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Targeting dorsal root ganglia and primary sensory neurons for the treatment of chronic pain

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Abstract

Introduction—Currently the treatment of chronic pain is inadequate and compromised by debilitating central nervous system side effects. Here we discuss new therapeutic strategies that target dorsal root ganglia (DRGs) in the peripheral nervous system for a better and safer treatment of chronic pain.

Areas covered—The DRGs contain the cell bodies of primary sensory neurons including nociceptive neurons. After painful injuries, primary sensory neurons demonstrate maladaptive molecular changes in DRG cell bodies and in their axons. These changes result in hypersensitivity and hyperexcitability of sensory neurons (peripheral sensitization) and are crucial for the onset and maintenance of chronic pain. We discuss the following new strategies to target DRGs and primary sensory neurons as a means of alleviating chronic pain and minimizing side effects: inhibition of sensory neuron-expressing ion channels such as TRPA1, TRPV1, and Nav1.7, selective blockade of C- and Aβ-afferent fibers, gene therapy, and implantation of bone marrow stem cells.

Expert opinion—These peripheral pharmacological treatments, as well as gene and cell therapies, aimed at DRG tissues and primary sensory neurons can offer better and safer treatments for inflammatory, neuropathic, cancer, and other chronic pain states.

1. Introduction

The dorsal root ganglia (DRGs) are located in the peripheral nervous system (PNS), between the dorsal horn of the spinal cord and the peripheral nerve terminals, and contain various cell types such as satellite glial cells, endothelial cells, macrophages and primary sensory neurons. DRG neurons are pseudo-bipolar neurons, with a peripheral branch that innervates their target organ and a central branch that carries the somatosensory information to the spinal cord. At the spinal cord, the DRG central branch synapses with secondary sensory

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neurons that transmit this information to the higher central nervous system (CNS) structures [1]. Because DRGs display no protective surrounding capsular membrane and have a high density of blood capillaries [2], the diverse DRG neurons can readily be targeted by systemic and local delivery approaches (Figure 1). The diversity of DRG neurons, marked by unique molecular, morphological, and functional features, is an important physiological and pathological feature allowing the discrimination between various types of sensations. For instance, DRG neurons with large cell bodies are low threshold, fast-conducting, and possess myelinated Aα and Aβ fibers that conduct proprioception and mechanoreception (e.g., touch); whereas those with small cell bodies are nociceptors, which transmit pain, that have either thinly myelinated medium-velocity Aδ fibers or unmyelinated slow-conducting C-fibers, most of which have a high threshold for activation. A recent *in vivo* characterization of DRG neurons shows that most of them are modality-specific in physiological conditions, but this specificity is compromised under pathological conditions, such as after tissue inflammation or injury [3].

Acute tissue inflammation or injury mostly results in acute pain, which is protective and can be efficiently managed by current drugs [4]. However, it is now clear that prolonged inflammation and injury can lead to chronic pain, a debilitating condition for which there are few and poor treatment options. Chronic pain affects 20% of the worldwide population and arises from various etiologies, including injury or dysfunction of the nervous system (neuropathic pain), tissue damage or inflammation (inflammatory pain), or tumor invasion (cancer pain), but can also occur with no apparent etiology (functional pain, e.g., fibromyalgia) [5,6]. Chronic pain is classically associated with symptoms such as spontaneous unprovoked pain, paresthesias, dysthesias, pain evoked by normally innocuous stimuli (allodynia), or exaggerated pain to noxious stimuli (hyperalgesia). The mechanisms underlying these various pathologies and symptoms are still incompletely understood, however, changes in the plasticity and modality of DRG neurons seem to be a hallmark of chronic pain (Table 1), focusing attention on these cells as targets for therapeutic interventions.

Current pharmacologic treatments for chronic pain are an outgrowth of drugs targeting acute pain and are often associated with side effects due to their actions in the central nervous system. Targeting DRG neurons specifically may result in safer therapeutic approaches. For instance, opioids are potent analgesics that act through opioid receptors expressed in the peripheral and central nervous system. Unfortunately, their CNS actions also result in respiratory depression, sedation, dizziness, somnolence, tolerance, and dependence. Interestingly, experimental and clinical studies have suggested that targeting only peripheral opioid receptors in DRG neurons is sufficient to produce significant analgesic and anti-inflammatory effects, without centrally mediated side effects [7].

Previous reviews have extensively discussed the various clinical approaches and advantages of targeting DRG [8,9]. Here, we focused on pre-clinical studies showing how unique molecular mechanisms operating in DRG neurons can offer new therapeutic targets; and these mechanisms can be targeted via delivering drugs, nucleic acids, and cells into DRG tissues as a mean to alleviate chronic pain. We will begin by describing systemic and local therapeutic approaches and end by proposing stem cell as specific drug carriers to injured

DRG neurons. We will also briefly discuss the opportunities and challenges to translate animal research into clinical therapies for chronic pain.

2. Targeting ion channels in DRG neurons and their axons via systemic or peripheral routes

Systemic administration is a common route of choice for many drugs, allowing the entire body to be affected via the circulatory system. The central nervous system is segregated from this due to the blood brain barrier, but the DRG tissues have rich vascularization with unique endothelial cells which allow for the penetration and accumulation of systemic drugs in this tissue [2]. Although higher concentration of drugs can be found in DRG tissues, current systemic pain drugs (e.g., opioids) are not selective for DRG tissues and affect their targets across multiple tissues often leading to serious side effects. Targeting molecules involved in pain mechanisms that are exclusively expressed or at least enriched in DRG neurons can overcome this problem.

One of the largest group of receptors that mediate pain in DRG neurons is transient receptor potential (TRP) channels. Among them, TRPV1 and TRPA1 are highly and primarily expressed in nociceptors [10]. TRPV1 is activated by noxious heat and capsaicin (the active ingredient of chili peppers) [11]. Interestingly, capsaicin has been used as a topical analgesic for centuries and an 8% capsaicin patch is FDA approved for postherpetic neuralgia. Its efficacy in other chronic pain states is still being investigated, but it holds promise for the treatment of a localized area of the body such as the feet in diabetic or HIV-related neuropathy or postsurgical neuropathic syndromes such as after a thoracotomy[12]. Multiple mechanisms targeting the peripheral sensory neurons underlie capsaicin-induced analgesia, including inactivation of voltage-gated sodium channels, intracellular calcium saturation, mitochondrial dysfunctions and desensitization of TRPV1[13]. TRPA1 recognizes an array of chemicals (e.g., mustard, cinnamon, wasabi, garlic and bradykinin) and appears to be involved in cold and mechanical noxious sensation [14-16]. Inflammatory signals and nerve injury alter TRPV1 and TRPA1 expression and function contributing to chronic pain [17-19]. Several companies have been conducting clinical trials for TRPV1 and TRPA1 antagonists. In particular, TRPV1 antagonists have elicited great interest in the past decades and yielded multiple clinical trials. Unfortunately, first generation TRPV1 antagonists demonstrated undesirable side effects such as hyperthermia or reduced heat pain threshold [10]. However, a second generation of antagonists directed to a modality-specific state of TRPV1 (e.g., AMG8562 and NEO6860) have been recently tested for their analgesic effects and seem not to produce the previous adverse effects [20].

In addition to a direct modulation of TRP channels by the aforementioned antagonists, these channels can be indirectly modulated by targeting scaffolding proteins and G protein–coupled receptors (GPCRs). Recently, we have identified SHANK3 as a critical scaffold protein for TRPV1. TRPV1 function in sensory neurons is largely impaired after deletion or knockdown of SHANK3 in both mouse and human DRG neurons [21]. Targeting the interaction of SHANK3 and TRPV1 may lead to safer treatment of chronic pain by adding specificity for sensory neurons. Endogenous pro-resolution lipid mediators (PRLMs) also

offer a unique therapeutic approach to indirectly target the analgesic function of TRPV1 and TRPA1 in inflammatory and neuropathic pain via GPCRs [22,23]. These PRLMs, which are derived from omega-3 unsaturated fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), include resolvin D1 (RvD1), RvD2, RvE1, and protectin D1 (NPD1). Interestingly, we have shown that these neuroprotectin and resolvins not only have anti-inflammatory and pro-resolution actions, but they are also strong analgesic through their actions on TRPV1 and TRPA1 signaling in sensory neurons. Different PRLMs modulate different TRP channels: NPD1 and RvE1 only inhibit TRPV1 while RvD1 only inhibits TRPA1, but RvD2 inhibits both TRPA1 and TRPV1 in DRG neurons [24,25]. Importantly, their actions are mediated by Gi/o-coupled GPCRs and they attenuate inflammatory and neuropathic pain without affecting basal pain processing or having other deleterious side effects. Although the specific GPCRs and downstream signaling responding to these lipid mediators in neurons remain to be determined, protectin and resolvins may allow novel treatment approaches for chronic pain. Notably, effective conversion of PRLMs from diet supplemented with DHA and EPA may be responsible for the dietary control of chronic headaches [26], suggesting new low-cost and low-risk treatments based on diet control.

Voltage-gated sodium channels (Na_vs) are another family of popular targets for chronic pain treatments. These channels contribute to the generation of the ectopic action potential found in sensory neurons in various chronic pain conditions and most importantly $Na_v1.7$, $Na_v1.8$ and $Na_v1.9$ are unique to the peripheral neurons [27]. We encourage our readers to read the recent review of Emery et al. in this very same journal for more details about targeting these subunits for pain relief [28].

Although the systemic delivery is the prevalent approach in clinical practice, dorsal root ganglion electrical stimulation and injections localized across the peripheral nervous system have also been used successfully to treat chronic pain while minimizing undesired side effects in animal studies and in clinical practice [29-33]. Various injection routes have been used to target DRG (Figure 1). Intrathecal injections are widely used in pre-clinical studies to deliver drugs to DRG neurons, but this approach cannot reliably restrict injected drugs to a single side or to a longitudinal range of vertebral levels. Alternatively perineuronal and intraganglionic injections are used and offer a better regional specificity over the intrathecal delivery, albeit with risk of direct needle trauma to the DRG. Furthermore, methods for injecting drugs directly into peripheral nerves using ultrasound guidance or using fluoroscopic guidance are well-established in clinic [31,32]. Selective spinal nerve blocks by delivery local anesthetics (e.g. lidocaine) into spinal nerves or DRG tissues have been used for diagnostic and therapeutic purposes in patients with chronic back pain, as well as to manage cancer pain [34]. However, chronic pain conditions would require repeated injections with increased technical challenges due to the inability to directly visualize the DRG fluoroscopically, risk of tissue injury, risk of injection of medication systemically, and patient discomfort.

Injections in the vicinity of the DRG can offer a less invasive approach and still provide a targeted and safe therapeutic option for chronic pain. Corticosteroids are commonly used as adjuvant analgesics in chronic pain treatment and unfortunately systemic administration affects multiple tissues and induces severe side effects such as candidiasis, hyperglycemia,

myopathy, peptic ulceration, and psychiatric disorders [35]. Interestingly, it has been shown that a single injection of corticosteroid in the vicinity of an injured DRG can mimic the effect of systemic administration in alleviating chronic pain in animals and patients while reducing systemic side effects[36,37].

Another therapeutic option for chronic pain recently established in clinic is the direct electrical stimulation of DRG neurons, which is delivered by electrical leads placed into the neuroforamen in proximity of the targeted DRG [38]. The mechanisms underlying the analgesic actions of this stimulation are still unclear. However, GABAergic DRG neurons have been recently identified and it has been demonstrated that chemogenetic or optogenetic depolarization of these neurons significantly reduce chronic inflammatory pain [39]. Electrical stimulation of DRG may results in a similar depolarization and action. Although clinical trials of this approach involve a limited number of patients and it is approved for use in the EU and USA, DRG electrical stimulation seems to be effective primarily in alleviating only neuropathic pain[29,40]. It also requires permanent implantation of hardware, carrying the risk of surgical trauma and further tissue damage. Peripheral nerve stimulation has been also proposed to treat neuropathic pain [41], but more studies are necessary to confirm the role and efficacy of this treatment in chronic pain and the implantable hardware to perform peripheral nerve stimulation is still relatively nascent.

3. Targeting DRG neurons by selective nerve blockade

Recent progress has been made in selective targeting of different subsets DRG neurons [42-47]. Local anesthetics are mostly uncharged molecules that penetrate the membrane of all neurons, blocking not only sensory neurons but also motor and autonomic neurons, generating undesired effects such as blood pressure changes and motor deficits. The seminal discovery that the lidocaine derivative QX-314 was able to block sodium channels only in nociceptors expressing TRPV1 channels [45] provided the framework for new strategies to selectively inhibit the neuronal activity in a specific population of sensory neurons. QX-314 is a permanently charged lidocaine derivative that cannot penetrate cell membranes, making it incapable of the intracellular blockade of sodium channels characteristic of the local anesthetics. However, the co-administration of capsaicin to activate and open TRPV1 channels enables QX-314 to enter the TRPV1+ neurons and block activation of these neurons. Co-administration of capsaicin and QX-314 in naïve animals results in long-lasting analgesia, completely blocking the neuronal response to noxious stimuli without impairing motor function or generally innocuous tactile sensitivity [45]. In animal models of inflammatory or neuropathic pain, the combination of capsaicin and QX-314 alleviates particular chronic pain behaviors. During inflammation, heat hyperalgesia, and mechanical allodynia were completely blocked by QX-314 and capsaicin [48]. Similar effect on mechanical allodynia, but not heat hyperalgesia, was observed for local co-injection of QX-314 and an agonist of TRPA1 [44]. This suggest that the TRPV1+ nociceptors mediate the heat and mechanical modalities, whereas TRPA1+ nociceptors contribute only to the mechanical modality during inflammation. This is supported by similar phenotypes which are exhibited by TRPV1 and TRPA1 knockout mice [14,49,50]. In contrast to inflammatory pain states, in which TRPV1 and TRPA1 expression levels are significantly increased in neurons, their expression levels decrease in response to peripheral nerve injury [17].

Interestingly, co-injection of QX-314 and capsaicin in a model of neuropathic pain only abolished the response to a noxious mechanical pressure with a pinch forceps, with only a mild effect on the mechanical allodynia induced by von Frey filaments [48]. This reinforces the concept that mechanical allodynia in neuropathic pain conditions can be processed by different neurons than the TRPV1-expressing C-fiber neurons.

Mechanical allodynia results from maladaptive plasticity in mechanoreceptors. Nerve injury causes neurons that normally convey light touch to be engaged by spinal pain circuits, turning light touch to pain, which clinically manifests as hyperalgesia. Recently, we have identified a unique distribution pattern of TLR5 in DRG neurons [46]. Immunohistochemical and electrophysiological experiments showed selective expression of TLR5 in mechanoreceptors. Furthermore, we demonstrated that activation of TLR5 via flagellin, a specific agonist of TLR5, led to selective QX-314 entry into TLR5-expressing DRG neurons and subsequent functional blockade of Aβ-fibers. In contrast to the co-administration of QX-314 with capsaicin, QX-314 with flagellin significantly reversed chemotherapy- and nerve injury–evoked mechanical allodynia as well as chemotherapy-induced ongoing pain [46]. The mechanism that allow TLR5/flagellin to deliver QX-314 into neurons remains to be elucidated but again shows the promise of targeted pharmacotherapy to DRG.

4. Targeting DRG neurons by gene therapy

Gene therapy delivered by a modified virus is emerging as a novel therapy for chronic pain. Gene therapy enables the stable knockdown or knock-in of genes for a sustained time, leveraging the natural homing and trafficking mechanism of a particular virus to target therapeutics to specific DRG neurons.

Vectors derived from the human parvovirus adeno-associated virus (AAV) have been successfully tested to target DRG neurons and alleviate chronic pain. AVV vectors offer numerous advantages including long-lasting gene expression, broad cellular tropism, and limited immune responses[51]. AAV vectors have various serotypes with distinct tropisms for distinct cell types. In particular, the serotypes AAV5, AAV6, and AAV8 have been used to deliver various gene to DRG neurons in various animal model of chronic pain. For instance, intraganglionic injection of AAV5 carrying a gene for short hairpin RNA (shRNA)targeting the $Na_v1.3$ channel resulted in alleviation of neuropathic pain in rats after spared nerve injury[52]. Similar injections of AVV8 carrying the recombinant gene for the serine protease inhibitor 3 also resulted in reduction of neuropathic pain after a similar nerve injury in mice [53].

Importantly, there is evidence for species and delivery route differences in the tropisms of different DRG neuron subpopulations by AAV serotypes. Notably, in mice AAV8 transfects indistinctly all DRG neurons[53], whereas in rats AAV8 preferentially targets large diameter DRG neurons (i.e. mechanoreceptors) [54]. In contrast, AAV6 carrying the green fluorescent protein (GFP) preferentially targets small diameter DRG neurons (i.e. nociceptors) [55]. However, sciatic nerve injections of the virus resulted in GFP expression in peptidergic nociceptors, whereas GFP expression was observed in non-peptidergic nociceptors when the

same virus was injected intrathecally. Although AAV vectors are very promising, they also display major drawbacks. AAV have minimal packaging capacity meaning that they cannot deliver very large genetic constructs and their broad tropisms can lead to the transfection of multiple undesired tissues and cells. Lumbar intrathecal injection of AAV6 resulted not only in transfection of lumbar DRG neurons, but also cervical DRG neurons [55]. Similar observations were reported after intrathecal injection of AVV8 in dogs, with an additional spread of the virus to the spinal cord, the liver, and the spleen[56].

In contrast to AAV, the viral vector HSV-1 from the herpes simplex virus offers the advantage of a large packaging capacity and the natural ability to target sensory neurons in discrete dermatomes[57]. HVS-1 has been used to alleviate pain behaviors in animal models of chronic pain by carrying different genes, such as the anti-inflammatory cytokine IL-4 or shRNA targeting $Na_v1.7$ channel [58,59]. Most importantly, the HSV-1 viral vector carrying the gene for the endogenous opioid polypeptide hormone proenkephalin reverses pain in animal models of both inflammatory and neuropathic pain, and a recent clinical trials has demonstrated its safety and effectiveness to treat cancer pain [60].

Lentiviral vectors also offer an interesting alternative to AVV and HSV-1 vectors for gene therapy applications due to their intrinsic ability to integrate into the host genome, allowing for stable and long-term expression (up to or greater than 6 months) in neurons[61]. We have recently used lentiviral vectors to knockdown and knock-in genes in DRG and spinal cord tissues. Subcutaneous administration of lentiviral vector encoding for a miRNA-30-based shRNA permanently knockdown the expression of the NMDA receptor subunit NR1 in DRG neurons and decreased inflammatory pain[62], whereas a single intraspinal injection of lentiviral vector encoding for the β-arrestin-2 gene has been shown to reverse spinal nerve injury-induced mechanical allodynia for 3 months [63].

However, a major challenge for the clinical translation of gene therapy is to anticipate the long-term effects of a potentially perennial change in gene expression. The use of small interfering RNA (siRNA) strategies has been reported to temporarily target gene expression in DRG neurons and alleviate chronic pain [64]. However, a major limitation of these siRNA strategies is the poor permeability of cell membranes to negatively charged nucleic acids. To circumvent this issues, researchers have used various mediators including polymers, lipids, and peptides to assist the delivery of siRNA into cells [65]. For instance, we have used intrathecal injections of the siRNA targeting the matrix metalloproteinase 9 (MMP9) complexed with the cationic polymer polyethyleneimine (PEI) to target MMP9 expression in DRG neurons and attenuate neuropathic pain [66]. Interestingly, Tan and colleagues were able to use subcutaneous injections of siRNA or shRNA vectors paired to PEI to silence the NMDA receptor subunit NR1 in DRG neurons and alleviate inflammatory pain[67,68].

However, PEI delivers siRNA or shRNA indistinctively to various cell types. Recently, new cell-penetrating peptides (CCPs) derived from viral capsid proteins have emerged for the efficient and specific delivery of siRNA into DRG neurons [69,70]. In particular, we have leveraged the property of the RVG peptide derived from rabies virus glycoprotein, which can transfect neuronal cells expressing the acetylcholine receptor [70], to deliver siRNA to DRG neurons and reduce pain in mice [71]. Specifically, peri-sciatic injection of the RVG-R9

peptide (i.e. RVG peptide fused to nine D-arginine residues to facilitate siRNA loading) combined with siRNA targeting caspase 6 greatly reduced formalin-evoked pain by retrograde transport of siRNA to the DRG neuronal somata and silencing of caspase 6 mRNA. Given that the TAT peptide derived from the human immunodeficiency virus can also target DRG neurons and the increasing availability of novel virus-derived peptides, we propose the strategy of combining CCPs and siRNA as an alternative and interesting option to virally mediated gene therapy. Indeed, a clinical trial of a siRNA targeting TRPV1 has recently reported positive Phase II results with siRNA SYL1001 in treating ocular pain (ClinicalTrials.gov Identifier: NCT02455999).

5. Targeting DRG neurons by stem cells

Engrafting of embryonic stem cells into the nervous system is also a very promising approach to control neurological diseases, including chronic pain [72]. However, potential limitations in the availability and immune rejection of these stem cells are a major therapeutic hurdle. It is also a health risk that pluripotent embryonic stem cells may turn into cancer cells. Bone marrow stromal cells (BMSCs) are progenitor cells present in the bone marrow of adults and have emerged as a major source for cell-based therapies [73]. BMSCs are readily accessible, easy to isolate and expand *ex vivo*, and their autologous or heterologous transplantation does not require immune suppressants [74]. Systemic and local injection of BMSCs has been shown to suppress inflammatory and neuropathic pain [75-80].

Recently, we have used intrathecal injection of BMSCs to reveal their actions and analgesic effect in nerve-injury induced neuropathic pain [81]. A major finding of our study is the demonstration of selective recruitment of BMSCs to DRG tissues with injured neurons via the CXCL12/CXCR4 axis, leading to long-term survival in these tissues and persistent analgesic effect. CXCL12 (or stromal cell-derived factor 1, SDF-1) belongs to the C-X-C subfamily of chemokine and exerts its function by binding to CXCR4. The migration of the BMSCs was triggered by their expression of CXCR4 and the upregulation of CXCL12 in the injured DRGs [81]. Interestingly, CXCL12 is upregulated in DRG in various chronic pain conditions such as following toxin-induced neuronal damage, opioid exposure, or different nerve injuries [81-84]. Most of the injected BMSCs were detected at the periphery of the injured DRG tissues and are almost completely gone by 84 days. Thus the potential health risk for BMSCs (e.g., conversion into tumor cells) should be very low. In contrast to a general substitutional role observed in many stem cell therapies, BMSC contribution seems mainly immunomodulatory [85]. We found that the observed analgesic effect is mediated and sustained via the local release of the anti-inflammatory growth factor TGF-β1 from BMSCs. Indeed, BMSCs and TGF-β1 both can highly inhibit nerve injury-induced infiltration of macrophages in DRG and spinal neuroinflammation. To note, intrathecal wide-spread delivery of TGF-β1 or small molecule mimics may cause side effects such as diabetes, suggesting that local delivery using a self-homing cellular vector may be more efficacious [86].

Besides the targeted delivery of TGF-β1, BMSC availability, low immunogenicity, and ability to home in on injured DRG tissues make them an ideal delivery vector for a variety of analgesic and anti-inflammatory mediators in chronic pain conditions. Although challenges

remain for translating a BMSC approach to clinical therapies, we anticipate that the existence of human BMSC lines and the engineering of these cells may lead to local disease modifying approaches in contrast to the current systemic pharmacological therapies that are directed at symptom management. Future advances may focus on enhancing the CXCL12/CXCR4 homing signaling to the injured DRG or on increasing production of TGF-β1 for a more robust analgesia.

6. Expert opinion

New therapeutic approaches for chronic pain are certainly needed because most of the current analgesic drugs lack satisfactory efficacy and produce undesirable side effects. Yet the failure for emergence of new pain drugs has discouraged the pharmaceutical industry and led to an overreliance on opioids with devastating individual and societal consequences such as abuse, tolerance, and dependence. Despite there are major differences between various forms of chronic pain, they all lead to shared pathological changes in DRG neurons. Defining these changes, when and how they occur, and what cellular and molecular mechanisms are responsible, will provide an exceptional opportunity for progression towards safer therapeutic approaches. In this review, we have attempted to provide an overview of the current clinical delivery approaches and proposed several new and innovative approaches with unique advantages and disadvantages (Table 2) to specifically deliver therapeutic molecules to DRG neurons for the treatment of chronic pain.

Systemic oral delivery is the route of choice for current human therapies in the ambulatory setting, but current therapeutics are accompanied by significant risks of non-therapeutic or deleterious effects. These side effects can be reduced by targeting receptors and channels that are enriched in DRG nociceptive neurons (e.g., TRPV1, TRPA1, and sodium channels) and by using molecules that do not cross the blood-brain barrier, such as monoclonal antibodies. Over the past years, the market for therapeutic antibodies has grown exponentially for cancer and inflammatory diseases. Several clinical trials are ongoing for antibodies for chronic pain treatment such as AMG334 for migraine treatment (ClinicalTrials.gov Identifier: NCT02174861), where a monoclonal antibody is directed to neutralize the calcitonin gene-related peptide released by the trigeminal ganglion's DRG neurons. Several local targeted interventions are also currently in use clinically. Peripheral application of resiniferatoxin, a potent agonist of TRPV1, which at high concentration is capable of ablating TRPV1+ neuronal fibers, has been used clinically to treat chronic pain, albeit with some concerns related to loss of heat sensitivity. Temporary blockade of neuronal fibers, leveraging specific receptors or channels on DRG neurons to deliver the conduction blocker QX314, may offer better therapeutic options, but concerns were raised recently about the toxicity of QX-314, similar to that of lidocaine or other local anesthetics, which warrants future investigations. Future investigations are also needed for a better understand of the cellular and molecular mechanisms of the electrical stimulation around the DRG, as this intervention carries far more surgical risk than a simple injection. However, DRG stimulation dose show promising results for chronic neuropathic pain patients.

In the last few years, there has been an increased number of clinical trials based on gene therapy and stem cell therapy. In a recently completed clinical study, patients suffering

diabetic neuropathy experienced a significant reduction in pain after taking VM202, a gene therapy in the form of a plasmid containing the neuroprotective hepatocyte growth factor [87]. The remarkable ability of HSV-1 and AAV gene therapy to target DRG, combined with recent clinical trials showing therapeutic successes and an acceptable safety record for these viral vectors, could accelerate the development of gene therapy as a new chronic pain therapeutics. Clinicians are also turning more and more to autologous mesenchymal stem cell therapy for chronic musculoskeletal pain. However, their regenerative, repair, and analgesic effects are still inconclusive with a great deal of conflicting clinical data and controversy on efficacy. An improved understanding of the mechanisms by which stem cells act as analgesics should provide a better framework for future stem cell therapeutic approaches in chronic pain. We have shown that bone marrow-derived stem cells are precisely carried at the damaged DRG via the CXCL12/CXCR4 homing signaling and release the anti-inflammatory and analgesic cytokine TGFβ1 in various chronic pain conditions. The identification of BMSCs mechanism of action, combined with the numerous advantages including minimally invasive harvesting, high cell viability rates, immune-privileged status, and the secretion of multiple trophic factors make bone marrow-derived stem cells a possible front-runner for clinical translation.

Therapeutic interventions targeting DRG must, however, take into account the different neuronal changes occurring in various forms of chronic pain and their temporal evolution during the progression of the disease. Furthermore, we need also to consider and determine the extent to which the immune and glial cells surrounding DRG neurons are linked to neuronal activity and influenced by the aforementioned therapeutic approaches. However, DRG neurons are active participants in chronic pain and we hope that the information provided in this review not only highlights current clinical practice, but will also assist in the development and translation of new therapeutic approaches.

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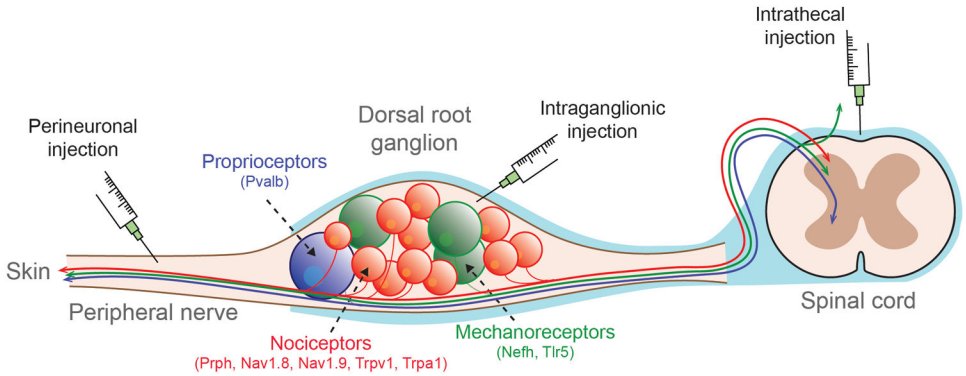

Figure 1.

Morphological, electrophysiological, and molecular studies have supported the specificity theory that different populations of DRG neurons are responsible for distinct sensory modalities. Noxious stimuli, including mechanical, chemical, and thermal noxious stimuli, are sensed by nociceptors, characterized by the expression of the neurofilament peripherin (Prph), voltage-gated sodium channels Nav1.8 and Nav1.9, as well as transient receptor potential cation channels Trpv1 and Trpa1. Low threshold mechanical stimuli such as light touch activate mechanoreceptors that specifically expressed neurofilament high (Nfh) and toll-like receptor 5 (Tlr5). Another type of DRG neuron is the proprioceptor that senses movement or vibration and it is generally characterized by the expression of parvalbumin (Pvalb).Information from DRG neuron subtypes arrives into different regions of the spinal cord and then is transmitted to the brain where the different stimuli are ultimately decoded. In chronic pain conditions DRG neurons undergo major cellular and molecular changes, which can be therapeutically targeted by using local drug delivery such as by peripheral nerve, intraganglionic, or intrathecal injections.

Table 1
Major chronic pain mechanisms occurring in DRG neurons

Mechanisms	Brief description
Peripheral sensitization	Peripheral sensitization represents a reduction in the threshold and/or an increase in the magnitude of responsiveness at the peripheral endings of sensory nerve fibers and at their cell bodies in DRGs. This occurs in response to the inflammatory mediators released at the site of tissue injury.
Ectopic neuronal activity	Spontaneous or abnormal propagation of ion flows through transmembrane channels that stimulate transmembrane electrical currents in axons after tissue and nerve injury.
Gene regulation	Dramatic transcriptional changes occur in DRG neurons contributing to the onset and maintenance of chronic pain after tissue and nerve injury.
Presynaptic modulation	Increased neurotransmitter release from nociceptors after nerve injury contributes to synaptic plasticity via presynaptic regulation.
Switch of sensory modality (phenotypic switch)	Sensory neurons acquire new modalities after injury. For example, mechanoreceptors start to transmit nociceptive information (i.e. mechanical allodynia) after nerve injury.

Table 2

Advantages and disadvantages of various therapeutic approaches to target DRG neurons

Approach	Advantages	Disadvantages
Systemic administration	Ease of the technique Widespread actions	Prone to side effects Temporary effects
Local injections	Precise tissue delivery Achieve high local concentrations	Limited to few tissues Can be difficult to perform Temporary
Dorsal root ganglia stimulation	Precise tissue delivery On demand and long-lasting therapy	Limited to few tissues Surgically implanted Unclear mechanism of action
Nerve blockade	Precise delivery to a subpopulation of DRG neurons Local actions	Potential toxicity of QX-314 Temporary
siRNA therapy	Target specifically DRG neurons Selective knockdown of virtually any gene	Transfection efficiency Temporary
Viral therapy	Target specific DRG neurons Long-lasting therapy Can be manipulated for knockdown, knockout, and knockin function	Immunoreactivity Potentially irreversible
Stem cell therapy	Precise migration to damaged DRG tissue Long-lasting pain relief Can be manipulated using recombination Can be cultured from patients	Dependency on CCL12-CCR4 signaling Limited availability of cells Risk of teratoma