Disease of the Small Intestine

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Abstract: Recent information on the small intestine is summarized. Concerning digestion and absorption, α-glycosidase inhibitor, which slows the absorption of carbohydrate, has become commercially available as a diabetic drug, and a number of transporters, such as peptide transporter (PepT1) that is involved in the efficient absorption of nitrogen source as well as drug absorption, have been discovered. In addition, a group of growth factors that are involved in the formation and regeneration of the small intestine have been found, and the importance of intraepithelial lymphocytes and glutamine has become known. In addition, the possibility that cells derived from the bone marrow might behave as a part of the epithelium of the digestive tract has been reported and has gained interest. Concerning intestinal motility, progress has been made in the analysis of interstitial cells of Cajal and various neurotransmitters. C-kit-positive stromal tumors were thoroughly investigated. The concept of GIST has been established and imatinib therapy for GIST has already begun. Although there is room for improvement in enteroscopy, is useful in the diagnosis of small intestinal diseases. The advancement of technology including virtual endoscopy is expected. In the area of surgery, the spread of laparoscopic surgeries as a minimally invasive approach has been marked.

Key words: Peptide transporter; Stem cells; Gastrointestinal stromal tumor (GIST); Enteroscopy; CT

Introduction

The small intestine, which plays a role in the absorption of nutrients that are essential to maintain life, is an important immune organ that serves as a barrier against foreign antigens, and its functions are while intricately interrelated with the autonomic nerves and endocrine system. However, it is also an organ where a direct approach such as endoscopy is difficult. Recent information on the small intestine, has been summarized firstly in terms of basic research and secondly in terms of clinical research.
Basic Research

1. Digestion and absorption

Food is degraded into glucose, amino acids, and others by digestive enzymes, and it is finally absorbed into the body through the villous epithelium in the small intestine. Carbohydrate is hydrolyzed by α-glycosidase during membrane digestion. The α-glycosidase inhibitor, which slows the hydrolysis of carbohydrate, is presently used in the treatment of diabetes, because it prevents the blood glucose level from rapidly increasing.

In addition to simple diffusion, various substrate-specific transporters are also employed in the absorption process of each nutrient from the villous epithelium into the body efficiently. Thus far, a number of transporters such as sodium-glucose cotransporters (SGLT1), glucose transporters (GLUT2) that function by facilitated diffusion, transporters of various amino acids, and sodium-dependent bile acid transporters (BAT) have been reported, and their properties are being revealed at a molecular biological level. Concerning absorption of nitrogen sources, the functions and regulation of peptide transporters (PepT1), which can absorb nitrogen sources in the form of oligopeptides, have become clear. PepT1 is known to have unique characteristics, such as maintaining its functions even in various pathological conditions and being involved in the absorption of some antibiotics.

More recently, monocarboxylic acid transporter (MCT1) and non-sodium-dependent organic anion transporters (OATP) have been newly discovered, and it is expected that many more transporters will be revealed in the future. These transporters may be applied not only to absorption of nutrients but also to drug delivery.1)

2. Process of villus formation and regeneration of mucosa

As mentioned above, expression of nutrient transporters are mostly specific to the small intestine. It has become evident that various transcription factors such as Cdx2 are involved in the phenotypic expression specific to the small intestine. Small intestinal epithelium differentiates from stem cells that exist near the bottom of the intestinal crypt, and the entire villus is thus formed through the maturation process of these cells. However, the mechanism by which the small intestinal mucosa acquires properties specific to the small intestine, is not yet clearly understood. This is one of the major research themes today.

In addition to transcription factors, various growth factors such as epidermal growth factor (EGF) and insulin-like growth factor-1 (IGF-1) are involved in this process. Among such growth factors, glucagon-like peptide-2 (GLP-2) in particular has drawn attention because its strong action for mucosa proliferation action has been proven through experiments.2) Moreover, stimulation by foreign antigens that has entered from the mouth and the presence of intraepithelial lymphocytes are also factors that cannot be ignored in the formation of mucosa.

In fact, the number of intraepithelial lymphocyte count in the small intestinal mucosa decreases over a short period in patients who receive parenteral nutrition, followed by a decrease in secretory IgA and finally causing villous atrophy. This induces bacterial translocation and increases the patient’s susceptibility to serious infections. To prevent such villous atrophy and infections, administering glutamine and dietary fibers are effective.

With regard to differentiation and proliferation of mucosa, one recent report concerning the regeneration of the intestinal tract was particularly noteworthy. The report showed that bone-marrow-derived cells might serve as stem cells for gastrointestinal mucosa when gastrointestinal mucosa has been seriously damaged.3) Since intestinal disorders caused by radiotherapy and carcinostatics often make treatment difficult to continue, exploring...
methods that can be used not only to prevent mucosal disorders but also to rapidly repair and regenerate mucosa is a very important project from a clinical standpoint.

3. Gastrointestinal motility and autonomic nerves

The small intestine transports food by peristaltic movement, which is appropriately regulated according to hunger, the ingestion of food, and other conditions. While it is known that sympathetic nerves (noradrenergic) and parasympathetic nerves (cholinergic) serve as autonomic nerves associated with gastrointestinal motility, the mechanisms of intestinal motility are also becoming more clearly understood. In particular, a nervous system that is operated by nonadrenergic and noncholinergic transmitters has been found in the intestinal wall.

Specifically, there is a nervous system that is sensitive to various substances including vasoactive intestinal poly-peptide (VIP), nitric oxide (NO), 5-hydroxytryptamine (5-HT), and calcitonin gene-related peptide (CGRP), and each of these substances is closely involved in regulating gastrointestinal motility and secretion. The actions of 5-HT (serotonin) for secretion have drawn attention thus far, and it is thought that changes in the sensitivity to 5-HT may cause abnormal intestinal motility.

Although 5-HT₃ receptor antagonists have already been put to clinical use as antiemetics for chemotherapy, a clinical attempt has been made to use them for diarrhea-type irritable bowel syndrome based on the idea that they suppress intestinal motility. It is also becoming clear that peristaltic movement of the digestive tract is regulated by the motilin level during hunger. The cause is still unknown as for intestinal pseudo-obstruction, which makes food intake impossible due to a marked decrease in intestinal motility, but a marked decrease in interstitial cells of Cajal has been reported in some patients.

Clinical Research

1. Enteral nutrition and home parenteral nutrition

The number of patients with severe malabsorption due to short-bowel syndrome and Crohn’s disease is increasing each year. In Japan, nutritional management using enteral nutrition is the first choice followed by home parenteral nutrition (HPN).

According to a survey done by an HPN Research Group, 149 out of 355 patients were given HPN each year due to a benign disease. It is striking that the majority of these patients, (132 cases) are able to return to work or to live at home because of HPN, which confirms the benefits derived from HPN.

In contrast, due to the patients who require nutritional management by enteral nutrition and HPN over one year, new problems concerning vitamins and trace elements have surfaced. For example, well-known trace element deficiencies such as copper deficiency and selenium deficiency cause anemia and heart dysfunction, respectively. Conversely, the excess manganese has become a problem, as studies have shown that manganese is deposited in the brain. Effective management methods of trace elements that do not cause deficiency or excess must be established through prescriptions and over-the-counter supplements of trace elements.

2. Tumors of the small intestine

Neoplastic diseases in the small intestine are not very common. In general, non-epithelial tumors are more common than epithelial tumors. Recently, new information on stromal-cell-derived tumors has become available.

Conventionally, it has been thought that stroma-derived tumors were mostly leiomyoma or leiomyosarcoma, and tumors originating from the nervous system were distinguished by immunostaining. Recently, however, the tumor originating from interstitial cells of Cajal has drawn attention. This tumor has been narrowly defined as a gastrointestinal stromal
Interstitial cells of Cajal, which are distributed in the muscularis propria throughout the digestive tract, serve as pacemaker cells for intestinal motility. Since interstitial cells of Cajal are c-kit- and CD34-positive cells, c-kit and CD34 are used as markers for diagnosis (Table 1). Re-evaluation of stromal tumors by this diagnostic method has revealed that many of the tumors that had been considered to be leiomyoma were tumors that had originated from the interstitial cells of Cajal (GIST). While GIST itself is said to be most commonly found in the stomach, it is a representative neoplastic disease of the small intestine where non-epithelial tumors are common. There is also a malignant GIST, and metastatic cases with this type of tumor have a very poor prognosis.

Recently, it has been reported that tyrosine kinase inhibitor (imatinib), which has been developed to treat chronic myelocytic leukemia, also inhibits the tyrosine kinase of GIST and exhibits a contractionary effect against tumors. Although the use of this drug has already become available in Japan, there remain unresolved problems concerning indications and adverse drug effects. One should note that the term GIST is occasionally used broadly to refer to stromal-cell-derived tumors.

### Table 1 Immunohistological Diagnosis of Gastrointestinal Stromal Tumors

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Marker Status</th>
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<tbody>
<tr>
<td>GIST</td>
<td>c-kit (+)</td>
</tr>
<tr>
<td>Leiomyoma</td>
<td>c-kit (-), SMA (+), desmin (+)</td>
</tr>
<tr>
<td>Neurogenic tumor</td>
<td>c-kit (-), S-100 (+)</td>
</tr>
</tbody>
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(SMA: smooth muscle actin)
(Excerpt from Fletcher, C.D. et al.: *Hum Pathol* 2002; 33: 459–465)

### 3. Recent developments in diagnostic imaging

Since popularization of helical CT has dramatically reduced the amount of time required for exposure and improved resolution, CT has become an imaging method that is very easy to use. Although there was a tendency to shun overdependence on CT, the situation seems to have somewhat changed with the appearance of helical CT, and CT is now viewed essential in acute abdomen examinations.

Contrast-enhanced CT is the first-line test for ileus, which is a disease that is encountered on a daily basis, and location of obstruction, degree of obstruction, and condition of intestinal ischemia can be grasped by CT. Makita, et al., have established six types of findings and reported that diagnosis of cases with intestinal necrosis was possible at a sensitivity of 94% and a specificity of 89%. This method has also made it possible for physicians to quickly determine surgical need. It is also particularly useful for confirming diseases that are difficult to find, such as obturator hernia.

Another new and noteworthy form of applied technology is virtual CT. With the popularization of hardware and software, the daily clinical application of virtual CT will become a common procedure in the near future.

### 4. Enteroscopy

In the field of endoscopy, a relatively thin push type video enteroscope has become popular and it is utilized for diagnosis or treatment of the upper jejunum. While the use is somewhat limited, as the small intestinal wall is weak, treatment such as polypectomy is possible by using this method. Attempts at deeper insertion of the enteroscope by using of a sliding tube and a balloon have been reported. Although widespread use of enteroscopy is hoped for, a remote-controlled capsule endoscopy, which is swallowed by the patient, has been developed recently. This method awaits clinical application in the very near future.

While diagnosis and treatment of hemorrhage from the small intestine often seem difficult, perioperative endoscopy has been known to be useful in identifying the source of small intestinal hemorrhage. In addition, when lapa-
rotomy is performed in patients with Peutz-Jeghers syndrome, it is recommended that small intestinal polyps be thoroughly searched and treated by perioperative endoscopy so that intussusception may be prevented.

5. Inflammatory bowel disease

A representative inflammatory bowel disease of the small intestine is Crohn’s disease, and the number of patients with the disease has been increasing yearly in Japan. While the true cause of the disease is still unknown, an abnormality was discovered in 2001 in a gene called NOD2, which is one of the innate immune mechanisms. This abnormality was seen in approximately 10% of patients in Western countries. However, this gene abnormality has not been found in Japan.

A topic of interest in the area of treatment is that monoclonal antibody therapy against tumor necrosis factor (TNFα), a representative inflammatory cytokine, is now covered by Japan’s national insurance system as of May 2002. Insurance coverage is applicable for cases with external fistulae or cases in which inflammation could not be relieved by other methods. However, as concerns for adverse drug reactions have been emphasized since the beginning and it has been pointed out that the treatment is not easy to use in cases with a strong stenosis, the type of cases in which the treatment would be appropriate needs to be determined in the future.

In the field of surgery, it seems that laparoscopic surgery is being used more widely. Laparoscopic surgery reduces invasiveness and makes it possible for patients to return to work earlier, and the procedure is not inferior in its effectiveness compared to open surgery. In addition, prevention of short-bowel syndrome caused by resection, a surgical method called strictureplasty rather than resection, is recommended to relieve the stenosis in cases of Crohn’s disease.

Intestinal adhesion has been a major problem for quite some time not only in cases with inflammatory bowel disease but also following laparotomy, and adhesion-induced ileus should be avoided when it can be helped. In recent years, a carboxyl methylcellulose membrane has become popular in preventing adhesion, serving as an effective adhesion prevention method. In fact, when patients with ulcerative colitis and familial adenomatous polyposis were randomly allocated to a group that used the membrane and a group that did not use the membrane in first-stage surgery, an examination of the degree of adhesion during the second-stage surgery revealed that adhesion had been prevented significantly in the group that used the membrane.

Conclusion

Since peptides common to both the central nervous system and the small intestine have been discovered, the small intestine is called the second brain. It works while intricately interrelating with the endocrine, the nervous, and the immune systems. The study of this organ is a major field with many topics remaining to be explored.

REFERENCES

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