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REVIEW

Interstitial cells of Cajal in the gut - A gastroenterologist's point of view

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Abstract

Alterations of normal function of interstitial cells of Cajal (ICC) are reported in many intestinal disorders. Diagnosis of their involvement is rare (infrequent), but necessary to propose a specific treatment. This article reviews the place of ICC in the pathogenesis of achalasia, gastroesophageal reflux disease, infantile hypertrophic pyloric stenosis, chronic intestinal pseudo-obstruction and slow transit constipation. Moreover we discuss the role of the Cajal cells in the development of stromal tumors of the gastrointestinal tract.

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Key words: Cajal cells; c-kit; Intestinal motility; Achalasia; Gastrointestinal stromal tumor

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INTRODUCTION

Digestive motility is highly coordinated and consists of local, non-propulsive mixing (segmental) and propulsive (peristaltic) movements. Mixing movements are produced by intrinsic pacemakers generating rhythmic contractions and peristalsis by intrinsic excitatory and inhibitory neural reflex pathways[1,2].

Even in the absence of stimulation, most regions of the gastrointestinal tract can generate some spontaneous electrical and mechanical activity. Recordings made from isolated muscle cells in the gastrointestinal tract show a regular discharge recorded as plateau and slow potentials. These pacemaker potentials are generated by a specialized population of cells, known as interstitial cells of Cajal (ICC)[3].

Together with the enteric nervous system, composed of both the myenteric (inter-muscular) plexus and the submucosal plexus, the ICC plays a major role in gastrointestinal motility[4]. The ICC was firstly described by Cajal SR in 1911[5]. He characterized "interstitial neurons" as "primitive accessory components that could modify smooth muscle contraction, subject themselves to regulation from principal neurons". Cajal provided detailed pictures of methylene blue-stained networks of interstitial cells, which were described as spindle shaped or stellate cells with long, ramified cell processes and large, oval, nuclei with sparse perinuclear cytoplasm, and intercalated between autonomic nerve endings and smooth muscle cells[5].

ICC constitutes networks that are widely distributed within the submucosal, intra-muscular and inter-muscular layers of the gastrointestinal tract from the lower esophagus to the internal anal sphincter.

These cells are defined by the expression of the CD117 (c-kit) protein which is a membrane receptor with tyrosine kinase activity[3,4,6].

In the past decade, knowledge of the role of ICC in the digestive physiology and pathology has progressed. In this review, we highlight some of these advances which could have clinical impact either in pathogenesis or treatment.

ESOPHAGUS

Achalasia

Achalasia is characterized by relaxation failure of lower

esophageal sphincter (LES) and lack of peristaltic contraction of esophageal body[7]. The etiology of this disorder is unknown and may be "idiopathic" or secondary to malignancy (local invasion or a paraneoplastic manifestation).

In primary or idiopathic achalasia, the failure of deglutitive inhibition is responsible for aperistalsis. This dysfunction is due to a loss of inhibitory nerves and progressive degeneration of ganglion cells containing vasoactive intestinal peptide (VIP) and nitric oxide (NO). Hypertensive LES is thought to result from a combination of the lack of tonic inhibitory nitrergic influence and an unopposed cholinergic activity.

The mechanism of inflammatory process responsible of these alterations is unclear. It is suggested to be an autoimmune disorder induced by a viral or food antigen in a patient genetically predisposed to the disease[8,9]. ICC involvement in achalasia is debated[10,11].

Electronic microscope studies of muscle coat of LES in seven patients with achalasia showed that muscle wall components (nerve endings, smooth muscle cells, ICC and connective tissue) were modified. ICC ultrastructure was altered, namely clear cytoplasm, fewer mitochondria, and scarce smooth endoplasmic reticulum. A reduced number of contacts between nerves and ICC were reported. Specific changes in smooth muscle cells were also documented, whereas the nerve endings had a normal ultrastructure. Alterations in older patients were more pronounced[12]. Since the LES components specifically altered in achalasia are the nerve endings and ICC, they are regarded as principally responsible for abnormal motility[12].

Achalasia is uncommon among pediatric population and some authors consider it as a different entity. Rare familial forms, combining early onset achalasia, alacrymia, ACTH insensitivity and dysautonomia, are known as Allgrove's syndrome or "four A" syndrome. Allgrove's syndrome is inherited in an autosomal recessive mode and may express in adulthood. Massive loss of neural elements and neuronal NO synthase as well as a marked fibrotic process of the muscle layers of the cardia have been observed in this syndrome[13]. ICC in cardia was also markedly decreased or absent while ICC (and neural structures) were preserved in pylorus[13].

Gastro-esophageal reflux disease (GERD)

GERD is a highly prevalent condition. Typical symptoms of heartburn and acid regurgitation are encountered in 15%-20% of the general population[14].

GERD represents the most common cause of esophagitis that may be complicated with esophageal ulcers, peptic stenosis and Barrett's esophagus, which carries a high risk of esophageal adenocarcinoma[14].

The role of the ICC in inhibitory transmission in the LES is still discussed.

In W/W_v mutant mice (lack of ICC) LOS pressure was lower than wild-type mice but a normal swallow still induced LOS relaxation, arguing against the role of ICC in inhibitory transmission[15]. Another study demonstrated that in W/W_v animals, cholinergic and nitrergic neurotransmission is greatly reduced pleading for the role of ICC in mediating neural inputs[16]. However enteric neurons, varicose processes, and the ability to release neurotransmitters are not reduced, and smooth muscle cells demonstrate responsiveness to exogenous transmitters[16].

Loss of ICC during development or in pathologic conditions would significantly compromise the ability of GI muscles to generate typical motor reflexes[17].

Esophagitis itself may be at the origin of an alteration of normal function of the Cajal cells: in advanced stages of GERD, inflammatory changes in the esophageal wall will also involve the ICC. That way, the more severe the esophagitis, the more severe is the ICC impairment. This destruction leads to loss of effective contraction of esophagus, maintaining reflux and thus aggravating the symptoms[18].

STOMACH

Gastroparesis

Delayed gastric emptying can be secondary to muscular, neural, humoral causes or use of anticholinergic and opiates medicines. In the absence of an identified cause, gastroparesis is termed as idiopathic[19]. Clinical features of gastroparesis are frequently indistinguishable from true mechanical obstruction and severity of symptoms is variable. Most patients present with early satiety, nausea, and abdominal pain. In some cases, symptoms can be highly incapacitating: chronic abdominal pain and vomiting leading to dehydration, electrolyte imbalance, nutritional impairment and weight loss[20,21].

ICC is involved in regulation of gastric emptying by generating slow waves.

A decrease in ICC density ranged from 60% to 100% depending on the area investigated was demonstrated in histologic studies of stomach of type 1 diabetic patients[6]. The number of immunopositive cells for c-kit was significantly decreased in the corpus and antrum of the gastroparesis patients compared with control tissues[21]. The loss of intra muscular ICC and associated nerves in the gastric fundus could explain the low basal gastric tone and increased compliance of the stomach. The hypomotility of the antrum can also be explained by the absence of slow wave generation by the ICC[21,22].

Infantile hypertrophic pyloric stenosis

This is a congenital disorder characterized by functional gastric-outlet obstruction. Dysfunction of pyloric inhibition has been implicated in the pathophysiology of hypertrophic pyloric stenosis. Normal inhibition process is mediated by peptidergic and NO enteric nerves and also may involve ICC. Although myenteric neurons appear normal, those innervating the circular-muscle layer of the pyloric sphincter lack NO synthetase[21]. In children with hypertrophic pyloric stenosis, there was a significant decrease in the number of ICC[22,23]. The following observations were made using electron microscopy in gastric specimens from patients with pyloric stenosis versus normal controls[24]. Muscle cells were primarily in a

proliferative phase and exhibited very few gap junctions between smooth muscle cells or ICC: (1) Near absence of nerve fibers containing large granular vesicles in the circular muscle layer; (2) Fewer nerve cell bodies in the myenteric plexus and lower total number of ganglia; (3) Decreased number of ICC. These findings may plead for a role of ICC in the pathogenesis.

SMALL INTESTINE AND COLON

Idiopathic chronic intestinal pseudo-obstruction (CIIP)

CIIP is characterized by defective gastrointestinal propulsion together with symptoms and signs of bowel obstruction in the absence of any lesions or mechanical obstacle[25]. CIIP is regarded as a neuropathy, myopathy or both[26,27].

A possible role played by the ICC is demonstrated by the alterations in ICC network reported in patients with CIIP. Electron microscopy and immunochemistry studies showed a decreased number of ICCs along with structural abnormalities such as loss of processes and damaged intracellular cytoskeleton and organelles[28].

Slow transit constipation (STC)

This is a very prevalent motility problem, but its mechanisms are unclear. Studies found that ICC density in the colon of patients with constipation was significantly decreased compared with those of normal patients[29]. Expression of *c-kit* mRNA and c-kit protein was significantly decreased in the colon of STC, suggesting that the c-kit signal pathway may play an important role in ICC reduction in STC[30-32].

Since slow-transit constipation is secondary to problems with the ENS, ICC, or smooth muscle cells, replacement of the missing or defective cells would be an attractive way of treatment[31]. Growing precursors of the defective cells from stem cells should be easy, but the distribution of the cells to their proper locations is still problematic[31,32]. For the moment this is a promise of genetic treatment.

TUMORS OF GASTROINTESTINAL TRACT

Gastrointestinal stromal tumors (GISTs)

GISTs have been recognized as a biologically distinctive tumor type, different from smooth muscle and neural tumors of the gastrointestinal tract. They constitute the majority of gastrointestinal mesenchymal tumors[33].

GISTs originate from the ICC. Their origin from the ICC has been proven by their immunophenotypic (CD117 positive) and ultrastructural resemblance and also by the presence of an embryonic smooth muscle myosin similar to the one present in the ICC[33-36] (Table 1). Approximately 80% of GISTs also express CD34.

Annual incidence of clinically detected new cases of GISTs in the United States has increased to 5000-6000 per year due to better diagnosis, and incidence is rising. Uncommonly, GISTs arise in families, and in these patients germline mutations of c-kit have been identified particularly in exons 11 and 13. A diffuse hyperplasia of the ICC, which is regarded as a pre-neoplastic lesion is noted in these patients[33]. The patients with exon 11 mutations develop cutaneous mastocytosis with or without cutaneous hyperpigmentation, but those with exon 13 mutations do not have these features[33,34]. The tumors under 3 cm in diameter are mostly benign, but all GISTs have a malignant potential[35].

Table 1 Immunohistochemical analysis of GI mesenchymal tumors[35,36]

Tumor	Positive immunohistochemical staining
GIST	CD 117
	CD 34
Malignant GIST	Ki 67
Smooth muscle tumor	Smooth muscle actin
	Desmin
Schwannoma	S100
Glomus tumor	Smooth muscle actin
	Vimentin

The majority of GISTs occurs in the stomach (60%-70%), small intestine (20%-30%) and only 10% or less in the esophagus, colon and rectum, and they affect mainly middle aged patients. Similar tumors, sometimes known as extra-gastrointestinal stromal tumors (E-GIST), may arise in the omentum, mesentery, or retroperitoneum and at least one case of pancreatic tumor was described[37,38]. The presence of ICC in normal pancreas was demonstrated recently[39].

The symptoms may vary from none or slight abdominal discomfort to brisk gastrointestinal hemorrhage, perforation or obstruction.

Imatinib mesylate, a synthetic tyrosine kinase inhibitor developed for the use in the management of interferon resistant chronic myeloid leukemia (CML), was shown to be effective against a number of other tyrosine kinases including c-kit and platelet derived growth factor (PDGF) and now it is considered to be the drug of choice for metastatic and inoperable GIST's[33,34].

CONCLUSION

Knowledge on the role of ICC in gastrointestinal disorders is increasing. However, with the exception of GIST's, no major breakthrough has been made in treatment. Further studies may provide new treatments.

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