東北大学脳科学GCOEセミナーのお知らせ

日時　2011 年 2 月 28 日（木）16:00～17:30

会場　星陵キャンパス・5 号館 2 階　201 号室

演者　Prof. Donald Newgreen, Ph.D.

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演題　Towards a stem/progenitor cell therapy for Hirschsprung's Disease: Neural progenitor cell transplantation into post-natal colon

Hirschsprung's disease is a potentially fatal birth defect in which the neural crest-derived enteric nervous system (ENS) is absent from the distal bowel, causing intractable constipation. Infants with Hirschsprung's disease require surgery to remove the affected region of bowel, but distressing motility problems often persist. Stem cell therapy has been suggested to augment or replace the missing ENS tissue in such patients. Previous studies in animal models have shown that neural stem/progenitor cells can colonize segments of embryonic gut in vitro and can differentiate in the gut wall into neurons and glial cells. However, to be therapeutically useful in human patients, this would have to be achieved in post-natal bowel. At present, it is unknown whether stem/progenitor cells can colonize and give rise to appropriate types of cells in vivo in the older stage bowel. Here, neurospheres were generated by dissociating gut from late embryonic and early post-natal transgenic mice in which ENS cells express fluorescent proteins. Neurospheres of ENS cells isolated by FACS sorting were transplanted into the distal colon of post-natal (P14-P21) wild-type mice. After 1-12 weeks, the recipient mice were killed and the colon examined. The neurosphere-derived cells migrated extensively and formed ganglion-like aggregates within the wall of the colon. Grafted cells showed markers of neural (Hu and PGP9.5) and glial differentiation (S100b). Moreover, some neurons had the characteristic morphology of Dogiel type I ENS neurons and expressed characteristic ENS neurotransmitter markers, nitric oxide synthase, choline acetyl transferase and vesicular acetylcholine transporter. The neurosphere-derived neurons projected axons, with synaptic markers, into the myenteric ganglia and circular muscle layer of the recipient. Electrophysiological recording from graft-derived neurons indicated that they could generate action potentials, and that they received cholinergic nerve synaptic input. Very recent results demonstrate two further points: neurospheres from post-natal mouse ENS show similar capacities to embryo-derived neurospheres, and similar graft cell spreading and differentiation occurred in post-natal aganglionic colon from EdnrB-/- (Hirschsprung model) mice. Together, these data from mouse models are very encouraging for potential human therapy, since they show that ENS stem/progenitor cells can migrate and undergo neuronal and glial differentiation in the post-natal bowel in vivo, and also achieve a considerable degree of nerve functionality.

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