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Coincidence of EGF Receptors and Somatostatin Receptors in Meningiomas but Inverse, Differentiation-Dependent Relationship in Glial Tumors

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Somatostatin (SS) receptors as well as EGF receptors have been shown to be present in various brain tumors such as meningiomas or glia-derived tumors. Using receptor autoradiography for both receptors, their localization on adjacent tumor sections was investigated and a correlation was attempted. In glia-derived tumors, there was an inverse relationship for the incidence of the two receptors in individual tumors: in a majority of cases (five of eight) of well-differentiated astrocytomas (I-II), SS receptors were present, but in none of the cases (zero of eight) EGF receptors were detected. In undifferentiated glioblastomas, the reverse situation was observed, no SS receptors were found (0 of 14) but EGF receptors were present in a majority of tumors (8 of 14). In astrocytomas III both types of receptors were normally seen. These data suggest that in glia-derived tumors, SS receptors are markers for the well-differentiated cases as opposed to EGF receptors. In meningiomas, SS receptors are found in all (27 of 27) tumors and EGF receptors in a large percentage (23 of 27) of the same tumors. However, in some cases a coincidence of both receptors on the same cell can be excluded. Furthermore, no effect of the SS analog SMS 201-995 on basal or EGF-stimulated growth of meningiomas in culture could be detected. Nevertheless, the coexistence of the two receptor types in meningiomas may be suggestive for a potential functional interaction between EGF and SS. (Am J Pathol 1989, 134:337–344)

Somatostatin (SS) receptors have been shown to be the molecular basis of SS action in normal tissue from laboratory animals as well as humans.[1–3] In addition, they may mediate SS actions in numerous human tumors, because a high incidence of SS receptors have recently been found in tumors originating from endocrine target tissues, in particular SS targets, such as GH-producing pituitary adenomas or hormone-producing gastroenteropancreatic tumors.[4–6] In an increasing number of patients SS analogs are being used as therapeutic tools to successfully treat many of these tumors.[7–9] It is assumed that SS acts basically by its pronounced physiologic action of hormone secretion inhibition mediated through SS receptors on the tumor site.

There have been a number of reports showing that a wide variety of human tumors, often not originating from established SS target tissues, also have a high quantity of SS receptors. This has been shown in all tested tumors derived from the leptomeninges, such as meningiomas, and also in a large proportion of well-differentiated glia-derived tumors, astrocytomas, and oligodendrogliomas, and finally in a smaller number of breast tumors.[10–12] This relatively ubiquitous distribution among brain and endocrine tumors may be of interest for pathology, in terms of tools for tumor characterisation, as steroid receptors are currently. However, the role of these SS receptors in tumors, specifically in those not originating from SS target tissues, is still far from being understood. It is not clear whether they mediate primarily an inhibition of hormone secretion or whether they play a more direct role in antiproliferative mechanisms, as suggested by recent reports of an interaction of SS with epidermal growth factor (EGF).[13–15]

The aim of this study was to further characterise the type of tumors bearing SS receptors by correlating their SS receptor status with their content of EGF receptors, a recently established tumor marker for low grades of differentiation and poor prognosis[16–18] in various types of

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tumors including brain tumors. This may also give clues about the existence of a molecular basis for a direct SS-EGF interaction. For this purpose, both SS and EGF receptors have been visualized with autoradiographic techniques on adjacent tissue sections originating from meningiomas and glia-derived tumors. Furthermore, we have studied the response of cultured meningioma cells to EGF and to the somatostatin analog SMS 201-995 (Sandostatin). We have tried to establish whether a similar functional relationship exists between these two peptides as has been shown previously in a number of cell lines.[13–15]

Methods

Samples

Fifty-three human tumors consisting of 27 meningiomas, 12 astrocytomas, and 14 glioblastomas were obtained at surgery from the University hospitals in Zürich and Rotterdam.

Receptor Autoradiography

Immediately after removal of the tumor, one part was taken for histologic examination, and the other part was processed as follows. The tissue was immediately placed on ice and within a maximal delay of 60 minutes frozen at −80 C. The storage time of the tumors at −80 C before autoradiographic processing ranged from 10 days to 5 years. Tumor sample diameters were between 2 and 20 mm.

Frozen material was cut on a cryostat for autoradiographic visualization of SS receptors as described previously[6,11] using the stable octapeptide ^{125}I-204-090, a Tyr^3 analogue of SMS 201-995, as well as the somatostatin-28 (SS-28) analogue ^{125}I-[Leu^8, D-Trp^{22}, Tyr^{25}]-SS-28 (^{125}I-LTT-SS-28). Both ligands were iodinated and purified as described previously and characterized in standard binding assays.[6,11] For autoradiography, the tumors were cut on a cryostat (Leitz 1720) in 10 μ sections, mounted on precleaned microscope slides, and stored at −20 C for at least 3 days to improve adhesion of the tissue to the slide. Sections were preincubated in TRIS-HCl buffer (50 mM, pH 7.4), containing $CaCl_2$ (2 mM) and KCl (5 mM), for 10 minutes at ambient temperature and then washed twice for 2 minutes in the same buffer without additional salts added. Incubation was carried out for 2 hours at ambient temperature in TRIS-HCl buffer (170 mM, pH 7.4), containing bovine serum albumin (1%), bacitracin (40 μg/ml), and $MgCl_2$ (5 mM) to inhibit endogenous proteases in the presence of iodinated ligand (0.16×10^6 dpm/ml, ca. 80 pM). Nonspecific binding was determined by adding unlabeled 204-090 or SS-28, depending on the radioligand used, at a concentration of 1 μM. Moreover, for specificity control, at least one section was incubated with 10^{-6} M of an unrelated peptide such as luteinizing-hormone-releasing-hormone (LHRH) or the biologically inactive SS-28 moiety SS-28 (1–12). Incubated sections were washed twice for 5 minutes in ice-cold incubation buffer containing 0.25% BSA. After a brief dip in distilled water to remove excess salts, the sections were dried quickly, apposed to [^{3}H]-LKB films and exposed for 1–3 weeks in x-ray cassettes.

EGF receptors were visualized on adjacent tumor tissue sections under the same experimental conditions as for SS receptors,[19,20] using a 2-hour incubation period at ambient temperature in the presence of 0.16×10^6 dpm/ml of ^{125}I-EGF (NEN, Boston, MA; specific activity, 1000 Ci/mmoles). Nonspecific binding was measured in presence of 10^{-7} M EGF. A tumor was considered to be receptor-positive on an autoradiogram if at least part of it had an optical density value for the total binding at least twice the value measured for the nonspecific binding.

Selected tumors in which both SS and EGF receptors were visualized with autoradiographic methods were also characterized biochemically in homogenate binding assay as described previously[10–12] to exclude any affinity of EGF for SS receptors or of SS analogs for EGF receptors.

Meningioma Cell Cultures

Samples of meningioma tissue were obtained within 30 minutes of surgery. They were cleaned of obvious non-meningiomal tissue (such as capsules and large adherent blood vessels), and minced to small pieces (approximately 1 cu mm). The minced tissue was washed twice with Ca^{2+} and Mg^{2+}-free Hanks' balanced salts solution (HBSS, Gibco Europe, Breda, The Netherlands) containing 1% human serum albumin (HSA, Centraal Laboratorium Bloedtransfusiedienst, Amsterdam, The Netherlands). The washed mince was incubated with dispase (2.4 U/g tissue; Boehringer Mannheim, Almere, The Netherlands) during 2 hours in a shaking waterbath at 37 C. After incubation the tissue was dispersed by repeated pipetting; remaining fragments were allowed to settle and the resulting cell suspension was layered on Ficoll-Isopaque (density, 1.077 g/ml, prepared by the pharmacy of the University Hospital Rotterdam, The Netherlands). After centrifugation (20 minutes, 450*g*) the viable cells were removed from the interphase, washed twice with HBSS/HSA, and suspended in Minimal Essential Medium (MEM, Gibco Europe) with 10% fetal bovine serum (FBS, Flow/Amstelstad, Zwanenburg, The Netherlands), 100 U/ml penicillin (Gist, Brocades, Delft, The Netherlands), 100 μg/ml streptomycin (Pharmachemie, Haarlem, The Netherlands), and 1.5 μg/ml fungizone (Squibb, Rijswijk, The Netherlands). The cells were seeded in 24-well tissue cul-

Table 1. *Distribution of SS-R and EGF-R in Meningiomas*

Case no.	Histology	Receptor incidence SS-R	EGF-R	R distribution*
A 9-1	Meningioma, transitional/syncytial	+	+	No overlapping
17227	Meningioma	+	−	
19116	Meningioma	+	+	
20194	Meningioma	+	+	
K-22	Meningioma, transitional	+	+	
E-45-6	Meningioma, transitional	+	+	
E-52-2	Meningioma, transitional/syncytial	+	+	No overlapping
E-43-10	Meningioma	+	+	No overlapping
E-42-15	Meningioma, psammomatous	+	+	No overlapping
A-264	Meningioma, transitional	+	+	No overlapping
A-234	Meningioma, transitional	+	+	
A-302	Meningioma, syncytial	+	+	
E-49-12	Meningioma, syncytial	+	+	No overlapping, R on different cell elements
80-12	Meningioma, syncytial	+	+	No overlapping
A-76	Meningioma, syncytial with mitoses	+	+	
A-148	Meningioma, syncytial	+	+	
A-241	Meningioma, syncytial, transitional	+	+	
A-248	Meningioma, syncytial, anaplastic, with mitoses	+	+	
A-243	Meningioma, transitional	+	+	
A-219	Meningioma, syncytial, transitional	+	+	
A-233	Meningioma, syncytial	+	+	
A-216	Meningioma, anaplastic, with mitoses	+	+	
34774	Meningioma	+	−	
34463	Meningioma	+	−	
122	Meningioma, recurrence of E-43-10	+	+	
80-7	Meningioma, recurrence of E-49-12	+	+	
7442-87	Meningioma	+	−	

+, presence; −, absence of receptor.
* Only cases without overlapping of both receptors over the same structure are listed.

ture plates (Costar Europe, Badhoevedorp, The Netherlands) at 100,000 cells per well in 1 ml of MEM/FBS. The cultures were maintained in a water-saturated 5% CO_2 atmosphere at 37 C. The culture medium was refreshed twice weekly.

Experiments with Cultured Meningioma Cells

To establish the effects of the somatostatin analog SMS 201-995 on the growth of meningioma cells *in vitro,* cultures were given fresh MEM/FBS and SMS 201-995 was added at concentrations ranging from 10^{-7} to 10^{-10} M. Twenty hours later 1 μCi of [methyl-^{3}H]-thymidine (60–90 Ci/mmol, Amersham Nederland, Houten, The Netherlands) was added. After 4 hours of additional incubation the cultures were washed, the cells were solubilized, and the incorporation of thymidine was measured by liquid scintillation counting. Effects of EGF (Boehringer Mannheim) and of the combination EGF/SMS 201-995 were measured in a similar way except that in this case the incubation medium was not MEM/FBS, but serum-free MEM to which a number of substances had been added (transferrin, 10 mg/l; biotin, 0.1 mg/l; Na_2SeO_3, 8 μg/l; DL-α-tocopherol, 2 mg/l; D-(+)-galactose, 7.5 mg/l; all from Sigma, St. Louis, MO).

Results

Table 1 summarizes the results of SS receptors and EGF receptor determination in 27 meningiomas; SS receptors were found in all tumors. In addition, all cases but four contained SS and EGF receptors simultaneously, demonstrating a coincidence of SS and EGF receptors in the same tumor. Although in some cases both types of receptors seem to be relatively homogeneously distributed over the entire tumor area, with sparing of connective tissue (Figure 1 left), we have no evidence yet that they are localized on the same tumor cells. On the contrary, a careful analysis seems to indicate that in some cases the pattern of distribution in a given tumor area is clearly different for both receptor types (Table 1), suggesting that each receptor is localized in specific areas of the tumor, possibly on distinct cells. A particularly impressive case is shown in Figure 1 right, where the topographic location of each receptor type seems to be complementary. The center of the tumor, which contains preferentially EGF receptors, is likely to be composed of necrotizing cells. The surroundings, composed of intact tumor cells, contain numerous SS receptors but no or very little EGF receptors. Figure 2 shows the high affinity and the pharmacologic specificity of each receptor in a membrane homogenate from a single meningioma. Only EGF but not SS analogs are able

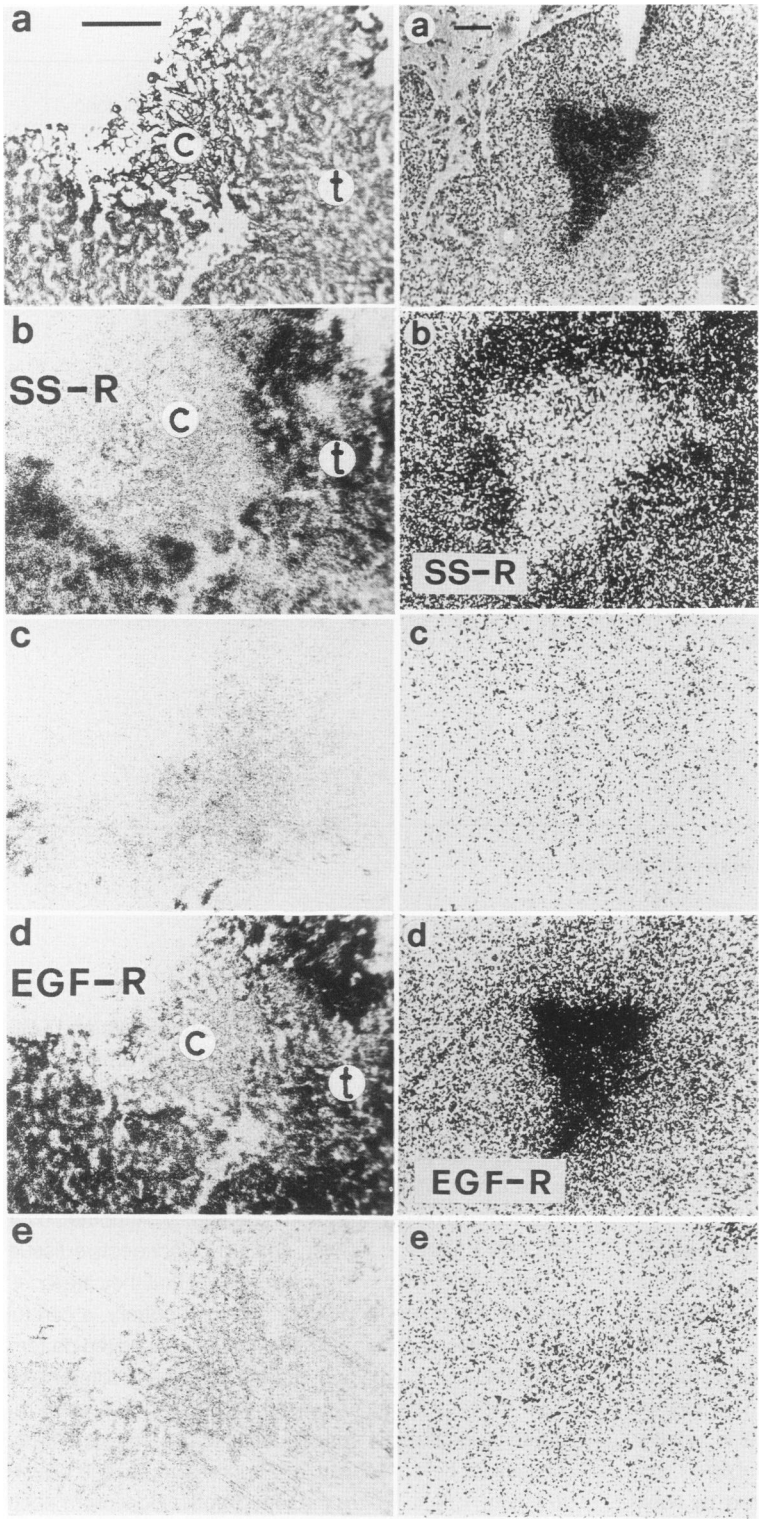

Figure 1. *Somatostatin and EGF receptors in two different meningiomas. Left: Case No. E 45.6. Right: Case No. E 49-12.* **a:** *Hematoxylin stained sections.* **b,c:** *Autoradiograms of SS receptors labeled with ^{125}I-LTT-SS-28.* **b:** *Total binding.* **c:** *Nonspecific binding in presence of 10^{-6} M SS-28.* **d,e:** *Autoradiograms of EGF receptors.* **d:** *Total binding.* **e:** *Nonspecific binding in presence of 10^{-7} M EGF. Left: The tumor area (t) contains both receptors, whereas connective tissue is free of receptors (c). Right: Tumor lobule with necrotising area in the center, which shows EGF receptors but no SS receptors. In the surrounding tumor area, more SS receptors than EGF receptors are seen. Exposure time: SS receptors: 1 week; EGF receptors: 3 weeks. Bars, 1 mm.*

to displace the ^{125}I-EGF radioligand in the high affinity range; only SS analogs but not EGF can displace the ^{125}I-LTT-SS-28 radioligand.

A different situation than in meningiomas is found in glia-derived brain tumors. As seen in Table 2, five of the eight well-differentiated astrocytomas have SS receptors but none has EGF receptors, whereas the contrary is observed in undifferentiated glioblastomas. None of the 14 tumors contained SS receptors but 8 of 14 glioblastomas contained EGF receptors. In four astrocytomas graded II or III, both SS and EGF receptors can be detected in varying concentrations. As examples, receptor status is

shown with autoradiography for an astrocytoma I (Figure 3 left), an astrocytoma III (Figure 3 right), and a glioblastoma (Figure 4). It should be noticed that in the example depicting the astrocytoma III, where both receptors seem present, only EGF receptors are present on the tumor whereas the SS receptors are exclusively located on healthy brain tissue.

Cultured Meningioma Cells

Six of the meningiomas mentioned in Table 1 were also studied in cell culture (E-52-2, A-9-1, 80-12, E-49-12, 80-7, and 122). No significant change of the incorporation of tritiated thymidine by these cultured meningioma cells was seen when they were incubated with SMS 201-995 in concentrations between 10^{-7} and 10^{-10} M. All of the meningiomas tested with EGF (0.1–100 ng/ml) showed increased incorporation of tritiated thymidine in response to exposure to EGF (E-52-2 and 80-12, Table 3). Increases of the incorporation of tritiated thymidine from 20–100% above basal level were seen.

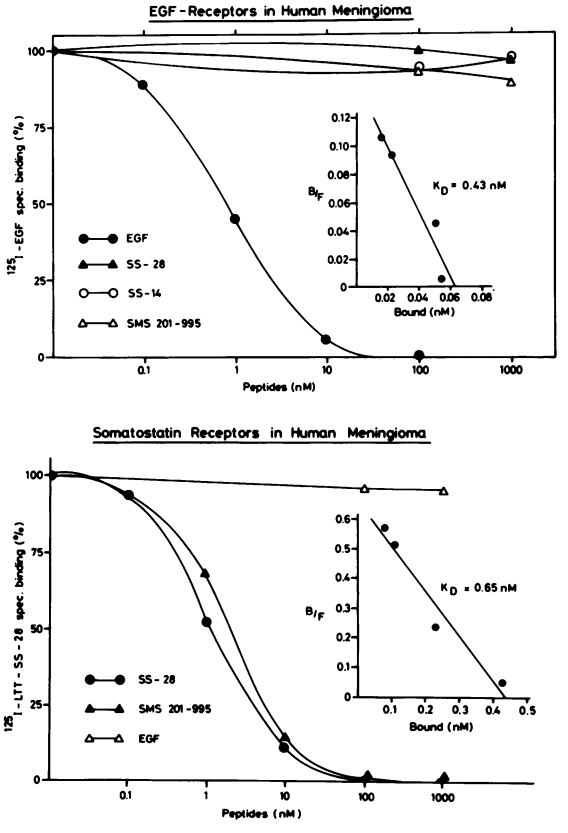

Figure 2. *Pharmacologic specificity of EGF and SS receptors in a single meningioma. Both graphs show a competition curve using a membrane homogenate of a meningioma. Upper graph: Only EGF (● —— ●) but not SS analogs (SS-28 ▲ —— ▲ SS-14 ○ —— ○, SMS 201-995 △ —— △) displace in the high affinity range the ^{125}I-EGF radioligand. Insert: Scatchard plot of the EGF binding. Lower graph: SS analogs (SS-28 ● —— ●, SMS 201-995 ▲ —— ▲) but not EGF (△ —— △) displace in the high affinity range the ^{125}I-LTT-SS-28 radioligand. Insert: Scatchard plot of SS-28 binding.*

Table 2. *Distribution of SS-R and EGF-R in Astrocytomas and Glioblastomas*

Case no.	Histology	Receptor incidence SS-R	EGF-R
29077	Astrocytoma I	+	−
3134	Astrocytoma I	−	−
29694	Astrocytoma I	−	−
9536	Astrocytoma I	−	−
26221	Astrocytoma II	+	−
17798	Astrocytoma II	+	−
5335	Astrocytoma II	+	−
27049	Astrocytoma II	+	−
80-2	Astrocytoma II–III	+	+
E-51-5	Astrocytoma II–III	+	+
5053	Astrocytoma III	+	+
2344	Astrocytoma III–IV	−	+
20195	Glioblastoma	−	−
19505	Glioblastoma	−	−
19177	Glioblastoma	−	−
19214	Glioblastoma	−	+
17679	Glioblastoma	−	+
16212	Glioblastoma	−	+
16209	Glioblastoma	−	+
28504	Glioblastoma	−	−
21219	Glioblastoma	−	+
28502	Glioblastoma	−	−
26945	Glioblastoma	−	−
26812	Glioblastoma	−	+
26090	Glioblastoma	−	+
29845	Glioblastoma	−	+

+, presence; −, absence of receptors.

Similar to the lack of effect of SMS 201-995 on basal, serum-stimulated incorporation of [^{3}H]thymidine, SMS 201-995 failed to inhibit the EGF-stimulated incorporation of tritiated thymidine in these two cultured meningiomas (Table 3). In one meningioma only, not otherwise included in this series, did we find that the EGF-induced stimulation of [^{3}H]thymidine-incorporation could be partially abolished by SMS 201-995.

The use of serum-free medium did not completely stop the cultured meningioma cells from incorporating tritiated thymidine. It is possible, however, that the cells become completely quiescent upon prolonged serum-deprivation. Furthermore, under serum-free medium conditions, the somatostatin analog SMS 201-995 did not influence the incorporation of tritiated thymidine by meningioma cells.

Discussion

This study confirms with autoradiographic techniques the presence of specific receptors for SS or EGF in various human brain tumors. Furthermore, it provides good evidence for the existence of an inverse relationship between the presence of SS and EGF receptors in glia-derived brain tumors, whereas in meningiomas a coincidence of both receptor types is observed.

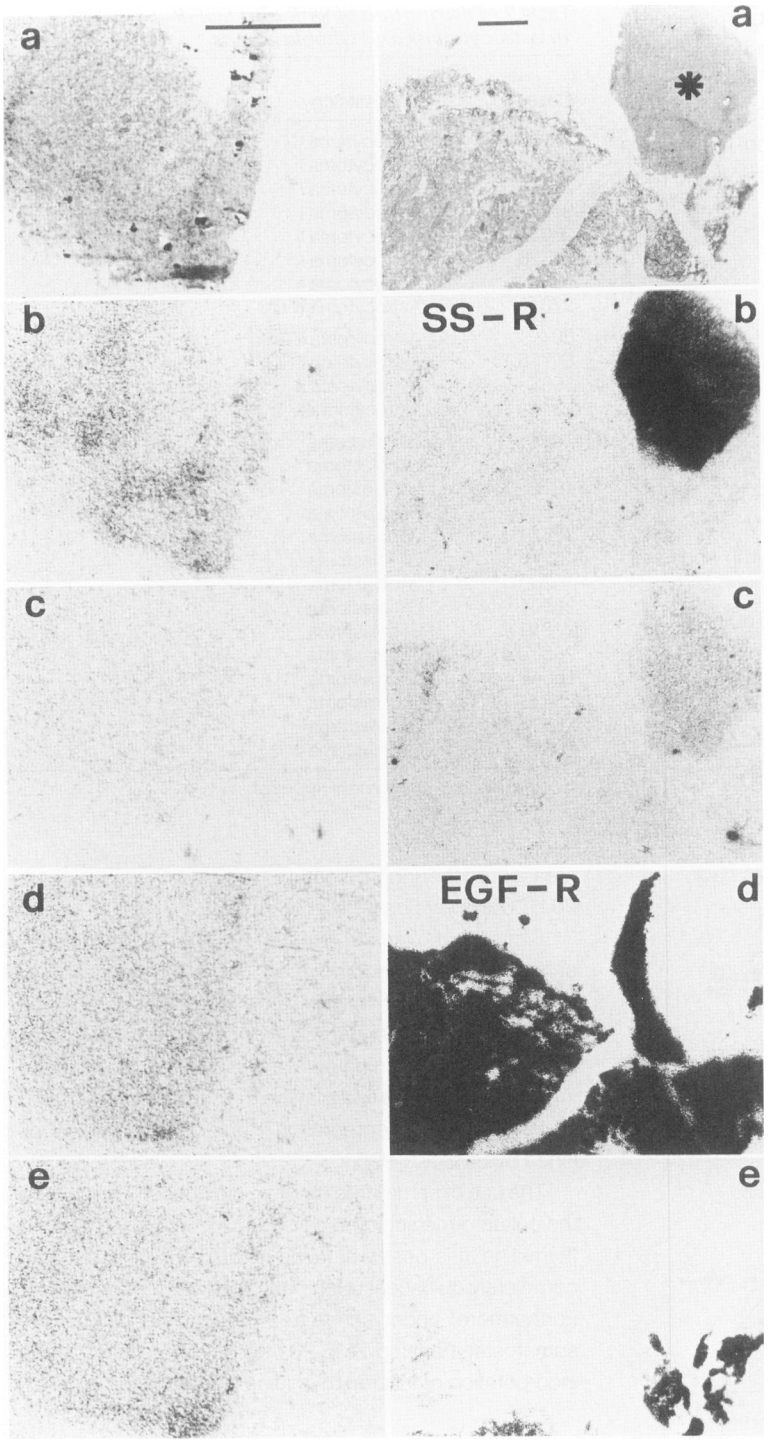

Figure 3. *Somatostatin and EGF receptors in two different cases of astrocytomas. Left: Astrocytoma I (No. 29077). Right: Astrocytoma III–IV (No. 2344).* **a:** *Hematoxylin stained sections.* **b,c:** *Autoradiograms of SS receptors labeled with ^{125}I-LTT-SS-28δ.* **b:** *Total binding.* **c:** *Nonspecific binding in presence of 10^{-6} M SS-28.* **d,e:** *Autoradiograms of EGF receptors.* **d:** *Total binding.* **e:** *Nonspecific binding in presence of 10^{-7} M EGF. The left case has only a low density of SS receptors, whereas the right case has a high density of EGF receptors on tumoral tissue, but SS receptors only in healthy brain tissue (*). Exposure time: SS receptors: 1 week; EGF receptors: 3 weeks (No. 29077) or 2 weeks (No. 2344). Bars, 1 mm.*

Recent reports seem to suggest that the inverse relationship between SS-R and EGF-R seen in glia-derived tumors may be generalized for other tumors as well: numerous well-differentiated tumors, in addition to the astrocytomas, contain SS receptors, such as GH-producing pituitary adenomas or hormone-producing gastrointestinal tumors; conversely, it has been shown that pituitary adenomas do not possess EGF receptors.[21,22] Moreover, many undifferentiated tumors bear EGF receptors: numerous breast tumors with poor prognosis,[23] or certain squamous cell tumors such as cervical, ovarial, oesophageal, and bladder carcinomas.[24,25] Most of these squa-

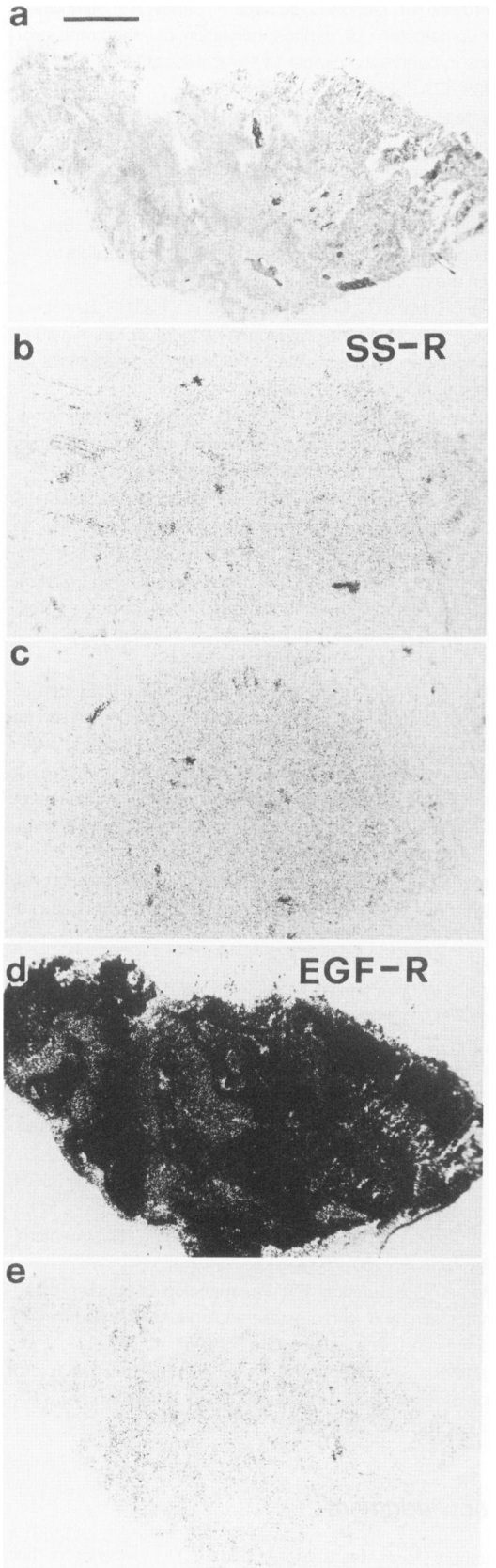

Figure 4. *Somatostatin and EGF receptors in an undifferentiated glioblastoma (case No. 26090).* **a:** *Hematoxylin stained section.* **b,c:** *Autoradiograms of SS receptors labeled with ^{125}I-LTT-SS-28.* **b:** *Total binding.* **c:** *Nonspecific binding in presence of 10^{-6} M SS-28.* **d,e:** *Autoradiograms of EGF receptors.* **d:** *Total binding.* **e:** *Nonspecific binding in presence of 10^{-7} M EGF. EGF but no SS receptors are found. Exposure time: SS receptors: 1 week; EGF receptors: 3 weeks. Bar, 1 mm.*

mous cell tumors seem to lack SS receptors, however.[12] The same is true for exocrine pancreatic adenocarcinomas, which may contain EGF receptors but no SS receptors.[26] The present data are a further indication that the presence of SS receptors is likely to be restricted to differentiated human tumors with low malignancy.

Meningiomas, which often contain both SS and EGF receptors in the same piece of tissue, seems therefore to represent an exception to the frequently found inverse relationship of EGF and SS receptor incidence. Careful evaluation of certain autoradiograms seems, however, to suggest that the two types of receptors are not necessarily located over identical cells. Furthermore, it seems difficult to demonstrate in cell culture experiments a clearly reproducible SS-EGF interaction on growth parameters in meningiomas. The lack of a direct effect of the somatostatin analog SMS 201-995 on the incorporation of [^{3}H]thymidine by meningioma cells may, however, be due in part to the fact that the method used may not be sufficiently sensitive to measure effects that may take longer than 24 hours to become apparent. In recent experiments we have obtained indications that it may be possible to show effects of SMS 201-995, after a 1 week period of incubation, by analysis of the DNA-content of the cultures with sensitive methods.

The present results suggest that a direct interaction between SS and EGF on tumor growth, originally described in tumor models of experimental animals,[13-15,27,28] may not be a general rule but rather restricted to particular tumors only.

Analogous to the role played by steroid receptors as tumor differentiation markers, whose incidence in some cancers also often shows an inverse relationship to that

Table 3. *Effect of EGF Alone (Control) or EGF in Presence of 10^{-7} M SMS 201-995 on the ^{3}H-thymidine Incorporation (cpm ± SEM) in Two Cultured Meningiomas*

Case no.	EGF (ng/ml)	Control (CPM ± SEM)	10^{-7} M SMS 201-995 (CPM ± SEM)
E-52-2	0.0	831 ± 164	1029 ± 84
	0.1	993 ± 44	1079 ± 59
	1.0	1149 ± 2	1201 ± 62
	10.0	1169 ± 75	1092 ± 80
	100.0	1263 ± 11	1135 ± 27
80-12	0.0	12703 ± 114	12601 ± 631
	20.0	20679 ± 94	19681 ± 1141

of EGF receptors,[16,23] SS receptors may be considered another valuable tumor differentiation marker. Therefore, it may be worthwhile to add the SS receptor status to future tumor screening procedures for the biochemical evaluation of certain tumors. It may help the pathologic diagnosis of tumors, because it may pick up tumor subtypes not seen with conventional methods.[4] Finally, because SS analogs are now available for therapy, SS receptor status may be influential in the strategy to be developed for the clinical management of such tumors.

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