Interstitial cells of Cajal, the Maestro in health and disease

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Abstract

Interstitial cells of Cajal (ICC) are important players in the symphony of gut motility. They have a very significant physiological role orchestrating the normal peristaltic activity of the digestive system. They are the pace-maker cells in gastrointestinal (GI) muscles. Absence, reduction in number or altered integrity of the ICC network may have a dramatic effect on GI system motility. More understanding of ICC physiology will foster advances in physiology of gut motility which will help in a future breakthrough in the pharmacological interventions to restore normal motor function of GI tract. This mini review describes what is known about the physiological function and role of ICCs in GI system motility and in a variety of GI system motility disorders.

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Key words: Interstitial cells of Cajal; Gastrointestinal motility; Peristalsis

 INTRODUCTION

Physiology of gut motility has been always a fascinating chapter in gastroenterology. It poses interesting challenges to physiologists. Our understanding of basic gut motility processes is advancing; a major emphasis is placed on elucidating gut regulatory mechanisms. A better appreciation of the importance of the presence of normal function of interstitial cells of Cajal (ICC) transformed this field of research. In 1893, Spanish Nobel Laureate physician and neuropathologist Santiago Ramon y Cajal, was the first to describe cells that are located between the nerve endings and smooth muscle cells in the gastrointestinal (GI) tract. Their location prompted him to call them “interstitial”. They are now known as the ICC. ICC may be considered to be a specialized population of smooth muscle cells. Both arise from common mesenchymal cells[1-3]. However, whereas smooth muscle cells develop an extensive array of contractile elements, ICC have few contractile elements but contain large numbers of mitochondria, an abundance of endoplasmic reticulum and distinct sets of channels in their membrane. The ICC consist of a fusiform cell body with a thin cytoplasm, a large oval nucleus and dendritic-like processes[4]. Two to five primary dendritic processes divide further into secondary and tertiary processes[5]. Many ICC express Kit, a tyrosine kinase receptor (Kit-ir); this allows them to be recognized by their ability to bind antibodies to Kit[6]. Similarly ICC readily react with...
antibodies to vimentin whereas nearby smooth muscle cells do not\(^9\). The presence of ICC is not restricted to the GI tract. They can be found in the bladder\(^{7,9}\), the ureteropelvic junction\(^8\), the vas deferens\(^{10}\), the prostate\(^{11}\), the penis\(^{12,13}\), the mammary gland, the uterus\(^{14}\), the pancreas\(^{15,16}\), blood vessels\(^{16}\) such as the portal vein\(^{17}\) and the vagina\(^{18}\). More recently, they have been found in the veriform appendix in childhood\(^{19}\). Some of these cells are thought to have a pacemaker function (such as those in the portal vein, in the lymphatics or prostate) but not those in the arteries, uterus (where the influence is, if any, an inhibitory one) or bladder\(^{24}\).

The motor activity of the GI tract is critical for life\(^{21}\). It is a complex process involving multiple cell types such as enteric neurons that can sense the contents of the GI tract, integrate information and devise a suitable motor pattern, ICC that transduce inputs from enteric motor neurons and generate intrinsic electrical rhythmicity, and smooth muscle cells that can interpret and integrate large arrays of inputs and develop appropriate responses\(^{22}\). ICC are a minor component of the tunica muscularis of the GI tract (only about 5% of cells present\(^{23}\)); however, these cells have very significant physiological roles in GI motility\(^{22}\).

Many tissues, isolated from different regions of the GI tract, contract rhythmically in the absence of neuronal or hormonal stimulation. When contractions and membrane potential are recorded simultaneously each contraction is seen to be triggered by a long lasting wave of depolarization: because of their low frequency of occurrence and long duration, the waves of depolarization have been termed slow waves\(^{24}\). The origin and basis of the generation of slow waves have been debated for many years. It was initially thought that the generation of slow waves reflected some properties of GI smooth muscle cells\(^{25,26}\), but studies on isolated smooth muscle cells have consistently failed to demonstrate a capability to generate slow wave activity\(^{27}\). It has also long been recognized that the generation of slow waves does not rely on the sequential activation of voltage-dependent ion channels as do cardiac pacemaker cells. Rather, many early studies raised the possibility that rhythmical activity relied on the cycling of one or more metabolic processes within cells of the gut wall. Thus Conner and his colleagues proposed that the generation of slow waves involved changes in the activity of the sodium pump\(^{28}\).

Subsequently Nakayama et al\(^{29}\) suggested an involvement of glycolytic pathways, again assuming that pace making activity originated in smooth muscle cells. Although ICC were first described in the intestine a century ago by Cajal, they were long viewed as an oddity. Their role in the generation of pacemaker activity in the GI tract was suggested on the basis of histological studies\(^{30}\). More recently, studies on mutants that lack subpopulations of ICC revealed their role in the generation of rhythmicity\(^{31}\).

Critically, whereas isolated smooth muscle cells rarely generate spontaneous electrical activity\(^{32}\), isolated ICC invariably do\(^{11,32}\).

### STRUCTURAL ORGANIZATION AND IDENTIFICATION OF SPECIFIC POPULATIONS OF ICC

The discovery that ICC express c-Kit, the proto-oncogene that encodes the receptor tyrosine kinase Kit has offered a simple and reliable immunohistochemical method for determining the structure and distribution of ICC networks\(^{33,34}\). ICC are found throughout the GI tract from the esophagus to the internal anal sphincter\(^{33,34}\). Hanani et al\(^{35}\) mentioned that while it is becoming clear that more than one type of ICC exists, based on both morphological and functional data, we still subdivide ICC based on location. Furthermore, Farrugia\(^{36}\) emphasized the importance of revisiting a classification based solely on location and move towards a classification that is based on function, suggesting a reasonable start, to subdivide ICC into those that have the machinery to, and generate, unitary potential and slow waves and those that do not. Morphological studies now supported by some functional evidence suggest that at least three separate functional groups of ICC exist. In most regions of the GI tract, a network of ICC are located within the intermuscular space at the level of the myenteric plexus (ICC-MY) between the circular and longitudinal muscle layers. ICC-MY are the pacemaker cells in the stomach and small intestine that trigger the generation of slow waves in the tunica muscularis\(^{37}\).

A second population of ICC (referred to as intramuscular ICC or ICC-IM) are found within the muscle layers of the GI tract and are innervated preferentially by enteric motor nerves\(^{37}\). ICC-IM are closely associated with not only enteric motor nerves but also vagal afferent nerves. Vagal afferent nerve fibers, labeled by the injection of neural tracers into the nodose ganglia, can terminate as intramuscular arrays within the musculature and as intraganglionic laminar ending within the myenteric ganglion of the stomach and duodenum. These afferent fibers transmit mechanoreceptive information from the muscle wall\(^{38,39}\). Horiguchi et al\(^{40}\) gave histological evidence that a third population of ICC, ICC-SEP, lies within the septa between the circular muscle bundles, and suggested that it may play a role in conducting electrical information from ICC-MY deep into the distant circular muscle bundles, Figure 1 showing functional organization of ICC in the canine gastric antrum\(^{41}\).

Electrophysiological data are presented which indicate that when the normal pathway from ICC-MY is sectioned, electrical stimulation of the cut ends of the muscle bundles can initiate slow waves over considerable distances. In the absence of stimulation, the muscle bundles isolated from ICC-MY can generate rhythmical activity but do so at low frequencies. Thus a distinct population of ICC, ICC-SEP, exists which can transfer pacemaker depolarization from ICC-MY deep into the distant bundles of circular muscle. Although ICC-SEP have the potential to generate pacemaker activity they are not normally the dominant pacemaker centre. As an analogy with the...
generation of pacemaker activity in the heart, the plexus of ICC-MY, like the sino-atrial node, is the dominant pacemaker centre. ICC-SEP, like Purkinje fibers, have the potential to generate pacemaker activity, but normally function to convey electrical activity from the dominant pacemaker region to more distant tissues\[^{41}\].

**PHYSIOLOGICAL FUNCTIONS OF ICC**

Peristaltic motor activity is a motor pattern orchestrated by complex sequencing of neural excitation and inhibition in cooperation with intrinsic muscular control mechanisms, including those residing in ICC\[^{42}\]. Peristalsis is defined as waves of contraction propagating along the GI tract for various distances as a means of mixing and propelling its content distally. Both the type of neural activity and the type of intrinsic myogenic control mechanism differ widely throughout the GI tract\[^{42}\]. Physiological activation of peristalsis will in most cases involve the stretching of a segment of stomach, intestine, or colon and it will occur by neural pathways that contain additional mechanisms to those required for the ascending excitatory reflex\[^{43}\]. When peristaltic motor activity occurs, in particular in stomach and proximal small intestine, the waves of contraction always have rhythmicity to it. This rhythmicity is determined by electrical slow wave activity in the musculature, referred to as pacemaker activity\[^{44}\].

New reagents, coupled with immunohistochemical techniques and new electrophysiological experimental approaches opened the door to recent progress in identification of the important roles of ICC as pacemakers, in propagation of slow waves and as mediators of inputs from enteric motor neurons\[^{45}\]. Other functions, such as mechanosensors have also been proposed, but little physiological evidence supporting this function has been published\[^{46}\].

**Laboratory approaches used for ICC study**

Isolated ICC have been examined using conventional patch clamp recording techniques. This approach, which has been applied to ICC-MY, allows a description of the specific populations of ion channels present in their membrane\[^{47,48}\] and an analysis of the cellular mechanisms which regulate the channels\[^{47,48}\]. Simple intracellular recording from smooth muscle cells in isolated segments of GI tissues and isolated segments of urethra, after blocking smooth muscle L-type Ca\(^{2+}\) channels, record primarily the activity of the ICC in the tissues. The properties of ICC-MY can be determined \textit{in situ} using sharp electrodes, allowing one to monitor the behavior of populations of interconnected ICC-MY and to determine how pacemaker potentials generate signals in adjacent smooth muscle layers\[^{47,49,50}\]. A third method used to study the properties of ICC IM involves recording from small isolated segments of circular muscles; if dissected appropriately the preparations are isopotential and contain up to 2000 smooth muscle cells linked to up to 200 ICC-IM. The membrane potential of both smooth muscle cells and ICC-IM, can be varied over a limited range and the effects of nerve stimulation can be analyzed\[^{47,49,50}\]. Finally, the use of mutant mice in which specific sets of ICC are either absent of dramatically reduced in numbers has allowed an evaluation of the physiological properties of tissues, with and without different sets of ICC\[^{47,49,50}\].

**PATHOPHYSIOLOGY OF ICCs**

Many GI motor disorders can be related to changes in number and/or structure and/or density of ICCs\[^{54-57}\]. These changes can be primary, due to toxin substances, neurotoxins or viral diseases, or secondary as a consequence of neural damage, degraded tissue or treatment effect\[^{54-57}\]. An absence or reduction in the number of ICCs causes abnormal electrical slow waves causing a decreased contractility of smooth muscle cells resulting in a diminished intestinal transit\[^{54-57}\]. Although the density decreases, the slow wave is still present in most affected patients but the frequency and duration are prolonged\[^{54-57}\].

**COMMON GI MOTILITY PROBLEMS**

**ICC in the human esophagus and cardia**

ICC in human esophagus has a myoid ultrastructure with abundant smooth endoplasmic reticulum, numerous mitochondria, intermediate filaments, scattered caveolae, and discontinuous basal lamina. They are most frequent in the esophageal part of the lower esophageal sphincter (LES)
but rare in the gastric part. They are in close contact with nerve terminals and make specific junctions with smooth muscle cells.\(^\text{[90,91]}\)

**Achalasia**: Achalasia is a disorder of esophageal motility that has been well documented for over 300 years.\(^\text{[81]}\) Achalasia is characterized by relaxation failure of the LES and lack of peristaltic contraction of the esophageal body.\(^\text{[62]}\) The mechanism of LES relaxation is complex, requiring the coordinated interaction of nerves, smooth muscle, ICC and hormones. The LES is a functional and anatomic barrier between the stomach and esophagus. It consists of a thickening of the circular smooth muscle layer of the esophagus at the gastroesophageal junction. It is anatomically asymmetric, and this is reflected in the physiology of the sphincter as demonstrated by ultrasound and pharmacologic manometric studies.\(^\text{[63]}\) The LES is tonically contracted. Initiation of a peristaltic wave in the esophagus is accompanied by a decrease in LES pressure as a result of smooth muscle relaxation. This allows the swallowed bolus to enter the stomach.\(^\text{[81]}\)

ICC involvement in achalasia is debated. Electron microscope studies of the muscle coat of the 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.\(^\text{[64]}\)

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 abnormal ultrastructure. Alterations in older patients were more pronounced.\(^\text{[68]}\) Since the LES components specifically altered in achalasia are the nerve endings and ICC, they are regarded as principally responsible for abnormal motility.\(^\text{[65]}\)

Achalasia is uncommon among the pediatric population. It is usually sporadic and affects mainly teenagers.\(^\text{[66]}\) A rare familial form combining early onset achalasia of cardia, alacrymia (absence of tears), and ACTH insensitivity, are known as Allgrove’s syndrome or “Triple A” syndrome.\(^\text{[69]}\) These forms are inherited in the autosomal recessive mode.\(^\text{[70]}\) Massive loss of neural elements and neuronal nitric oxide synthase as well as a marked fibrotic process of the muscle layers of the cardia have been observed in “Triple A” syndrome.\(^\text{[71]}\) ICC in the cardia are also markedly diminished or are completely absent while ICC (and neural structures) are preserved in the pylorus.\(^\text{[72]}\)

**Gastroesophageal reflux**: Gastroesophageal reflux (GERD) is a common condition and its prevalence varies in different parts of the World.\(^\text{[73]}\) Typical symptoms of heartburn and acid regurgitation are encountered in 15%-20% of the general population.\(^\text{[62]}\) The major mechanism for GERD is transient relaxation of the LES.\(^\text{[74]}\) The role of the ICC in inhibitory transmission in the LES is still being discussed.\(^\text{[65]}\)

In W/Wv mutant mice (lack of ICC) LES pressure was lower than wild-type mice but a normal swallow still induced LES relaxation, arguing against the role of ICC in inhibitory transmission.\(^\text{[75]}\) Another study demonstrated that in W/Wv animals, cholinergic and nitrogic neurotransmission is greatly reduced pleading for the role of ICC in mediating neural inputs.\(^\text{[76]}\) However, enteric neurons, varicose processes, and the ability to release neurotransmitters are not reduced, and smooth muscle cells demonstrate responsiveness to exogenous transmitters.\(^\text{[77]}\)

Loss of ICC during development or in pathologic conditions would significantly compromise the ability of GI muscles to generate typical motor reflexes.\(^\text{[78]}\)

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.\(^\text{[79]}\)

**ICC in the human stomach and pylorus**

**Gastroparesis**: The pathogenesis of gastroparesis is complicated and poorly understood. This lack of understanding remains a major impediment to the development of effective therapies for this condition. Most of the scientific information available on the pathogenesis of gastroparesis has been derived from experimental studies of diabetes in animals. These studies suggest that the disease process can affect nerves (particularly those producing nitric oxide, but also the vagus nerve), ICC and smooth muscle.\(^\text{[70]}\) It is broadly defined as disordered gastric emptying, and is a commonly encountered clinical problem.\(^\text{[80]}\) Delayed gastric emptying can be secondary to muscular, neural, humoral causes or use of anticholinergic and opiate medicines. In the absence of an identified cause, gastroparesis is termed as idiopathic.\(^\text{[70]}\) Gastroparesis has a broad range of clinical presentations ranging from dyspeptic symptoms to nausea, vomiting, abdominal pain, malnutrition, frequent hospitalizations and incapacitation.\(^\text{[81]}\) Chronic abdominal pain and vomiting leading to dehydration, electrolyte imbalance, nutritional impairment and weight loss.\(^\text{[82]}\)

The ICC are fundamental in the generation of gastric slow waves.\(^\text{[79]}\) A decrease in ICC density ranging from 60%-100% depending on the area investigated was demonstrated in histologic studies of the stomach of type 1 diabetic patients.\(^\text{[81]}\) The number of immunopositive cells for c-kit was significantly decreased in the corpus and antrum of the gastroparesis patients compared with control tissues.\(^\text{[62]}\) The loss of intramuscular 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.\(^\text{[83]}\)

**Infantile hypertrophic pyloric stenosis**: Infantile hy-
Hypertrophic pyloric stenosis (IHPS) is common in infants, characterized by marked delayed gastric emptying and hypertrophy of the inner (circular) muscle layer of the pylorus. IHPS has been known for more than a century, but it remains a puzzling disorder. The genetic susceptibility to development of IHPS seems to be multifactorial. Hypertrophy of the pyloric musculature develops after birth and produces the characteristic palpable pyloric “olive.” The pyloric lumen is however not fully occluded and can be intubated relatively easily, suggesting that the obstruction of the gastric outlet in IHPS is not merely due to a mechanical obstruction by the hypertrophied musculature. The extent of muscle hypertrophy appeared to be unrelated to the age or duration of symptoms.

Various neurotransmitters and the neuronal isoform of NO synthase are reduced or lacking in the hypertrophic musculature. The increased thickness of the pyloric muscular coats appears to be due to hypertrophy, rather than to hyperplasia, of the smooth muscle cells. ICC, identified either by electron microscopy or by Kit-ir, were consistently lacking in the hypertrophic circular muscle layer. However, Kit+ cells, similar to Kit-ir ICC observed in controls, were observed in the innermost part of the hypertrophic pylorus and in the antrum, indicating that the lack of Kit-ir is restricted to the hypertrophic pyloric musculature.

The lack of ICC in IHPS may interfere with the propagation of slow waves and may be, at least partly, involved in antro pyloric incoordination. Homozygous transgenic mice carrying inactivated genes (“knockout”) coding for the neuronal NO synthase developed hypertrophy of the pylorus. The link between the lack of ICC, the lack of inhibitory nitrergic neurotransmission, and the hypertrophy of the smooth musculature in IHPS remains to be elucidated.

**Small intestine and colon**

**Hirschsprung’s disease:** Hirschsprung’s disease (HD) is characterized by the lack of intrinsic enteric nervous system (ENS) in the distal part of the GI tract (“aganglionosis”). The affected segment extends cranially from the anus and encompasses a variable portion of the gut. Functionally, the lack of propulsive movements may lead either to an early obstructive syndrome in infancy or to a severe constipation. Lack of slow wave activity in the aganglionic segment has been identified. Kit immunohistochemistry identified ICC in HD. However, the cellular density of Kit+ ICC appeared markedly reduced in the aganglionic segment. ICC-MP were rather abundant in the (aganglionic) space between the muscle layers. Kit+ ICC were specially scarce in the inner part of the circular musculature and in the submucosal plexus. However, the presence of some ICC-SMP was confirmed by electron microscopy.

In contrast, another study reported a distribution of Kit+ ICC in HD comparable to controls and claimed that Kit1 ICC-MP form “normal” networks in aganglionic segments when studied by confocal microscopy on whole mount preparations.

Differences in interpretation may be less significant than it appears as there is an agreement in the literature to acknowledge the presence of a number of interconnected ICC-MP in aganglionic segments but there is no objective criterion to assess the “normality” of networks. Considering the very close relationships of ICC with intrinsic nerves and glial cells in the normal gut, a normal arrangement of ICC appears quite unlikely in the absence of both intrinsic nerves and glial cells as encountered in aganglionic segments. In the embryonic chicken or mouse gut experimentally deprived of neural crest derivatives, ICC develop in the absence of ENS, confirming the mesenchymal nature of ICC. But it has not been established if ICC fully develop morphologically and functionally in such conditions.

HD is a heterogenous, multigenic disease and reviewing its genetic aspects is beyond the scope of this paper. Several systems regulating neural crest migration have recently been identified. Some genes are expressed by the neural crest, others by the mesenchyme of the gut. Kit has previously been considered as a possible candidate in the search for genes involved in hereditary forms of HD, but the absence of linkage between HD and the region of the Kit gene has been more recently reported. The genetic defects leading to aganglionosis in the HD patients enrolled in all studies on ICC published so far have not been assessed. Subtle differences may explain the discrepancies observed between studies, and a link between some specific genetic defect leading to aganglionosis and the differentiation of ICC in HD patients cannot be ruled out.

**Intestinal neural dysplasia:** A clinical condition that resembles HD was first described by Meier-Ruge in 1971 as a malformation of the enteric plexus. In 1983, Fadda et al. subclassified intestinal neural dysplasia (IND) into two clinically and histologically distinct subtypes. Type A occurs in less than 5% of cases, is characterized by congenital aplasia or hypoplasia of the sympathetic innervations, and presents acutely in the neonatal period with episodes of intestinal obstruction, diarrhea and bloody stools. The clinical picture of Type B resembles HD and is characterized by malformation of the parasympathetic submucous and myenteric plexuses and accounts for over 95% of cases of isolated IND. IND occurring in association with HD is of Type B. IND have been reported to be associated with loss or deficiency of ICC networks.

**Chronic intestinal pseudo-obstruction:** Chronic intestinal pseudo-obstruction (CIFO) is characterized by defective GI propulsion together with symptoms and signs of bowel obstruction in the absence of any lesions or mechanical obstacle. It is generally a serious, even life-threatening, condition with frequent need for long-term parenteral nutrition. CIFO can either be restricted to the intestine, can involve other parts of the GI tract, or can be part of...
a multisystemic disorder[59]. CIPO can be secondary to a number of identified disorders or can be “idiopathic”[113]. Very little is known about the etiology of idiopathic CIPO. Pathological features of CIPO are pleomorphic. A number of alterations of the ENS (“neuropathic” forms)[112] and “myopathic” forms, limited to the musculature of the GI tract or involving also the musculature of the urinary system[113,114], have been described.

**Slow transit constipation:** Functional constipation encompasses a group of functional disorders that exhibit persistent difficult, infrequent, or seemingly incomplete defecation and infrequent, lumpy, or hard stools[115,116]. This symptom is very common and may occur in up to 20% of populations, depending on demographic factors, sampling, and the definitions employed[115,117]. The term constipation is probably better viewed as a sort of semantic umbrella, covering pathophysiologic subtypes, among which 2 major groups may now be identified: slow transit constipation (STC) and pelvic floor dysfunction[58].

STC is thought to have, as a primary defect, slower than normal movement of contents from the cecum to the rectum[119]. This is a very prevalent motility problem, but its mechanisms are unclear[26]. Although STC may not be a congenital disease, the frequent onset in adolescence and strong female predominance suggest that STC could be a result of a sex modified multifactorial disorder of the GI tract with a genetic basis[120].

ICC volume was significantly lower in the STC patients across all colonic regions[21]. 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[121]. Shafik et al[23] concluded that a disorder of the ICC, which generate electric activity, may have a role in inducing diminished or absent colonic motor activity, a point that should be further investigated.

**TUMORS OF GI TRACT**

GI stromal tumors (GISTs) have been recognized as a biologically distinctive tumor type, different from smooth muscle and neural tumors of the GI tract. They constitute the majority of GI mesenchymal tumors[124].

GISTs exhibit considerable phenotypic heterogeneity[125]. Their origin remains unclear, although origin in smooth muscle cells has been proposed[124,125]. CD34-ir is often present in GIST[125,126-128], a property shared with various other solid tumors[129,131,133].

Kit-ir may be a suitable marker for GIST[125] and superior to CD34-ir[128-129]. Mutations (usually activating) of the proto-oncogene Kit have been identified in GIST[127,131-133,135]. GIST with Kit mutation appear to have a poorer prognosis[125,131,133-135]. Therefore Kit mutations may merely be part of the oncogenic process rather than an indication of the origin of these tumors.

Recent studies suggesting that ICC in the human gut were both Kit-ir and CD34-ir raised the idea that Kit+CD34+ GIST may derive from ICC[128,131,132].

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-GIST, may arise in the omentum, mesentery, or retroperitoneum and at least one case of pancreatic tumor was described[139,140]. The presence of ICC in normal pancreas was demonstrated recently[139].

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

Imatinib mesylate, a synthetic tyrosine kinase inhibitor developed for the use in the management of interferon resistant chronic myeloid leukemia, was shown to be effective against a number of other tyrosine kinases including c-kit and platelet derived growth factor and now it is considered to be the drug of choice for metastatic and inoperable GISTs[137].

**CONCLUSION**

Knowledge on the role of ICC in GI disorders is increasing and there is currently overwhelming evidence to support the idea that ICC play important roles in GI motility in laboratory animals. Studies of several animal models have shown that the lack of specific ICC subpopulations produces major disturbances of GI motility. ICC are unique cell types with a central role in the control of gut function. Further studies of ICC may, therefore, lead to a major breakthrough in more understanding of GI physiology which may be considered as a promising target, at least in the long run, for specific pharmacological interventions to restore the normal physiology and motor functions of the GI tract.

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**REFERENCES**

1. Lecoin L, Gabella G, Le Douarin N. Origin of the c-kit-positive interstitial cells in the avian bowel. *Development* 1996; 122: 725-733
2. Young HM, Ciampoli D, Johnson PJ, Stebbing MJ. Inhibitory transmission to the longitudinal muscle of the mouse caecum is mediated largely by nitric oxide acting via soluble guanylyl cyclase. *J Auton Nerv Syst* 1996; 59: 103-108
3. Young HM. Embryological origin of interstitial cells of Cajal. *Microsc Res Tech* 1999; 47: 303-308
4. Sanders KM. A case for interstitial cells of Cajal as pacemakers and mediators of neurotransmission in the gastrointestinal tract. *Gastroenterology* 1996; 111: 492-515
5. Faussone-Pellegrini MS, Thuneberg L. Guide to the identi-
Gastrointestinal peristalsis: joint action of...to feders. Biol Reprod 2004; 70: 371-378

Shafik A, El-Sibai O, Shakif AA. Identification of c-kit-positive cells in the human prostate: the interstitial cells of Cajal. Arch Androl 2005; 51: 345-351

Hashitani H, Suzuki H. Identification of interstitial cells of Cajal in corporeal tissues of the guinea-pig penis. Br J Pharmacol 2004; 141: 199-204

Shafik A. Study of interstitial cells in the penis: human study. J Sex Med 2007; 4: 66-71

Shafik A, El-Sibai O, Shakif I. Identification of c-kit-positive cells in the uterus. Int J Gynaecol Obstet 2004; 87: 254-255

Popescu LM, Hinescu ME, Ionescu N, Ciotreiu D, Ardelean C. Interstitial cells of Cajal in pancreas. J Cell Mol Med 2005; 9: 169-190

Harhun MI, Pucovský V, Povstyan OV, Gordienko DV, Bolton TB. Interstitial cells in the vasculature. J Cell Mol Med 2005; 9: 232-243

Povstyan OV, Gordienko DV, Harhun MI, Bolton TB. Identification of interstitial cells of Cajal in the rabbit portal vein. Cell Calcium 2003; 33: 223-239

Shafik A, El-Sibai O, Shakif I, Shakif AA. Immunohistochemical identification of the pacemaker cajal cells in the normal human vagina. Arch Gynecol Obstet 2005; 272: 13-16

Richter A, Wit C, Vanderwinden JM, Wit J, Barthlen W. Interstitial cells of Cajal in the vermiform appendix in childhood. Ear J Pediatr Surg 2009; 19: 30-33

McHale N, Hollywood M, Sergeant G, Thornbury K. Origin of spontaneous rhythmicity in smooth muscle. J Physiol 2006; 570: 23-28

Huizinga JD, Lammers WJ. Gut peristalsis is governed by a multitude of cooperating mechanisms. Am J Physiol Gastrointest Liver Physiol 2009; 296: G1-G8

Sanders KM, Ward SM. Kit mutants and gastrointestinal physiology. J Physiol 2007; 578: 33-42

Ford T, Redelman D, Horváth VJ, Miller LJ, Horowitz B, Sanders KM. Quantitative analysis by flow cytometry of interstitial cells of Cajal, pacemakers, and mediators of neurotransmission in the gastrointestinal tract. Cytotherapy 2004; 62: 139-149

Hirst GD, Ward SM. Interstitial cells: involvement in rhythmicity and neural control of gut smooth muscle. J Physiol 2003; 550: 337-346

Connor JA, Prosser CL, Weems WA. A study of pace-maker activity in intestinal smooth muscle. J Physiol 1974; 230: 671-701

El-Sharkaway TY, Daniel EE. Ionic mechanisms of intestinal electrical control activity. Am J Physiol 1975; 229: 1287-1298

Farrugia G. Ionic conductances in gastrointestinal smooth muscles and interstitial cells of Cajal. Annu Rev Physiol 1999; 61: 45-84

Nakayama S, Chihara S, Clark JP, Huang SM, Horuchi T, Tomita T. Consequences of metabolic inhibition in smooth muscle isolated from guinea-pig stomach. J Physiol 1997; 505 (Pt 1): 229-240

Thuneberg L. Interstitial cells of Cajal: intestinal pacemaker cells? Adv Anat Embryol Cell Biol 1992; 71: 1-100

Huizinga JD, Thuneberg L, Klüppel M, Malyss J, Mikkelsen HB, Bernstein A. W/kit gene required for interstitial cells of Cajal and for intestinal pacemaker activity. Nature 1995; 373: 347-349

Langton P, Ward SM, Carl A, Norell MA, Sanders KM. Spontaneous electrical activity of interstitial cells of Cajal isolated from canine proximal colon. Proc Natl Acad Sci USA 1989; 86: 7280-7284

Tokutomi N, Maeda H, Tokutomi Y, Sato D, Sugita M, Nishikawa S, Nishikawa S, Nakao J, Imamura T, Nishi K. Rhythmic CI current and physiological roles of the intestinal c-kit-positive cells. Pfugers Arch 1995; 431: 169-177

Daniel EE, Posey-Daniel V. Neuromuscular structures in opossum esophagus: role of interstitial cells of Cajal. Am J Physiol 1984; 246: G305-G315

Hagger R, Grasea S, Finlayson C, Kumar D. Distribution of the interstitial cells of Cajal in the human anorectum. J Auton Nerv Syst 1998; 73: 75-79

Hanani M, Farrugia G, Komuro T. Intercellular coupling of interstitial cells of cajal in the digestive tract. Int Rev Cytol 2005; 224-249-262

Farrugia G. Interstitial cells of Cajal in health and disease. Neurogastroenterol Motil 2008; 20 Suppl 1: 54-63

Ward SM, Beckett EA, Wang X, Baker F, Khoi M, Sanders KM. Interstitial cells of Cajal mediate cholinergic neurotransmission from enteric motor neurons. J Neurosci 2000; 20: 1393-1403

Iino S, Horiguchi K. Interstitial cells of cajal are involved in neurotransmission in the gastrointestinal tract. Acta Histochem Cytochem 2006; 39: 145-153

Fox EA, Phillips RJ, Martinson FA, Baronsowsky EA, Powley TL. Vagal afferent innervation of smooth muscle in the stomach and duodenum of the mouse: morphology and topography. J Comp Neurol 2000; 428: 558-576

Horiguchi K, Semple GS, Sanders KM, Ward SM. Distribution of pacemaker function through the tunica muscularis of the canine gastric antrum. J Physiol 2001; 537: 237-250

Hirst GD. An additional role for ICC in the control of gastrointestinal motility? J Physiol 2001; 537: 1

Huizinga JD. Gastrointestinal peristalsis: joint action of enteric nerves, smooth muscle, and interstitial cells of Cajal. Microsc Res Tech 1999; 47: 239-247

Tonini M, Costa M, Brookes SJ, Humphreys CM. Dissociation of the ascending excitatory reflex from peristalsis in the guinea-pig small intestine. Neuroscience 1996; 73: 287-297

Huizinga JD, Thuneberg L, Vanderwinden JM, Rumessen JJ. Interstitial cells of Cajal as targets for pharmacological intervention in gastrointestinal motor disorders. Trends Pharmacol Sci 1997; 18: 393-403

Sanders KM, Oradog T, Ward SM. Physiology and pathophysiology of the interstitial cells of Cajal: from bench to bedside. IV. Genetic and animal models of GI motility disorders caused by loss of interstitial cells of Cajal. Am J Physiol Gastrointest Liver Physiol 2002; 282: G747-G756

Lee HK, Sanders KM. Comparison of ionic currents from interstitial cells and smooth muscle cells of canine colon. J Physiol 1993; 460: 135-152

Ward SM, Oradog T, Koh SD, Baker SA, Jun JY, Amberg G, Monaghan K, Sanders KM. Pacemaking in interstitial cells of Cajal depends upon calcium handling by endoplasmic reticulum and mitochondria. J Physiol 2000; 525 Pt 2: 355-361

Koh SD, Jun JY, Kim TW, Sanders KM. A Ca(2+)-inhibited non-selective cation conductance contributes to pacemaker currents in mouse interstitial cell of Cajal. J Physiol 2002; 540: 803-814
Mostafa RM et al. ICC, the Maestro in health and disease

49 Hirst GD, Edwards FR. Generation of slow waves in the antral region of guinea-pig stomach—a stochastic process. J Physiol 2001; 535: 165-180

50 Dickens EJ, Hirst GD, Tomita T. Identification of rhythmically active cells in guinea-pig stomach. J Physiol 1999; 514 (Pt 2): 515-531

51 Suzuki H, Hirst GD. Regenerative potentials evoked in circular smooth muscle of the antral region of guinea-pig stomach. J Physiol 1999; 517 (Pt 2): 563-573

52 Suzuki H, Ward SM, Bayguinov VR, Edwards FR, Hirst GD. Involvement of intramuscular interstitial cells in nitricergic inhibition in the mouse gastric antrum. J Physiol 2003; 546: 751-763

53 Edwards FR, Hirst GD, Suzuki H. Unitary nature of regenerative potentials recorded from circular smooth muscle of guinea-pig antrum. J Physiol 1999; 519 Pt 1: 235-250

54 Hudson N, Mayhew I, Pearson G. A reduction in interstitial cells of Cajal in horses with equine dysautonomia (graze sickness). Auton Neurosci 2001; 92: 37-44

55 Long QL, Fang DC, Shi HT, Luo YH. Gastro-electro dysrhythm and lack of gastric interstitial cells of cajal. World J Gastroenterol 2004; 10: 1227-1230

56 Rolle U, Piotrowska AP, Nemeth L, Puri P. Altered distribution of interstitial cells of Cajal in Hirschsprung disease. Arch Pathol Lab Med 2002; 126: 928-933

57 Zarate N, Mearin F, Wang XY, Hewlett B, Huizinga JD, Malagelada JR. Severe idiopathic gastroparesis due to neuronal and interstitial cells of Cajal degeneration: pathological findings and management. Gut 2003; 52: 966-970

58 Fintl C, Hudson NP, Mayhew IG, Edwards GB, Proudmann CJ, Pearson GT. Interstitial cells of Cajal (ICC) in equine colic: an immunohistochemical study of horses with obstructive disorders of the small and large intestines. Equine Vet J 2004; 36: 474-479

59 Vanderwinden JM, Rumessen J. Interstitial cells of Cajal in human gut and gastrointestinal disease. Microsc Res Tech 1999; 47: 344-360

60 Torihashi S, Horisawa M, Watanabe Y. c-Kit immunoreactive interstitial cells in the human gastrointestinal tract. J Auton Nerv Syst 1999; 75: 38-50

61 Kraichely RE, Farrugia G. Achalasia: physiology and etiopathogenesis. Dis Esophagus 2006; 19: 213-223

62 Negrean LM, Assor P, Mateescu B, Cirstoiu C. Intestinal cells of Cajal in the gut—a gastroenterologist’s point of view. World J Gastroenterol 2008; 14: 6285-6288

63 Richardson BJ, Welch RW. Differential effect of atropine on rightward and leftward lower esophageal sphincter pressure. Gastroenterology 1981; 81: 85-89

64 Ward SM, Morris G, Reese L, Wang XY, Sanders KM. Intestinal cells of Cajal mediate enteric inhibitory neurotransmission in the lower esophageal sphincter and pyloric sphincters. Gastroenterology 1998; 115: 314-329

65 Faussone-Pellegrini MS, Cortesi C. The muscle coat of the lower esophageal sphincter in patients with achalasia and hypertensive sphincter. An electron microscopic study. J Submicrosc Cytol 1985; 17: 673-685

66 Myers NA, Jolley SG, Taylor R. Achalasia of the cardi a in children: a worldwide survey. J Pediatr Surg 1994; 29: 1375-1379

67 Allgrove J, Clayton GS, Grant DB, Macaulay JC. Familial glucocorticoid deficiency with achalasia of the cardia and deficient tear production. Lancet 1978; 1: 1284-1286

68 Moore PS, Couch RM, Perry YS, Shuckett EP, Winter JS. Allgrove syndrome: an autosomal recessive syndrome of ACTH insensitivity, achalasia and alacrima. Clin Endocrinol (Oxf) 1991; 34: 107-114

69 Dugardyn C, Anooshiravani M, Christophe C, Goyens P, Perlmutter N. Achalasia-alacrima-ACHT insensitivity syndrome (Tripole-A-syndrome). J Belge Radiol 1993; 76: 167-168

70 Weber A, Wienker TF, Jung M, Easton D, Dean HJ, Heinrichs C, Reis A, Clark AJ. Linkage of the gene for the triple A syndrome to chromosome 12q13 near the type II keratin gene cluster. Hum Mol Genet 1996; 5: 2061-2066

71 Lui H, Vanderwinden JM, Ji P, De Laet MH. Nitric oxide synthase distribution in the enteric nervous system of children with cardiac achalasia. Chin Med J (Engl) 1997; 110: 358-361

72 Yamagishi H, Koike T, Ohara S, Kobayashi S, Arizumi K, Aye B, Iijima K, Imatani A, Inomata Y, Kato K, Shibuya D, Aida S, Shimosegawa T. Prevalence of gastroesophageal reflux symptoms in a large unsselected general population in Japan. World J Gastroenterol 2005: 11: 1358-1364

73 Kaltenbach T, Crockett S, Gerson LB. Are lifestyle measures effective in patients with gastroesophageal reflux disease? An evidence-based approach. Arch Intern Med 2006; 166: 965-971

74 Dickens EJ, Edwards FR, Hirst GD. Selective knockout of intramuscular interstitial cells reveals their role in the generation of slow waves in mouse stomach. J Physiol 2001; 531: 827-833

75 Ward SM, Sanders KM. Physiology and pathophysiology of the interstitial cell of Cajal: from bench to bedside. I. Functional development and plasticity of interstitial cells of Cajal networks. Am J Physiol Gastrointest Liver Physiol 2001; 281: G602-G611

76 Shafik A, El-Sibai O, Shafik I, Shafik A. Electrogastrograph in gastroesophageal reflux disease with a new theory on the pathogenesis of its electric changes. BMC Surg 2004; 4: 13

77 Vittal H, Farrugia G, Gomez G, Pasricha PJ. Mechanisms of disease: the pathological basis of gastroaerpasis—a review of experimental and clinical studies. Nat Clin Pract Gastroenterol Hepatol 2007; 4: 336-346

78 Abeli TL, Malinowski S, Minocha A. Nutrition aspects of gastroaerpasis and therapies for drug-refractory patients. Nutr Clin Pract 2006; 21: 23-47

79 Forster J, Damjanov I, Lin Z, Sarosiek I, Wetzel P, McCallum RW. Absence of the interstitial cells of Cajal in patients with gastroaerpasis and correlation with clinical findings. J Gastrointest Surg 2005; 9: 102-108

80 Reddymas SC, McCallum RW. Pharmacotherapy of gastroaerpasis. Expert Opin Pharmacother 2009; 10: 469-484

81 Hirst GD, Edwards FR. Role of interstitial cells of Cajal in the control of gastric motility. J Pharmacol Sci 2004; 96: 1-10

82 Hayes MA, Goldenberg IS. The problems of infantile pyloric stenosis. Surg Clin North Am 1957; 104: 105-138

83 Rogers JM. The enigma of pyloric stenosis. Some thoughts on the aetiology. Acta Paediatr 1997; 86: 6-9

84 Mitchell LE, Risch N. The genetics of infantile hypertrophic pyloric stenosis. A reappraisal. Am J Dis Child 1993; 147: 1203-1211

85 Rollins MD, Shields MD, Quinn RJ, Woolridge MA. Pyloric stenosis: congenital or acquired? Arch Dis Child 1989; 64: 138-139

86 Lynn HB. The mechanism of pyloric stenosis and its relationship to preoperative preparation. Arch Surg 1960; 81: 453-459

87 Yamashiro Y, Mayama H, Yamamoto K, Sato M, Navate G. Conservative management of infantile pyloric stenosis by nasoduodenal feeding. Eur J Pediatr Surg 1981; 136: 187-192

88 Ukabiala O, Lister J. The extent of muscle hypertrophy in infantile hypertrophic pyloric stenosis does not depend on age and duration of symptoms. J Pediatr Surg 1987; 22: 200-202

89 Kobayashi H, O’Brien DS, Puri P. Immunochromosomal characterisation of neural cell adhesion molecule (NCAM), nitric oxide synthase, and neurofilament protein expression in pyloric muscle of patients with pyloric stenosis. J Pediatr Gastroenterol Nutr 1995; 20: 319-325

90 Schröder JM, Dieter R, Skopnik H, Steinau G. Immunohistochemical reactivity of neuropeptides in plastic-embedded semithin sections of the myenteric plexus in infantile hypertrophic pyloric stenosis. Acta Histochern Suppl 1992; 42: 341-344
Wattchow DA, Cass DT, Furness JB, Costa M, O'Brien PE, Little KE, Pitkin J. Abnormalities of peptide-containing nerve fibers in infantile hypertrophic pyloric stenosis. *Gastroenterology* 1997; 113: 443-448

Vanderwiden JM, Maillieux P, Schifflmann SN, Vanderhaegen JJ, De Laet MH. Nitric oxide synthase activity in infantile hypertrophic pyloric stenosis. *N Engl J Med* 1992; 327: 511-515

Tam PK. Observations and perspectives of the pathology and possible aetiology of infantile hypertrophic pyloric stenosis -a histological, biochemical, histochemical and immunocytochemical study. *Ann Acad Med Singapore* 1985; 14: 523-529

Langer JC, Berezn I, Daniel EE. Hypertrophic pyloric stenosis: ultrastructural abnormalities of enteric nerves and the interstitial cells of Cajal. *J Pediatr Surg* 1995; 30: 1535-1543

Vanderwiden JM, Liu H, De Laet MH, Vanderhaegen JJ. Study of the intestinal cells of Cajal in infantile hypertrophic pyloric stenosis. *Gastroenterology* 1996; 111: 279-288

Yamataka A, Fujiwara T, Kato Y, Okazaki T, Sunagawa M, Miyano T. Lack of intestinal pacemaker (C-KIT-positive) cells in infantile hypertrophic pyloric stenosis. *J Pediatr Surg* 1996; 31: 96-98; discussion 98-99

Huang FL, Dawson TM, Bredt DS, Snyder SH, Fishman MC. Targeted disruption of the neuronal nitric oxide synthase gene. *Cell* 1993; 75: 1273-1286

Meier-Ruge W, Gambazzi F, Käufeler RE, Schmid P, Schmidt CP. The neuropathological diagnosis of neuronal intestinal dysplasia (NID B). *Eur J Pediatr* 1994; 4: 267-273

Kubota M, Ito Y, Ikeda K. Membrane properties and innervation of smooth muscle cells in Hirschprung's disease. *Am J Physiol* 1983; 244: G406-G415

Yamataka A, Kato Y, Tiboobol D, Murata Y, Sueyoshi N, Fujiimoto T, Nishiyi H, Miyano T. A lack of intestinal pacemaker (c-kit) positive cells in isolated and syndromic Hirschsprung disease. *Eur J Hum Genet* 1997; 5: 247-257

Kapur RP. Contemporary approaches toward understanding the pathogenesis of Hirschsprung disease. *Pediatr Pathol* 1993; 13: 83-100

Dow E, Cross S, Wolgemuth DJ, Lyonnet S, Mulligan LM, Mascari M, Ladda R, Williamson R. Second locus for Hirschsprung disease/Waardenburg syndrome in a large Mennonite kindred. *Am J Med* 1994; 97: 75-80

Meier-Ruge W. *Casuistic of colon disorder with symptoms of Hirschsprung's disease (author's trans)*) *Verh Dtsch Ges Pathol* 1971; 55: 506-510

Fadda B, Maier WA, Meier-Ruge W, Schäfli A, Daum R. *Neuronal intestinal dysplasia. Critical 10-years' analysis of clinical and biopsy diagnosis* Z Kinderchir 1983; 38: 305-311

Puri P. Intestinal neuronal dysplasia. *Semin Pediatr Surg* 2003; 12: 259-264

Rolle U, Piasecka-Piotrowska A, Puri P. Intestinal cells of Cajal in the normal gut and in intestinal motility disorders of childhood. *Pediatr Surg Int* 2007; 23: 1139-1152

Di Giorgio R, Sarnelli G, Corinaldesi R, Stanghellini V. Advances in our understanding of the pathology of chronic intestinal pseudo-obstruction. *Gut* 2004; 53: 1549-1552

Rudolph CD, Hyman PE, Altschuler SM, Christensen J, Colletti RB, Cucchiara S, Di Lorenzo C, Flores AF, Hillemeier AC, McCallum RW, Vanderhoof JA. Diagnosis and treatment of chronic intestinal pseudo-obstruction in children: report of consensus workshop. *J Pediatr Gastroenterol Nutr* 1997; 24: 102-112

Krishnamurthy S, Heng Y, Schuffler MD. Chronic intestinal pseudo-obstruction in infants and children caused by diverse abnormalities of the myenteric plexus. *Gastroenterology* 1993; 104: 1398-1408

Anuras S, Mitros FA, Soper RT, Pringle KC, Maves BV, Younoszai MK, Franken EA Jr, Whittington P. Chronic intestinal pseudoobstruction in young children. *Gastroenterology* 1986; 91: 62-70

Smith VV, Miller PJ. Histological phenotypes of enteric smooth muscle disease causing functional intestinal obstruction in childhood. *Histopathology* 1997; 31: 112-122

Bassotti G, Chistolini F, Nzepe FS, Morelli A. Colonic propulsive impairment in intractable slow-transit constipation. *Arch Surg* 2003; 138: 1302-1304

Camilleri M, Thompson WG, Fleshman JW, Pemberton JH. Clinical management of intractable constipation. *Ann Intern Med* 1994; 121: 520-528

Locke GR 3rd. The epidemiology of functional gastrointestinal disorders in North America. *Gastroenterol Clin North Am* 1996; 25: 1-19

Locke GR 3rd, Pemberton JH, Phillips SF. AGA technical review on constipation. American Gastroenterological Association. *Gastroenterology* 2000; 119: 1766-1778

Nyma DC, Pemberton JH. Long-term results of lateral internal sphincterotomy for chronic anal fissure with particular reference to incidence of fecal incontinence. *Dis Colon Rectum* 1999; 42: 1306-1310

Tong WD, Liu BH, Zhang LY, Zhang SB. Analysis of the c-kit gene in patients with slow transit constipation. *Gut* 2006; 55: 1207-1208

Lyford GL, He CL, Sofier E, Hull TL, Strong SA, Senagore AJ, Burgart LJ, Young-Fadok T, Szurszewski JH, Farrugia G. Pan-colonic decrease in intestinal cells of Cajal in patients with slow transit constipation. *Gut* 2002; 51: 496-501

Schiller LR. New and emerging treatment options for chronic constipation. *Rev Gastroenterol Disord* 2004; 4 Suppl 2: S43-S51

Shafik A, Shafik AA, El-Sibai O, Mostafa RM. Electric activity of the colon in subjects with constipation due to total colonic inertia: an electrophysiologic study. *Arch Surg* 2003; 138: 1007-1011; discussion 1011

D’Amato G, Steinert DM, McAuliffe JC, Trent JC. Update on the biology and therapy of gastrointestinal stromal tumors. *Cancer Control* 2005; 12: 44-56

Erlandson RA, Klimstra DS, Woodruff JM. Subclassification of gastrointestinal stromal tumors based on evaluation by electron microscopy and immunohistochemistry. *Ultrastruct Pathol* 1996; 20: 373-393

Saul SH, Rast ML, Brooks JJ. The immunohistochemistry of gastrointestinal stromal tumors. Evidence supporting an origin from smooth muscle. *Am J Surg Pathol* 1987; 11: 464-473

Mikami T, Terada T, Nakamura K, Okayasu I. The gastric hypercellular microleiomyoma as a precursor lesion for clinical gastrointestinal stromal tumors. *Hum Pathol* 1997; 28: 1355-1360

Sakurai S, Fukasawa T, Chong JM, Tanaka A, Fukayama M. Embryonic form of smooth muscle myosin heavy chain (SMMb/MHC-B) in gastrointestinal stromal tumor and interstitial cells of Cajal. *Am J Pathol* 1999; 154: 23-28

Monihan JM, Carr NJ, Sotin LH. CD34 immunoreactivity in stromal tumors of the gastrointestinal tract and in mesenteric fibromatoses. *Histopathology* 1994; 25: 469-473

Miettinen M, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumors. *Ann Clin Gynaecol* 1998; 87: 278-281

Silverman JS, Tamson A. Mammary fibroadenoma and some phyllodes tumour stroma are composed of CD34+ fibroblasts
and factor XIIIa+ dendrophages. Histopathology 1996; 29: 411-419
132 Chaubal A, Paetau A, Zoltick P, Miettinen M. CD34 immunoreactivity in nervous system tumors. Acta Neuropathol 1994; 88: 454-458
133 Kindblom LG, Remotti HE, Aldenborg F, Meis-Kindblom JM. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am J Pathol 1998; 152: 1259-1269
134 Sarlomo-Rikala M, Kovatch AJ, Barussevicius A, Miettinen M. CD117: a sensitive marker for gastrointestinal stromal tumors that is more specific than CD34. Mod Pathol 1998; 11: 728-734
135 Nakahara M, Isozaki K, Hirota S, Miyagawa J, Hase-Sawada N, Taniguchi M, Nishida T, Kanayama S, Kitamura Y, Shinomura Y, Matsuura Y. A novel gain-of-function mutation of c-kit gene in gastrointestinal stromal tumors. Gastroenterology 1998; 115: 1090-1095
136 Lasota J, Jasinski M, Sarlomo-Rikala M, Miettinen M. Mutations in exon 11 of c-Kit occur preferentially in malignant versus benign gastrointestinal stromal tumors and do not occur in leiomyomas or leiomyosarcomas. Am J Pathol 1999; 154: 53-60
137 Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, Kawano K, Hanada M, Kurata A, Takeda M, Muhammad Tunio G, Matsuzawa Y, Kanakura Y, Shinomura Y, Kitamura Y. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998; 279: 577-580
138 Ernst SI, Hubbs AE, Przygodzki RM, Emory TS, Sobin LH, O’Leary TJ. KIT mutation portends poor prognosis in gastrointestinal stromal/smooth muscle tumors. Lab Invest 1998; 78: 1633-1636
139 Yamaura K, Kato K, Miyazawa M, Haba Y, Muramatsu A, Miyata K, Koide N. Stromal tumor of the pancreas with expression of c-kit protein: report of a case. J Gastroenterol Hepatol 2004; 19: 467-470
140 Nakagawa M, Akasaka Y, Kanai T, Yamashita T, Kuroda M, Takayama H, Miyazawa N. Extragastrintestinal stromal tumor of the greater omentum: case report and review of the literature. Hepatogastroenterology 2003; 50: 691-695
141 de Silva CM, Reid R. Gastrointestinal stromal tumors (GIST): C-kit mutations, CD117 expression, differential diagnosis and targeted cancer therapy with Imatinib. Pathol Oncol Res 2003; 9: 13-19

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