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Generation of self-organized central nervous system-like tissue resembling normal spinal cord following intrathecal transplantation of embryonic stem cells

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Embryonic stem cells (ESCs) have been emerging as a promising therapeutic approach to repair damaged organs. In the normal embryo, ESCs have the unique ability to self-organize into spatially appropriate arrangements of cells, but this capacity has not been demonstrated outside of embryonic development. In this study, ESCs transplanted into the intrathecal space of normal adult rat spinal cord self-organized into central nervous system (CNS)- like tissue whose gross and ultrastructural anatomy resembled that of the developing spinal cord. By 3-4.5 months after transplantation, grafts contained primarily the three principle neural cell types: astrocytes, oligodendrocytes, and neurons. ESC-derived astrocytes had created a glial limitans similar to the layer covering the normal cord; ESC-derived oligodendrocytes had produced mature patterns of myelination; and the ESC neurons exhibited features of cholinergic motor neurons in clusters mimicking the ventral horn. Many axons within the ESC graft were wrapped by myelin and there were numerous bouton-like nerve endings, some of which were shown to express specific molecular markers such as vGlut1, 5-HT or tyrosine hydroxylase (TH). Neuronal tract tracing revealed that the ESC-derived graft had connections with the host. The graft also showed vascular formation with features of CNS blood brain barrier structures. Cell ablation studies also highlighted the importance of Flk-1-positive ESCs for development of neural tissue. This study furthers our understanding of self-organization and organogenesis, which are essential to the development of effective therapeutic strategies for organ repair, particularly for complex organs such as the CNS.

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