Deriving Dorsal Spinal Sensory Interneurons from Human Pluripotent Stem Cells.

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Authors: Sandeep Gupta, Daniel Sivalingam, Samantha Hain, Christian Makkar, Enrique Sosa, Amander Clark, Samantha J Butler

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Public Summary:
In work that has been ongoing for two decades, scientists have been using growth factors to direct pluripotent stem cells, the undifferentiated cells that can become any cell type, into neurons. Many studies, increasingly successfully, have defined the conditions necessary to make stem cell-derived spinal motor neurons. These cells, in turn, have permitted major breakthroughs in our understanding of the degenerative diseases that affect motor neurons, such as amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy, and have raised the possibility that patients with spinal cord injuries may be able to recover the ability to walk. In contrast, very little progress has been made in defining the conditions that can direct stem cells to become spinal sensory relay neurons, which would allow patients to recover their ability to feel. There are multiple categories of sensory relay neurons present in the spinal cord, which encode touch, nociception (pain) and proprioception (our unconscious knowledge of the position of our bodies in space). Our work assessing the role of BMPs directing the identity of sensory relay neurons during embryonic development had suggested that one BMP - BMP4 - was particularly potent, able to make large numbers of two categories of sensory relay neurons: the proprioceptors, and one class of touch neuron. We thus assessed whether BMP4, in combination with retinoic acid, was able to direct human embryonic stem cells into sensory relay neurons. We found that it was, moreover we were able to define the key window of opportunity when neural progenitors have the greatest capacity to generate these two key classes of sensory relay neurons. We were further demonstrated that this protocol generated the identical mixture of sensory neurons when BMP4 and retinoic acid were added to induced pluripotent stem cells. These special stem cells are produced by reprogramming a patient's own mature cells, such as their skin cells, thereby maintaining the patient's genetic code. The ability to create sensory neurons with a patient's own reprogrammed cells holds the most potential for creating a cell-based treatment that restores the sense of touch without immune suppression.

Scientific Abstract:
Cellular replacement therapies for neurological conditions use human embryonic stem cell (hESC)- or induced pluripotent stem cell (hiPSC)-derived neurons to replace damaged or diseased populations of neurons. For the spinal cord, significant progress has been made generating the in-vitro-derived motor neurons required to restore coordinated movement. However, there is as yet no protocol to generate in-vitro-derived sensory interneurons (INs), which permit perception of the environment. Here, we report on the development of a directed differentiation protocol to derive sensory INs for both hESCs and hiPSCs. Two developmentally relevant factors, retinoic acid in combination with bone morphogenetic protein 4, can be used to generate three classes of sensory INs: the proprioceptive dI1s, the dI2s, and mechanosensory dI3s. Critical to this protocol is the competence state of the neural progenitors, which changes over time. This protocol will facilitate developing cellular replacement therapies to reestablish sensory connections in injured patients.