Congenital GI motility disorders: Clinical overview and stem cell therapy

Naoki Shimojima
Department of Surgery, Keio University School of Medicine

Hirschsprung disease (HD), also called aganglionosis, is a developmental disorder of distal intestine characterized by a constipation and an abdominal distension which usually seen shortly after birth. The nature of this disease is lacks of normal enteric nerves in the distal part of intestine. Enteric nerves, known as ganglion cells, are derived from the neural crest and the etiology of HD is thought to be a migration arrest of neural crest derived cells in a developmental period. This disease occurs in 1 in 5000 births. To date, the only treatment available is a surgery, which requires the removal of the aganglionic bowel.

Variant Hirschsprung disease (VHD) is a group of diseases which resembles HD in clinical symptoms in spite of the presence of ganglion cells in the whole intestines. VHD can be divided into two categories, a group with histologically intact ganglion cells and a group with histologically abnormal ganglion cells. In the former group, causes of disease can be abnormality of smooth muscles or interstitial cells of Cajal (ICC), but the exact etiologies are not well understood. The incidence of these diseases is much fewer than that of HD. In many cases clinicians face difficulties in treatment as entire intestines are affected and patients are dependent with total parenteral nutrition in VHD.

Motility patterns in HD and VHD are different from normal patterns. In normal small bowel, contractions propagate from oral to aboral smoothly, called “peristalsis”. In contrast, in HD or VHD, intestines can contract but each contraction is not well coordinated and luminal contents go back and forth. ICC distributions in HD and VHD are still controversial. Some previous reports described loss or decrease of ICC in HD or VHD. But according to our experiences, distributions of ICC are different among cases. It is difficult to evaluate how the alteration of ICC distribution affected to motility impairment in HD and VHD. But I believe ICC play a key role in normal intestine and abnormal intestine in HD and VHD as well.

To treat HD and VHD, surgical resections are required. In some severe cases, it may be difficult to wean from total parenteral nutrition. And the only remaining choice of treatment would be a small bowel transplantation (SBTx). As small bowel is easy to be rejected by immune system, long-term result of SBTx is not satisfying.

Recently, stem cell therapy has been spotlighted as a novel alternative therapy in this field. In our group, to regenerate enteric nerves and ICC transplantation of neural crest stem cells and mesenchymal stem cells has been examined. To date, migrations, engraftments, and differentiations of transplanted cells were confirmed in animal experiments. Our latest data and reports from other groups will be reviewed.