Amino Acids (2007) 32: 395–400
DOI 10.1007/s00726-006-0386-y
Printed in The Netherlands

Amino Acids

Somatostatin analogues, a series of tissue transglutaminase inducers, as a new tool for therapy of mesenchimal tumors of the gastrointestinal tract

G. Palmieri[1], **L. Montella**[1], **C. Aiello**[2], **F. Barbieri**[3], **D. Di Vizio**[4], **S. Schulz**[5], **S. Beninati**[6], **A. Budillon**[7], **M. Caraglia**[7], **L. Insabato**[4], and **T. Florio**[3]

[1] Department of Molecular and Clinical Endocrinology and Oncology, ''Federico II'' University, Naples, Italy
[2] Pharmacology and Neuroscience, National Institute for Cancer Research, Genova, Italy
[3] Section of Pharmacology, Department of Oncology, Biology and Genetics, University of Genova, Genova, Italy
[4] Department of Biomorphological and Functional Science, Unit of Pathology, University ''Federico II'', Naples, Italy
[5] Department of Pharmacology and Toxicology, Otto-von-Guericke-University, Magdeburg, Germany
[6] Department of Biology, Second University of Rome ''Tor Vergata'', Rome, Italy
[7] Department of Experimental Oncology, Experimental Pharmacology Unit, National Institute of Tumours ''G. Pascale'', Naples, Italy

Received June 6, 2006
Accepted July 14, 2006
Published online February 6, 2007;

Summary. Imatinib, a tyrosine kinase inhibitor directed against the enzymatic domain of KIT protein, was found to produce dramatic clinical responses in metastatic gastrointestinal stromal tumors (GISTs). However, resistance usually develops thus determining treatment failure. The present study was performed to analyse the expression of somatostatin receptor (SSTR) subtypes, modulators of tissue transglutaminase, in a series of GISTs and leiomyosarcomas by immunohistochemistry to identify a new potential therapeutic target. Sixteen cases (8 males and 8 females, age range: 38–73; 11 GISTs, 4 leiomyosarcomas, 1 leiomyoma) were studied. Immunohistochemical detection of the relevant SSTRs was performed on paraffin-embedded tissue sections, stained with polyclonal antibodies directed against the five somatostatin receptor subtypes. We found 7 out of 16 (44%) tumors expressing all SSTRs and 14 out of 16 (87%) tumors positive for at least 3 subtypes. $SSTR2_A$ was the most represented subtype in the tumors studied, being expressed in approximately 70% of cases exhibiting an intense labeling in most of these cases. The significant expression of SSTRs shown in this series of GISTs and gastrointestinal leiomyosarcomas suggests a potential therapeutic target to be explored alone and/or in combination with other therapeutic agents in the setting of refractory GI stromal tumors.

Keywords: GIST – Gastrointestinal leiomyosarcomas – Tissue transglutaminase – Somatostatin receptor – Immunohistochemistry – Imatinib

Introduction

Mesenchymal tumors of the gastrointestinal (GI) tract, showing evidence of smooth muscle differentiation may occur in any portion of the intestine, but mostly in the large intestine, while most gastrointestinal stromal tumors (GISTs) occur in the stomach and small intestine. GISTs are rare tumors, although they are the most common mesenchymal tumors of the GI tract. They account for 2.2% of gastric cancer, 13.9% of small bowel cancer, and 0.1% of all colorectal cancers (Thomas and Sobin, 1995). These tumors are still object of discussion about their origin, histopathological classification and prognostic factors. They are defined and diagnosed by the expression of CD117, a receptor tyrosine kinase encoded by c-kit proto-oncogene (de Silva and Reid, 2003). Recently, a new risk classification for aggressive tumors, based on tumor size and mitotic index, divided GISTs in 6 categories. Tumors assigned to groups 1 and 2 were considered to be benign or probably benign, group 3 represents GISTs with uncertain malignant potential, and groups 4, 5, and 6 were considered with malignant potential (Lasota et al., 2003). Recently, the analysis of a large series of cases has assessed clinicopathological features with a potential prognostic impact (Miettinen et al., 2005). These investigations may be helpful in defining new risk categories of tumors that are candidate for a selected therapeutic strategy. A major clinical advance has been driven by the relatively recent recognition of activating kit mutations in the pathogenesis of GISTs (Hirota et al., 1998). The prognostic meaning of KIT mutations is controversial and until now not clearly related to the biologic behavior of GISTs (Koh et al., 2004). KIT-wild type GISTs have also shown mutually

exclusive platelet-derived growth factor receptor (PDGFR) mutation and activation (Heinrich et al., 2003).

Recently, a small molecule tyrosine kinase inhibitor (STI-571, imatinib mesylate, Gleevec, Novartis Europharm Ltd., West Sussex, U.K.) directed against the enzymatic domain of KIT protein was found to produce dramatic clinical responses, used as monotherapy for metastatic GISTs and changed the history of these chemorefractory tumors (van Oosterom et al., 2001; Joensuu et al., 2000). In most of GISTs, the identified mutations involve regulatory sites of KIT. In these instances, imatinib retains the binding to the KIT protein, thus blocking its activity. However, when the mutations modify the enzymatic site, a structural protein change occurs, resulting in resistance to imatinib and treatment failure. This condition, ultimately, results in increasing need for a better understanding of histogenesis, biological/clinical behavior and alternative therapeutic strategies in GISTs.

Somatostatin (SS), initially described as a powerful inhibitor of the secretion of different pituitary and gastrointestinal hormones (Lamberts et al., 1996) and known to be a regulator of tissue transglutaminase (TTGase) expression (Szende et al., 1991), was recognized to be also an active anti-proliferative agent for different epithelial and neuroendocrine tumors (Schally, 1988; Reubi and Laissue, 1995). This activity is mediated via direct anti-proliferative effects also occurring through TTGase modulation, and, indirectly reducing growth factor release (for example insulin-like growth factor-1) or by inhibition of tumor neo-angiogenesis (Albini et al., 1999; Florio et al., 2003a).

To date five somatostatin receptor (SSTR) genes, named from SSTR1 up to SSTR5, have been cloned with different pharmacological properties, i.e. somatostatin analogs selectivity, tissue distribution, regulation and intracellular signaling (Schonbrunn, 1999). SSTRs have been reported to exert their biological effects through the inhibition of cAMP formation, the modulation of Ca^{++} and K^{+} channel activities (Florio and Schettini, 1996a) and the induction of a phosphotyrosine phosphatase (PTP) activity that was proposed to be responsible for the direct anti-proliferative activity of this peptide in different normal and transformed cells (Pan et al., 1992; Buscail et al., 1994; Florio et al., 1996b, 2001). In detail, the SS-dependent PTP activity was reported to directly inhibit ERK1/2 activation leading to a $p27^{kip1}$-dependent arrest of the cell cycle in G0/G1 (Florio et al., 2001; Massa et al., 2004a).

The detection of SSTR by both in vivo and in vitro tools has usually provided the rationale for therapeutic use of SS analogs. Therefore, in line with previous investigations from our group (Florio et al., 2003b), the present study was performed to analyse the expression of SSTR subtypes in a series of GI stromal tumors by immunohistochemistry possibly identifying alternative therapeutic targets.

Materials and methods

Origin of tissue samples

Sixteen cases of mesenchymal tumors of GI tract (8 males and 8 females, age range: 38–73 years, median age: 60 years) diagnosed at University "Federico II" of Naples were studied. All characteristics of the tumors are comprehensively reported in the Table 1. Eleven GISTs, four leiomyosarcomas and one leiomyoma were included. GISTs were located in the stomach, in the small intestine and in the mesenterium respectively in six, four and one patients. Leiomyosarcomas arised in the stomach in two patients, in the small intestine and the colon in the other two patients of the present series. One patient with a gastric leiomyosarcoma (pt.1) was evaluated twice as both primitive tumor and metastatic lung lesion. The only leiomyoma included was located in the oesophagus. All GISTs of this series were positive for c-Kit, while the other tumors were negative.

Immunohistochemistry

Analysis was performed on one representative block from each case by using the avidin biotin peroxidase complex detection system (LSAB kit from Dako, Carpinteria, CA, USA), with diaminobenzidine as the chromogen. Antibodies to the following antigens were used: KIT (CD117), CD34, α-smooth muscle actin, desmin, and S-100 protein (Dako). All GISTs displayed strong immunoreactivity for CD117. The staining was in the cytoplasm, with a granular and homogeneous quality. In four gastric GISTs a strong positivity for CD34 in the neoplastic cells was observed. The leiomyosarcomas and the leiomyoma showed reactivity for muscle actin and, focally, for desmin and were negative for CD117, CD34, and S-100 protein.

Immunohistochemical detection of the relevant SSTRs was performed on sections (4 μm) of paraffin-embedded tissue stained with the following monoclonal antibodies: anti-SSTR1, anti-$SSTR2_A$, anti-SSTR3, anti-SSTR4 and anti-SSTR5 that were generated as reported. Twenty–three antisera were used at the dilution of 1:100. Sections were subjected to routine deparaffinization and rehydration, and then deepen in sodium citrate buffer (pH 6.0), heated in a microwave oven for 2 min, and then allowed to cool for 10 min. Subsequently, sections, treated in PBS containing 0.3% Triton for 10 min and rinsed in TBS buffer (0.05 M Tris–HCl, 0.15 M NaCl, pH 7.6), were saturated with 10% normal goat serum in TBS for 20 min and then incubated with the primary antibodies at a 1:100 dilution in CHEM-MAT^{TM} solution (Dako) at 4 °C overnight. After three washes in TBS, the sections were incubated with biotinylated secondary antibodies anti-rabbit (Dako, dilution 1:500) for 30 min. Finally, the sections were washed and incubated for 20 min with StreptABComplex/AP (Dako), according to the manufacturer's instructions revealed with BCIP/NBT/INT substrate system (Dako) and counterstained with hematoxylin before being mounted with Mowiol (Calbiochem). Negative controls were included in all the immunohistochemical analyses by omitting the primary antibodies. Microphotographs were obtained with a Nikon DS digital camera. The positive labelling was scored as faint (+) and strong (++) labelling, to differentiate low from high level of receptor expression.

Statistical analysis

Data, grouped into categories (number of mitosis vs. SSTR subtypes expression), were analyzed by correlations with the χ^2 test (Statistical 4.1

program, StatSoft, Inc). Values of p equal or lower than 0.05 were considered statistically significant.

Results

The analysis of SSTR subtype expression in our series, summarized in Table 1, showed a cytoplasmic expression of all receptor subtypes in 8 out of 16 tumors (50%) while at least 3 out of 5 subtypes were expressed in 14 out of 16 (87%) tumors. Generally neoplastic cells from both GIST and leiomyosarcomas showed expression of SSTR. Representative immunostaining for one GIST and one leiomyosarcoma (cases 16 and 4, respectively) is reported in Fig. 1.

GIST no.16 showed a strong expression of SSTR1 and $SSTR2_A$ (see Fig. 1, left panel). Another case (no. 5), corresponding to a leiomyoma arising in the oesophagus, displayed faint labeling for $SSTR2_A$ and SSTR4. $SSTR2_A$ was the most represented subtype in the tumors studied, being expressed in approximately 70% of cases and usually exhibiting an intense labeling. Similarly, SSTR1 and SSTR4 were also strongly expressed in many cases (63 and 56%, respectively). On the other hand, SSTR3 and SSTR5 were identified in a minority of the tumors studied (31 and 19%, respectively) and usually presented a faint pattern of expression.

In detail, immunohistochemistry analysis revealed a significant expression of SSTRs in GISTs studied. In fact, all GISTs resulted positive for more than two SSTR subtypes except for case 13 corresponding to a tumor located in the mesenterium which did not express any SSTR (Table 1). All SSTRs were expressed in 5 out of 11 GISTs (45%). $SSTR2_A$, SSTR1 and SSTR4 were strongly expressed respectively in 8 out of 11 (72%), 7 out of 11 (64%) and 6 out of 11 (54%) GISTs. The remaining subtypes were strongly expressed in $\leq$36% GISTs examined.

Interestingly, statistical analysis showed that high level of expression of SSTR4 correlated, in a significant manner ($p = 0.037$) with GIST showing a low mitotic index (<5 mitosis per HPF, see Table 1). Also the expression of SSTR1 was more often associated with a low number of mitosis, although it was not statistically significant ($p = 0.069$). Conversely, no correlation was observed with the expression of $SSTR2_A$ ($p = 0.621$), SSTR3 ($p = 0.819$) and SSTR5 ($p = 0.153$).

All 4 leiomyosarcomas of this series expressed SSTRs. SSTR4 and SSTR5 were detected in all cases. Figure 1 (right panel) show case no. 4, expressing all SSTRs except for SSTR1 and SSTR3. Two leiomyosarcomas (nos. 1 and 3) arising in the stomach expressed all subtypes. One leiomyosarcoma (no. 1) was evaluated as concerning the primitive site (stomach) and the lung metastasis. The primitive lesion resulted positive for all SSTRs with SSTR1 and $SSTR2_A$ showing a strong pattern of labeling, while the metastasis was strongly positive for SSTR3 and SSTR4 and weakly positive for SSTR5.

Table 1. Characteristics of tissue samples of mesenchymal tumors

Patient	Sex/Age	Location	Size (cm)	C-Kit	Mitosis	Diagnosis	SSTR1	$SSTR2_A$	SSTR3	SSTR4	SSTR5
1	M/65	Stomach	8.5	Neg	2	LMS	++	++	+	+	+
	M/65	Lung	4	Neg	2	Met	−	−	++	++	+
2	M/50	Small intestine	8	Neg	2	LMS	++	−	++	++	++
3	M/60	Stomach	12	Neg	2	LMS	++	++	+	++	+
4	M/65	Colon	10	Neg	2	LMS	−	++	−	+	+
5	M/38	Oesophagus	5	Neg	1	LM	−	+	−	+	−
6	F/63	Stomach	5	Pos	1	GIST	++	++	+	++	++
7	F/67	Small intestine	3.5	Pos	1	GIST	+	++	++	++	+
8	M/48	Small intestine	13	Pos	1	GIST	++	+	−	++	++
9	M/54	Stomach	10	Pos	1	GIST	++	+	+	++	+
10	F/48	Stomach	25	Pos	2	GIST	+	++	++	++	+
11	M/51	Stomach	10	Pos	2	GIST	+	++	++	+	+
12	F/62	Stomach	5	Pos	1	GIST	++	++	+	++	+
13	F/73	Mesenterium	5.3	Pos	2	GIST	−	−	−	−	−
14	F/46	Small intestine	8	Pos	2	GIST	++	++	−	+	+
15	F/71	Stomach	8	Pos	1	GIST	++	++	++	−	−
16	F/52	Small intestine	13	Pos	2	GIST	++	++	−	−	−
Rate of strong labelling							10/16 (62.5%)	11/16 (68.7%)	6/16 (37.5%)	9/16 (56%)	3/16 (18.7%)

M Male, *F* female, *LMS* leiomyosarcoma, *LM* leiomyoma, *Met* metastasis, *GIST* gastrointestinal stromal tumors
1: <5 mitosis × 50 HPF; 2: >5 mitosis × 50 HPF; − no labelling, + faint labelling, ++ strong labelling.

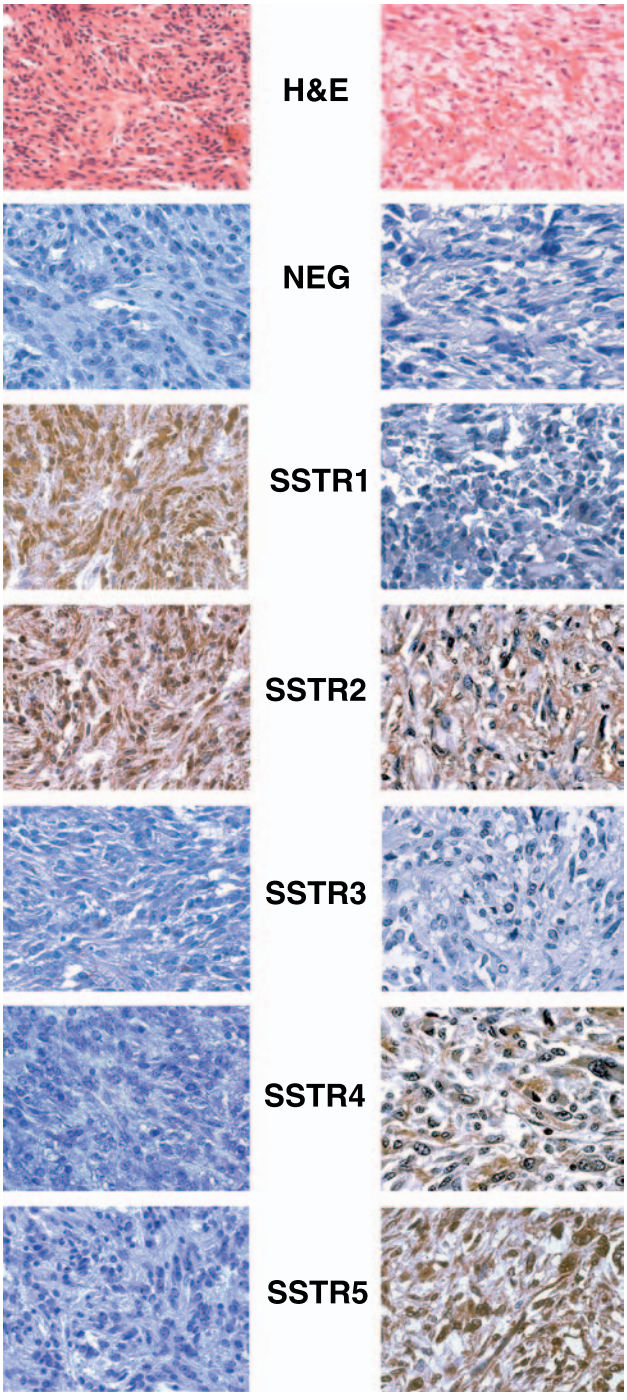

Fig. 1. Representative immunostaining with SSTR1–5 antibody of a GIST (left column) and a leiomyosarcoma (LMS) (right column). The selected cases correspond to cases no. 16 and 4, as reported in Table 1. Positive staining is indicated as a brown precipitate whereas unstained nuclei appear blue because of the hematoxylin counterstain. Hematoxylin-eosin (H&E, *1–2*) stain and negative controls (stained with the secondary antibody) (NEG, *3–4*) are also reported. *5–6* SSTR1, *7–8* SSTR2, *9–10* SSTR3, *11–12* SSTR4, *13–14* SSTR5

Discussion

Although imatinib can reasonably be considered as the always wished "wonderful bullet" in some malignancies and among them GISTs, the occurrence of therapeutic resistance leads to further biological and clinical investigations. Some studies are investigating increasing doses of imatinib, others are testing new inhibitors of tyrosine kinases, such as SU11248 or the combination of imatinib with novel agents. In this respect, the significant expression of different SSTRs reported here can represent an interesting field of research. Interestingly, we identified in our GIST series a significant correlation between the proliferating fraction of tumor cells and high level of expression of SSTR4 and SSTR1, although the latter did not reached the statistical significance. Therefore, although further studies will be required to confirm this observation due to the limited number of tumor analyzed, our data suggest that the expression of SSTR subtypes can be correlated to reduced proliferation of these tumors.

SSTR1 and $SSTR2_A$ were not detected in a metastatic lesion, while visualized in the primitive corresponding tumor, suggesting the occurrence of a progressive loss of differentiation markers during the progression of the disease. Any consideration on possible changes in patterns of SSTR expression cannot be made because only one sample was evaluable for primitive and metastatic lesions. Similar restrictions hampered the evaluation of changes in pattern of SSTR expression between leiomyoma and leiomyosarcoma. However, the malignant tumors of the present series showed a more significant SSTR expression than the benign counterpart.

Human mesenchymal tumors, and bone and vessel-derived malignancies preferentially, expressed SSTRs, as demonstrated by Reubi et al. (1996) with autoradiography. SSTRs were shown to be expressed in 84% of 31 human intermediate and malignant soft tissue tumors studied by reverse transcription-polymerase chain reaction (RT-PCR) (Florio et al., 2003a). Those series included also 3 non-GI-leiomyosarcomas and 2 GISTs. Except for the absence of SSTR4 in one case, all SSTRs have been found in the three leiomyosarcomas examined. The two GISTs expressed SSTR2 mRNA, with a variable pattern of expression of the remaining SSTRs (Florio et al., 2003b).

SSTRs have been previously detected in the non-neoplastic gut mucosa as well as lymphoid tissue, nerve plexus, circular smooth muscle at the mucosa directed margin, and the vasculature by in vitro receptor autoradiography (Gugger et al., 2004). In detail, the duodenum and prox-

imal jejunum contain a high number while distal jejunum and ileum present a low number of $SSTR2_A$ positive cells (Gugger et al., 2004). Both human gastrointestinal lymphatic and nervous components express $SSTR2_A$ (Gugger et al., 2004; Reubi et al., 1999). In fact, $SSTR2_A$ expression was identified in nerve elements entering and/or leaving the plexus and possibly in the membrane of ganglion cells (Reubi et al., 1999). It was hypothesized that $SSTR2_A$ expressed in the myenteric plexus was involved in the regulation of peristalsis and motility (Massa et al., 2004b). The wide expression of the different SSTRs and the strong labeling in a large percentage of cases studied are agreement with both our data and the proposed origin of GISTs by the interstitial cell of Cajal or ''pacemaker cells'', which play a neuromotor role in normal gut motility.

In the past years the activation of PTPs emerged as possible relevant intracellular mechanism involved in SS antiproliferative activity. In detail, it was reported that in glioma cells, SS activated a specific PTP (PTPη/DEP-1) able to directly dephosphorylate and inactivate ERK1/2 (Massa et al., 2004a). Interestingly, the recently developed antitumoral drugs that selectively inhibit the tyrosine kinase activity of different growth factor receptors may be nicely integrated by compounds able to activate PTP. Thus, the activation of SSTR by SS analogues, via the activation of specific PTP may synergize with compounds acting on the same intracellular pathway via different mechanisms. In the case of GIST, the inhibition of c-kit activity induced by imatinib, resulting in inhibition of ERK1/2 activation that in turn mediates proliferation, may be greatly increased by the direct inhibition of ERK1/2 via SSTR, resulting in a significant synergism and allowing a better clinical output (Wandzioch et al., 2004).

Altogether these considerations make particularly appealing the promise of a possible therapeutic association of imatinib and SS analogs, that are known as TTGase modulators, in this clinical setting.

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Authors' address: Dr. Giovannella Palmieri, Department of Molecular and Clinical Endocrinology and Oncology, "Federico II" University, via Pansini 5, 80131 Naples, Italy,
Fax: +39-081-7462114, E-mail: giovannella.palmieri@email.it