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Review

Gene therapy for the treatment of chronic peripheral nervous system pain

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ABSTRACT

Chronic pain is a major health concern affecting 80 million Americans at some time in their lives with significant associated morbidity and effects on individual quality of life. Chronic pain can result from a variety of inflammatory and nerve damaging events that include cancer, infectious diseases, autoimmune-related syndromes and surgery. Current pharmacotherapies have not provided an effective long-term solution as they are limited by drug tolerance and potential abuse. These concerns have led to the development and testing of gene therapy approaches to treat chronic pain. The potential efficacy of gene therapy for pain has been reported in numerous pre-clinical studies that demonstrate pain control at the level of the spinal cord. This promise has been recently supported by a Phase-I human trial in which a replication-defective herpes simplex virus (HSV) vector was used to deliver the human pre-proenkephalin (hPPE) gene, encoding the natural opioid peptides met- and leu-enkephalin (ENK), to cancer patients with intractable pain resulting from bone metastases (Fink et al., 2011). The study showed that the therapy was well tolerated and that patients receiving the higher doses of therapeutic vector experienced a substantial reduction in their overall pain scores for up to a month post vector injection. These exciting early clinical results await further patient testing to demonstrate treatment efficacy and will likely pave the way for other gene therapies to treat chronic pain.

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Introduction

Pain is one of the most prevalent disease complications and is now included as the fifth vital sign by most hospitals. It is estimated that 60–80 million patients within the US suffer from some form of chronic pain. As defined by the International Association for the Study of Pain, chronic pain is a severe and ever-present pain that persists for at least 3 months post initial injury or tissue damage. Chronic pain is often debilitating, leading to substantial loss of productivity and impaired quality of life. In 2005, chronic back and neck pain affected 22 million patients creating an estimated $86 billion in health care expenditures (Martin et al., 2009). Arthritis, another common cause of chronic pain, is predicted to affect 25% of the adult population by the year 2030, with 25 million experiencing activity limitations resulting from chronic pain (Hootman and Helmick, 2006). The societal burden from chronic pain patients will continue to increase as the population ages.

Nature of the chronic pain state

Chronic pain can result from inflammation and nerve damage. Nociceptive pain of an inflammatory nature is associated with a typical immune response to tissue injury or infection whereas neuropathic pain results from damage to neural structures, often in the absence of accompanying injury to non-neural tissues. Nociceptive pain is quite common and results from a variety of disease states in which short-term or long-term inflammation leads to prolonged changes in nociception. The most common incidence occurs in patients with rheumatoid or osteoarthritis, pancreatitis, or inflammatory bowel disease. Other associated conditions include interstitial cystitis (IC) or chronic pelvic pain syndrome of the bladder. Common immune mediators, such as the inflammatory cytokines interleukin-1 (IL-1), IL-6 and tumor necrosis factor-alpha (TNFα), contribute to a localized inflammatory response in the afflicted tissue or organ. They act to induce the mobilization of immune cells that amplifies their production and results in prolonged painful responses (Moalem and Tracey, 2006). The same pro-inflammatory cytokines are also secreted by glia within the spinal cord and astrocytes in response to peripheral organ and tissue inflammation, which impacts the nociceptive processes in the spinal cord (Moalem and Tracey, 2006; Sloane et al., 2009). Animal models of acute and chronic nociceptive pain have been created by injection of (i) immunogenic substances, including complete Freund's adjuvant (CFA), carrageenan and LPS, (ii) chemicals such as formalin, capsaicin, or dibutyltin dichloride, or (iii) acids like monoiodoacetate to create a model of monoarthritis or acetic acid to induce lower urinary tract pain in rats.

Neuropathic or neurogenic pain is defined as pain initiated or caused by a primary lesion or dysfunction of the nervous system. This can be the result of (i) spinal cord injury (SCI), (ii) peripheral nerve damage resulting from diabetes or other autoimmune diseases, (iii) treatment with anti-cancer drugs that affect axon integrity, or (iv) post-herpetic neuralgia (PHN). A variety of animal models mimic neuropathic pain: (i) surgical models of nerve damage, including chronic constriction injury (CCI) and spared nerve injury (SNI), (ii) streptozotocin-induced painful diabetic neuropathy and transgenic diabetic pain models, (iii) treatment with anti-cancer drugs and models of bone cancer pain established by introduction of sarcoma cells into the femur (Goss et al., 2002; Lan et al., 2010), and (iv) PHN induced by footpad injection of HSV (Kuraishi et al., 2004; Takasaki et al., 2001) or VZV (Garry et al., 2005; Hasnie et al., 2007).

The first event in pain signaling in response to inflammatory and/or mechanical damage to peripheral tissues/organs is an increase in the extracellular levels of mediators such as bradykinin, substance P (SP), ATP, hydrogen ions, histamine, prostaglandins and inflammatory cytokines such as TNFα and IL-1. It is likely that besides the peripheral signals which can induce the chronic pain response, central signals may also lead to the establishment of chronic pain, both centrally and also can manifest itself as peripheral chronic pain. The inflammatory cytokines and prostaglandins are secreted by inflammatory cells, such as resident mast cells and macrophages recruited to the initial insult *via* mast cell-released cytokines, or Schwann cells and microglia that are local to the site of nerve damage (Moalem and Tracey, 2006). Release of these molecules by the damaged tissue results in 'peripheral sensitization,' i.e. stimulation of primary afferents *via* specific receptors or ion channels sensitive to heat, mechanical impulses, protons, or cold. These stimuli activate second messenger systems, including protein kinases A and C, which results in ectopic discharge due to increased sensitivity of endogenous voltage-gated sodium and calcium channels leading to hyperalgesia, a heightened response to painful stimuli, and allodynia, pain in response to normally non-painful stimuli (Julius and Basbaum, 2001; Scholz and Woolf, 2002). In addition, the increased levels of intracellular calcium can lead to the release of neuropeptides such as SP, CGRP and neurokinin A from vesicles at the cell termini; extracellular accumulation of these factors increases their receptor occupancy in the damaged tissue, thereby amplifying the pain signal. These stimulated afferent nerve fibers carry impulses to second order neurons located within the dorsal horn of the spinal cord, the site where control and processing of the initial nociceptive signal takes place.

Pain usually occurs in two phases. The first is sharp in intensity, short in duration, very focal in nature, and is mediated by Aδ-afferents that display firing rates that correlate with the intensity of the painful stimulus. In contrast, the second phase is rather dull in intensity, displays a more prolonged duration, is not localized in nature, and is mediated by unmyelinated C-fiber afferents that display a progressive increase in their discharge rate toward second order neurons in the spinal cord (Woolf, 1996). These second-order neurons, projecting centrally to the thalamus, the dorsal reticular nucleus and periaqueductal gray, ultimately relay the signal to the cortex enabling pain perception. In addition, there are descending signaling pathways from the brain back down to the dorsal horn of the spinal cord where release of endogenous opioid peptides such as the enkephalins, ß-endorphin, dynorphins and endomorphin occurs as the body's natural pain management response (Basbaum and Fields, 1984). Chronic pain is a result of continuous or altered signaling within the activation loop. Additionally, proinflammatory agents such as prostaglandin E_2, serotonin, histamine and adenosine, and neurotrophic factors such as NGF, can induce functional changes in C-fiber afferents that can lead to hyperactivation or hyperexcitability of relatively unexcitable afferents (Gold et al., 1996). Although pain can manifest itself both centrally, such as headache, or peripherally, such as arthritis or lower back pain, this review will concentrate