modulating cell differentiation in SC, as its activation increases osteogenic differentiation in human bone marrow MSC[59].

The use of SC in pain treatment is also based on the ability of these cells to act on the CNS since they have the ability to desensitize the CNS by inhibiting glutamate-related pathways (reduction of NMDAR expression and TGF- β 1 secretion) [60]. Furthermore, SC can decrease central sensitization, *via* reduced glial cell activity, once again contributing to the attenuation of hyperalgesia[61] (Figure 3), these points will be discussed in further details in the following topics.

SC IN THE TREATMENT OF INFLAMMATORY DISEASES AND INFLAMMATORY PAIN

The number of articles investigating the relationship between pain and SC is still small, so this section was divided into two parts: (1) The use of SC to treat inflammatory diseases. This part is of interest in terms of the perspective of application to inflammatory pain since inflammatory mediators can induce nociceptor sensitization mechanisms; and (2) Articles that analyze the analgesic activity of SC treatment.

SC in the treatment of inflammatory diseases without the assessment of pain

In this topic we will present the mechanisms behind the ability of SC to modulate the inflammatory response, and the most recent discoveries involving SC and inflammation. Reducing pain is a potential outcome since inflammation was reduced in these studies, however, this specific disease symptom was not tested.

As previously discussed, the inflammatory process is composed of a series of signals. Through the release of inflammatory molecules (cytokines, leukotrienes, and prostanoids), which are used for cellular communication, tissue resident immune cells start the inflammatory response process. Examples of these inflammatory molecules include, for instance, IL-1 β , IL-5, IL-6, IL-17A, TNF- α , nerve growth factor (NGF), LTB $_4$, 5-HT and PGE $_2$. They have a role in the recruitment and activation of leukocytes and some can also activate receptors expressed by the primary afferent nociceptor sensory neurons inducing the activation (causing depolarization) or sensitization (causing an enhancement of response upon other chemical, mechanical or thermal stimulation) of these neurons. This neuro-immune interaction is relevant to pain and inflammation[62] and we will discuss how SC can interfere with it.

Neutrophils are the most abundant cell type in the blood and large numbers are recruited in acute inflammation[63]. SC activity on neutrophils may present two distinct patterns[64]. MSC can suppress hydrogen peroxide production in activated neutrophils *in vitro*. On the other hand, tissue resident glandular MSC seem to play an early role in lipopolysaccharide (LPS)-triggered inflammation by producing cytokines and chemokines to recruit neutrophils. These polymorphonuclear leukocytes presented an increase in their lifespan, chemokine production and response to LPS stimulation[65]. This MSC-dependent response is protective in the sense that LPS stimulation represents part of an infection. On the other hand, neutrophils can participate in the induction of pain by producing LTB $_4$ and PGE $_2$, which activate and sensitize nociceptor neurons[66,67]. Reactive oxygen species can also activate nociceptor neurons[9].

One of the most important anti-inflammatory mechanisms of SC is to induce a class switch in the pattern of macrophages from M1 phenotype to M2 phenotype. This ability was observed in models of osteoarthritis using the treatment with exosomes from iPSC and MSC. The M2 macrophage phenotype is involved in tissue repair as well as in the resolution phase of inflammation[68]. Upon inducing this macrophage phenotype switch, there is a decrease in the production of pro-inflammatory cytokines IL-1 β and TNF- α produced by M1 macrophages[68,69]. Interestingly, this activity seems to be related to SC-derived PGE $_2$. Contrasting with the hyperalgesic role of PGE $_2$ in inflammation by sensitizing primary nociceptive sensory neurons[70], this prostanoid also has other regulatory functions. For instance, when dendritic cells are stimulated to produce PGE $_2$ and IL-10, these antigen presenting cells reduce the expression of major histocompatibility complex (MHC)-II and CD86, thus, reducing their function of presenting antigens. As a result, there is a reduction of lymphocyte proliferation and adaptive immune response[71]. This evidence points to specific roles of PGE $_2$ and how somewhat opposing effects can be triggered by this prostanoid depending on the site of production and cellular target as well as explain anti-inflammatory activities of SC. Furthermore, PGE $_2$ can induce the production of TSG-6[72], which is capable of converting the macrophage phenotype from pro-inflammatory to anti-inflammatory[73]. Finally, MSC can recruit monocytes and macrophages through the production of chemokines such as C-C motif chemokine ligand (CCL)2, CCL3 and CCL12 in inflamed tissue, which contributes to the tissue repair[72,74].

Another characteristic of SC is their ability to interfere with the lymphocytic pattern. In Crohn's disease patients, it was observed that treatment using MSC was able to decrease lymphocyte proliferation, the proportion of CD4+ T cells, and decreases the levels of TNF- α and IL-6. The authors also demonstrated an increase in regulatory T cells (Tregs) and IL-10 production, thus, suggesting that an MSC would shift the T cell population towards an increase of Tregs that produce IL-10 to limit inflammation and reducing CD4+ T cells[75]. It has also been reported that SC are able to inhibit the prolifer-

eration of B lymphocytes[76]. The mechanism by which SC can affect these changes in both T and B lymphocytes is not fully elucidated. However, Lin *et al*[77] demonstrated that SC express adhesion molecules vascular cellular adhesion molecule-1 and intracellular adhesion molecule 1, which lead to adhesion to lymphocytes indicating a possible SC contact dependent regulation of lymphocyte function[78]. In addition, SC release NO, PGE₂ and hepatocyte growth factor[79], as well as activate the programmed cell death 1 death receptor[80], suggesting that SC could reduce lymphocyte proliferation and survival[81-83].

In addition to its influence on the immune system, it is also interesting to note the opposite. One of the reasons why most studies use MSC is due to their ability to evade the immune system explained by their lack of HLA class I and II surface markers. Both molecules are necessary for recognition by immune cells, thus, lacking such molecules is an essential characteristic to avoid the rejection of the transplanted SC and also leaves open the possibility of transplanting cells from one donor to a patient, and not solely autologous transplantation[77]. Despite this characteristic, most human studies involving SC and inflammation use MSC in a non-randomized manner. It is also noteworthy that MSC are believed to be the only SC with immunoregulatory and regenerative capabilities, in addition to presenting almost all of the effects mentioned above in this topic[77].

Application of SC in the treatment of inflammatory pain

Inflammatory pain occurs when afferent sensory neurons detect specific molecules that are able to sensitize or activate these neurons, such as cytokines, peptides, and other molecules[84]. Most of these molecules are secreted by immune and glial cells, which normally communicate in a controlled and homeostatic manner. In inflammatory diseases, there is an imbalance between pro and anti-inflammatory molecules, leading to the activation of membrane receptors in nociceptive neurons and the consequent activity of sodium channels and TRP channels resulting in neuronal sensitization and activation[9]. Inflammation also leads to neuronal plasticity in which they express higher levels of ion channels, additional receptors, and present enhanced activity and response when compared to a non-sensitized neuron. These plastic alterations cause the transition from an acute to a chronic pain state[85].

Table 2 summarizes the current literature in which SC treatment was applied to reduce pain; taking as a principle that these cells can reduce the production of pro-hyperalgesic molecules. It is noteworthy that studies on the analgesic activity of SC in inflammatory pain have been increasing in the last 10 years. Before that, the articles were mainly focused on the mechanisms of inflammation control using SC, but not necessarily on pain. Evidence supports that the mechanism by which SC reduce thermal and mechanical hypersensitivity is based on three perspectives: (1) Targeting the inflammatory response: By having the ability to reduce the secretion of pro-inflammatory cytokines (capable of sensitizing nociceptors) such as IL-6, TNF- α and IL-17[69,86,87] as well as increasing IL-4 levels, a cytokine capable of mediating analgesia[88]; (2) Modifying cell phenotype: the effects of these cytokines (mentioned in the perspective 1) are also based on the ability of SC to induce a change in the macrophages phenotype from M1 to M2 (non-phlogistic macrophage)[88], in addition to decreasing CCL2, CCL5 and CXCL10 (macrophage recruiting factors)[87]. Additionally, SC participate in the reduction of mast cell degranulation, which would result in the secretion of varied molecules with nociceptive activities such as 5-HT, histamine, LTB₄ and cytokines[89]; and (3) Neuronal and glial effects: The treatment with SC can decrease the expression in the spinal cord of calcitonin gene-related peptide (CGRP)[90] and ionized calcium-binding adaptor molecule 1 (IBA-1) (marker of glial activation, related to central sensitization)[91] and decrease the activity of immune cells. The current understanding is that SC activity occurs through the secretion of TSG-6[92], a soluble chemokine-binding protein. In turn, TSG-6 acts through inhibiting the expression of protein kinase C- γ [87] and suppressing the Toll-like receptor 2 (TLR2)/myeloid differentiation factor-88 adaptor protein (MyD88)/nuclear factor kappa B (NF- κ B)[91] signaling pathway. This TLR2/MyD88/NF- κ B cascade occurs in glial cells in the spinal cord and its activation leads to the production of pro-inflammatory/hyperalgesic cytokines.

The studies that address treatment in humans do not address possible signaling mechanisms of SC. However, SC treatment decreases pain for 6 mo [autologous bone marrow concentrate, one treatment, (0.5-1) \times 10⁶ cells][93] to 1 year (autologous adipose-derived stromal vascular cells, one treatment, 14 \times 10⁶ cells)[90] in knee osteoarthritis patients and for 2 years for discogenic back pain patients[93]. Thus, although the analgesic mechanisms of SC in humans remains elusive, the data supports the analgesic effect of clinical SC treatment.

SC TREATMENT OF PATHOGEN-INDUCED PAIN

In general, treatment using SC has great analgesic and anti-inflammatory potential. Similarly to sterile inflammatory diseases, infections also cause inflammation, however, there is a dual role in which inflammation involves the immune response against the pathogen as well as being responsible for tissue damage. Finding the balance between these two effects is difficult[94]. Studies involving SC and infections caused by bacteria and viruses are restricted only to the inflammatory context of infections. On this topic we will present data that demonstrate a potential analgesic effect in diseases caused by SC in bacterial and viral infections.

Bacteria-induced pain

Bacterial infections can commonly cause discomfort and pain[95]. It is believed that pain caused by bacteria and their bacterial components can occur in two different manners: The first and most classic one occurs through the activation of immune cells, production of pro-inflammatory cytokines, and the consequent nociceptor sensitization by neuronal effects of inflammatory molecules[96,97]. The second occurs through the direct activation of nociceptor neurons by bacterial virulence components, such as α -hemolysin, capable of forming pores (as its primary activity), thus activating both

Table 2 Articles that used stem cells to treat inflammatory pain (stem cell-based treatment of inflammatory pain or in models where pain is certainly involved, but was not investigated)

Ref.	Stem cell therapy design	Key findings	Pain-related highlights	Route of administration	Number of cells or amount of extracellular vesicles and exosomes
Hsueh <i>et al</i> [69], 2023	iPSC-derived EVs for the treatment of rabbit articular cartilage OA in an <i>in vivo</i> model and an <i>in vitro</i> interleukin (IL)-1 β -induced model	Improvement in both <i>in vivo</i> and <i>in vitro</i> models of OA by stimulation of chondrocytes proliferation and decreasing senescence were accompanied by: Decreasing of TNF- α ; IL-6; protein 21 (p21); MMP 13; ADAMTS5; and increasing of collagen II	Indirect: Specific pain receptors/pathways weren't investigated	i.a.	100 μ g iPSC-EV
Gao <i>et al</i> [184], 2022	Small EVs from iPSC-derived mesenchymal stem-cells ameliorate tendinopathy pain by inhibiting mast cell activation	The treatment was able to decrease acute pain in tendinopathy, as well as inhibit infiltration of activated mast cells and interactions with nerve fibers <i>in vivo</i> . In the <i>in vitro</i> experiments, the treatment decreased mast cell degranulation and the expression of pro-inflammatory cytokines and genes involved in the hypoxia inducible factor-1 signaling pathway	Pain behavior was measured by the von Frey method. And the weight distribution on the knees by SWB; immunofluorescence staining of tendon sections for tryptase (mast cell marker) and PGP9.5 (nerve fiber marker) was performed to assess the number of activated mast cells and the anatomical interaction between mast cells and nerve fibers. In addition, the SWB and CatWalk test was also carried out	Local injection (quadriceps tendon)	1 \times 10 ⁹ particles
Yu <i>et al</i> [185], 2022	Intravital imaging and single cell transcriptomic analysis for engraftment of mesenchymal stem-cells in an animal model of interstitial cystitis/bladder pain syndrome	The transplanted cells formed a perivascular-like structure. They were also shown to express cyclin-dependent FOSe kinase-1 which played a key role in modulating the migration, engraftment and anti-inflammatory functions of multipotent MSCs, which determined their therapeutic potency <i>in vivo</i>	<i>In vivo</i> two-photon intravital microscopy and single-cell transcriptome analysis were used to assess the effects of stem cell treatment on interstitial cystitis/bladder pain syndrome	Injected into the outer layer of the anterior wall and dome of the bladder	10 ⁶
Zhang <i>et al</i> [186], 2022	EVs derived from MSCs alleviate neuroinflammation and mechanical allodynia in interstitial cystitis rats by inhibiting NLRP3 inflammasome activation	SC treatment decreased suprapubic mechanical allodynia and frequent urination in rats with interstitial cystitis. It also decreased glial cell activity as well as neuroinflammation in the spinal cord. Furthermore, the treatment was able to decrease the activation of NLRP3 inflammasomes and the TLR4/NF- κ B signaling pathway	Behavioral test (von Frey) was performed to measure allodynia and western blot and immunofluorescence for protein related to inflammation and central sensitization analysis: CD9, CD63, CD81, ALIX, TNF- α , IL-1 β , IL-6, IBA-1, GFAP, NLRP3, Caspase-1, IL-18, TLR4, p65 NK- κ B, phospho-p65 NK- κ B (western blot). NLRP3, neuron-specific nuclear protein, GFAP and OX-42 labeling (immunofluorescence)	i.t.	20 μ g
González-Cubero <i>et al</i> [86], 2022	EV and soluble fractions of adipose tissue-derived MSCs secretome induce inflammatory cytokines modulation in an <i>in vitro</i> model of discogenic pain	There was a decrease in the expression of IL-6, IL-8 and IL-17	Indirect method: The authors measured the regulatory capacity of EVs on the inflammatory molecules IL-1 α , IL-1 β , IL-6, IL-8, IL-17, nerve growth factor, brain-derived neurotrophic factor, IFN- γ , NF- κ B and TNF and MMP-1, MMP-2, MMP-3, MMP-13 and ADAMTS-5	<i>In vitro</i> model	1 \times 10 ⁶
Yang <i>et al</i> [91], 2020	Anti-inflammatory protein TSG-6 secreted by bone marrow MSCs attenuates neuropathic pain by inhibiting the TLR2/MyD88/NF- κ B signaling pathway in spinal microglia	Stem cells are capable of secreting TSG-6. This article demonstrated that i.t. administration of this protein leads to a decrease in mechanical allodynia and heat hyperalgesia. In addition to inhibiting neuroinflammation in the spinal cord (IBA-1), the protein administration inhibited the activation of the TLR2/MyD88/NF- κ B pathway in the dorsal horn of the ipsilateral spinal cord by the secretion of TSG-	The activation of the TLR2/MyD88/NF- κ B signaling pathway was evaluated by western blot and by immunofluorescence. Mechanical allodynia and heat hyperalgesia were observed by behavioral tests	i.t.	5 \times 10 ⁶

		6 and reduced the production levels of pro-inflammatory cytokines, such as IL-1 β , IL-6 and TNF- α			
Zhang <i>et al</i> [187], 2019	MSCs exosomes alleviate temporomandibular joint OA by attenuating inflammation and restoring matrix homeostasis	It was observed that the treatment led to repair of the temporomandibular joint, along with a reduction in inflammation and pain. Treatment increased IL-1 β -impaired sulfated glycosaminoglycan synthesis and suppressed IL-1 β -induced nitric oxide and MMP13 production. These effects were partially abrogated by inhibitors of adenosine receptor, protein kinase B, ERK and adenosine monophosphate activated protein kinase phosphorylation	Mechanical hyper-nociception was assessed using the von Frey microfilament. The expression of inflammatory mediators and other components was measured using quantitative polymerase chain reaction	i.a.	100 μ g
Ebbinghaus <i>et al</i> [88], 2018	A promising new approach for the treatment of inflammatory pain: Transfer of stem cell-derived tyrosine hydroxylase-positive cells (mouse model)	It has been demonstrated that the administration of endogenous tyrosine hydroxylase positive cells (iTH+) cells, prior to the induction of antigen-induced arthritis, was not sufficient to suppress the disease. However, the treatment was able to decrease pain behavior evoked by inflammation, largely due to the production of IL-4 induced by iTH+ cells. Furthermore, the treatment was able to reduce the levels of pro-inflammatory molecules, in addition to increasing the number of M2 macrophages in dorsal root ganglia	Inflammatory molecules were quantified, such as: IFN- γ , IL-2, IL-4, IL-6, IL-10, CCL3, CCL5, CXCL1, CXCL2, CXCL10, and CXCL12. Additionally, pain-related behavior tests and IBA-1 and arginase 1 labeling in the dorsal root ganglion <i>via</i> immunofluorescence was performed	i.v.	10 ⁶
Ichiseki <i>et al</i> [92], 2018	I.a.-injected MSC stimulate anti-inflammatory molecules and inhibits pain related protein and chondrolytic enzymes in a monoiodoacetate-induced rat arthritis model	The treatment was able to inhibit central pain sensitization (decreased expression of CGRP in the spinal cord) and increase the secretion of TSG-6 by stem cells, an anti-inflammatory factor and cartilage protector	For the evaluation of central sensitization, CGRP staining was performed by immunofluorescence. And the histochemical technique was also used for the evidence in the joint of ADAMTS5 and TSG-6	i.a.	5.0 \times 10 ⁶
Fodor and Paulseth [90], 2016	Adipose derived stromal cell injections for pain management of OA in the human knee joint	After 3 mo of treatment, patients showed improvement in WOMAC and VAS scores, which were maintained for 1 yr. ROM and TUG improved until the third month. All patients achieved full activity with decreased knee pain and no infections or adverse effects reported	Patients were evaluated by following scores on the WOMAC, VAS pain scale, ROM, TUG, and magnetic resonance imaging	i.a.	14.1 \times 10 ⁶ nucleated stromal vascular fraction cells per knee
Pettine <i>et al</i> [93], 2016	Treatment of discogenic back pain with autologous bone marrow concentrate injection with minimum two-year follow-up (humans)	Stem cell treatment reduced visual analog scale and Initial Oswestry Disability Index scores. In addition to reducing pain in patients. The treatment proved to be effective for up to 2 yr after the injection	Pain was assessed using scores provided by patients	Intradiscal injection	(0.5-1) \times 10 ⁶
Durand <i>et al</i> [89], 2015	Persistent visceral allodynia in rats exposed to colorectal irradiation is reversed by MSC treatment	Induced a time-dependent reversion of the visceral allodynia and a reduction of the number of anatomical interactions between mast cells and PGP9.51 nerve fibers	Spinal sensitization (was available for labeling of phospho-ERK neurons), colonic neuroplasticity (as increased density of substance P1 nerve fibers); s, visceral sensitivity was evaluated by studying the contraction of the abdominal muscles in response to colorectal distension	i.v.	1.5 \times 10 ⁶
Watanabe <i>et al</i> [87], 2015	Early transplantation of MSC after SCI relieves pain hypersensitivity through suppression of pain-related signaling cascades and reduced inflammatory cell	The treatment was able to decrease thermal and mechanical hypersensitivity. Improvements in pain were mediated by suppression of PKC- γ and p-CREB expression in dorsal horn neurons. The authors also reported a decrease in the levels of	Mechanical allodynia and thermal sensitivity were recorded. In addition, immunofluorescence was performed on spinal cord sections, labeling for: PKC- γ or p-CREB, GFAP, cD11B and phospho-protein 38. For immunoblot analysis,	Injection into the middle of the contusion site, identified as the middle point of the laminectomy area	2.0 \times 10 ⁵

recruitment	pro-inflammatory cytokines (TNF- α , IL-6), mediators of early secondary vascular pathogenesis (MMP9) and macrophage recruitment factors (CCL2, CCL5 and CXCL10). All in addition to increased levels of a microglial stimulating factor GM-CSF)	components of the mitogen-activated protein kinase family, inflammatory mediators (TNF- α , IL-6, MMP-9), macrophage recruiting factors (CCL2, CCL5, and CXCL10) and GM-CSF (a microglial stimulating factor) were analyzed		
Emadedin <i>et al</i> [188], 2012	Intra-articular injection of autologous MSC in six patients with knee OA	The treatment was able to improve scores related to pain, the functional status of the knee and the distance covered up to six months after the injection	VAS which is a subjective assessment that represents the patient's perception of the current pain state with a higher score reflecting more severe pain. Functional status of the knee was assessed by WOMAC OA index. This index evaluates pain, joint stiffness, physical and social function of patients with OA of the knee	i.a. (20-24) $\times 10^6$

iPSC: Induced pluripotent stem cells; OA: Osteoarthritis; IL: Interleukin; TNF- α : Tumor necrosis factor alpha; p21: Protein 21; MMP: matrix metalloproteinase; ADAMTS5: A disintegrin and metalloproteinase with thrombospondin motifs 5; i.a.: Intra-articular; EV: Extracellular vesicle; SWB: Static weight bearing; PGP9.5: Protein gene product 9.5; CDK1: Cyclin-dependent kinase 1; MSC: Mesenchymal stem cells; NLRP3: NOD-like receptor protein 3; i.t.: Intrathecal; TLR: Toll-like receptor; NF- κ B: Nuclear factor kappa B; IBA-1: Ionized calcium-binding adapter molecule 1; GFAP: Glial fibrillary acidic protein; CD: Cluster of differentiation; IFN- γ : interferon-gamma; TSG-6: Tumor necrosis factor alpha-stimulated gene 6; MyD88: Myeloid differentiation primary response 88; ERK: Extracellular signal-regulated kinase 1; iTH+: Tyrosine hydroxylase positive cells; CCL: C-C motif chemokine ligand; CXCL: C-X-C motif chemokine ligand; DRG: Dorsal root ganglion; i.v.: Intravenous; CGRP: Calcitonin gene-related peptide; WOMAC: Western Ontario and McMaster Universities Arthritis Index; VAS: Visual Analogue Scale; ROM: Range of motion; TUG: Timed ascent and descent; PKC- γ : Protein kinase C gamma; GM-CSF: Granulocyte-macrophage colony stimulating factor; p-CREB: Phospho cyclic AMP response element binding protein; p-p38: Phospho-protein 38.

Nav1.8+ and TRPV1+ neurons[98,99]; or by LPS, which is capable of activating TLR4 expressed by neurons or be sensed by TRPA1 (at lower doses) and even TRPV1 (at higher doses)[100,101]. Thus, bacteria can induce nociceptor sensory neuron sensitization indirectly by activating immune cells that will produce nociceptor sensitization molecules or directly by activating neuronal receptors and triggering nociceptor depolarization by forming membrane pores[96].

As discussed in the topic "SC in the treatment of inflammatory diseases and inflammatory pain", the effects of SC activity on bacterial infections have two main characteristics. The first is that treatment with SC can increase phagocytic activity and neutrophil survival in bacterial infections[102,103]. Second, SC treatment can attenuate exacerbated immune responses, as seen in a murine model of endotoxemia induced by LPS, the administration of MSC by the intraperitoneal route is capable of reducing the severity of the disease, mainly by reducing the levels of IL-1 β , IL-6, IL-8 and TNF- α and increasing IL-10 in the plasma, as well as reducing the recruitment of neutrophils in the liver[104].

Despite demonstrating great analgesic potential by reducing the levels of cytokines causing hypersensitivity and increasing bacterial clearance, no articles were found that investigated a possible decrease in pain in models that use bacteria and SC treatment. This fact highlights a gap in the literature and potential field to be explored.

Viral infection-induced pain

In general, viral infections can cause pain. Depending on the type of virus and site of infection, an inflammatory process begins, characterized by the high release of inflammatory mediators. The detection of these mediators can occur through the central or peripheral nervous system[11]. A recent study demonstrated that most of the symptoms of intranasal H1N1 infection (reduction in food intake, water intake, and mobility during early-stage infection and improved survival) come from the detection of PGE₂. This prostanoid activates EP3 receptors, which are expressed in both the hypothalamus and circumventricular organs, as well as in nerve endings in the nasopharynx[105]. It has also been demonstrated that the herpes simplex virus 1 can also infect the neurons present in the DRG, and the persistence of the virus leads to the recruitment of leukocytes to the region, TNF- α secretion and neuronal hypersensitivity[106]. While the pain caused by Chikungunya virus depends on its envelope protein E2 activation of TRPV1+ nociceptor sensory neurons[107].

As discussed earlier, SC have a high anti-inflammatory capacity. This characteristic is also observed against viruses since treatment with SC can decrease the levels of cytokines[108] that sensitize nociceptors. An interesting fact about SC is that these cells have IFN-responsive genetic machinery. Therefore, upon detecting the presence of the signal produced in viral infections (flavivirus, dengue and Chikungunya virus), they express genes related to IFN-induced transmembrane proteins, which prevents the contamination of these cells[109]. In murine models, treatment with MSC reduces the levels of IL-1 α , IL-6, TNF- α and IFN- γ in response to H9N2 infection[110]. It has also been described that the administration of extracellular vesicles derived from MSC was able to reduce the viral load in lung epithelial cells of pigs infected with H1N1/H7N2/H9N5[111]. Recent evidence demonstrates that extracellular cells derived from MSC have the *in vitro* capacity to inhibit the replication of the Influenza virus and severe acute respiratory syndrome coronavirus 2[112]. It is also important to report that recently a number of clinical studies have been carried out in humans using MSC treatment in coronavirus disease (results not yet reported)[113-117]. Despite the potential of SC treatment to reduce pain and the fact that viral infections can cause pain, there is a gap in the literature of studies investigating the analgesic effectiveness of SC in the treatment of viral infection-triggered pain.

SC-BASED TREATMENTS FOR NP

Studies involving inflammation and pain are still somewhat restricted when compared to the volume of articles that study NP and treatment using SC. On this topic, we will present an overview of the mechanisms involved in the development of NP and then explain the mechanisms underpinning SC therapy.

What mechanisms are involved in the development of NP?

To fully comprehend the mechanisms that modulate NP, it is essential to understand how our body processes the external and internal stimuli that can lead to nociceptive alterations. Pain sensation is the product of higher brain center perception and can be influenced by a number of factors like attention, affective dimensions, autonomic variables, immune variables, and hormones[118].

In normal tissue, pain is triggered by intense or noxious stimuli that leads to the activation of high threshold transmembrane ion channels, a process defined as nociceptive pain. These ion channels present on nociceptor neurons convert mechanical, thermal or chemical stimuli - that can vary from pinpricks and light touch to vibrations, indentations, gravity and sound waves - into biochemical regulated electrical signals that are directed to the brain through the generation and conduction of action potentials, characterizing mechanotransduction[119].

NP, on the other hand, occurs when a pathological process leads to nerve damage, and the healing process of the nervous system results in maladaptation observed by the lower unbalanced threshold of neuronal activation that can involve numerous pain-related processes, from the detection by the nociceptor neuron to the acknowledgement of nociceptive signaling by the brain[120]. NP comprises peripheral neuropathy, postherpetic neuralgia, trigeminal neuralgia, nerve root pain, and phantom limb pain; and can be caused by lesions or diseases involving the primary afferent sensory neurons of the somatosensory nervous system, including peripheral fibers (A β , A δ and C fibers) and CNS neurons[121-123].

The extensive modulatory possibilities that can unravel during the healing process of nervous tissue make evident the importance of neuroplasticity, a phenomenon that can be defined as the ability of the nervous system to adapt its responses according to intrinsic or extrinsic stimuli by reorganizing its structure, functions, or connections after injuries. Thus, neuroplasticity is a key factor in the development of NP[124].

NP typically arises from an incorrect healing process due to an imbalance between neuroimmune interactions, glial cells, and neurotrophic factors. Briefly, a nervous system lesion triggers inflammatory and repair responses that are not always successful. Unsuccessful nerve repair will lead to plastic changes causing the sensitization of nociceptive neurons, sympathetic sprouting forming basket structures that explain sympathetic maintained chronic pain, incorrect formation of novel synapses causing the stimulation of second order neurons upon touch (causing allodynia). Maladaptive tissue repair can also involve the activation of glial cells that further stimulate nociceptive neurons causing retrograde sensitization and boosting second order nociceptive signaling to the brain when a nervous fiber is sectioned. Cellular events occur at the site of injury and in the neuronal soma corresponding to the area in the DRG. These cellular events include, for instance, local immune cell signaling *via* purinergic P2 receptors-ATP signaling[125]. Nerve damage is, therefore, an initiating event, but it is not the sole orchestrating factor. Neuronal plastic changes include the alteration of ion channel properties, affecting spinal and brain sensory signaling, shifting pain perception so that normal innocuous stimuli can result in pain by facilitating neuronal depolarization upon thermal and mechanical stimulation as a result of nociceptor neuron sensitization owing to increased membrane excitability. Spontaneous neuronal firing can also be observed[119, 125, 126].

The regeneration process can be divided into five steps: (1) Fluid phase; (2) Matrix phase; (3) Cellular migration phase; (4) Axonal phase; and (5) Myelination phase[127]. After injury, neuronal genetic expression is altered to induce the release of neurotrophic and angiogenic factors like NGF, brain-derived neurotrophic factor, glial cell-derived neurotrophic factor (GDNF), vascular endothelial growth factor-A and angiopoietin-1[128], and to upregulate the expression of their corresponding receptors. These growth factors support the axonal lengthening of the injured nerve from its proximal fragment, as the damaged axons in the distal nerve fragments undergo degeneration, a process known as Wallerian degeneration[127]. Infiltrating macrophages and Schwann cells also take part by clearing myelin debris and retro feeding the secretion of neurotrophic and pro-angiogenic factors, enabling the formation of connective tissue bridging the nerve clefts, as Schwann cells create an endoneurial tube that guides the axonal regeneration process starting from a growth cone located at the Ranvier's node[129].

The accurate balance between compensatory and decompensatory reactions of the nervous system when facing neural damage is of the utmost importance, because many of the changes that occur in response to neural injury are potentially adaptive, such as the removal of cell and myelin debris, regulation of receptors that counterbalance the loss of input, and appropriate signaling in order to dampen ion fluxes and metabolic stress after the acute injury[130]. Among the adaptive modifications, we can also cite anti-apoptotic signaling to prevent neuronal cell death, induction of axonal growth and sprouting, synaptic remodeling, and remyelination[131].

A defining characteristic that is often present in NP is the absence of an identifiable stimulus upon spontaneous pain. Such abnormal sensitization can be generated at any anatomical level related to the nociceptive sensory experience: (1) The site of the injury that induced the NP in the first place and underwent maladaptive healing - or neuroma - where the regenerated axon can get misdirected and become unable to reach the desired target[132]; (2) Cell death of the corresponding DRG neurons; (3) Alterations in gene regulation and expression of the surrounding intact afferent fibers; (4) Central sensitization and altered connectivity in the spinal cord of low-threshold large myelinated afferents *via* synaptic facilitation and loss of inhibition at multiple levels of the neuraxis; and (5) Voltage-gated channel-related generation of spontaneous ectopic activity in nociceptors, a mechanism whose importance is supported by the effectiveness of nonselective sodium channel blockers as local anesthetics[133]. Increased synaptic strength enables previously sub-

threshold inputs to activate nociceptive neurons, reducing their threshold and enhancing their responsiveness, which results in the expansion of their receptive fields. In addition, phenomena like conduction slowing or blocking, reduced inhibition, inappropriate connectivity, altered processing of both nociceptive and innocuous afferent input, abortive growth, neuronal loss, and glial scarring can be decisive factors underlying the pathogenesis of NP and the onset of spontaneous pain[126,134].

It is important to note that once NP is generated, the sensory hypersensitivity tends to persist for prolonged periods, even though the original initiator factor may have long since disappeared[126]. The complexity and abundance of factors involved in the central and peripheral nervous system modifications, make the treatment of NP challenging and expensive[51].

The use of SC as a therapy for NP

Given the fact that current treatments for NP are not fully effective, there is a need for improving NP treatment. Among the characteristics that stand out in the use of SC for NP is the ability of these cells to migrate to the injured site and repair damaged cells, even when administered systemically[135]. Most literature reports address SC treatment in the context of NP models, in which strategies are based on replacing damaged nerve cells and induce the production of neurotrophic factors. In addition, SC inhibit apoptosis and degeneration processes, and increase the survival of both injured and uninjured nerves[136] (Table 3). Furthermore, the mechanisms of action of SC modulating NP vary according to the stimulus in question (disease model/condition), since each disorder presents its own alterations that can be classified as peripheral and/or central, we will follow this rationale in the next sections.

Peripheral nervous system-related analgesic mechanisms of SC

The peripheral actions of SC focus on their anti-neuro-inflammatory capacity and their neuroprotective potential and ability to promote growth. SC anti-neuro-inflammatory capacity (described in the previous topics) includes the ability to reduce the levels of pro-inflammatory cytokines IL-1 β , IL-6[137] and TNF- α [87]. These cytokines are extremely important in peripheral sensitization, because they are capable of sensitizing nociceptors and increase the expression of TRP and Na channels, consequently leading to mechanical and thermal sensitization[9]. In addition to reducing the production of hyperalgesic cytokines, SC can increase IL-10 levels in NP models[137], which also explains the decrease in the pro-inflammatory cytokine production[138] and induction of the class switch of macrophages from an M1 to an M2 profile. M1 macrophages are responsible for proinflammatory responses, overexpress CD80, CD86, and CD16/32 which are essential for activating lymphocytes and thus adaptive immunity. Moreover, M1 phenotype macrophages are capable of secreting pro-inflammatory cytokines[139]. In contrast, M2 macrophages express chemokines CCL17 and CCL22 that mediate the control of Treg cell biology[140], mannose receptor (CD206) that induces endocytosis[141], as well as anti-inflammatory responses and contribute to the repair of damaged tissues by the phagocytosis of debris[138]. Moreover, M2 macrophages can be manipulated *in vitro* to produce an opioid-mediated analgesic effect, demonstrated by its complete blockade by the opioid receptor antagonist naloxone methiodide in an *in vivo* model of chronic constriction injury (CCI) of the sciatic nerve induced NP[142]. Although there is no data on SC and microglia polarization, considering the activity of SC to polarize macrophages towards a M2 profile, if this activity is also true for microglia polarization to an M2 profile, this would be an important analgesic mechanism in NP. M1 microglia are actively involved in NP by producing mediators that sensitize nociceptors[143].

SC are also able to directly interact with the DRG neurons through GDNF production[144]. GDNF is of great importance for studies where there is neuronal damage, such as in sciatic nerve injury[136]. Since the administration of GDNF is capable of decreasing pain-related behaviors, due to its inhibitory action on the molecules such as activating transcription factor 3 - marker of neuronal injury and IB4 (a nociceptive neuron marker of a neuronal population that do not express CGRP, and that downregulate NGF and receptor tyrosine kinase)[145,146].

The actions of SC on DRG neurons also affect the production of neuropeptides related to pain signaling. In models of CCI-induced NP, SC treatment was able to decrease nociceptive behavior by releasing TGF- β 1, which activates neuronal TGF- β 1R[147], as well as reducing the production of hyperalgesic cytokines IL-1 β and TNF- α [148].

CNS-RELATED ANALGESIC MECHANISMS OF SC

The actions of SC treatment targeting mechanisms in the CNS environment are based on three hypotheses: (1) Desensitization of the CNS; (2) Inhibition of glial cells; and (3) Reduction in apoptosis and autophagy[149].

The SC mechanisms that are dependent on: (1) Desensitizing the CNS in NP mainly involve the downregulation of glutamate neurotransmission. After the damage of peripheral neurons, glutamate is released in the spinal cord as well as N-methyl-d-aspartate (NMDA) and an increase of its receptor (NMDAR) expression is seen. This mechanism aims to maintain the transmission of the captured noxious signal to the cerebral cortex, where it will be interpreted as pain[150]. Treatment with SC decreases the CNS expression of NMDAR, interrupting the maintenance of nociceptive signaling [150]. In addition, SC can secrete TGF- β 1, which inhibits the signaling carried out by glutamate that would otherwise stimulate nociceptive signaling by the activation and proliferation of microglia and astrocytes in NP. TGF- β 1 also reduces the expression of proinflammatory cytokines in the CNS in NP, thus, reducing neuroinflammation and nociceptor neuron sensitization[147].

Second, glial cells play a key role in central sensitization. As previously explained, after the detection of noxious stimuli by nociceptors, primary sensory afferent neurons secrete neuropeptides in the spinal cord dorsal horn, where central signaling takes place. If the noxious stimulus persists, glial cells can be activated by these neuropeptides (CGRP and

Table 3 Articles that used stem cells for neuropathic pain treatment (stem cell-based treatment of neuropathic pain)

Ref.	Stem cell therapy design	Key findings	Pain-related highlights	Delivery route	Number of cells or amount of extracellular vesicles and exosomes
Gao <i>et al</i> [189], 2023	Huc-MSCs-derived exosomes attenuate neuropathic pain by inhibiting activation of the TLR2/MyD88/NF-κB signaling pathway in the spinal microglia by targeting radical S-adenosyl methionine domain containing 2	Huc-MSCs-derived decreased protein levels of TLR2, MyD88, and p-p65 that were significantly upregulated in the CCI group in model rats	The protein levels of TLR2, MyD88, p65, and p-p65 were examined by western blotting	i.t.	5 μg
Miyano <i>et al</i> [190], 2022	I.v. administration of human MSCs derived from adipose tissue and umbilical cord improves neuropathic pain <i>via</i> suppression of neuronal damage and anti-inflammatory actions in rats	Both the mechanical threshold and the differences in weight bearing of the right and left hind paws improved significantly. In addition, the authors also reported a decrease in the ATF-3 and IBA-1 in DRG. The authors also reported that the treatment significantly improved the partial sciatic nerve ligation-induced decrease in the level of myelin basic protein in the sciatic nerve	Was performed by von Frey and dynamic weight bearing. Also, the authors did I against ATF-3, IBA-1, myelin basic protein, NeuN, neurofilament (NF) 200	i.v.	5 × 10 ⁶
González-Cubero <i>et al</i> [191], 2022	Application of adipose-derived MSCs in an <i>in vivo</i> model of peripheral nerve damage	Rat sciatic nerve damage models both <i>ex vivo</i> , on TNF-induced Schwann cells, and <i>in vivo</i> using biomaterial implants containing TNF. Upregulation of c-Jun and downregulation of early growth response protein 2 myelin-associated transcription factors were induced by TNF-related damage, but the addition of ASCs or ASC-conditioned medium (secretome) were able to revert the profile	qPCR, western blot, and confocal microscopy were chosen to quantify nerve healing-related protein expression and production <i>in vivo</i> and <i>ex vivo</i> . The sciatic functional index was calculated to assess nerve regeneration, but no pain-specific mechanisms were investigated	Sciatic nerve	<i>ex vivo</i> 0.5 × 10 ⁶ cells; <i>in vivo</i> 4 × 10 ⁶ ASCs
An <i>et al</i> [192], 2022	Immortalized bone MSCs with inducible galanin expression produce controllable pain relief in neuropathic rats	hTERT-BMSCs/Tet-on/GAL cells were able to induce controllable pain relief by spared nerve injury of sciatic nerve under the transcriptional control of doxycycline	To determine the analgesic efficacy acted through GalR1, GalR2, and phospho-protein kinase Mζ expression levels in spinal dorsal horn were analyzed by western blot assay	Subarachnoid space	10 ⁶
Lee <i>et al</i> [193], 2022	MSCs spheroids alleviate neuropathic pain by modulating chronic inflammatory response genes	The authors report a decrease in mechanical allodynia, related to a decrease in TNF-α and IFN-γ levels. In addition to a smaller number of cells marked with cluster of differentiation (CD) 68 in the region	The von Frey test was performed to assess mechanical allodynia, while immunofluorescence was used to observe changes in CD68 and IBA-1 levels. TNF-α and IFN-γ levels were assessed by the ELISA assay	Intramuscular	10 ⁶
Chen <i>et al</i> [194], 2022	Synergic Effect of early administration of probiotics and adipose-derived MSCs on alleviating inflammation-induced chronic neuropathic pain in rodents	The authors demonstrate that treatment with stem cells alone can reduce thermal hyperalgesia and mechanical allodynia, with the potentiated effects after combined treatment with probiotics. Interestingly, they found a reverse correlation between protein expressions of inflammatory (phospho-NF-κB, IL-1β, TNF-α and MMP-9), apoptotic (cleaved-caspase-3, cleaved-PARP), oxidative-stress (NOX-1, NOX-2), deoxyribonucleic acid (DNA)-damaged (γ-H2AX) and MAPK-family (p-P38, p-JNK, p-ERK 1/2) biomarkers as	To observe pain-related behavior alterations, Hargreaves and von Frey tests were applied. Immunofluorescence was performed for p-p38; NF200; peripherin, 53BP1, β3 Tubulin analysis. Western blot was chosen to identify alteration of p-NF-κB, IL-1β, TNF-α, MMP-9, NOX-1, NOX-2, caspase 3, cleaved-PARP, γ-H2AX, p-ERK1/2, p-JNK, p-p38, Nav.1.3, Nav.1.8, Nav.1.9 and immunoglobulin G	i.v.	3.0 × 10 ⁵

		well as the protein levels of voltage-gated sodium channels (Nav.) 1.3, Nav.1.8, and Nav.1.9 in L4-L5 in DRG to the pain-behavior results obtained by thermal hyperalgesia and mechanical allodynia testing, characterizing a set of "pain-connived cells" presenting the following profiles: Nav1.8+/peripherin+, p-ERK+/peripherin+, p-p38+/peripherin+ and p-p38+/NF200+. Mainly by suppressing inflammation and oxidative stress, the combination of probiotic and ASCs therapy was found superior for alleviating CCI-induced neuropathic pain			
Zhang <i>et al</i> [195], 2021	Lncenc1 is identified as a novel regulator in neuropathic pain by interacting with EZH2 and downregulating the expression of Bai1 in mouse microglia	Virgin embryonic stem cells express Lncenc1, which can activate microglia in DRG and induce the production of TNF- α , IL-1 β , and MCP-1. Lncenc1 silencing reduced mechanical and thermal hyperalgesia, as well as lower levels of pro-inflammatory cytokines	The mechanical withdrawal threshold was measured by von Frey filaments and thermal hyperalgesia <i>via</i> hot plate assay. Immunofluorescence was performed to analyze OX-42, western blot to assess EZH2, suppressor of zeste 12, embryonic ectoderm development, BAI1, trimethylation of histone 3 lysine 27 (H3K27me3), H3K27ac, total histone H3, glyceraldehyde-3-phosphate dehydrogenase and OX-42. RT-qPCR was performed to identify expression alterations on Lncenc1, EZH2, BAI1, OX-42, inflammatory factors TNF- α , IL-1 β and chemokine MCP-1. TNF- α , IL-1 β and MCP-1 protein changes were assessed by ELISA	Not informed	Not informed
Masoodifar <i>et al</i> [161], 2021	Effect of the conditioned medium of MSCs on the expression levels of P2X4 and P2X7 purinergic receptors in the spinal cord of rats with neuropathic pain	Animals treated with the conditioned medium (stem cells secretome) showed a reduction in mechanical and thermal hyperalgesia. A decrease in the expression of P2X4 and P2X7 receptors was related to the interaction of neurons and glial cells in neuropathic pain	The von Frey and hot plate tests were applied to measure mechanical and thermal hyperalgesia, respectively. In addition, qPCR was performed to measure the expression of P2X4 and P2X7 receptors	i.p.	1 \times 10 ⁵
Kotb <i>et al</i> [196], 2021	Preemptive stem cells ameliorate neuropathic pain in rats: A central component of preemptive analgesia	MSCs-treatment increased allodynia, mechanical hyperalgesia, and thermal hyperalgesia thresholds. Stem cells were able to reach the cerebral cortex, as the CCI group had few stem cells expressing PCNA, CD117 and nestin in the cerebral cortex. The treated group had numerous CD117-, nestin-, PCNA-positive stem cells recently proliferated in the cerebral cortex. Together, the results indicate a potential central analgesic effect of i.v. MSC-treatment	To evaluate pain behavior, von Frey, Randall and Selitto, and hot plate tests were performed. Immunohistochemical analyses of GFAP, PCNA and nestin were also performed	i.v.	1 \times 10 ⁶
Zhang <i>et al</i> [197], 2021	Therapeutic effects of peripherally administered neural crest stem cells on pain and spinal cord changes after sciatic nerve transection	The treatment was able to induce thermal and mechanical analgesia, possibly by decreasing the expression of TRPV1, cFOS, p-ERK, ERK, iNOS and NF- κ B, p65 and increasing BDNF and GAP-43 in the spinal cord	To assess mechanical allodynia, the authors used the BEM-404 device (similar to the von Frey). For thermal withdrawal latency, they use Hargreaves. In the western blot, they had the following targets: BDNF, cFOS, GAP-43, p-ERK, ERK 1/2, TRPV1 and iNOS. Immunofluorescence: IBA-1, GFAP and CGRP were assessed	Local injection	2 \times 10 ⁶
Yang <i>et al</i> [91], 2020	Anti-inflammatory protein TSG-6 secreted by BMSCs attenuates neuropathic pain by inhibiting the TLR2/MyD88/NF- κ B	I.t. administration of TSG-6 secreted from stem cells decreases mechanical allodynia and thermal hyperalgesia, inhibiting IBA-1 and the activation of the	The activation of the TLR2/MyD88/NF- κ B signaling pathway was evaluated by western blot and immunofluorescence, while allodynia and hyperalgesia were assessed by the behavioral tests Dynamic Plantar Aesthesiometer, Hargreaves and	i.t.	5 \times 10 ⁶

	signaling pathway in spinal microglia	TLR2/MyD88/NF-κB pathway in the dorsal horn of the ipsilateral spinal cord. Levels of pro-inflammatory cytokines, such as IL-1β, IL-6 and TNF-α, were also reduced	rotarod system		
Jwa <i>et al</i> [198], 2020	ASCs alleviate cold allodynia in a rat spinal nerve ligation model of neuropathic pain	ASCs or ASC-derived culture medium decreased neuropathic pain behaviors in a rat model with L5 spinal nerve ligation	Mechanical and cold allodynia were assessed by von Frey filaments and acetone assay, respectively. Mechanisms were not assessed	Intrathecal or injection into the right retro-orbital sinus	10 ⁶
Gama <i>et al</i> [164], 2018	Conditioned medium of BMSCs as a therapeutic approach to neuropathic pain: A preclinical evaluation	The animals showed improvement in thermal hyperalgesia and mechanical allodynia. They also showed reduced levels of IL-1β, TNF-α and IL-6 and increased IL-10 in the spinal cord and sciatic nerve	To evaluate thermal hyperalgesia, the Hargreaves test was performed, and von Frey mechanical allodynia. To evaluate the motor function test, the rotarod test was performed. Using the ELISA method, TNF-α, IL-1β, IL-6 and IL-10 were quantified	i.v.	10 ⁶
Lin <i>et al</i> [165], 2017	Autologous ASCs reduce burn-induced neuropathic pain in a rat model	There was no difference between the groups regarding thermal hyperalgesia, whereas in mechanical allodynia, the treated group presented analgesia from the 3 rd wk of the first treatment. Western blot analyses revealed a decrease in p-Akt/Akt and Bax/Bcl-2 and levels of LC3B-II and Beclin 1 in the spinal cord, suggesting that the treatment also decreased apoptosis and autophagy. This effect was accompanied by a reduction in COX-2, iNOS and nNOS. The treated group also showed lower expression of p-JNK (an inflammatory marker), TUNEL (apoptosis marker), phospho-NFκB (inflammatory marker) and increased p-IκB (an inhibitor of NFκB activation)	Immunofluorescence were performed to analyze p-IκB; NeuN, GFAP, phospho-NFκB and p-JNK; and western blot for COX-2, iNOS, nNOS, Akt/protein kinase B, p-Akt, B-cell lymphoma 2, Bcl-2-associated X protein, β-actin, LC3B and Beclin 1	Subcutaneous into the scar tissue of the right hind paw	10 ⁶
Vaquero <i>et al</i> [199], 2018	I.t. administration of autologous bone marrow stromal cells improves neuropathic pain in patients with SCI	Treatment with mesenchymal stromal cells for human chronic SCI: Pain scores demonstrated a continuous decrease in neuropathic pain from the first month until the 10 th	Intensity of neuropathic pain was evaluated by standard numerical rating scale (visual analogue scale) from 0 to 10. Mechanisms were not assessed	i.t.	10 ⁶
Sun <i>et al</i> [200], 2017	I.t. administration of hBMSCs genetically modified with human proenkephalin gene decrease nociceptive pain in neuropathic rats	hBMSCs engineered with human proenkephalin gene were used on sciatic nerve (CCI)-induced model to reduce neuropathic pain in rats	Mechanical withdrawal threshold (von Frey filaments) and paw thermal withdrawal assays were used to assess the changes in pain-related behavior. Levels of Leu-enkephalin, a neurotransmitter that activates opioid receptors and is released by hBMSCs were found augmented <i>via</i> ELISA assay in genetically modified BMSCs compared to secretions released by naive BMSCs	i.t.	6 × 10 ⁶
Fischer <i>et al</i> [201], 2017	Inhibition of neuropathic hyperalgesia by i.t. BMSCs is associated with alteration of multiple soluble factors in cerebrospinal fluid	BMSCs decrease the levels of intracellular adhesion molecule 1, IL-1β, hepatocyte growth factor), IL-10, and Nope protein relacionated by Tibial nerve injury	Antibody array analysis was performed and the levels of cytokines and other soluble factors in cerebrospinal fluid samples was measured	i.t.	2.5 × 10 ⁵
Xie <i>et al</i> [202], 2017	Active nerve regeneration with failed target reinnervation drives persistent neuropathic pain	Semaphorin 3A, an inhibitory axonal guidance molecule, reduces functional regeneration, spontaneous activity, and pain behaviors when applied to the injury site <i>in vivo</i> . Silencing of the upregulated GAP43 with interfering RNA injected into the axotomized sensory ganglion reduced pain behaviors	Behavior assays: von Frey filaments acetone cold sensitivity, dynamic tactile allodynia with a wisp of cotton across the plantar surface of the hindpaws, and spontaneous guarding behavior score. Immunohistochemistry for GAP43 tracer methods to assess anatomical nerve regeneration	Injury site	

Brini <i>et al</i> [203], 2017	Therapeutic effect of human ASCs and their secretome in experimental diabetic pain	Treatments with both human ASC and their secretome were able to reverse mechanical, thermal allodynia and thermal hyperalgesia inducing high IL-1 β , IL-6 and TNF- α and low IL-10 levels, restoring cytokine balance, Th1/Th2 balance and preventing skin innervation loss in neuropathic STZ-diabetic mice model	Mechanical allodynia was tested using the Dynamic Plantar aesthesiometer, a drop (50 μ L) of acetone was placed in the middle of the plantar surface of the hind paw to evaluate cold allodynia and the hot-plate test was used to assess thermal hyperalgesia. Immunohistochemistry and ELISA were performed for cytokines assessment	i.v.	1×10^6
Watanabe <i>et al</i> [87], 2015	Early transplantation of MSCs after SCI relieves pain hypersensitivity through suppression of pain-related signaling cascades and reduced inflammatory cell recruitment	BMSC improved SCI model <i>via</i> : Down of protein kinase C- γ and phosphocyclic AMP response element binding protein on DRG neurons, both of which are upregulated in association with at-level allodynia after contusion spinal cord. Decreased activation of MAPK signaling in injured spinal cord by p-p38 and p-ERK1/2 decrease. Decreasing macrophage recruitment through. Down TNF- α , IL-6, MMP-9, CCL2, CCL5, and C-X-C motif chemokine ligand 10. Decreased microglia stimulation factor, granulocyte-macrophage colony stimulating factor, platelet-derived growth factor receptor α	For behavioral and sensory testing, the Basso Mouse Locomotor Scale, the Dynamic Plantar Aesthesiometer (allodynia), and the Plantar Test Apparatus (thermal sensitivity) were assessed. immunohistochemistry, flow cytometry and immunoblot assays were performed to determine protein levels	BMSCs were injected into the middle of the contusion site, identified as the middle point of the laminectomy area	2×10^5
Zhang <i>et al</i> [204], 2014	I.t. administration of MSCs reduces the ROS and pain behavior in neuropathic rats	I.t. rat MSCs injection reduced pain response and ROS production in the dorsal horn of neuropathic rats induced by spinal nerve L5 ligation model	Mechanical sensitivity was assessed using von Frey filaments and production of ROS <i>via</i> dihydroethidium fluorescent staining	i.t.	10^5
Liu <i>et al</i> [205], 2014	MSCs inhibit lipopolysaccharide-induced inflammatory responses of BV2 microglial cells through TSG-6	Anti-inflammatory effects of MSCs and TSG-6 in an <i>in vitro</i> LPS-induced BV2 microglial activation model inhibiting NF- κ B and MAPK pathways. MSCs can modulate microglia activation through TSG-6 and TSG-6 attenuates the inflammatory cascade in activated microglia	RT-qPCR, western blot, electrophoretic mobility shift assay, immunofluorescence and laser-scanning confocal microscopy techniques were used	<i>In vitro</i>	1.0×10^5 LPS-activated MSCs
Vicker <i>et al</i> [206], 2014	A preliminary report on stem cell therapy for neuropathic pain in humans	Treatment led to a reduction in stem cell treatment pain intensity scores in 7/9 patients (two with marginal improvement and five subjects with good to excellent pain reduction). Five of these positive responders also reduced their need for gabapentin medication	Patients were assessed for: Change in pain intensity and the secondary outcome was any reduction in daily consumption of anti-neuropathic medication	Perineural, directly in the center or source of pain, and in the adjacent pain field of the affected branches of the trigeminal nerve	Number of cells not reported, but extracted from 100-200 g of patient tissue
Tao <i>et al</i> [154], 2013	Role of NRG1/ErbB signaling in stem cell therapy for SCI-induced chronic neuropathic pain	The treatment induces remyelination in the injured spinal cord and reduces SCI-injury-induced chronic neuropathic pain. In addition to increasing levels of NRG1 and ErbB4 slightly reduced by SCI. Also, the author related that Stem cells differentiated into oligodendrocytes	To evaluate mechanical allodynia, the von Frey filament test was applied. Immunofluorescence for NG2, APC-CC1, GFAP, NeuN, and western blot for NRG1 and ErbB4 levels assessment	i.t.	10^6
Xu <i>et al</i> [207], 2013	I.t. transplantation of NSCs appears to alleviate neuropathic pain in rats through release of GDNF	The treatment was able to cause thermal and mechanical analgesia. Accompanied by an increase in GDNF in the DRG and spinal cord. The authors also suspected that these changes occurred due to the transformation of stem cells into astrocytes in the spinal cord	To evaluate the mechanical withdrawal threshold, the Electric von Frey test was used. For thermal withdrawal latency, a method with a high-intensity projection lamp bulb was used. For immunofluorescence: Nestin; β III-tubulin; GFAP. For ELISA: BDNF and GDNF	i.t.	10^6

Choi <i>et al</i> [208], 2013	Core-shell nanoparticle controlled human adipose tissue-derived stem cells neurogenesis for neuropathic pain therapy	Treatment activated biochemical functions of Dicer, Oct4, Sox2, Nanog, and glutathione peroxidase 3 improving stem cells self-renewal and differentiation abilities	von Frey and Hargreaves behavior tests were performed to assess mechanical and thermal hyperalgesia changes, respectively. Immunofluorescence, western blot and RT-qPCR techniques were used to study alterations in protein production/expression/localization	i.t.	Unspecified
Franchi <i>et al</i> [137], 2012	I.v. NSCs abolish nociceptive hypersensitivity and trigger nerve regeneration in experimental neuropathy	NSCs administration in CCI mouse model significantly decreased proinflammatory (IL-1 β , IL-6), activated anti-inflammatory (IL-10) cytokines in the sciatic nerve, and reduced spinal cord Fos expression in laminae I-VI	Thermal hyperalgesia was tested according to the Hargreaves using a Plantar Test Apparatus, while mechanical allodynia was assessed using the Dynamic Plantar Aesthesiometer. Immunohistochemistry, immunofluorescence, and qPCR plus ELISA assays were performed for Fos and GFPI; substance P and CGRP; and IL-1 β , IL-6 and IL-10, respectively	i.v.	10 ⁶
Sacerdote <i>et al</i> [209], 2013	Systemic aAdministration of human ASCs reverts nociceptive hypersensitivity in an experimental model of neuropathy	Human ASCs were able to completely revert neuropathic pain symptoms in a murine CCI model by: IL-1 β decreased and IL-10 increased in the lesioned nerve. Restored normal iNOS expression	Thermal hyperalgesia was tested according to the Hargreaves, while mechanical allodynia was assessed using the Dynamic Plantar Aesthesiometer (von Frey filament)	i.v.	1 \times 10 ⁶ , 3 \times 10 ⁶ and 6 \times 10 ⁶
Choi <i>et al</i> [73], 2011	Anti-inflammatory protein TSG-6 secreted by activated MSCs attenuates zymosan-induced mouse peritonitis by decreasing TLR2/NF- κ B signaling in resident macrophages	TSG-6 interacts through the CD44 receptor on resident macrophages to decrease zymosan/TLR2-mediated nuclear translocation of the NF- κ B	RT-qPCR, ELISA, NF- κ B translocation assays and isolation of resident macrophage RNA was performed	i.p.	1.6 \times 10 ⁶
Siniscalco <i>et al</i> [210], 2011	Long-lasting effects of human MSCs systemic administration on pain-like behaviors, cellular, and biomolecular modifications in neuropathic mice	The treatment was able to reduce pain-like behaviors such as mechanical allodynia and thermal hyperalgesia. In addition to reducing IL-1 β and IL-17 levels and increasing IL-10 in the spinal cord and reducing labeling for alternatively activated macrophages (CD106)	For behavior analysis, the following tests were applied: von Frey filaments, Rotarod and Hargreaves. Immunofluorescence: CD73; IL-1 β ; IL-17; CD4; GFAP; IBA-1; western blot: IL-1 β , IL-17, IL-10 e CD106	i.v.	2 \times 10 ⁶

Huc-MSCs: Human umbilical cord mesenchymal stem cells; TLR2: Toll-like receptor 2; MyD88: Myeloid differentiation primary response 88; NF- κ B: Nuclear factor kappa B; Rsad2: Radical S-adenosyl methionine domain containing 2; p-p65: Phospho-protein 65; CCI: Chronic constriction injury; i.t.: Intrathecal; i.v.: Intravenous; MSCs: Mesenchymal stem cells; ATF-3: Activating transcription factor 3; IBA-1: Ionized calcium-binding adapter molecule 1; DRG: Dorsal root ganglion; MBP: Myelin basic protein; NeuN: Neuron-specific nuclear protein; NF: Neurofilament; TNF: Tumor necrosis factor; ASCs: Adipose tissue derived-mesenchymal stem cells; RT-qPCR: Real time quantitative polymerase chain reaction; hTERT-BMSCs/Tet-on/GAL: Rafted human telomerase reverse transcriptase-immortalized bone marrow mesenchymal stromal cells with inducible galanin expression; GalR: Galanin receptor; SDH: Spinal dorsal horn; IFN- γ : Interferon gamma; CD: Cluster of differentiation; ELISA: Enzyme-linked immunosorbent assay; i.m.: Intramuscular; IL: Interleukin; MMP: Matrix metalloproteinase; P/ARP: Poly ADP-ribose polymerase; NOX: NADPH oxidase; MAPK: Mitogen-activated protein kinase; p-JNK: Phosphorylated Jun N-terminal kinase, p-ERK: Phospho-extracellular signal-regulated kinase; Nav: Voltage-gated sodium channels; LncRNA: Long-chain noncoding ribonucleic acid; Lncnc1: Long-chain noncoding RNA embryonic stem cells expressed 1; EZH2: Enhancer of zeste homologue 2; MCP-1: Monocyte chemoattractant protein-1; SUZ12: Suppressor of zeste 12; EED: Embryonic ectoderm development; BAI1: Brain-specific angiogenesis inhibitor 1; H3K27me3: Tri-methylation of histone 3 lysine 27; P2X4: P2X purinoceptor 4; i.p.: Intraperitoneal; PCNA: Proliferating cell nuclear antigen; GFAP: Glial fibrillary acidic protein; TRPV1: Transient receptor potential cation channel subfamily vanilloid 1; iNOS: Inducible nitric oxide synthase; p65: Protein 65; BDNF: Brain-derived neurotrophic factor; GAP-43: Growth-associated protein 43; CGRP: Calcitonin gene-related peptide; TSG-6: Tumor necrosis factor- α -stimulated gene 6 protein; BMSC: Bone marrow mesenchymal stem cells; p-Akt: Phospho protein kinase B; LC3B: Light chain-3B; COX-2: Cyclooxygenase 2; nNOS: Neural nitric oxide synthase; hBMSCs: Human bone marrow stem cells; CSF: Cerebrospinal fluid; Th1: Type 1 helper; SCI: Spinal cord injury; p-CREB: Phosphocyclic AMP response element binding protein; CCL: C-C motif chemokine ligand; CXCL: C-X-C motif chemokine ligand; GM-CSF: Granulocyte-macrophage colony stimulating factor; PDGFR- α : Platelet-derived growth factor receptor α ; ROS: Reactive oxygen species; LPS: Lipopolysaccharides; NRG1: Neuregulin-1; GDNF: Glial cell derived neurotrophic factor; NSC: Neural stem cells.

substance P)[151]. When activated, glial cells' function will be related to the maintenance and enhancement of the interaction between the peripheral and CNSs, secreting, for instance, cytokines that will activate spinal cord neurons [152]. Interestingly, this glial activation can be detected by the expression of some targets, such as IBA-1 for microglia and glial fibrillary acidic protein (GFAP) for astrocytes[61]. These glial cells are responsible for the subsequent release of cytokines inducing a series of cellular responses, such as upregulation of glucocorticoids and glutamate receptors, leading to spinal cord excitation and neuroplasticity[136].

It has been reported that in experimental conditions involving spinal cord injury and spinal cord treatment with SC, embryonic stem (ES) cells differentiate into oligodendrocytes using positive selection and mechanical enrichment[153],

promoting functional recovery after a spinal cord injury producing myelination[154]. Spinal cord SC treatment also decreases GFAP[155] and IBA1[156] indicating the down-regulation of astrocyte and microglia activation, respectively. SC express high levels of CXCL12[157]. CXCL12 can reduce the activation of astrocytes and microglia in spinal nerve ligation models, thus, potentially contributing to the activity of SC in NP[158]. There are other potential repercussions of glial inhibition. For instance, the decrease of IBA1 also occurs by inhibiting gasdermin D-induced microglia pyroptosis, thus, promoting autophagy[159]. In fact, impaired autophagic flux aggravates NP by increasing neuroinflammation[160]. Moreover, the mitogen-activated protein kinase signal pathway is activated after microglial activation, which promotes long-term potentiation and central sensitization in pain[136].

Another mechanism of action of SC that explains their analgesic activity by down-modulating glial cell activation is the capability they have at reducing the expression of purinergic P2X purinoceptor 4 (P2X4) and P2X7 receptors in a rat model of NP induced by CCI of the sciatic nerve[161]. P2X4 and P2X7 receptor activation mainly by ATP (coming from nerve damage) leads to the activation of glial cells and the release of IL-1 β , TNF- α and IL-6, capable of sensitizing nociceptors and perpetuating NP[162,163].

In a different perspective, it has also been shown that SC are capable of increasing IL-10 levels in the spinal cord[164], in addition to secreting TSG-6 in the spinal cord[91], and decreasing IBA-1 activity by inhibiting the TLR2/MyD88/NF- κ B signaling pathway in spinal microglia. These activities reduce nociceptor neuron activation and neuronal plasticity.

The third analgesic mechanism of SC in the CNS involves the inhibition of neuronal death in the CNS. SC treatment can reduce the levels of p-Akt/Akt and Bax/Bcl-2, LC3B-II, Beclin 1 and TUNEL (markers of cellular death) in the dorsal horn of lumbar spinal cords in burn-induced NP. Thus, suggesting that SC can reduce the levels of apoptosis, necrosis and autophagy related to inflammation in spinal cord neurons of dorsal horn cells[165].

SC TECHNOLOGY AS A TOOL FOR INVESTIGATING PAIN-RELATED MECHANISMS

Although most of the efforts in scientific research regarding SC and pain are guided towards finding suitable painkillers, it is worth mentioning that SC technology can also be proven valuable to create different experimental models, which can contribute to understanding pathophysiological mechanism of pain and thus, evolving towards therapy. As an example, Kaneski *et al*[166] developed a human ESC (hESC)-based model to study the poorly understood pathophysiology of pain in Fabry disease. This X-linked glycolipid storage disorder that results in a deficiency in the lysosomal enzyme alpha galactosidase A (AGA) can cause recurrent attacks of excruciating pain ("Fabry pain crisis") that occur spontaneously or in response to extreme temperatures, fever, fatigue, stress, overheating, or exercise. The group generated two AGA-deficient hESC clones using CRISPR-Cas9 gene editing techniques and demonstrated that AGA-deficient human SC could be differentiated into peripheral neurons with nociceptor properties, offering a tool for the investigation of cellular mechanisms for this and other peripheral neuropathies[166].

Some studies utilized dental pulp SC to investigate the possible effects of sirtuin 6 (SIRT6) - an NAD-dependent protein deacetylase known for its role as a differentiation regulator - as a modulation factor using a model of LPS-induced pulpitis (inflammation in the dental pulp). LPS is the major virulence component of gram-negative bacteria cell walls and is widely recognized as a potent activator of inflammation[167]. Their results demonstrated that injection of lentiviral vector-expression SIRT6 leads to SIRT6 overexpression in rats, reduced LPS-induced neutrophils infiltration, a marked decrease in proinflammatory cytokines (IL-6, IL-1 β , and TNF- α) and deactivation of the NF- κ B pathway. LPS-induced pulpitis in turn, upregulated TRPV1 expression and activity, by downregulating SIRT6. Interestingly, CGRP release was induced by pulpitis while the overexpression of SIRT6 inhibited TRPV1 expression and CGRP release. The expression of inflammatory cytokines, dentin matrix acidic phosphoprotein 1, and NF- κ B activation were upregulated after the addition of capsaicin, a TRPV1 channel agonist. Taken together, their results suggest that SIRT6 may be both a negative regulator of pulpitis and an inflammatory pain modulator[168].

DOWNSIDES AND POSSIBLE TREATMENT SIDE-EFFECTS

The biggest concern surrounding SC treatment is the onset of tumors as a result of the therapy, particularly *via* systemic administration routes. This concern is due to the proliferation potential that these cells have, thus, raising the possibility of tumor development if they continue to proliferate after transplantation[169]. The literature lacks *in vivo* studies evaluating the tumorigenic effect of SC treatment. However, it is currently acknowledged that tumorigenicity can develop through three different manners. Firstly, the presence of undifferentiated SC anchored in other already differentiated lineages can lead to tumor formation, due to their high replication rate[169]. Second, reprogramming factors may remain active in transplanted SC, promoting the transformation of these cells and, consequently, tumorigenic transplantation[169]. Finally, tumorigenicity can also develop during *in vitro* culture through genetic mutations[169]. Studies demonstrate that a significant rate of SC derived from bone marrow undergo spontaneous transformations towards a malignant profile in long-term cultures (5 to 106 wk), showing an increase in the rate of proliferation and morphological and phenotypic changes[170].

Another disadvantage is the possible development of cellular rejections. This can occur when the individual's immune system recognizes the SC as foreign antigens and develops an immune response against them[25,169]. Polymorphic molecules of the MHC are an example of immunologically recognized molecules that induce rejection[171]. In fact, studies have already demonstrated that the administration of ESC in the myocardium of allogeneic mice results in the development of an immune response with significant infiltration of T lymphocytes and dendritic cells[172]. Likewise,

abnormal gene expression in cells differentiated from iPSC can induce a T cell-dependent immune response^[173]. Finally, even though there are studies that demonstrate the effects of systemic administration of SC, there is a lack of data in the literature that assess their distribution and actions in the body after treatment.

CONCLUSION

In this review, we provide evidence on the therapeutic potential of the use of SC in pain treatment. Analgesia was observed with SC administration as well as SC extracellular vesicle administration. This analgesic effect was found to be achieved with a variety of routes, such as intra-articular, intravenous, intrathecal, intramuscular, intraganglionic, perineural, subcutaneous, and local injection. Additionally, the SC load for these administrations varied between 1.0×10^5 to 24×10^6 for SC, and 1×10^6 to 1×10^9 for SC extracellular vesicle. The specific conditions of each experiment can be appreciated in the Tables 2 and 3.

This review discussed that the analgesic mechanism of action of SC treatment can be indirect by acting on inflammation, changing the pattern from pro-inflammatory to anti-inflammatory mediators. SC can decrease the levels of cytokines that have a role in mechanical and thermal hyperalgesia in addition to promoting the secretion of cytokines with analgesic roles. These anti-inflammatory analgesic mechanisms have been demonstrated in peripheral tissue. In the CNS, SC can cause analgesia by inhibiting the effects of glutamate on spinal cord neurons and by its ability to decrease glial activity and therefore central sensitization.

There are still gaps in the elucidation of the mechanism of action of SC, since most of the articles in the literature aim mainly at the treatment of NP. Among the literature hiatus we can cite the lack of studies on the analgesic mechanisms of SC in models using microorganisms as stimuli. Confirmatory studies on SC therapy long-term safety are also missing. SC rejection is also a potential drawback and there are no studies comparing the success of therapy using autologous cells to the patient, and cells of exogenous origin. On the other hand, much of the success of therapy using SC comes from the use of MSC, which have a lower possibility of rejection, as well as greater effectiveness in the treatment.

Even with all the limitations and shortcomings, there are already clinical studies using SC both in the treatment of inflammatory diseases and in NP. In all reports, treatments were able to decrease pain scores and restore mobility-related functions. Therefore, SC treatment is a potential approach for pain relief and to achieve such biotechnological advancements, there is a need to fill the current knowledge gaps in order to develop efficient and safe therapies based on SC.

FOOTNOTES

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