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Comparison, Selection, and Combined Use of Mesenchymal Stem Cells and Their Exosomes in the Field of Analgesia

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Abstract. Chronic pain belongs to a class of persistent pain syndromes with a high morbidity rate and complex pathogenesis. Conventional drug treatment methods not only have limited efficacy, but also bring more adverse reactions. Mesenchymal stem cells (MSCs) and their exosomes (MSC-Exos) provide a new research direction for chronic pain treatment with their diverse and unique mechanisms of action. This article compares the characteristics of the two in the field of analgesia and their practical clinical application value, sorts out and analyses the respective analgesic mechanisms of MSCs and MSC-Exos, and compares the differences in the onset speed and efficacy maintenance time of the two. The analysis results show that MSCs take effect slowly, but the duration of the drug effect is longer; such cells can dynamically regulate the neuroimmune microenvironment and repair damaged tissue, which is more suitable for the long-term intervention of chronic neuropathic pain. In comparison, MSC-Exos have faster onset of effect, better overall safety, and are more suitable for the rapid treatment of acute breakthrough pain and central-mediated pain. The two types of treatment can complement each other. Follow-up research can focus on exploring the combined drug administration scheme of the two, taking into account the dual goals of rapid analgesia and long-term tissue repair; at the same time, standardise the timing, ratio and dosage of drug administration, and promote the implementation of relevant therapies into standardised clinical work.

Keywords: Chronicpain, Mesenchymalstemcells, Exosomes, Analgesicmechanisms, Combination therapy

1. Introduction

The International Classification of Diseases (ICD-11) defines chronic pain as a pain syndrome that persists or occurs repeatedly for more than three months. The global prevalence of this disease is about 20%-25%, among which neuropathic pain accounts for the highest proportion [1]. Although traditional analgesic drugs such as gabapentin, pregabalin (a calcium channel blocker), tricyclic antidepressants and opioids can relieve symptoms to a certain extent, they only act on the appearance of pain and cannot intervene in the root cause of the disease. Such drugs can neither reverse nor repair damaged nerve tissue, nor prevent pain from evolving into a chronic state. Many patients with intractable pain can only rely on drugs to control their condition for a long time, and

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the effect of the medicine will continue to weaken over time. In addition, the use of traditional analgesics will also cause serious adverse reactions such as dizziness, lethargy and respiratory depression. Mesenchymal stem cell (MSC) treatment improves this limitation from the root, which can make up for the defect that traditional drugs can only achieve pain relief but cannot complete tissue repair. MSCs have multilineage differentiation potential, low immunogenicity, and potent paracrine functions, and have attracted considerable attention in the field of regenerative medicine. Recent studies have shown that the analgesic effect of MSCs depends mainly on the biologically active molecules they secrete, which can regulate the neuroimmune microenvironment.

As the core paracrine vector of MSCs, exosomes (MSC-Exos) can carry molecular cargos such as proteins, mRNA, and microRNA to mediate intercellular communication and are considered a potential substitute for MSCs [2]. However, MSC-Exos differ fundamentally from living MSCs in terms of analgesic mechanism, onset time and duration of analgesia, accessibility to target organs, and dynamic adaptability. This article aims to systematically compare the analgesic mechanisms and therapeutic effects of the two, explore the prospects for their clinical application, and propose future directions for engineering modifications and combined application.

2. Mechanism of pain generation

The occurrence of pain involves the activation of peripheral and central inflammatory pathways and the remodelling of the neuroimmune microenvironment, which is a complex set of physiological processes. When mechanical, chemical or thermal harmful stimuli act on peripheral sensory receptors, that is, free nerve endings, cells will release inflammatory mediators such as leukotrienes, prostaglandins, and various growth factors. These mediators act on the ion channels on the receptors, including the transient receptor potential (TRP) channels and the voltage-gated sodium channels (Nav), which induces action potentials. The action potentials are transmitted to the dorsal root ganglia (DRG) through the myelinated Aδ fibres and the unmyelinated C fibres, and then projected to the dorsal horn of the spinal cord to complete the transmission of primary afferent signals. At the same time, microglia and astrocytes are activated to release pro-inflammatory factors. If the harmful stimulus continues to enter, glial cells will maintain a long-term activated state, resulting in long-term potentiation (LTP) of the synaptic transmission efficiency of spinal cord dorsal horn neurons; even if the peripheral stimulation weakens or even disappears completely, the central nervous system will continue to generate pain signals. This phenomenon is central sensitisation, which is also a key factor for acute pain to turn into chronic pain [3]. After the signals are integrated in the dorsal horn neurons of the spinal cord, they are transmitted to the thalamus through ascending pathways such as the spinothalamic tract, and then further projected to the sensory cortex, limbic system and prefrontal cortex, thus forming a complete pain perception and emotional experience.

In addition, the central nervous system itself can also regulate pain signals. Brain areas such as the periaqueductal gray (PAG) of the midbrain and the rostral ventromedial medulla (RVM) can regulate the excitability of spinal cord dorsal horn neurons through the descending pathways, including the descending facilitatory system and the descending inhibitory system, and enhance or inhibit pain signals [4]. The onset, persistence, and chronification of pain are closely related to the release of peripheral inflammatory factors, glial cell activation, and central sensitization, which is the core reason why acute and chronic pain are clinically difficult to cure and prone to recurrent attacks. Currently, conventional clinical analgesic methods are mainly single-target approaches aimed at pain relief, whereas MSCs and their exosomes, with their multiple mechanisms including

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anti-inflammatory effects, regulation of neural cells, and inhibition of central sensitization, have emerged as a new therapeutic approach for chronic pain.

3. Comparison of mechanisms of action between MSCs and MSC-Exos

3.1. Mechanism of action of MSCs

MSCs actively migrate to and engraft at sites of inflammation or nerve injury by sensing chemokines released by damaged tissues (such as SDF-1/CXCL12); they then coordinately remodel the neuroimmune microenvironment at the peripheral, spinal, and brainstem levels. In the peripheral nervous system, MSCs inhibit the activation of inflammatory pathways in macrophages by secreting TSG-6 and releasing TGF-β1, IDO, and PGE2, and they promote the polarization of pro-inflammatory M1 macrophages toward the anti-inflammatory M2 phenotype, thereby reducing the release of inflammatory factors such as TNF-α and IL-1β [5]. In the spinal dorsal horn, MSCs inhibit microglial phosphorylation through paracrine pathways, reduce the release of inflammatory factors, and prevent the establishment of central sensitization; they also promote the transformation of neurotoxic A1 astrocytes into protective A2 astrocytes [6].

At the brainstem level, MSCs can sustainably upregulate the expression of μ-opioid receptors (MOR) in the rostral ventromedial medulla (RVM) and enhance the function of the endogenous descending pain-inhibitory system. In addition, during their residence, MSCs can sense the intensity of inflammation, hypoxia, and pH changes in the local microenvironment and dynamically regulate their secretory profile—for example, increasing the expression of IDO and TSG-6 under highly inflammatory conditions—while establishing direct connections with host cells through tunneling nanotubes and persistently releasing functional exosomes containing miRNAs, proteins, and other molecules.

3.2. Mechanism of action of MSC-Exos

The diameter of MSC-Exos is in the range of 30-150 nanometers. After administration, these exosomes spread with blood circulation, and the chemotactic signals released by the damaged tissue can guide them to migrate to the inflammatory or injured sites in a targeted manner. Relying on cellular active uptake and transcytosis, MSC-Exos can also pass through the blood-brain barrier and blood-spinal cord barrier, and efficiently deliver the contents carried inside to the target cells; this feature gives them a unique advantage in treating pain related to the central nervous system [7]. In addition, MSC-Exos can also load and release miRNAs to achieve precise gene regulation. On the one hand, they can act on the inflammatory pathway in a targeted manner. miRNAs can inhibit the release of pro-inflammatory factors and prevent the activation of microglia. For example, exosomal miR-181c-5p can bind to the 3'UTR of TLR4 mRNA, inhibit the molecular translation process, block the MyD88/NF-κB inflammatory pathway, and thus reduce the neuroinflammatory response [8].

On the other hand, they can target and regulate ion channels. miRNAs directly act on the dorsal root ganglion (DRG) neurons with the help of seed sequences to regulate the expression of functional proteins such as voltage-gated sodium channels. For example, miR-101b-3p can target and inhibit the Nav1.6 sodium channel and reduce the abnormal firing of neurons [9]. Another point is that they can regulate the state of cell polarisation, deliver specific miRNAs to microglia or macrophages, lower the expression of pro-inflammatory genes at the post-transcriptional level, and change the cell phenotype. For example, exosomal miR-99b-3p activates the autophagy pathway

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after entering the microglia, promoting the cells to convert from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype [8]. However, exosomes themselves are static molecular carriers. They do not have the environmental perception ability of living cells, and they cannot dynamically adjust the secretion function. They cannot continuously upregulate the expression of central MOR, and at the same time, have no tissue-homing effect, and have no ability to repair the tissue structure.

4. Comparison of analgesic effects between MSCs and MSC-Exos

4.1. Analgesic effects of MSCs

The analgesic effect of MSCs is a delayed and sustained process characterized by dynamic responsiveness, with a long onset time of approximately 10 to 30 days, and the analgesic effect can last for at least 1 to 3 months. A study on the analgesic effects of bone marrow MSCs on resin toxin-induced neuropathic pain revealed that after mice were intravenously infused with bone marrow MSCs via the tail vein, the MSCs exerted their effects by homing to the spinal cord, inhibiting microglial activation and the p38 MAPK pathway, with significant improvement in mechanical pain threshold observed on day 20 post-transplantation, and the analgesic effect lasting until day 30 post-transplantation [10]. A clinical study on autologous adipose-derived MSC treatment for postherpetic neuralgia confirmed that one month after stem cell injection, the VAS score decreased significantly, indicating the onset of analgesia, and three months post-treatment, the VAS score remained significantly lower than that of the control group, suggesting that the analgesic effect can last at least three months [11]. In a spared nerve injury (SNI) mouse model, human umbilical cord MSCs (hUC-MSCs) were injected via the tail vein on the fourth day post-surgery. Assessment using mechanical allodynia and thermal hyperalgesia tests showed that in the hUC-MSC-treated SNI mice, the mechanical pain threshold was significantly higher at all time points from day 11 to day 90 post-surgery compared to the untreated group, and the thermal withdrawal latency was significantly longer than that of the untreated group [12].

4.2. Analgesic effects of MSC-Exos

The analgesic effect of MSC-Exos is characterized by precise delivery and a rapid-short-term process, showing significant pain relief within 15 minutes to several hours. The duration of a single dose typically lasts for a few hours, and its analgesic action diminishes as the vesicles are cleared, displaying a relatively short action window that requires repeated administration or reliance on a sustained-release system to maintain longer-term analgesic effects. A study by Zhou et al. confirmed that in a rat model of osteoarthritis, a single intra-articular injection of umbilical cord-derived MSC exosomes led to a significant increase in mechanical and thermal pain thresholds observed on the 7th day, with analgesic effects persisting until day 28 post-administration [13]. Another related study demonstrated that a single injection of human umbilical cord MSC-derived exosomes, at a dose of 12 micrograms of total protein, produced effects within 15 minutes and maintained analgesia for up to 24 hours. Notably, exosomes have low immunogenicity and a lower risk of tumorigenesis and embolism formation, allowing for repeated administration. Continuous hourly injections of the same dose for 7 days could achieve an additional 7-day analgesic effect post-treatment [14]. MSCs have a slow onset of analgesia but produce long-lasting effects; the delayed effect is due to the need for MSCs to home, engraft, and continuously remodel the neuroimmune microenvironment, while the longevity relies on paracrine signaling and exosome release during their residence, making them

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suitable for long-term intervention in chronic pain. In contrast, MSC-Exos act rapidly, providing pain relief shortly after administration, and although the action window of a single dose is limited, their low immunogenicity supports repeated administration, which compensates for their short-term limitations.

5. MSCs and MSC-Exos optimization strategies

5.1. Optimization strategies for MSCs

Three-dimensional (3D) culture techniques can significantly enhance the analgesic efficacy of MSCs. Lee et al. found that compared to two-dimensional monolayer culture, MSCs cultured as 3D spheroids showed longer survival after transplantation, stronger expression of anti-inflammatory genes, and more pronounced analgesic effects [15]. In addition, genetic modification strategies, such as overexpressing glial cell line-derived neurotrophic factor (GDNF) or human preproenkephalin (hPPE) in MSCs, can enhance their neurotrophic and analgesic capabilities. By using a lentiviral vector to introduce the GDNF gene into rat bone marrow-derived MSCs, a stable GDNF-overexpressing transgenic MSC line was established and directly injected into the dorsal root ganglia (DRG) of rats with chronic constriction injury (CCI) of the sciatic nerve. Results showed that, compared with control MSCs, the GDNF-MSC transplantation group exhibited a significant reduction in mechanical and thermal hyperalgesia as early as postoperative day 3, with analgesic effects persisting until the end of the experiment [16]. Apart from neurotrophic factors, overexpression of endogenous opioid peptide precursors represents another effective genetic modification approach. Using a recombinant adeno-associated virus vector to introduce the hPPE gene into human bone marrow-derived MSCs, a transgenic cell line capable of sustained secretion of leucine-enkephalin (L-EK) was established. In the rat CCI model, intrathecal transplantation of hPPE-modified MSCs led to significant improvement in both mechanical and thermal hyperalgesia, and the analgesic effect could be completely reversed by the opioid receptor antagonist naloxone, confirming that the analgesic mechanism depends on activation of the endogenous opioid peptide system [17].

5.2. Optimization strategies for MSC-Exos

Inflammatory preconditioning is an effective strategy for enhancing the analgesic effect of exosomes. Zhang et al. found that MSC-derived exosomes pretreated with TNF-α (T-EVs) were enriched in miR-101b-3p, which targets and inhibits the Nav1.6 sodium channel in DRG neurons; their analgesic effect was significantly greater than that of untreated exosomes and lasted as long as two weeks [9]. Hypoxic preconditioning can promote the expression of HIF-1α, angiogenic factors (VEGF, angiopoietin-1, erythropoietin), survival proteins, and anti-apoptotic proteins (Bcl-xL, Bcl-2) in MSC-derived exosomes, thereby significantly improving their tissue repair and neuroprotective capacity [18]. In terms of delivery systems, hydrogel loading, collagen-binding domain (CBD) modification, and 3D-printed scaffolds can achieve sustained local release of exosomes and prolong their duration of action. For example, adhesive hydrogels used as an exosome delivery platform can support continuous exosome release, exert neuroprotective effects, and promote tissue repair. Fixing human MSC-derived exosomes in an adhesive hydrogel (Exo-pGel) achieves local delivery and sustained release at the spinal cord injury site, significantly promoting nerve repair [19]. In summary, optimization strategies for MSCs focus mainly on enhancing cell survival and shortening the onset time: 3D spheroid culture can improve the survival and anti-inflammatory capacity of cells

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in vivo, while genetic modification to overexpress GDNF or hPPE can enhance neurotrophic effects or activate the endogenous opioid pathway, thereby initiating and prolonging the analgesic effect. Optimization strategies for MSC-Exos focus on prolonging the duration of analgesia: inflammatory or hypoxic preconditioning can remodel exosomes to enhance analgesia and neuroprotection, and combination with hydrogels, scaffolds, and other delivery systems can achieve sustained local release, overcoming the limitation of rapid exosome clearance.

6. Strategies for the analgesic application of MSCs and MSC-Exos

6.1. Clinical significance

Based on the aforementioned mechanisms and differences in efficacy, MSCs and MSC-Exos should be viewed as complementary tools targeting different pathological stages and time windows in clinical pain management, rather than as substitutes. For acute pain or breakthrough pain, MSC-Exos are preferred. They can take effect 15 minutes after administration, which is very suitable for situations where pain needs to be quickly controlled, such as postoperative acute pain and cancer-related breakthrough pain. At the same time, the preparation has low immunogenicity and no risk of causing tumours, which supports repeated administration. Chronic neuropathic pain is more suitable for living mesenchymal stem cells (MSCs). Their analgesic effect can be maintained for several months, which is suitable for diseases that require long-term intervention, such as diabetic peripheral neuropathy and post-herpetic neuralgia. MSCs also have the ability of tissue repair and can also up-regulate the expression of central MOR, which forms a unique advantage in chronic pain treatment. As for central pain, such as pain after spinal cord injury and pain after stroke, MSC-Exos are given clinical priority. This kind of exosome can penetrate the blood-brain barrier and can act on the central nervous system by intravenous administration, thus avoiding the invasive operation caused by intrathecal injection of living cells. To prevent chronic postsurgical pain (CPSP), exosomes can be administered intravenously during or immediately after surgery to rapidly control the inflammatory storm, followed by local MSC transplantation 1–2 weeks after surgery to block central sensitization; at 1–3 months, the need for repeated intervention can be reassessed. For patients with special conditions, such as immunosuppression, a history of tumors, or the need for repeated interventions, exosomes are more suitable due to their low immunogenicity, non-tumorigenicity, and repeatable dosing. In cases of long-term treatment regimens with limited economic resources, single-use stem cells may be more affordable.

6.2. Future research directions: combined strategies of exosomes and stem cells

The combined therapeutic paradigm of rapid-acting exosomes and long-term maintenance by live cells represents an important direction in the future of stem cell-based analgesia. However, a combined strategy does not mean simply overlaying the two therapies; rather, it leverages the mechanisms of both modalities to achieve complementarity. The analgesic pathways of the two are inherently complementary in terms of time and space. Temporally, exosomes can quickly control acute pain and inflammatory storms after administration, buying time for stem cells to home and engraft. Subsequently, stem cells establish a stable therapeutic microenvironment within 6–7 days, maintaining long-term analgesic effects for months through continuous secretion and in situ exosome production. Spatially, the combined strategy involves "local stem cells repairing peripheral tissue and systemic exosomes modulating the central system." Locally transplanted live MSCs can engraft in injured tissues to achieve peripheral tissue repair and local analgesia. Meanwhile,

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exosomes administered intravenously or intranasally can cross the blood-brain and blood-spinal cord barriers to reach the central nervous system, inhibit central sensitization, and reconstruct the descending pain inhibitory system.

7. Conclusion

This paper systematically compares the mechanisms of action, analgesic effects, and optimization strategies of MSCs and MSC-Exos in the treatment of chronic pain, and proposes clinical application directions as well as strategies for their combined use. The results indicate that the two possess different analgesic characteristics—MSCs are characterized by dynamic responsiveness, with a slow onset but long-lasting pain relief, and have the abilities of tissue homing, dynamic secretion, and upregulation of central MOR; MSC-Exos, on the other hand, are characterized by precise delivery, with rapid onset but relatively short duration of action, capable of crossing the blood-brain barrier and targeting the regulation of inflammatory pathways, ion channels, and cell phenotypes. The two have spatiotemporal complementarity in terms of mechanism of action and efficacy, and cannot replace each other. Instead, they adapt to different pathological stages and treatment time windows respectively, which can provide a theoretical basis for the selection of clinical plans. The combination of these two analgesic means is expected to rely on the effect of "quick onset-long-term maintenance" to achieve a coordinated improvement in analgesic effect. However, the analysis in this article is mainly based on preclinical research and a small amount of early clinical data, and there is still a lack of large-sample randomised controlled trials and long-term safety results. Follow-up research needs to promote clinical translation experiments, continue to explore the feasible strategies of drug-delivery optimisation and combined treatment, and promote the research in this direction to practical clinical application.

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