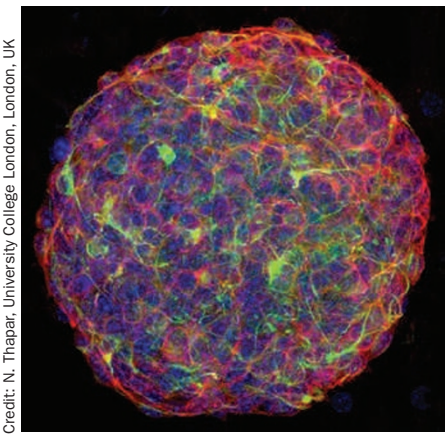
MOTILITY

Stem cells—therapy for gut neuromuscular disease?

Stem cells of the enteric nervous system can be isolated from endoscopic gut mucosal biopsy samples, and may have potential as a treatment for neuromuscular disorders of the gut, claim UK researchers. The isolated stem cells proliferated, were able to differentiate into cells of neuronal and glial lineages, and could integrate into recipient aganglionic gut tissue after transplantation. "The findings will form the backbone of further work to develop definitive therapies for enteric neural disorders", explains Nikhil Thapar, lead investigator of the study.

Therapeutic options for patients with gut disorders that result from absent or defective enteric neuromusculature are limited. Hirschsprung disease—characterized by functional intestinal obstruction—is the most common recognizable developmental disorder of the enteric nervous system, and is caused by an absence of enteric ganglia in part of the distal bowel. Current treatment for Hirschsprung disease involves surgical resection of the aganglionic bowel segment, but morbidity for patients with this disease remains high and new treatment options are warranted.

Stem cells that can integrate into the diseased gut and have the capacity to generate ganglia of the enteric nervous system could potentially cure neuromuscular disorders of the gut, such as Hirschsprung disease. Previous studies demonstrated the presence of cells with stem-cell characteristics in the postnatal human gut. These cells could self-renew, proliferate, and differentiate into components of a functional enteric nervous system, which suggested they might be able to replace absent or damaged enteric nervous system cells and 'functionally rescue' patients with gut neuromuscular disorders. The therapeutic potential of these cells was limited, however, because



Credit: N. Thapar, University College London, London, UK

they were sourced from full-thickness gut specimens obtained by surgical resection. "Not only did this represent a limited source [of cells], but the source also had limited implications for autologous cell transplantation", explains Thapar.

Thapar and colleagues' new study overcomes these limitations; they identified and isolated enteric stem cells from gut biopsy tissue specimens obtained by conventional endoscopic procedures. Gut mucosal biopsy specimens were obtained from patients aged 9 months to 17.3 years old who were undergoing endoscopic investigation for gastrointestinal disorders. Immunohistochemical staining of biopsy specimens revealed the presence of stem cells of the enteric nervous system. Dissociated cells from the biopsy tissue were cultured as neurosphere-like bodies, in conditions that promote survival and propagation of neural-crest-derived progenitor cells. Immunohistochemistry and biological assays confirmed the presence of stem cells of the enteric nervous system in the cultures. The characteristics of stem-cell-containing neurospheres generated from gut mucosa were similar to those obtained from full-thickness gut specimens.

"Not only was it possible to identify putative enteric nervous system stem cells within gut mucosa, but such cells could also be generated within cell cultures established from dissociated gut mucosal samples from all postnatal ages examined", summarizes Thapar. Transplantation of the cells into cultured aganglionic chick hindgut explants showed that the propagated enteric nervous system stem cells colonized the recipient tissue. The stem cells were also grafted onto cultured human hindgut explants from patients with Hirschsprung disease. Within a few days the transplanted cells had extended neuronal processes away from the neurosphere-like body.

The researchers say these findings demonstrate the ability of grafted stem cells to colonize and integrate with host tissue to generate a 'neoenteric' nervous system. Thapar believes their findings may herald the development of new curative therapies for patients with gut neuromuscular disorders, such as Hirschsprung disease, because "…conventional endoscopy provides a more practical and repeatedly accessible source of tissue [than tissue from surgical resections] that is also capable of regeneration". These researchers aim to test these enteric stem cells further in established models of human disease to assess their safety profile and to characterize the functional rescue of aganglionic tissue. Such studies, Thapar says, will be used to develop future pilot studies in human patients and will expedite the development of stem cell therapies for enteric neuromuscular diseases.

Susan J. Allison

Original article Metzger, M. *et al.* Enteric nervous system stem cells derived from human gut mucosa for the treatment of aganglionic gut disorders. *Gastroenterology* **136**, 2214–2225 (2009).