Histol Histopathol (2000) 15: 1293-1301

http://www.ehu.es/histol-histopathol

Histology and Histopathology

Cellular and Molecular Biology

Invited Review

Biological and clinical review of stromal tumors in the gastrointestinal tract

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Summary. Submucosal tumors of the gastrointestinal tract (GI tract) mainly consist of gastrointestinal mesenchymal tumors (GIMTs) that are distributed in the GI tract from the esophagus through the rectum. GIMTs include myogenic tumors, neurogenic tumors and gastrointestinal stromal tumors (GISTs). The term "GIST" is now preferentially used for the tumors that express CD34 and KIT. GIMTs are composed of spindle or epithelioid cells, and 20% to 30% show malignant behavior, including peritoneal dissemination and hematogenous metastasis. KIT expression and mutations in the *c-kit* gene are found only in GISTs, but not in myogenic or neurogenic tumors. Mutation in the *c-kit* gene is associated with aggressive features and poor prognosis, and malignant GISTs frequently have mutations in the *c-kit* gene. The clinicopathological features of GISTs with or without *c-kit* mutations are markedly different. Therefore, GIMTs may be divided into four major categories based on histochemical and genetic data: myogenic tumors; neurogenic tumors; GISTs with *c-kit* mutation; and GISTs without *c-kit* mutation. The origin of GISTs is not fully understood. However, phenotypical resemblance to the interstitial cells of Cajal (ICCs) and gain-of-function mutations in the *c-kit* gene may suggest origin from ICCs and/or multipotential mesenchymal cells that differentiate into ICCs.

Key words: Gastrointestinal tract, Gastrointestinal stromal tumor, *c-kit*, Interstitial cells of Cajal

Abbreviations. GI tract: gastrointestinal tract; GANT: gastrointestinal autonomic nerve tumor; GIMT: gastrointestinal mesenchymal tumor; GIPACT: gastrointestinal pacemaker cell tumor; GIST: gastrointestinal stromal tumor; ICC: Interstitial Cell of Cajal; NSE: neuron-specific enolase; SCF: stem cell factor.

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Comments: The term "Gastrointestinal Stromal Tumor (GIST)" is occasionally used for all types of stromal tumors in the gastrointestinal tract. However, in this review, "GIST" is used for the group of mesenchymal tumors that specially express CD34 and/or KIT. These tumors were previously classified as Gastrointestinal Stromal Tumor-uncommitted type. In this review the term "Gastrointestinal Mesenchymal Tumor (GIMT)" is used for mesenchymal origin-stromal tumors, including GISTs, myogenic tumors, and neurogenic tumors.

Introduction

Mesenchymal tumors in the gastrointestinal (GI) tract show similar clinical presentation. Traditionally, gastrointestinal mesenchymal tumors (GIMTs) have been classified as smooth muscle tumors (leiomyomas, cellular leiomyomas, or leiomyosarcomas) or neurogenic tumors (schwannomas) based on their morphological resemblance either to smooth muscle or neurogenic cells (schwann cells). Currently, GIMTs are divided into three major categories including myogenic tumors (leiomyomas or leiomyosarcomas), neurogenic tumors (i.e. schwannomas), and gastrointestinal stromal tumors (GISTs) according to the expression of marker proteins and ultrastructural characteristics (see the following pages and Batts and Barwick, 1996; Lechago and Genta, 1996; Rosai, 1996; Miettinen et al., 1999b).

Although the term "GIST" may be used for all mesenchymal tumors in the GI tract, including myogenic tumors, neurogenic tumors, and gastrointestinal stromal tumors-uncommitted type, in this review, the term is used to designate gastrointestinal stromal tumors-uncommitted type which express CD34 and/or KIT (CD117) proteins (Monihan et al., 1994; Miettinen et al., 1995, 1999b; Hirota et al., 1998; Kindblom et al., 1998; Sarlomo-Rikala et al., 1998; Seidal and Edvardsson, 1999). GISTs appear to be a heterogeneous group of mesenchymal cell-origin tumors but show similar histological features and clinical behavior, and thus are considered to have similar oncological backgrounds (Miettinen et al., 1999b). The two major problems in the

diagnosis of GIMTs are the differentiation of benign from malignant tumors and the determination of cellular origin (Franquemont, 1995; Batts and Barwick, 1996). Recent advances in understanding the tumor biology indicate that GISTs are genetically and histologically distinct from the groups of myogenic and neurogenic tumors. Although GISTs constitute a large majority of mesenchymal tumors in the GI tract, there still exist a small number of true leiomyomas and schwannomas. This review will focus on the biological basis for the clinical behavior of GIMTs, especially of GISTs. Because discrimination of malignant tumors from benign is sometimes difficult in stromal tumors in the GI tract, both benign and malignant myogenic, neurogenic and gastrointestinal stromal tumors are treated in this review.

Clinical features

GIMTs occur predominantly in middle-aged persons, and are subdivided into GISTs, myogenic tumors and neurogenic tumors as described above (Rosai, 1996; Miettinen et al., 1999b). Among them, GISTs account for nearly 80% of GIMTs and are the most common mesenchymal tumors in the human GI tract. Myogenic tumors account for 10% to 15%, and the remainder are neurogenic tumors. Approximately 70% of GIMTs occur in the stomach, 20% in the small intestine, and 10% in the esophagus and colorectum. Although GIMTs show site-dependent differences in their frequency (Rosai, 1996; Tworek et al., 1997, 1999a,b; Miettinen et al., 1999b), clinical presentation and behavior, current histochemical and molecular genetic data suggest that GIMTs have fundamental similarities independent of the site of occurrence (Rosai, 1996; Miettinen et al., 1999b).

Major symptoms include gastrointestinal bleeding, vague abdominal pain or dyspepsia, and palpable abdominal mass (Chou et al., 1996). These symptoms are associated with relatively large tumors, which may accompany poorer prognosis than those found asymptomatically. In Japan, over 40% of GIMTs in the stomach have been found by screening examinations. Most tumors are solitary and less than 5% of tumors are multicentric. Multiple tumors are reported in leiomyomas (leiomyomatosis), GISTs and gastrointestinal autonomic nerve tumors (GANTs) and patients suffering from these tumors are considered to have associated genetic factors (Marshall et al., 1990; Rosen, 1990; El-Omar et al., 1994; Nishida et al., 1998; O'Brien et al., 1999). Depending on the medical center or hospital situation, 20% to 30% of GIMTs behave clinically as malignant tumors (Miettinen et al., 1999b). Relapse and recurrences usually occur within two to three years after surgery, but occasionally recurrences may occur even after 5 years. Recurrences may be local relapse, hematogenous metastasis, or peritoneal dissemination. Hematogenous metastatic recurrences to the liver are predominant, followed by peritoneal dissemination and local relapse (Ng et al., 1992; Chou et al., 1996). Invasion into surrounding structures at diagnosis is found in nearly 10% of cases, and peritoneal dissemination and distant metastasis at diagnosis are much rarer. Metastasis predominantly occurs via the hematogenous rather than the lymphatic pathway.

Histological diagnosis

Histologically, GIMTs are divided into three major categories: myogenic tumors, neurogenic tumors and GISTs (Table 1). Differentiation of these tumors is mainly based on immunohistochemical expression of marker proteins (van de Rijn et al., 1994; Batts and Barwick, 1996; Lechago and Genta, 1996; Rosai, 1996; Miettinen et al., 1999b; Prévot al., 1999). Tumors can be diagnosed as myogenic when they are positive for desmin, as neurogenic when they are positive for S-100 protein, or as GISTs when they are positive for CD34 and/or KIT. Myogenic tumors may express α-smooth muscle actin, calponin and muscle-specific actin (HHF35) but are basically negative for vimentin, CD34 and KIT (Miettinen et al., 1999c). Typical leiomyomas (benign myogenic tumors) are hypocellular and consist of elongated spindle cells with abundant eosinophilic

Table 1. Subclassification of gastrointestinal mesenchymal tumors.

SUBCLASSIFICATION	MYOGENIC TUMOR	NEUROGENIC TUMOR	GIST		
			c-kit mutation (-)	occasional hyaliniztion	*c-kit* mutation (+)
c-kit mutation	-	-	-		+
Histological features	spindle cell	spindle cell	spindle cell sometimes epithelioid		
palisading	rare	often	sometimes		sometimes
cellularity	low	relatively high	relatively high		high
polymorphism	rare	sometimes	sometimes		frequent
	eosinophilic cytoplasm	lymphocyte infiltration	occasional hyalinization		
Immunohistochemistry					
Desmin	+	-	-		-
α-smooth muscle actin	+	-	-~+		-~+
S-100	-	+	-~+		-~+
Vimentin	-~(+)	+~(-)	+		+
CD34	-	-	+		+
KIT	-	-	+		+

cytoplasm. Myogenic tumors are relatively frequent in the esophagus. Neurogenic tumors may express glial fibrillary acidic protein and neuron-specific enolase (NSE). Neurogenic tumors most often occur in the stomach. Typical schwannomas (benign neurogenic tumors) are well circumscribed but not encapsulated and show interlacing bundles of well-defined spindle cells with mild nuclear atypia. Schwannomas may be accompanied by lymphoid infiltration surrounding the tumor.

GISTs frequently express vimentin and consist of spindle (nearly 80%) or epithelioid (polygonal) cells (20%). Significant numbers of GISTs are immunohistochemically positive for myogenic or neurogenic markers including α-smooth muscle actin, h-caldesmon, S-100 and NSE (Franquemont and Frierson, 1992; Ueyama et al., 1992; Miettinen et al., 1995, 1999b,c; Sakurai et al., 1999a). GISTs tend to have relatively higher degrees of cellularity and pleomorphism than myogenic or neurogenic tumors. These results suggest that GISTs appear to have histologically more aggressive features than myogenic and neurogenic tumors. Occasional but relatively specific association of hyalinization with GISTs is reported. The term GANT is used to designate tumors with characteristic features of (1) axon-like cytoplasmic processes (2) synapse-like structure with dense-core granules (3) intracellular fibrils ("skeinoid fibers") and (4) absence of myogenic marker proteins (Ojanguren et al., 1996). GANTs show immunohisto-chemical reactions for S-100 and NSE, and are also reported to be positive for CD34, vimentin, and KIT (Rosai, 1996; Miettinen et al., 1999b). Recently, multiple GANTs with hyperplasia of Interstitial cells of Cajal (ICCs) is reported to be caused by germline mutation of the *c-kit* gene (Hirota et al., 2000). These results suggest that the concepts of GIST and GANT overlap, and the former may include the latter.

Table 2. Prognostic factors of GIMTs.

FACTOR	COMMENT	REFERENCES
Clinical		
Tumor size	Tumor size (>5 cm) shows poor prognosis. Cut-off value may be 6, 7 or 8 cm.	Chou et al., 1996; Ma et al., 1993; Ng et al., 1992; Lechago and Genta, 1996; Rosai, 1996 Sanders et al., 1996; Ueyama et al., 1992
Invasion	Macroscopic invasion into surrounding structures and organs is an ominous prognostic factor	Chou et al., 1996; Ng et al., 1992; Rosai, 1996; Tworek et al., 1997
Metastasis	Metastasis at diagnosis is associated with worse prognosis. The liver is the main locus.	Ng et al., 1992; Rosai, 1996; Tworek et al., 1997
Dissemination	Peritoneal dissemination indicates worse prognosis. Disseminated tumors form multiple nodules without massive ascites.	Ng et al., 1992
Tumor rupture	Tumor rupture at surgery appears to have similar prognostic significance to peritoneal dissemination.	Ng et al., 1992
Incomplete resection	Incomplete resection is associated with poor prognosis.	Chou et al., 1996; Ng et al., 1992
Histological		
Mitosis	Tumors showing high mitotic figures (5/10HPF) are malignant and those with 1/10HPF to 5/10HPF mitotic figures are considered as intermediate malignant. Ki67, PCNA, S-phase fraction, and ploidy may indicate proliferation activity and are important prognostic factors.	Chou et al., 1996; Lechago and Genta, 1996; Ng et al., 1992; Ma et al, 1993; Rosai, 1996; Miettinen et al., 1999b; Tornoczky et al., 1999 Kiyabu et al., 1988; Shimamoto et al., 1992; Yu et al., 1992; Vrettou et al., 1995; Franquemont and Frierson, 1995; Chou et al., 1996
Cellularity	High cellularity indicates malignancy.	Lechago and Genta, 1996; Rosai, 1996
Pleomorphism	Tumors showing marked pleomorphism, which usually accompanies high cellularity, are aggressive and have poor prognosis.	Lechago and Genta, 1996; Rosai, 1996
Histological necrosis	The presence of necrosis indicates rapid increase of tumor size. Histological hemorrhage may have similar prognostic significance to necrosis.	Rosai, 1996
Histological grade	Histological grade is usually determined by mitotic number, cellularity, and pleomorphism. High grade tumors show poorer prognosis than intermediate or low grade tumors.	Batts and Barwick, 1996; Chou et al., 1996; Sanders et al., 1996; Seidal and Edvardsson, 1999
Molecular genetic		
c-kit mutation	Mutation in the *c-kit* gene is associated with poor prognosis.	Ernst et al., 1998; Moskaluk et al., 1999; Taniguchi et al., 1999; Sakurai et al., 1999b

Other clinical factors such as bleeding and locus of tumors and histological factor such as disappearance of marker proteins may affect the prognosis but they seem to be less important than the factors listed here.

Prognostic factors and risk assessment

One of the most important issues in the diagnosis of stromal tumors is the differentiation and discrimination of malignant tumors from benign (Table 2). Numerous studies have attempted to address this problem based on clinical and pathological factors (Franquemont, 1995; Miettinen et al., 1999b). However, no definite criteria have been established. Among macroscopic findings, larger tumor size (>5 cm), invasion into surrounding structures, metastasis at diagnosis, and peritoneal dissemination or tumor rupture at surgery have been reported to be correlated with poor prognosis (Ng et al., 1992; Ma et al, 1993; Chou et al., 1996; Rosai, 1996; Miettinen et al., 1999b). Many investigators consider that tumors over 5 cm are malignant, while others may consider tumors over 6, 7, or 8 cm as malignant tumors (Ueyama et al., 1992; Lechago and Genta, 1996; Sanders et al., 1996). Ruptured tumors are reported to have a similar clinical outcome as tumors with peritoneal dissemination at surgery (Ng et al., 1992). Some reports showed that GIMTs in the esophagus appeared to have a benign course and that intestinal GIMTs showed poorer prognosis than gastric GIMTs (Miettinen et al., 1999b). Large tumors may be accompanied by macroscopic necrosis, which may result in poor outcome (Ueyama et al., 1992; Rosai, 1996). However, location of tumors, central necrosis and hemorrhage are not always predictive of clinical behavior.

Among histological findings, the most important prognostic factor is the mitotic count of tumor cells (Ng et al., 1992; Ma et al, 1993; Chou et al., 1996; Lechago and Genta, 1996; Rosai, 1996; Tornoczky et al., 1999). A mitotic rate over 5/10 high power field (HPF) is considered to indicate an aggressive and malignant tumor (Franquemont, 1995; Batts and Barwick, 1996; Miettinen et al., 1999b). Tumors with mitotic frequency over 5/10 HPF are usually diagnosed as high-grade malignancy, and those with mitotic frequency between 1 to 2/50 HPF and 5/10 HPF are diagnosed as intermediate-grade malignancy. Benign tumors show no mitotic figures or less than 1/50 HPF even if present. Other methods of evaluating proliferation activity, including DNA flow cytometry (S-phase fraction and ploidy), the number of nuclear organizing regions (AgNOR), proliferating cell nuclear antigen (PCNA) and Ki-67 may be correlated with mitotic count and offer additional diagnostic information (Kiyabu et al., 1988; Shimamoto et al., 1992; Yu et al., 1992; Franquemont and Frierson, 1995; Vrettou et al., 1995; Chou et al., 1996).

Other important histological factors indicating poor prognosis are high cellularity, marked pleomorphism, and the presence of histologic necrosis and hemorrhage (Batts and Barwick, 1996; Lechago and Genta, 1996; Rosai, 1996; Miettinen et al., 1999b). An increase in cellularity is correlated with an increase in biological aggressiveness. Tumors with marked pleomorphism and cellular atypia are rare but show significantly poor clinical outcome. The presence of histological necrosis or hemorrhage may reflect rapid growth of tumor cells, and considerable numbers of tumors with these features may be associated with poor prognosis. Histological grade based on these factors is also prognostic. In this connection, histological grade, cellularity, frequency of mitosis, and histological necrosis are reported to have prognostic importance in soft tissue sarcomas (Tsujimoto et al., 1988). GISTs show histologically aggressive features compared to myogenic and neurogenic tumors, i.e., GISTs may show relatively higher cellularity, more frequent mitotic count and more marked pleomorphism than the latter two tumors. The former may be thought to have poorer prognosis than the latter two. However, tumor cell type (spindle or epithelioid), subclassification of GIMT (myogenic, neurogenic or GIST), and expression of differentiation marker proteins may offer additional diagnostic information but are not considered to be important prognostic factors.

Recently, it was reported that mutations in the *c-kit* gene are associated with poor prognosis (Ernst et al., 1998; Moskaluk et al., 1999; Taniguchi et al., 1999; Sakurai et al., 1999b). GISTs with *c-kit* mutations recurred more frequently than GISTs without mutations. Patients with GISTs with *c-kit* mutations showed significantly poorer prognosis than patients with GISTs without such mutations. Thus, size of the tumor, mitotic rate, and *c-kit* mutation are considered to be the most reliable indicators of the prognosis.

c-kit gene mutation and other possible genetic changes in GIST

The *c-kit* gene is the cellular homologue of the oncogene, *v-kit* of the HZ4 feline sarcoma virus. KIT, of which the ligand is stem cell factor (SCF) (Anderson et al., 1990; Huang et al., 1990; Williams et al., 1990; Zsebo et al., 1990), is a type III receptor tyrosine kinase and structurally similar to receptors of macrophage colony-stimulating factor and platelet-derived growth factor (Yarden et al., 1987; Chabot et al., 1988; Geissler et al., 1998; Qiu et al., 1988). KIT plays important roles in hematopoiesis, melanogenesis, gametogenesis, and the development and survival of mast cells and ICCs.

Although gain-of-function mutations of the *c-kit* gene are found in both mast cell neoplasms and GISTs, the location of *c-kit* mutations differs between human mast cell neoplasms and human GISTs (Furitsu et al., 1993; Tsujimura et al., 1994; Nagata et al., 1995; Hirota et al., 1998; Nakahara et al., 1998; Lasota et al., 1999; Longley et al., 1999). A particular amino acid in the tyrosine kinase domain (Exon 17) is changed in mast cell neoplasms (e.g., point mutation in codon 816 changes aspartic acid to valine), whereas various mutations consisting of insertions, deletions, and/or point mutations of amino acids in the juxtamembrane domain (Exon 11) are observed in GISTs. The most frequent mutations in GISTs are frame deletions of 3 to 30 base pairs and less frequent mutations include frame

insertions and/or point mutations, which result in amino acid deletions, insertions and/or substitutions. Recently reported *c-kit* gene mutations in germ cell tumors including seminomas and dysgerminomas are also located in the kinase domain (Tian et al., 1999). The amino acid substitution in the kinase domain causes autophosphorylation of KIT, which results in constitutive activation of KIT without its ligand (Furitsu et al., 1993; Kitayama et al., 1995). On the other hand, mutations in the juxtamembrane domain are postulated to cause changes in the α-helical conformation of this domain, which results in loss of its inhibitory function for KIT dimerization (Ma et al., 1999). Thus, mutations in the juxtamembrane domain cause dimerization and autophosphorylation of KIT. It is still unknown which intracellular signaling pathways, including PI3 kinases, MAP kinases, STAT, and JAK2 pathways, are important for tumor cell growth and promotion (Weiler et al., 1996; Vosseller et al., 1997; Hemesath et al., 1998; Timokhina et al., 1998; Brizzi et al., 1999). Recently, new mutations were found in the extracellular domain (Exon 9) and in the other kinase domain (Exon 13), that were associated with constitutive phosphorylation of KIT tyrosine (Marcia et al., 2000). The mutations described above are found only in neoplastic cells of sporadic tumors, and not in the germline of patients bearing sporadic GISTs.

In this connection, a family with multiple GISTs and *c-kit* mutation has been reported (Nishida et al., 1998). Germline mutations of the *c-kit* gene were found in a patient with urticaria pigmentosa and aggressive mastocytosis or patients with multiple GISTs (Longley et al., 1996; Nishida et al., 1998). Both reported mutations are gain-of-function mutations. It is interesting that the mutation locus in the *c-kit* gene of the patients with aggressive mastocytosis or multiple GISTs is the tyrosine kinase domain (Exon 17) or juxtamembrane domain (Exon 11), respectively. Various types of loss-of-function mutation are reported in both domains of the gene in piebaldism (Giebel and Spritz, 1991; Nomura et al., 1998; Spritz and Beighton, 1998). Thus, gain-of-function mutations in the juxtamembrane domain are causative for GISTs.

Among GIMTs, only GISTs express KIT and have mutations in the *c-kit* gene (Taniguchi et al., 1999). Practically all GISTs express KIT, whereas neither myogenic nor neurogenic tumors express it. However, mutations in the *c-kit* gene were found in only half of GISTs (Taniguchi et al., 1999). Other reports have described lower or higher frequency of *c-kit* mutations in GISTs (Lasota et al., 1999; Miettinen et al., 1999b; Moskaluk et al., 1999; Sakurai et al., 1999b). No *c-kit* mutations have been found in myogenic or neurogenic tumors. The different rates of *c-kit* mutation found in GISTs may have been due to the small numbers of patients in each study, to differences in malignant tumor rates, and/or to different backgrounds of patients in each study. Whether mutation in the *c-kit* gene is an early oncogenic event is problematic, but no GISTs have been found to have new or additional mutations in the *c-kit* gene after relapse or recurrence (Taniguchi et al., 1999). Family members with multiple GISTs and germline mutation in the *c-kit* gene suffer from tumors with mostly benign and later malignant features from a young age and show the same mutation in the germline, benign GISTs, and malignant GISTs. Thus, mutation in the *c-kit* gene appears to be an early oncogenic event.

The concept that GISTs with *c-kit* mutation have higher proliferative activity may be supported by the following facts: 1) Mutations found in GISTs are gain-of-function mutations and have been shown to promote autonomous cell growth (Hirota et al., 1998; Nakahara et al., 1998); 2) GISTs with *c-kit* mutations showed higher mitotic counts (Table 2; Taniguchi et al., 1999); and 3) The frequent presence of histological necrosis and hemorrhage in GISTs with *c-kit* mutations is also consistent with this concept (Lasota et al., 1999; Taniguchi et al., 1999). Histologically aggressive features are correlated with poor clinical outcome. GISTs with *c-kit* mutations are larger and more frequently invade surrounding structures than those without mutations (Taniguchi et al., 1999). Thus, GISTs with *c-kit* mutations have aggressive histological and clinical features. Patients with mutation-positive GISTs suffered from more frequent recurrences and had higher mortality than those with mutation-negative GISTs (Ernst et al., 1998; Taniguchi et al., 1999). Although *c-kit* mutation was correlated with mitotic count, cellularity, pleomorphism, frequent presence of histological necrosis and hemorrhage, tumor size and invasion, in a multivariate analysis, mutation in the *c-kit* gene was an independent prognostic factor, like the previously reported prognostic factors of tumor size and mitotic count (Taniguchi et al., 1999).

Immunohistochemical features of mutation-positive GISTs are similar to those of mutation-negative GISTs and differ from those of myogenic and neurogenic tumors. However, histological aggressiveness and clinical outcome of mutation-positive GISTs are different from those of mutation-negative GISTs. The latter tumors have histological aggressiveness similar to that of myogenic and neurogenic tumors. No new mutation in the *c-kit* gene has been found in relapsed originally mutation-negative GISTs (Taniguchi et al., 1999). Thus, GISTs may be divided into mutation-positive and -negative subtypes (Table 2). These two subtypes seem to have somewhat different oncogenic background and clinical behavior. Therefore, GIMTs may be classifiable into tumors with myogenic and neurogenic differentiation, but the majority consist of a heterogeneous group of GISTs. The last group is dividable into at least two groups, that is, GISTs with *c-kit* mutation and GISTs without the mutation. The former group contains the most aggressive tumors and shows poorest prognosis among the four groups.

Mutation in the *c-kit* gene is causative for GIST, but additional oncogenic mechanisms exist. However, other genetic information about GISTs is scarce. Comparative genomic hybridization (CGH) indicated loss of 14q and

22q, and structural aberrations of chromosome 1 (El-Rifai et al., 1996; Miettinen et al., 1999b). These alterations are specific for GISTs and not for myogenic or neurogenic tumors. Carney et al. (1977) reported the association of gastrointestinal leiomyosarcoma, pulmonary chondroma, and functioning extra-adrenal paraganglioma in young women, which is called Carney Triad. Most previously diagnosed leiomyosarcomas are re-diagnosed as GISTs these days. Although a specific genetic background is postulated in Carney Triad (Carney, 1999), at present no detailed genetic data are available. Neurofibromatosis type I (von Recklinghausen's disease) is caused by mutations of NF1, and some pathogenetic relationship between neurofibromatosis and GISTs is postulated because of the high frequency of non-random association (Fuller and Williams, 1991; Ishida et al., 1996).

Origin of GIST and interstitial cells of Cajal

Interstitial cells of Cajal (ICCs) are derived from immature mesenchymal cells, and not from neural crest cells (Lecoin et al., 1996; Young et al., 1996). In fetal stomach and intestine, *c-kit* was expressed extensively throughout the presumptive smooth muscle layer at the gestational age of 9.5 weeks (Kenny et al., 1999). Without SCF, *c-kit*-positive cells are considered to differentiate into smooth muscle cells that express smooth muscle markers including α-smooth muscle actin and desmin (Torihashi et al., 1997, 1999). These cells are destined to lose KIT expression perinatally. Activation of the KIT signaling pathway by SCF ligand, which is expressed in neural crest-derived cells of the myenteric plexus, maintains KIT expression and induces characteristic spindle cells with long branching processes (Wester et al., 1999). Postnatally, expression of KIT/*c-kit* is localized in cells near the plexus, that is, ICCs. Thus, KIT expression in precursor cells of ICCs and concomitant expression of SCF in neighboring cells are important for normal development of ICCs (Maeda et al., 1992; Huizinga et al., 1995). No neural cells, including ganglion and Schwann cells, express KIT throughout development. CD34 is expressed in immature mesenchymal cells, vascular endothelial cells and ICCs.

GISTs express KIT and CD34 and show histological similarity to ICCs by ultrastructural examination (Hirota et al., 1998; Kindblom et al., 1998; Sircar et al., 1999). Co-expression of KIT and the embryonic form of smooth muscle myosin was observed both in GISTs and ICCs (Miettinen et al., 1995, 1999b; Sircar et al., 1999). Gain-of-function mutations in the *c-kit* gene cause GISTs (Hirota et al., 1998; Nishida et al., 1999). Loss-of-function mutations are associated with lack of ICCs and intestinal pacemaker activity, which results in decreased contractile activity and peristalsis and appears as paralytic ileus (Maeda et al., 1992; Huizinga et al., 1995; Isozaki et al., 1997). These results suggest a histological relationship between ICCs and GISTs. Kindblom et al. (1998) concluded that GISTs were tumors of ICCs, the gastrointestinal pacemaker cells, and named GISTs "gastrointestinal pacemaker cell tumors (GIPACTs)". However, some investigators consider that GISTs are not originated from ICCs (Chan, 1999; Miettinen et al., 1999b). Most omental and mesenteric mesenchymal tumors express KIT and show histological features similar to GISTs (Miettinen et al., 1999a). Most GISTs consistently show h-caldesmon reactivity but have no reactivity for calponin, suggesting traits of smooth muscle differentiation (Miettinen et al., 1999c). KIT is expressed in multipotential mesenchymal cells that differentiate into ICCs and smooth muscle cells as described above. Thus, Miettinen et al. (1999b) proposed that GISTs may arise from multipotential mesenchymal cells that can differentiate into both ICCs and smooth muscle cells.

GISTs consist of heterogeneous groups of mesenchymal tumors and include tumors showing phenotypically various differentiated features resembling those of cells ranging from multipotential mesenchymal cells to ICCs. Some differentiated tumors may show phenotypic features similar to those of ICCs and highly de-differentiated tumors may phenotypically resemble multipotential mesenchymal cells.

In summary, GIMTs can be divided into myogenic tumors, neurogenic tumors, GISTs without *c-kit* mutations, and GISTs with *c-kit* mutations. GIMTs are composed of spindle or epithelioid cells and 20% to 30% show malignant behavior including peritoneal dissemination and hematogenous metastasis mainly to the liver. Mutations in the *c-kit* gene are found only in GISTs and are associated with aggressive features. Metastasis, invasion, size of the tumor, mitotic rate, and *c-kit* mutation are the most reliable indicators of prognosis. The origin of GISTs is not fully understood; however, it is thought that they may originate from ICCs and/or multipotential mesenchymal cells that can differentiate into both ICCs and smooth muscle cells.

Acknowledgements. The authors are grateful for the helpful comments from Drs. Jun-ichi Nakamura and Masahiko Taniguchi, Department of Surgery, E1, Osaka University Graduate School of Medicine, and from Dr. Masahiko Tsujimoto, Department of Pathology, Osaka Police Hospital. This work was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture of Japan.

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Accepted June 14, 2000