Transplant-mediated repair of spinal cord GABAergic inhibitory circuitry to treat the “disease” of neuropathic pain

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Neuropathic pain arises from injury to the peripheral or central nervous system and is characterized by ongoing (often burning) pain and mechanical hypersensitivity (alldynia). Among the many mechanisms that have been implicated in the generation of neuropathic pain is an NMDA receptor-mediated central sensitization of spinal cord pain processing circuits. Other studies suggest that neuropathic pain is an epileptic-like condition resulting from reduced GABAergic inhibition. Consistent with this hypothesis is that anticonvulsants are among the most effective pharmacological approaches to treat neuropathic pain. An alternative approach to reducing the ongoing pain and mechanical allodynia is to re-establish the inhibitory tone lost in the setting of nerve injury. We have now demonstrated that it is possible to restore inhibitory tone by transplanting GABAergic precursor neurons derived from the embryonic cortex into the spinal cord of nerve-injured mice. These precursor neurons develop in the spinal cord, differentiate into GABAergic interneurons and integrate into the host circuitry. Most importantly, peripheral nerve injury-induced mechanical hypersensitivity can be completely normalized, within weeks of the transplantation. More recently, we reported that chronic neuropathic itch, a condition that in humans is extremely difficult to manage is also responsive to the transplantation approach. With a view to translating these preclinical findings to patients, we have now initiated studies using human pluripotent stem cells modified to assume the properties of GABAergic neurons. Preliminary studies indicate that these cells have the capacity to integrate and influence host circuits. Taken together these studies suggest that a therapy targeted at treating the “disease” of neuropathic pain, namely the pathophysiological alterations in CNS function that are characteristic of this condition, is a viable and novel approach to the management of neuropathic pain.