Stem cells make the bowel nervous

In Hirschsprung disease, the enteric nervous system (ENS) is missing from the distal bowel. It emerges that postnatal transplantation of stem-cell–derived ENS precursors can prevent death in a mouse model of the disease.

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The enteric nervous system (ENS) is a network of neurons and supporting glial cells in the bowel wall that is essential for digestion. When ENS precursor cells fail to migrate through the full length of the bowel during the first trimester of pregnancy, a life-threatening birth defect called Hirschsprung disease ensues—a prominent symptom of which is constant contraction of the affected bowel regions. The standard treatment for children with Hirschsprung disease is removal of the abnormal bowel, but many children continue to have bowel problems after surgery. In a paper online in Nature, Fattahi et al. describe a method for generating ENS precursors from stem cells. Remarkably, transplantation of these cells into an animal model of Hirschsprung disease prevented premature death.

The ENS contains about as many neurons as the spinal cord, and its diversity of neuronal subtypes rivals that of the brain. This complexity allows the ENS to recognize sensory input from both the bowel wall and within the bowel, and to produce integrated bowel motility patterns that facilitate nutrient absorption. The ENS also influences bowel inflammatory cells, blood vessels, smooth muscle, intestinal pacemakers and the epithelial cells that line the bowel.

It is therefore not surprising that children with Hirschsprung disease develop abdominal distension, vomiting and constipation, fail to grow normally and can die from sepsis (a bacterial infection of the bloodstream). At least one-third of children with Hirschsprung disease continue to have serious problems after surgery, including a life-threatening syndrome called enterocolitis. Furthermore, some children with this disease have so little bowel that they require intravenous nutrient delivery to survive.

Exciting work suggests that regenerative medicine could one day offer an alternative to surgery for treating Hirschsprung disease. In this approach, stem cells would be transplanted into and would restore function in bowel regions in which the ENS is missing. Ideally, the transplanted cells would come from the affected child (known as autologous transplantation) to avoid immune rejection, and non-surgical methods would be used for cell delivery.

Figure 1 | Help for a model of Hirschsprung disease. Hirschsprung disease is a birth defect in which the enteric nervous system (ENS) fails to colonize the full length of the bowel during early pregnancy. To investigate possible therapies for the disease, Fattahi et al. grew human embryonic stem (ES) cells (which can give rise to every cell type of the body) in vitro under conditions that encouraged them to differentiate into cells resembling ENS precursors. The authors transplanted these cultured cells into the colons of mice with a genetic mutation that causes a Hirschsprung-like disease. The transplant prevented premature death in these mice, although how the cells achieved this feat is not clear.

Of particular interest for this type of therapy are gut-derived ENS stem cells, which can be isolated from the human bowel at all ages and cultured in vitro. Following culture, these stem cells can be reimplanted in the bowel wall. They then migrate to the normal site of the ENS and differentiate into neurons and glial cells that mimic those of the native ENS. However, this therapeutic approach faces several challenges, including difficulty producing enough gut-derived cells, limited cell migration, limited data about long-term safety and minimal information about the ability of these cells to restore gut function.

Fattahi et al. address some of these problems using human embryonic stem (ES) cells, which are derived from early embryos and can give rise to every cell type in the body. To direct differentiation of human ES cells towards an ENS precursor lineage, the authors modulated signalling pathways that control development by inhibiting SMAD and glycogen synthase kinase proteins, and then treated the cells with the metabolite retinoic acid. Under these conditions, human ES cells differentiated into cells that resemble ENS precursors from the vagal region of the developing spinal cord (called the vagal neural crest). The authors refer to these cells as enteric neural-crest (ENC) precursors.

These ENC precursors shared several key features with ENS precursors. For instance, when transplanted into the vagal neural-crest regions of developing chick embryos, ENC precursors often migrated to the bowel, like normal ENS precursors. When transplanted to the colon of young mice, ENC precursors populated the bowel close to the location of the normal ENS, but migrated even more quickly than fetal ENS-derived cells. When grown alongside human ES-cell–derived smooth-muscle cells, ENC precursors enhanced muscle differentiation and became neurons that could induce muscle contraction when activated. Following an extended period of in vitro culture with vitamin C and the growth factor GDNF, ENC precursors produced diverse neuronal and glial cells similar to those of the ENS. Most impressively, when ENC precursors were transplanted into the colons of mice with Hirschsprung-like disease, survival rates improved dramatically over a short time interval (Fig. 1).

Finally, Fattahi et al. used ENC precursors harbouring a genetic mutation that predisposes humans to Hirschsprung disease to perform an in vitro drug screen, and discovered that inhibiting the protease enzyme BACE2 enhanced ENC-precursor migration. The gene that encodes BACE2 is located in a region of chromosome 21 whose duplication increases the risk of Hirschsprung disease. This finding may be relevant to Down syndrome, in...
which children are born with three copies of chromosome 21 and rates of Hirschsprung disease are increased by as much as 100-fold. This study establishes a potentially limitless source of cells similar to those of the vagal neural crest that could be tested for use in transplants to treat children with Hirschsprung disease or other disorders in which the ENS is defective. In an ideal therapy, ENC precursors would be produced from induced pluripotent stem cells, which closely resemble human ES cells, but can be derived from the skin or blood cells of affected children, removing the need for embryo-derived cells and post-transplant immunosuppression. Fattahi and colleagues provide preliminary data to suggest that this strategy will work well. Furthermore, the human ES-cell-derived ENC precursors they produced migrate efficiently through the bowel and could potentially be delivered through an endoscope, avoiding invasive surgery. Although these advances are exciting, many questions remain. In particular, it is unlikely that transplanted ENC precursors recreated a normal ENS in the Hirschsprung model mice, given the rapidity with which transplantation rescued lethal bowel disease. Instead, minimally organized ENC precursors might have modulated immune activity or enhanced epithelial-cell function and repair by releasing neurotransmitter molecules (or other factors). Identifying these ENC-precursor-derived factors might lead to the development of other treatment or prevention strategies that obviate the need for cell-based therapies. Similarly, BACE2 targets that influence ENC-precursor migration could be used to enhance stem-cell therapy or to prevent Hirschsprung disease.

Finally, the effect of transplanted ENC precursors on bowel motility and long-term safety needs to be addressed. Nonetheless, Fattahi and colleagues’ study moves us one step closer to a time when autologous stem-cell therapy could replace surgery as a primary treatment for children with Hirschsprung disease. ■

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