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Review

Cell Transplantation as a Pain Therapy Targets Both Analgesia and Neural Repair

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Cell transplantation is a potentially powerful approach for the alleviation of chronic pain. The strategy of cell transplantation for the treatment of pain is focused on cell-based analgesia and neural repair. (1) Adrenal medullary chromaffin cells and the PC12 cell line have been used to treat cancer pain and neuropathic pain in both animal models and human cases. As biological or living minipumps, these cells produce and secrete pain-reducing neuroactive substances if administered directly into the spinal subarachnoid space. (2) Cell implantation for pain neurorestorative therapy is a new concept and an emerging research field for pain control along with neural repair. Possible neurorestorative mechanisms include neuroprotective, neurotrophic, neuroreparative, neuroregenerative, neuromodulation, or neuroconstructive interventions, as well as immunomodulation and enhancing the microcirculation. These factors may ultimately restore the damaged or irritated condition of the lesioned nerves. The growing preclinical and clinical data show that neural stem/progenitor cells, olfactory ensheathing cells, mesenchymal stromal cells, and $CD34^+$ cells have the capacity to manage intractable pain and improve neurological functions. Cell delivery routes include local, intrathecal, or intravascular implants. Although these strategies are still in their infancy phase for pain neurorestoratology, cell-based therapies could open up new avenues for the relief of pain. In this review, these aspects are critically analyzed based on our own investigations. This manuscript is published as part of the International Association of Neurorestoratology (IANR) supplement issue of *Cell Transplantation*.

Key words: Cell transplantation; Pain; Analgesia; Neural repair; Neurorestorative therapy; Pain neurorestoratology

INTRODUCTION

The management of chronic pain syndromes presents a difficult challenge. Some of the most severe chronic pain disorders are associated with peripheral or central nerve lesions leading to chronic neuropathic pain (NP) syndrome, such as spinal cord injuries and diabetic/alcoholic polyneuropathies. The treatment of such neuropathies has been far from successful with the currently available therapeutic interventions.

Increasing evidence suggests that cellular transplantation may be a powerful approach for the alleviation of chronic pain (29–31). Adrenal medullary chromaffin cells were chosen first as the donor source, followed by the PC12 (rat pheochromocytoma-derived) cell line, as these cells produce and secrete both opioid peptides and catecholamines; they could act as a living or biological minipump to relieve pain.

Although the occurrence and development of intractable neuropathic pain mechanisms are complex topics (Table 1), it is obvious that pain is always caused by nerve damage or irritation. Thus, we could treat the original source of pain using the new medical strategies of nonanesthesia or non-nerve blocks. For example, one can repair abnormal and damaged nerve construction. We could restore the balance of neural pathway and network signals. Alternatively, we could modulate the microenvironment for pain sensors.

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Table 1. Pathological Mechanisms of Intractable Neuropathic Pain

- Impact on the spinal nociceptive network, thereby opening the "gate" to higher brain centers involved in the perception of pain
- Ectopia
- Sensitization of nociceptors
- Phenotypic switching
- Structural malignant plasticity
- Disinhibition
- Neuroinflammation (3)
- Neurocutaneous inflammatory signaling (38)
- Activation of glutamate receptors and glial cells in the spinal dorsal horn (53)
- Local inflammatory pain (50)
- Peripheral immune cell-mediated analgesia (28)
- Activated microglia in nociception (68)

These are the pertinent aspects of novel therapies for NP syndrome that requires detailed investigation.

Recently, several new types of cells including neural stem/progenitor cells, olfactory ensheathing cells, γ-aminobutyric acid (GABA)ergic cells, various mesenchymal stromal cells, peripheral blood mononuclear cells, and cluster of differentiation 34-positive ($CD34^+$) cells have been shown to play a neurorestorative role in both the central nervous system (CNS) and peripheral nervous system (PNS). These cells are also able to effectively reduce some of the severe chronic pain syndromes, particularly NP. Interestingly, chromaffin cells have been reported to secrete a variety of neurotrophic factors, cytokines, and other neuropeptides, a "trophic cocktail," which may also stimulate the restoration of spinal cord functions following peripheral nerve injuries.

Thus, cell implantation for pain neurorestorative therapy is the critical aspect of pain neurorestoratology (PN). PN is an important branch of neurorestoratology that reveals how to intervene with pain, especially refractory NP, under the new theories and methods of neurorestoratology (30,31,34). The fundamental principles of PN are to promote nerve repair, regulate immunity, improve microcirculation, and modulate neurotransmission, among other mechanisms.

The PN treatment is not completely identical to the etiological treatments. So, PN is more active on the treatment of ideas, which is not comparable to the straightforward anatomical structural repair but emphasizes the neural painless remodeling and/or benign neural network plasticity. The PN treatment thus represents the etiological treatment in addition to the benign neural network plasticity. Cell implantation as a pain neurorestorative therapy aims to relieve pain, together with functional recovery, with more modulation and less destruction. In this article, we reviewed recent clinical results on cell transplantation pain therapeutics from both allogeneic and xenogeneic sources in animal models and in patients with chronic refractory pain due to spinal cord injuries, stroke, diabetes, aging, muscle strain, sports injuries, and other related conditions based on our own observations.

CELL-BASED ANALGESIA

Chromaffin Cells

Development of tissue and cellular strategies for intractable pain has progressed in the past 30 years (17). The earliest cell therapy studies for pain relief include adrenal medullary tissue, which is composed of chromaffin cells that produce several neuroactive substances, including catecholamines and opioid peptides. These cells confer pain relief after being transplanted into the spinal cord (60) or reduce pain sensitivity when injected into the midbrain periaqueductal gray (59). Electron microscopic studies also showed pronounced myelination that occurred both in the graft and in the host tissue 8 weeks after transplantation. The new myelin formation in the graft resembles PNS myelination and CNS myelination in the host. Chromaffin cells occasionally formed synapses and were observed extending into the host CNS tissue. Grafts may contribute to both postsynaptic and presynaptic components of the synaptic junctions (58,59). Transplantation of adrenal medullary tissue grafts into the spinal subarachnoid space of rats with adjuvant-induced arthritis alleviated chronic pain and attenuated body weight reduction in a naloxone (opiate antagonist)-dependent and phentolamine (α-adrenergic antagonist)-dependent fashion, implying opioid release (61).

Allografted adrenal medulla in the lumbar intrathecal space could reduce pain in an NP model caused by transection of the sciatic and saphenous nerves. Pain symptoms including allodynia, hyperalgesia, and dysesthesia (27), and limb self-injury (23) were markedly decreased in peripheral mononeuropathy rats through adrenal medullary tissue transplantation. Long-term alleviation of allodynia by intrathecal bovine chromaffin cell implantation may occur due to opioid and α-adrenoceptor activation as a consequence of cells acting as a long-term source of antinociceptive agents (80).

Grafts of adrenal medullary chromaffin cell grafts may also markedly reduce forelimb and hindlimb mechanical and thermal allodynia in chronic central pain (26), offer similar control over deafferentation pain to that observed in posttraumatic brachial plexus avulsion in humans (25), and prevent the development of QUIS-induced behavioral changes, which can mirror the pathological characteristics of ischemic and traumatic SCI (6).

One of the major limitations for widespread application of grafts is the availability of donor tissue or cells in adequate quantities. Prevention of long-term graft rejection could allow for the use of xenogeneic donors. Xenografts

of isolated bovine chromaffin cells can survive for at least 3 months in the rat periaqueductal gray following a short-term course of immunosuppressant treatment. Synaptic integration of transplanted bovine chromaffin cells with host neurons was observed along with physical integration into the host parenchyma (57).

One possible method to limit rejection is to encapsulate cells in semipermeable polymer membranes. Implantation of encapsulated bovine chromaffin cells into the rat spinal subarachnoid space demonstrated decreased pain sensitivity for 3 months after implantation in a naloxone- and phentolamine-dependent fashion, which suggests that opioid peptides and catecholamines contribute to these pain responses. In vitro studies using previously transplanted encapsulated cells demonstrated a sustained release of Met-enkephalin and catecholamines (62).

The first trial of encapsulated xenogeneic (bovine) cells in humans was performed by Buchser and colleagues. They implanted bovine chromaffin cells into the subarachnoid space of seven patients with severe chronic pain. No pharmacologic immunosuppression was administered to the patients. After 41 to 176 days in vivo, the implant was removed, and the survival of the encapsulated cells was confirmed. Their biochemical function was validated by assessment of secretory function. Several patients were able to reduce their need for morphine, and their pain ratings improved (7).

In the absence of encapsulation, additional purification of tissue, such as removal of immunological cells, may be necessary, especially for long-term or multiple grafting procedures. Clinical evidence from 15 patients revealed that intrathecal grafting of unencapsulated, nonhuman leukocyte antigen (HLA)-matched adrenal medullary tissue resulted in the migration of CD4 T lymphocytes into the CSF. While the graft was tolerated in most cases, the cells retained the ability to release inflammatory cytokines to promote an immune response, and impairment of the local immunosuppressive balance could cause rejection (72). A highly purified bovine cell preparation resulted in a considerably weaker stimulation of rat lymphocyte proliferation in vitro, compared to a semipurified preparation (49). Intrathecal transplantation demonstrated that the purer the transplanted bovine chromaffin cells, the less chance of immunorejection of the xenogeneic transplants and the greater the antinociception over time.

A homogeneous source can also be provided by using embryonic and neonatal chromaffin cells. They can ameliorate NP after nerve injury and SCI and reverse chronic pain due to their ability to deliver antinociceptive molecules (19). Another alternative to the use of these cells is to generate immortalized chromaffin cell lines by oncogene insertion. However, the genes must be excised before the cells could be used clinically. Eaton et al. found that the Cre/lox site could be used to remove the immortalizing oncogene from immortalized chromaffin cells and that these cells were still able to secrete neuroactive molecules. Transplantation of either immortalized or disimmortalized cells was able to reverse the behavioral hypersensitivity induced by a partial nerve injury (18).

The abnormal sensory hyperexcitability subsequent to peripheral injury may arise from activation of spinal *N*-methyl-D-aspartate (NMDA) receptors, promoting sensory responses and the maintenance of pathological pain. Adrenal medullary grafts can suppress this via α-adrenergic modulation and other neuroprotective mechanisms (65) including reducing spinal cGMP content (63), which are normally increased due to NMDA–nitric oxide (NO) synthase activity (24,63).

Acute and chronic pain alleviation is mediated by distinct mechanisms. Suppression of the acute pain by adrenal medullary implants is dependent on naloxone and partially dependent on phentolamine, but the antinociceptive effect on the tonic phase of the formalin response is not affected by these antagonists (64). Moreover, porcine and bovine chromaffin cells transplanted into the spinal subarachnoid space of the rat equally ameliorate formalin-evoked c-Fos expression in the spinal cord as well as nociceptive behaviors in the tonic phase of the formalin response (69).

In another study, various quantities of adrenal medullary tissue were transplanted into an SCI animal model to explore the optimization of adrenal medullary allograft conditions for pain alleviation. Sustained antinociception was obtained with only a small quantity of adrenal medullary tissue even after culturing for 30 days prior to transplantation (74). A prospective phase II clinical study further supported the feasibility of using chromaffin cell grafts for long-term relief of cancer pain. In this study, 15 patients with intractable cancer pain had chromaffin cell graft transplantation, and 12 exhibited profound control of the pain. The analgesic response appeared to be related to CSF Met-enkephalin levels in the majority of cases (45). Early clinical studies initiated for terminal cancer patients have also shown promising outcomes. Eight patients with an average follow-up of 5 months demonstrated some degree of control of cancer pain; intrathecal and oral morphine was no longer necessary in two cases and stabilized in five other patients. Met-enkephalin release was gradually reduced from 2 to 4 months after transplantation (44). Further promising results came from a preliminary clinical study of spinal subarachnoid adrenal medullary transplantation for alleviating cancer pain (55). Bés et al. (4) reported 1-year morphological and functional evidence of chromaffin cell allograft survival in cancer patients with chronic pain. In these studies, the analgesic effect was associated with CSF Met-enkephalin levels and the survival of transplanted chromaffin cells in the subarachnoid space.

PC12 Cells

A semipermeable membrane was used to microencapsulate PC12 cells, which were then utilized to treat NP in a rat model induced by chronic constriction injury (CCI) of the sciatic nerve. After implantation into the lumbar subarachnoid space, cold allodynia was significantly decreased in the rats of the cell-loaded group for up to 28 days (77).

Genetically Modified Embryonal Carcinoma Cell Line

Ishii et al. established a genetically modified embryonic carcinoma cell line (P19) with dexamethasone-dependent expression of β-endorphin (β-EP). Transplantation of these cells into the subarachnoid space in rats resulted in strong analgesic effects for a month. These effects were potentiated by an IP injection of dexamethasone (35).

CELL IMPLANTATION AS A PAIN NEURORESTORATIVE THERAPY

Bone Marrow-Derived Stromal Cells

Human bone marrow-derived stromal cells (hBMSCs) have been shown to reduce astrocytic and microglial cell activation and mechanical allodynia and thermal hyperalgesia within 6 days of transplantation into the lateral cerebral ventricle of mice 4 days after sciatic nerve surgery. The levels of proinflammatory cytokines and neural β-galactosidase, markers of astrocytic and microglial cell activation, were found to be reduced (66). A similar effect was seen with human mesenchymal stromal cells (hMSCs) injected via the tail vein into mice 4 days after sciatic nerve surgery (67). The authors proposed that the restorative mechanisms of MSCs may involve [1] a cell-to-cell contact activation whereby proinflammatory macrophages may be switched to anti-inflammatory macrophages by the homing of the cells to the spinal cord and [2] communication with multiple cell types via secretion of a broad spectrum of molecules (67). Another finding showed that intravenous BMSCs and subcutaneous synthetic immunostimulatory oligodeoxynucleotide IMT504, which contains a cytosine [(C)/thymine (T) or Py][C/T/adenine (A)/guanine (G) or N]TTTTGT motif, were both able to prevent the development of mechanical and thermal allodynia when they were administered in rats following a sciatic nerve crush injury. IMT504 may work by potentially stimulating MSC proliferation (12). On the contrary, a clinical study from Egypt revealed that intrathecal autologous bone marrow mesenchymal stem cell therapy may have serious side effects in chronic spinal cord injury patients, including developing pain and spasticity (40). Therefore, further study is needed to elucidate whether MSCs could be beneficial in the clinical setting.

MSCs could also be a novel tool for the treatment of painful diabetic neuropathy. Cells were injected into the unilateral hindlimb muscles of rats at an early stage of streptozotocin-induced diabetes. Mechanical hyperalgesia, cold allodynia, reductions in sciatic motor nerve conduction velocity, sensory nerve conduction velocity, and sciatic nerve blood flow were all improved following transplantation. The decreased mRNA expression of neurotrophin-3 (NT-3) in diabetic rats was also partially reversed by the cell transplant (52).

Intervertebral disc degeneration is a major cause of lower back pain. Cryopreserved allogeneic intervertebral disc transplantation has been shown to relieve pain and preserve motion, but the absence of sufficient viable cells means that the transplanted discs continue to deteriorate. Fortunately, BMSC implantation has been shown to delay degeneration (8). Additionally, BMSCs transplanted along with transforming growth factor-β1 contained within pure fibrinous gelatin were observed to inhibit apoptosis and reduced intervertebral disc degeneration (78). Yoshikawa et al. (79) were the first to report the clinical experience of intervertebral disc regeneration therapy. Two old female patients, suffering from lumbago, leg pain, and numbness, had collagen sponge pieces embedded with autologous BMSCs grafted percutaneously to their degenerated intervertebral discs. Two years later, radiograph, computed tomography, and magnetic resonance imaging all showed improvements in the lumbar discs. In addition, clinical symptoms were alleviated (79). Another clinical study further suggested that BMSC therapy may be a valid alternative for the treatment of chronic back pain caused by degenerative disc diseases. The advantages of BMSCs over current therapy may include a simpler and less invasive intervention without surgery, similar or enhanced pain relief, and no deviation of normal biomechanics (54).

Atherosclerosis often is accompanied by atherosclerotic peripheral artery disease, whereby the occlusion of large limb arteries may cause critical limb ischemia (CLI), pain, and ultimately amputation. BMSCs have been used in several preclinical studies with some success, which has led to several small clinical trials of BMSC therapy for CLI. Clinical benefits from these trials include pain reduction, improved ankle–brachial index, increased transcutaneous partial pressure of oxygen, and decreased amputation [reviewed by Lawall et al. (43)]. Recently, Murphy et al. (51) reported that autologous BMSC therapy is quite safe and promotes amputation-free survival and decreases pain at rest in patients with CLI. Other clinical trials have also shown similar results (16,20–22,56,71).

MSC transplantation may also help relieve pain in other diseases. For instance, intradermal injection of autologous MSCs led to dermis/subcutis border congregation of lymphocytes and enhanced vascularization in a Göttingen minipig cutaneous radiation syndrome model. Improvements in pain control and wound healing were also observed (1). Treatment of early avascular necrosis of the femoral head with a combined therapy of core

decompression and autologous BMSC transplantation was found to be more effective than core decompression alone for the relief of pain (9). The immune system-dependent cartilage degeneration of knee osteoarthritis was treated using autologous BMSCs in four patients who demonstrated some improvement in their pain as measured by walking time and stair climbing (14).

$CD34^+$ Cells

Granulocyte colony-stimulating factor (GCSF)-mobilized $CD34^+$ cells were transplanted intramuscularly in a phase I/IIa clinical trial of 15 patients with atherosclerotic peripheral artery disease or Buerger's disease with CLI. Some improvements in the Wong–Baker FACES pain rating scale, toe brachial pressure index, transcutaneous partial oxygen pressure, total or pain-free walking distance, and ulcer size were observed in all patients during the 12-week follow-up (37). Long-term observations (208 weeks) of 17 patients provided further support for this therapy (39). Another study compared the intramuscular and intra-arterial delivery of autologous bone marrow cells in 41 patients and found both routes to be equally effective, though higher $CD34^+$ cell concentrations and less inflammation resulted in a greater therapeutic response (41).

Olfactory Ensheathing Cells

Olfactory ensheathing cells (OECs) are a promising tool for improving functional outcomes after SCI (32). OEC transplantation could effectively attenuate NP associated with dorsal root injury, which included spontaneous pain behavior, tactile allodynia, and thermal hyperalgesia (76). OECs may mediate the antinociceptive effect by modulating inflammation and/or astrogliosis.

Seventeen patients who had suffered intractable chronic NP for 6 to 309 months after SCI were treated by fetal OEC implants into the spinal cord at opposing ends of the injury site. The degree of pain was compared before operation and long-term follow-up of 0.5–88 months based on the International Association of Neurorestoratology Spinal Cord Injury Functional Rating Scale (IANR-SCIFRS), in which 0 point represents extreme uncontrolled pain, 1 point represents severe pain that requires and responds to narcotics, 2 points represent mild pain that responds to ordinary pain killers, and 3 points represent no pain. Mean pain amelioration was 1.2 points (10). In addition, one central poststroke patient was relieved almost completely of pain following fetal OEC intracranial transplant, with 4 weeks follow-up (48).

GABA Cells

Injury or dysfunction of the nervous system frequently culminates in spontaneous pain, hyperalgesia, and/or allodynia. The early development of chronic NP may rely on spinal GABA levels, so an early intervention to restore GABA has been shown to prevent the pain development (70). Immature telencephalic GABAergic interneurons derived from mouse medial ganglionic eminence (MGE) that are transplanted into the spinal cord can completely reverse the peripheral nerve injury-induced mechanical hypersensitivity. The cells have also been shown to functionally synapse with both primary afferent and spinal cord neurons (5).

Spinal Progenitor Cells

Intrathecal implantation of spinal progenitor cells (SPCs) can alleviate NP as demonstrated by an attenuated response to thermal stimuli in CCI rats, which may relate to their expression of GABA (47).

Neuroblastoma Cells

Intrathecal implantation of the human neuroblastoma cell line NB69 has been shown to decrease heat hyperalgesia and cold allodynia in the NP rat following sciatic nerve CCI. This corresponded with elevated CSF concentrations of dopamine and serotonin metabolites (15).

Human Neuronal Cell Lines

Intrathecal transplantation of the human embryonal carcinoma-derived neuronal cell line hNT2.17 is able to reverse behavioral hypersensitivity following excitotoxic SCI in rats (75) as well as CCI-induced peripheral nerve injury (73). SCI caused reduced GABA expression in the spinal dorsal horn, and cell transplantation was observed to promote GABA expression, suggesting that the mode of action may be via restoration of the cellular GABAergic pathway.

Adipose Tissue Stromal Cells

Intrathecal grafting of adipose tissue-derived stromal cells (ADSCs) transduced to secrete levodopa demonstrated long-term survival and adherence to the spinal cord and nerve root meninges. However, no long-term elevation of CSF levodopa and dopamine metabolites or antiallodynic effects was observed, suggesting that transgene silencing may have occurred (11). In one study, multiple intramuscular ADSC injections were used in 15 CLI patients to attempt to restore blood flow. Significant improvement in pain rating scales, walking distance, and other clinical signs was observed at 6 months of follow-up after ADSC therapy (46). Infrapatellar fat pad-derived mesenchymal cells were shown to ameliorate pain and improve clinical function based on their Lysholm, Tegner activity scale, and VAS scores when percutaneously injected into 25 patients with arthritic knees (42).

Schwann Cells

Following peripheral nerve injury, Schwann cells can aid axonal regrowth by becoming migratory and

regulating the expression of inflammatory cytokines. This would appear to be dependent on erythropoietin since Schwann cells express erythropoietin and its receptor, and the migration and extracellular matrix remodeling are enhanced in erythropoietin's presence. In this way, NP can also be minimized by Schwann cells (33).

Immortalized Astrocytes

Exogenous galanin (GAL) has been shown to aid chronic pain management after nerve injury following spinal infusion. Immortalized astrocytes (IAST) can be transduced to express GAL and act as biological cytokine minipumps. Subarachnoid transplantation of such cells into rats with a sciatic nerve injury was shown to alleviate chronic NP in a GAL-dependent fashion (2).

Neural Stem/Progenitor Cells

Extensive migration and integration of engrafted neural stem/progenitor cells has been shown within the spinal cord of SCI rats. Oligodendrocytic differentiation was frequently observed but, while enhanced functional repair and plasticity was present, no modification of the "deformed" pain afferents or effect on NP was determined (36). Upregulation of NO has previously been demonstrated in spinal cord injury and may also contribute to NP occurrence (24,63). Therefore, a possible mode of action for benefit would be to decrease the upregulation of NO. One study demonstrated that embryonic neural stem cell transplantation into the hemisected cavity of the spine (which had been replaced by collagen matrix) reduced the acute pain response in an NO-dependent fashion (13).

SUMMARY

Cell transplantation as a pain therapy has been revolutionized from the "destructive" stage to a "constructive" stage. The future development of these various new approaches will depend on a close interplay between basic science and clinical applications. There are four future directions of cell transplantation pain therapeutics: (1) to treat chronic intractable pain for which there are currently unavailable methods; (2) to improve the outcome of traditional pain therapy; (3) to relieve pain in conjunction with nerve repair and reconstruction of the vascular and blood circulation in patients with central pain after spinal cord trauma, stroke, and neurodegenerative impairments; and (4) to provide new ideas for current treatment protocols. Several different cell types appear to show some degree of promise toward the relief of pain as outlined in this review.

Future research questions include exploring if we can treat trigeminal neuralgia by cell therapy instead of through surgical vascular decompression. Perhaps we could control spinal cord pain by using cell therapy with electric stimulation. We believe that this promising and fast developing research field will greatly enrich our perspective and be helpful for improving the level of intractable pain management in the future.

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