Expression of Somatostatin Receptors in Uveal Melanomas

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Purpose. To investigate the distribution of somatostatin receptor (SSR) subtypes 2, 3, and 5 in uveal melanomas and their diagnostic and possible therapeutic value.

Methods. SSRs were investigated in 25 paraffin-embedded eyes with uveal melanomas and in 6 normal eyes without any disease, by using polyclonal antiserum directed to SSR2A, -2B, -3, and -5. Antigen expression was evaluated by a semiquantitative method. The expression pattern of SSR was correlated with the patients' ad vitam prognosis by use of the Kaplan-Meier survival curve. Six different human melanoma cell lines were incubated with octreotide and vapreotide, and a proliferation assay was performed by determining [^{3}H]-TdR uptake. [111-Indium-DTPA-D-Phe1]-octreotide scintigraphy was performed in the eyes of four patients with known uveal melanomas.

Results. All uveal melanomas were positive for SSR2. SSR2A was expressed in 15 of 25, SSR2B in 23 of 25, SSR3 in 7 of 25, and SSR5 in 13 of 25 uveal melanomas. A Kaplan-Meier survival curve showed a significantly better ad vitam prognosis for patients with tumors expressing high levels of SSR2. Cell proliferation was inhibited up to 36% ± 6% in three of six melanoma cell lines at a concentration of 10^{-4} M octreotide or vapreotide. Eyes of two patients with uveal melanomas showed positive uptake of [111-Indium-DTPA-D-Phe1]-octreotide.

Conclusions. SSR2, -3, and -5 are expressed in human uveal melanomas and patients with a high amount of SSR2 in the melanoma tissue have a better ad vitam prognosis. Because a melanoma cell proliferation assay showed an inhibitory effect of up to 36% ± 6% using octreotide or vapreotide, somatostatin analogues may be beneficial in the treatment of patients with ocular melanomas. (*Invest Ophthalmol Vis Sci.* 2003;44: 980–987) DOI:10.1167/iovs.02-0481

Somatostatin was initially discovered as a hypothalamic neurohormone.[1] This peptide is widely distributed in the central and peripheral nervous systems and has also been found in the endocrine pancreas, gut, thyroid, adrenals, and kidneys.[2,3]

In mammals, two different forms of bioactive peptides are produced. Somatostatin 14 is a cyclic peptide consisting of 14 amino acids, and somatostatin 28 consists of 28.[4–6] Somatostatin acts on various targets, including the brain, pituitary, endocrine pancreas, gut, adrenals, thyroid, kidney, vascular system, and immune system. It acts mostly as an inhibitory factor in cell secretion and proliferation.[2,7]

The biological effects of somatostatin are mediated by specific plasma membrane receptors. To date, five different somatostatin receptor (SSR) subtypes have been cloned from human libraries.[4] These subtypes are identical in 42% to 60% of their amino acid sequences. Because the genes for these subtypes are located on different chromosomes, it has been suggested that they have different functions in different organs.[3,4,8] Human SSR types 1 to 5 are encoded by five genes located on 14q13, 17q24, 22q13.1, 20p11.2, and 16p13.3. SSR1 and SSR3, -4, and -5 are intronless, and SSR2 is alternatively spliced to generate two isoforms named SSR2A and SSR2B, which differ in their C-terminal sequences. They all bind somatostatin 14 amino acids and somatostatin 28 with high affinity (in the nanomolar range), but they have a slightly higher affinity with somatostatin 14.[9]

The binding of somatostatin to its receptor initiates pertussis-toxin–sensitive, G protein–dependent cell growth arrest or apoptosis, depending on the receptor subtype.[3,4,10,11]

SSRs have been identified in normal, inflammatory, and neoplastic tissues of neuroectodermal and neuroendocrine tissues, as well as in tissues of non-neural origin, such as pituitary adenomas, islet tumors, carcinoids, adenocarcinomas of the breast, lymphomas, astrocytomas, medulloblastomas, and dermal melanomas.[2,9,12–16] Even if each tumor expresses more than one subtype of SSRs, SSR2 is the most frequently detected.

Uveal melanomas develop from uveal melanocytes, which are of neuroectodermal-neural crest origin.[17–19] Thus, we hypothesized that these tumors might also express SSRs. Therefore, we looked at the expression pattern of SSR in uveal melanomas. Because somatostatin has an antiproliferative effect on cells that express SSRs,[3,20] uveal melanoma cell lines were analyzed for proliferation capacity during incubation with octreotide and vapreotide, two somatostatin analogues. To further evaluate the diagnostic value of SSR expression in uveal melanomas, in vivo octreotide scintigraphy was performed in patients with known uveal melanomas.

Methods

Demographic Data of Patients with Uveal Melanomas

The average age of the 25 patients enrolled in the study was 69 ± 11 years (±SD) at the time of enucleation, and the mean follow-up of the patients was 46 ± 30 months. Fourteen of the patients were women, 11 were men. The data on each patient are provided in Table 1.

Tissue Preparation of Uveal Melanomas

Twenty-five eyes with clinically diagnosed uveal melanoma were immediately fixed in 10% buffered formaldehyde for 2 days after enucleation. On day 2, each eye was cut in two pieces through the largest diameter of the tumor. The tissue was then embedded in paraffin and 5-μm sections were made on coated slides (ChemMate capillary gap microscope slides 75 μm; Dako, Carpinteria, CA).

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TABLE 1. Demographic Data on the Patients and the Results of Immunohistochemical Staining

Patient	Gender/Age	Location	Cell Type	Metastasis	FU	SSR 2A	SSR 2B	SSR 2A+B	SSR 3	SSR 5	Survival
1	M/65*	C	MC	None	12	+	++	++	++	−	NRD
2	F/68	C	EC	None	22	+	++	++	−	−	A
3	F/75	C	MC	None	24	+	−	+	−	+	A
4	M/57	C	SC	None	29	−	++	++	−	−	NRD
5	M/75	C	SC	None	45	+	++	++	−	+	A
6	M/58	C	MC	None	48	−	++	++	−	+	A
7	F/57	C	SC	None	49	+	++	++	−	+	A
8	M/52	C	SC	None	50	−	++	++	++	+	A
9	F/71	C	SC	None	62	+	++	++	−	−	A
10	M/83	C	EC	None	68	−	++	++	++	+	A
11	M/66	C	EC	None	82	++	+	++	++	++	A
12	F/74	CB	EC	None	83	−	++	++	++	+	A
13	M/93	C	SC	None	96	−	++	++	−	−	NRD
14	F/84	C	SC	None	97	+	+	+	−	−	NRD
15	F/66	C	EC	None	102	−	++	++	−	−	A
16	F/72	C	MC	Liver, Brain	5	−	+	+	−	++	MRD
17	F/58	C	SC	Liver	9	+	−	+	−	−	MRD
18	M/76†	C	MC	Liver	11	+	++	++	−	−	MRD
19	F/75	CB	EC	Liver	17	+	+	+	−	+	MRD
20	F/58	C	MC	Liver	27	+	+	+	−	−	MRD
21	F/77	C	MC	Liver	32	−	+	+	−	++	MRD
22	F/77	CB	MC	Liver	34	+	+	+	−	+	MRD
23	M/49	C	MC	Liver	36	+	++	++	++	−	MRD
24	F/68	C	EC	Liver	37	−	+	+	−	+	MRD
25	M/62	C	MC	Liver	73	++	++	++	++	+	MRD

C, choroid; CB, ciliary body; EC, epithelioid-cell type melanoma; SC, spindle-cell type melanoma; MC, mixed-cell type melanoma; FU, follow-up in months; survival, patients life status at the end of follow-up. A, alive; NRD, nonmelanoma-related death; MRD, melanoma-related death.

* Relates to figure 2e–h.

† Relates to Figures 2a–d.

The specimens were stained with hematoxylin-eosin and Masson trichrome for histologic evaluation. Because of their cytologic appearance, the melanomas were divided into tumors with spindle-cell growth, epithelioid-cell growth, and mixed-cell growth, according to the criteria of Rummelt and Naumann.[18] The tumor extensions were measured macroscopically after formalin fixation of the eyes. None of the uveal melanomas received treatment before enucleation.

Tissue Preparation of Normal Eyes

Both normal eyes of three donors (mean age, 67 ± 13 years) were enucleated 4 to 8 hours after death and fixed in 10% buffered formaldehyde for 2 days. On day 2, the eye was cut horizontally through the optic nerve and macroscopically evaluated for intraocular disease. Afterward, the tissues were embedded in paraffin and cut in 5-μm sections on coated slides (ChemMate; Dako). Hematoxylin-eosin and Masson trichrome staining was performed and histologically evaluated to ensure that the eyes did not have any disease.

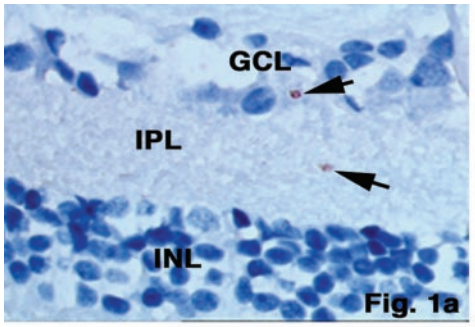
Immunohistochemistry

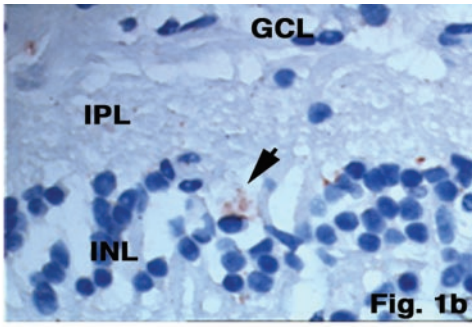
Paraffin-embedded sections (5 μm thick) were dewaxed and rehydrated. The samples were then rinsed in running tap water for 15 minutes, placed in sodium citrate buffer (pH 6.2) and incubated at 80°C overnight. The next day, the slides were washed again in running tap water for 15 minutes. Afterward, they were rinsed twice with PBS, and the endogenous peroxidase activity of the investigated specimens was quenched by incubating the sections in 3% H_2O_2 in H_2O for 10 minutes. The tissues were then incubated with 2% bovine serum albumin for 30 minutes. The serum was tapped off, and the slides were incubated with the panel of antiserum for 60 minutes at room temperature. All antibodies were rabbit anti-human SSRs. Anti-SSR2A and anti-SSR2B were used at 3.3 μg/mL and anti-SSR3 and anti-SSR5 at 2 μg/mL (all antiserums recognize the C-terminal part of the human SSR and were commercially obtained from Gramsch Laboratories, Schwabhausen, Germany).[21–23] The sections were washed three times with PBS, and further immunohistochemical staining was performed with a streptavidin-biotin-peroxidase complex technique (LSAB plus Kit; Dako). Immunoreactivity was visualized with 3-amino-9-ethylcarbazole (AEC).[24] Rabbit IgG anti-biotin (3.3 μg/mL Rb anti-biotin; Dako) was substituted for the primary antibodies as the negative control. The optic nerve and an eye with bacterial endophthalmitis served as the positive control. Three nonserial sections of each tissue were stained for each SSR. All sections were examined by two investigators (NA, YE). The antigen expression was semiquantitatively evaluated scoring the number of positive cells in three different areas of the tumor at a ×50 magnification under a light microscope (Axioplan; Carl Zeiss, Wetzlar, Germany). The final score was an average of the scores in all three areas graded in each of the three sections examined by both investigators.

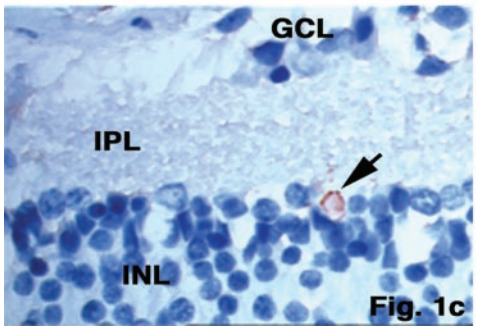
Grading of the immunohistochemically positive tissue was as follows[25]: (−) less than 10% of the tumor positively stained; (+) 11% to 50% positive; (++) 51% to 80% positive; and (+++) more than 81% positive.

Fluorescence Staining of the Uveal Melanoma Cell Lines for SSRs

Cell lines were grown on coated slides (ChemMate; Dako) for 8 hours under sterile conditions and then washed in PBS and dried at room temperature overnight. All uveal melanoma cell lines (OMM2.3, -92.1; OCM3, -8; Mel270, -290) were a generous gift of Jerry Niederkorn (Southwestern Medical School, Dallas, Texas) and Bruce Ksander (Schepens Eye Institute, Harvard Medical School, Boston, Massachusetts).[26] The cells were then fixed in ethanol-acetone (1:1) for 10 minutes at room temperature, washed three times in PBS and incubated with the primary rabbit anti-human SSR antibody or irrelevant antibody (as mentioned earlier) for 60 minutes at room temperature. Afterward, the cells were again washed three times and incubated with







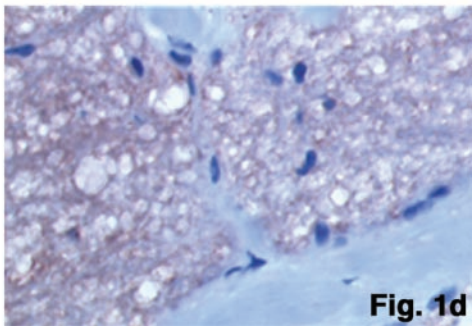


FIGURE 1. SSR expression in normal retina and optic nerve. Immunohistochemical staining of the normal retina shows some faint staining for SSR2A (**a**, *arrow*), SSR2B (**b**, *arrow*), and SSR3 (**c**, *arrow*) in the inner plexiform layer (IPL) of the retina. (**d**) Optic nerve expressing SSR2B in the axons but not in the glial cells. GCL, ganglion cell layer; INL, inner nuclear layer.

an FITC-conjugated swine anti-rabbit antibody (1:40; Dako). The cells were washed three times, dried at room temperature after washing in 100% ethanol for a few seconds, and mounted with a fluorescence mounting medium (Dako) containing 4′,6′-diamino-2-phenylindole (1 μL/mL; DAPI; Vector Laboratories, Peterborough, UK).

The sections were examined with a fluorescence microscope (3D Deconvolution microscope; Carl Zeiss). Micrographs were taken with a ×20 objective magnification, and positive cells were counted on the screen.

Proliferation Assay of the Melanoma Cell Lines

Cells were split and 200 μL of medium containing the melanoma cells (1×10^4 cell) and different concentrations (10^{-4} M, 10^{-6} M, and 10^{-8} M) of octreotide (Novartis, Basel, Switzerland), vapreotide (Debiopharm, Lausanne, Switzerland), or ornithine-octreotide (as the negative control; Novartis) were added to each well. The plate was cultured at 37°C in 5% CO_2 for 24 hours before being pulsed with 1 μCi/well [^{3}H]-TdR for 16 hours.[27]

Octreotide Scintigraphy

Octreotide scintigraphy as described in the next paragraph was performed in the eyes of four patients with uveal melanomas. The melanomas were localized in the ciliary body in two patients and in the choroid in the other two. The height of one the ciliary body melanomas as well as one of the choroidal melanomas was 15 mm. The other two melanomas, one ciliary body and one choroidal, had heights of 6 and 8 mm, respectively.

Single-photon emission computed tomographic (SPECT) images were obtained with a gamma camera at 4 hours after intravenous (IV) injection of 110 MBq [111-Indium-DTPA-D-Phe1]-octreotide (Mallinckrodt, St. Louis, MO). Sixty-four frames of 40 seconds each were collected during a 360° rotation, and scans were analyzed visually.[28]

The clinical trial protocol and informed consent forms followed Austrian national guidelines and were approved by the institutional Ethics and Research Committee; written informed consent was obtained from all patients. The study's protocol conformed to the tenets of the Declaration of Helsinki, as revised in 1989.

Statistics

The survival analysis was based on uveal melanoma–related deaths and calculated with the Kaplan-Meier nonparametric estimation.[29] The log-rank test was used to evaluate statistical significance. The statistical significance of the proliferation assay was obtained with Student's *t*-test. $P < 0.01$ was considered significant for the log-rank test and $P < 0.05$ was considered significant for the Student's *t*-test. Only significant probabilities are shown.

RESULTS

Immunohistochemical Staining of Normal Eyes

Faint staining for SSR2A, -2B, and -3 was found in the inner plexiform layer of the retina (Figs. 1a, b, c). SSR 5 was negative in the entire neuroretinal tissue in all six cases. All four investigated SSRs were found in the axons, but not in the glial cells, of the optic nerve (Fig. 1d). The uveal tract did not express any of the SSRs investigated (data not shown).

Immunohistochemical Staining of Uveal Melanomas

Fifteen (60%) of 25 melanomas were positive for SSR2A. Expression of SSR2A was graded + in 13 of 15 melanomas and ++ in the remaining 2 (Figs. 2a, 2e). SSR2B was expressed in 23 cases (Fig. 2b, 2f). Semiquantitative analysis revealed an expression pattern of + in 8 and ++ in 15 cases. Combining both antibodies (anti-SSR2A and -SSR2B), SSR2 was detected in all melanomas. Whereas 9 melanomas expressed SSR2 graded + the remaining 16 had a expression pattern graded ++. SSR3 was present in only 7 of 25 cases, but the level of expression was ++ in all cases (Fig. 2g). SSR5 was expressed in 14 of 25 melanomas. Eleven of these 14 cases showed an expression pattern graded + and the remaining 3 showed SSR5 graded at ++.

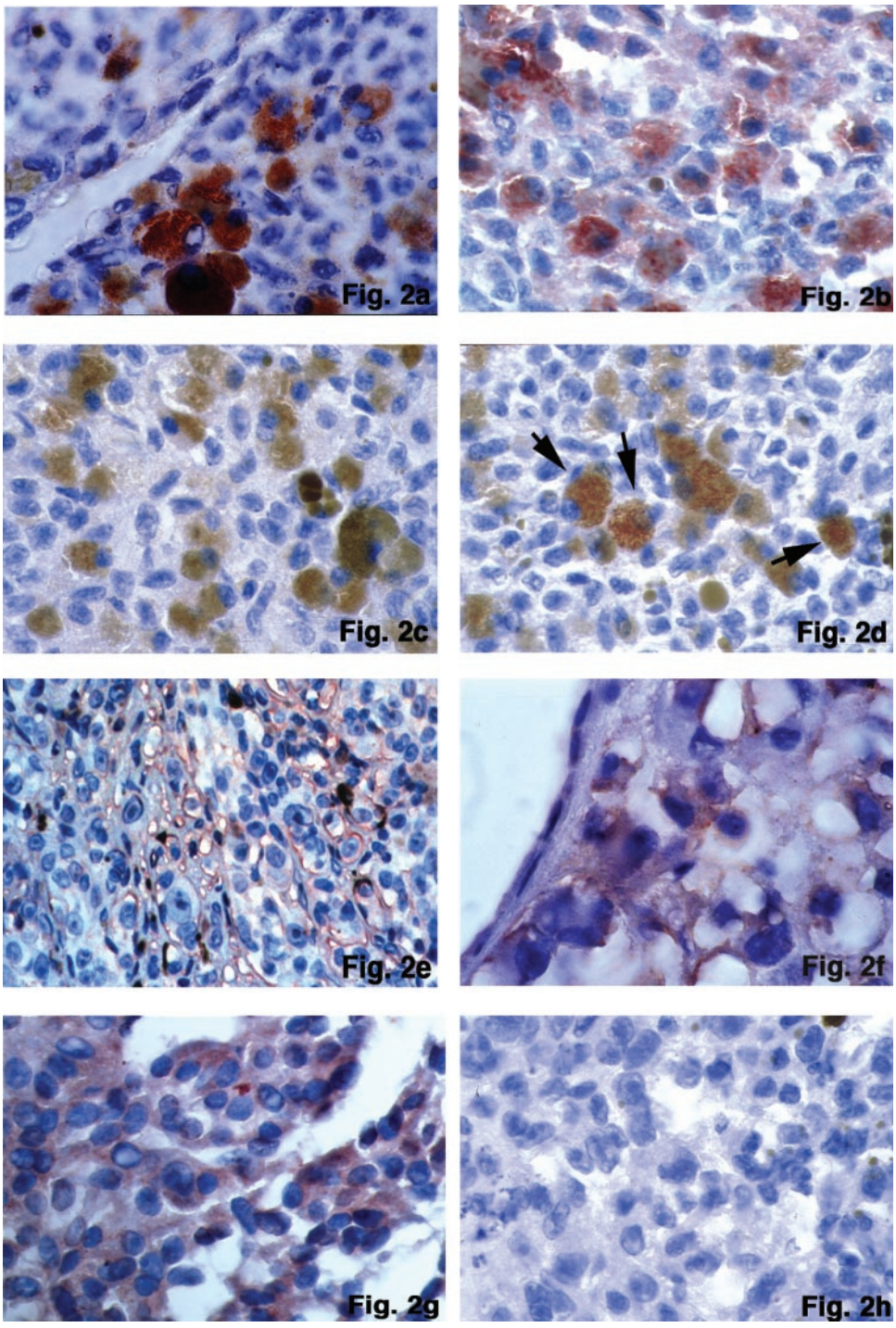


FIGURE 2. Expression of SSRs shown by immunohistochemical staining of two representative uveal melanomas: (**a**–**d**) a melanoma (patient 18 in Table 1) expressing low level of SSR2A (**a**) and higher levels of SSR2B (**b**). Staining for SSR3 was absolutely negative (**c**) and SSR5 expression was only found in a few cells (**d**; *arrows*); (**e**–**h**) a melanoma (patient 1 in Table 1) showing a moderate expression of SSR2A (**e**) and high expression of SSR2B (**f**) and -3 (**g**). Staining for SSR5 was negative (**h**). Original magnification, ×250.

Immunohistochemical Staining of Uveal Melanoma Cell Lines

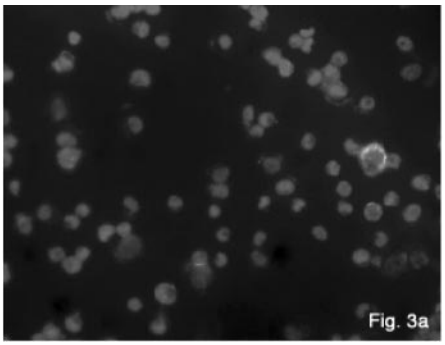
The expression pattern of the uveal melanoma cell types altered, depending on the investigated SSR and the melanoma cell line (Fig. 3). The level of SSR expression is outlined in Table 2.

Proliferation Assay

A proliferation assay using three different concentrations of octreotide or vapreotide showed a dose-dependent inhibitory effect on cell proliferation in three melanoma cell lines. In the case of OMM2.3 cells the inhibitory effect of both octreotide and vapreotide was up to 36% at a concentration of 10^{-4} M ($P < 0.04$). A significant inhibitory effect could also be seen at the concentration of 10^{-6} and 10^{-8} M ($P < 0.04$; Fig. 4b). The proliferation of the melanoma cell lines OCM8 and Mel270 was also significantly inhibited ($P < 0.04$ for OCM8 and $P < 0.03$ for Mel 270), but only at a concentration of 10^{-4} M (Figs. 4d, 4e). Even if the inhibition of proliferation was not statistically significant in the other three melanoma cell lines, a dose-dependent difference in proliferation was recorded at 10^{-4}, 10^{-6}, and 10^{-8} M (Figs. 4a, 4c, 4f).

Survival Analysis

Patients expressing high levels (++) of SSR2 in their uveal melanomas had a significant better survival rate than those



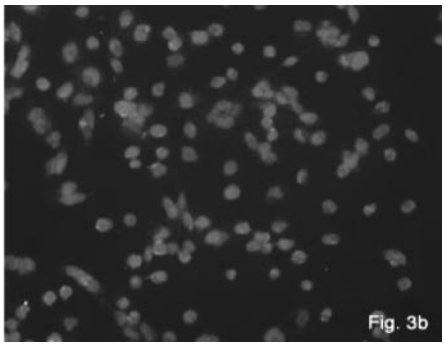


FIGURE 3. Representative examples of SSR expression in two cell lines. SSR2B was expressed in the uveal melanoma cell lines Mel290 (**a**) and Mel270 (**b**). Indirect immunofluorescence staining. Original magnification, ×75.

TABLE 2. Evaluation of Fluorescence-Stained Cell Lines

	OMM 2.3	92.1	OCM3	OCM8	Mel 270	Mel 290
SSR2A	86	13	20	89	91	56
SSR2B	59	60	26	50	70	23
SSR3	83	0	55	50	94	70
SSR5	82	16	64	90	92	31

Percentage of positivity of the uveal melanoma cell lines after indirect fluorescence staining for SSR2A, -2B, -3, and -5.

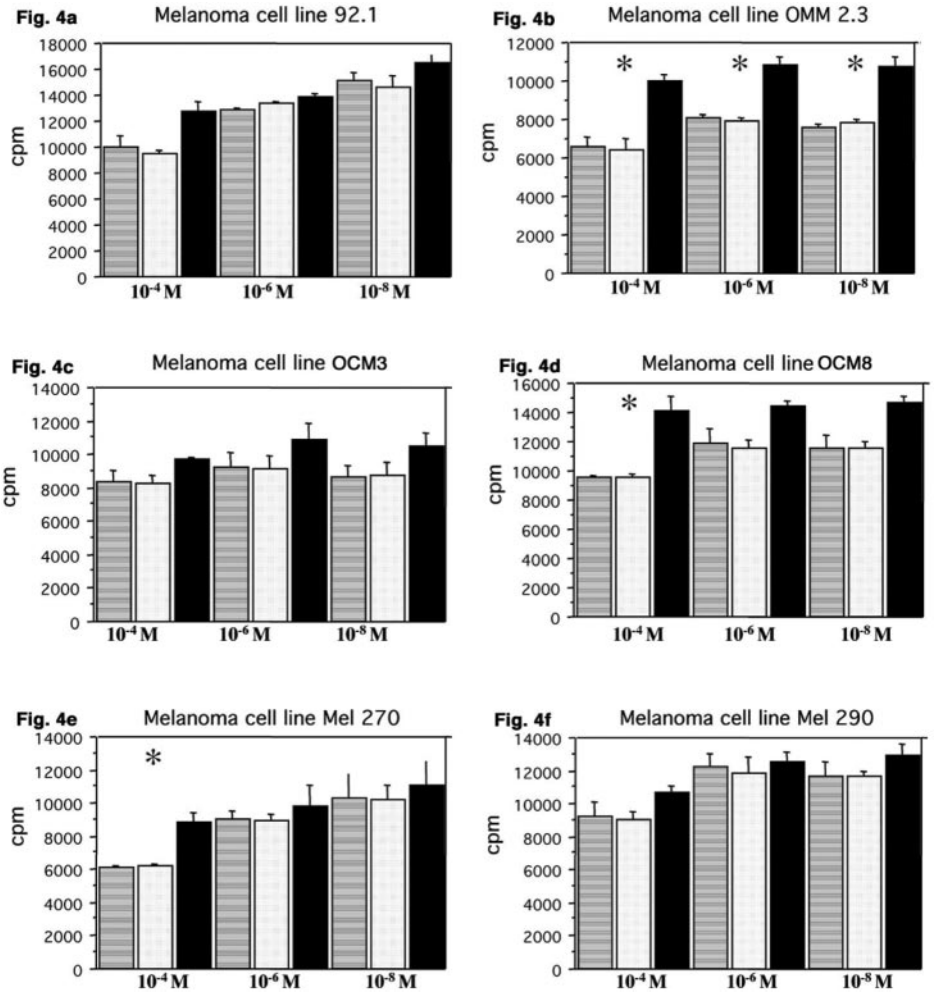


FIGURE 4. Uveal melanoma cell proliferation assays. Inhibition of proliferation could be seen in all melanoma cell lines at concentrations of 10^{-4}, 10^{-6}, and 10^{-8} M octreotide or vapreotide: (**a**) 92.1, (**b**) OMM2.3, (**c**) OCM3, (**d**) OCM8, (**e**) Mel270, and (**f**) Mel290. Statistically significant inhibition in OMM2.3 at all three different concentrations ($P < 0.04$), OC8 ($^*P < 0.04$), and Mel270 ($^*P < 0.03$) at 10^{-4} M. (▨) Octreotide, (□) vapreotide, (■) ornithine-octreotide (negative control).

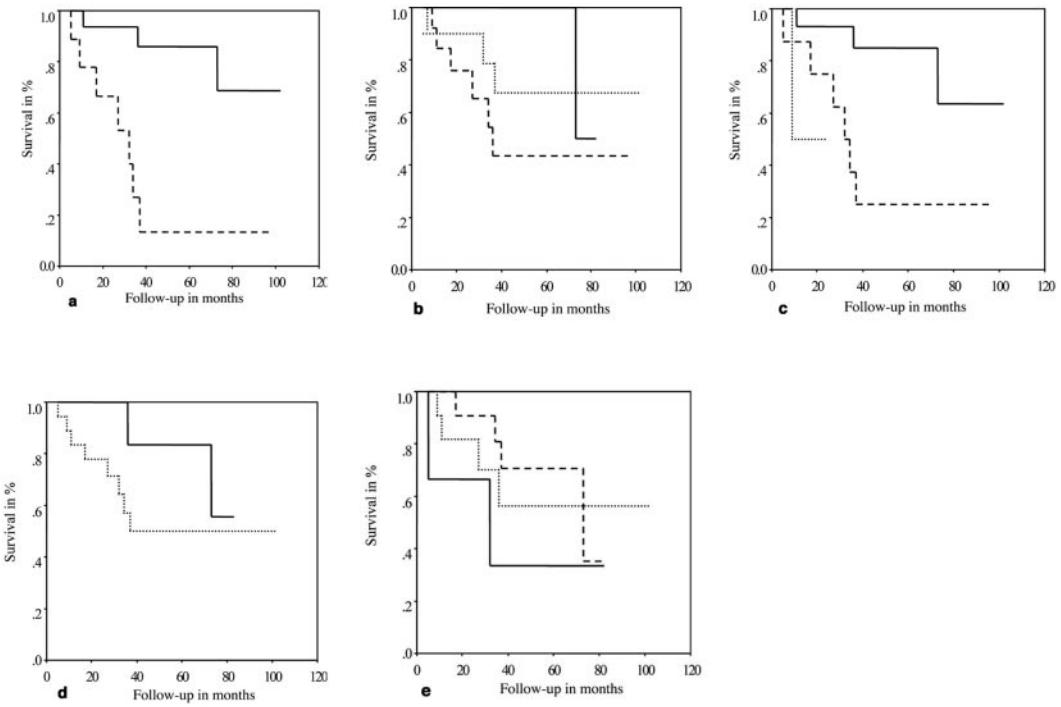


FIGURE 5. Kaplan-Meier survival curves of patients with uveal melanoma demonstrate a significant better survival rate in patients with tumors expressing high levels of SSR2 (A+B) (**a**) +, $n = 9$; ++, $n = 16$; $P = 0.0009$. A subgroup analysis of SSR2 did not show a significant difference for SSR2A or SSR2B: (**b**) −, $n = 10$; +, $n = 13$; ++, $n = 2$; (**c**) −, $n = 2$; +, $n = 8$; ++, $n = 15$, respectively; however, there was a tendency toward significance of SSR2B (+ versus ++, $P = 0.016$). There was no influence on the ad vitam prognosis of expression of SSR3 or SSR5: (**d**) −, $n = 18$; ++, $n = 7$; (**e**) −, $n = 11$; +, $n = 11$; ++, $n = 3$, respectively. The results of the survival curves were limited by the small number of patients in some groups. *Dotted line*, −; *dashed line*, +; *solid line*, ++.

with a low level (+) of SSR2 ($P = 0.0009$; Fig. 5a). Subgroup analysis of SSR2 showed no significant influence on the ad vitam prognosis with SSR2A (Fig. 5b), but a tendency toward better survival in patients with high levels of SSR2B in their tumors ($P = 0.016$; Fig. 5c). The expression of SSR3 (Fig. 5d) and SSR5 (Fig. 5e) in the tumors did not influence the patients' ad vitam prognoses.

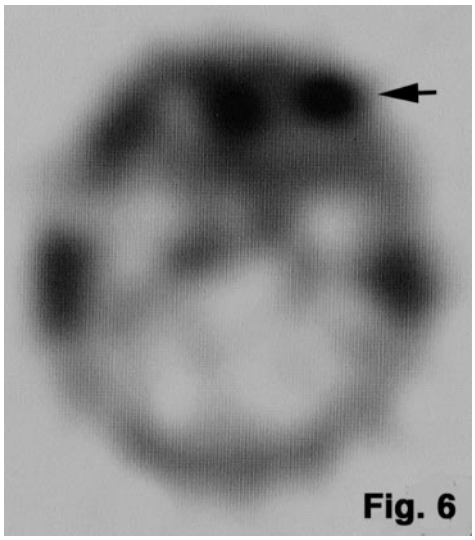


FIGURE 6. Octreotide scintigraphy of a melanoma tumor shows pathologic uptake of [111-indium-DTPA-D-Phe1]-octreotide in the left eye of a patient with a choroidal melanoma 15 mm in height (*arrow*). The other eye showed no positivity.

Octreotide Scintigraphy

A positive uptake of [111-indium-DTPA-D-Phe1]-octreotide occurred in two eyes with a tumor height of 15 mm (Fig. 6). The other two choroidal melanomas with a height of 6 and 8 mm could not be visualized by octreotide scintigraphy.

DISCUSSION

In this study we investigated the expression level of SSRs in uveal melanomas and its diagnostic and possible therapeutic value in future using in vivo octreotide scintigraphy and an in vitro proliferation assay.

Immunohistochemical staining showed positivity for SSR2 (Table 1; A+B) in all uveal melanomas. SSR3 was found in 29% and SSR5 in 58% of the tumors. Of the SSR2 subsets, SSR2B was the receptor most commonly expressed. Comparable results have been demonstrated in cutaneous melanomas, where expression of SSR mRNA has been shown, with mRNAs for SSR1 and SSR2 being the ones identified most frequently. Cutaneous melanomas were imaged in 63% of cases by octreotide scintigraphy using [111-indium-DTPA-D-Phe1]-octreotide, indicating that mRNA is transcribed into functionally active SSR.[2,30–32]

In contrast to Klisovic et al.,[14] who found high expression of SSR2 in the retina and choroid, our study revealed only faint staining for SSR2 in the inner plexiform layer of the retina. This discrepancy might be explained by the targeted epitope of the receptor. Whereas our antibody detected the C-terminal of the subgroups SSR2A and SSR2B, that antibody used in the study of Klisovic et al. targeted the N-terminal part of the SSR2 receptor.

Because somatostatin and its analogues have been shown to have antiproliferative capabilities through its binding to specific receptors, six uveal melanoma cell lines have been incu-

bated with two different somatostatin analogues. Octreotide, a synthetic peptide with a high affinity to SSR2 and -5 and a low affinity to SSR3,[3] showed a significant dose-dependent inhibition of proliferation in three melanoma cell lines. Similar results have been published by other investigators using a cutaneous melanoma cell culture model showing an inhibition of melanoma cell proliferation with different somatostatin analogues.[4,10,11] Schwab et al.[11] showed long-term survival in mice inoculated with cutaneous melanoma cells during treatment with a new somatostatin analogue. Even if experimental animal studies and in vitro models have shown that somatostatin analogues have an antineoplastic effect on different malignancies, the results of many clinical trials have so far been rather disappointing. However, it has to be considered that most early clinical trials for different malignancies had no control group. Kouroumalis et al.[33] have shown in a randomized controlled study that treatment with octreotide can be a valuable alternative for inoperable hepatocellular carcinomas after adjustment for tumor staging or tumor size. Patients with tumors smaller than 3 cm or Okuda index stage I had a significantly longer survival time. Furthermore, clinical trials with octreotide have also shown promising results for the treatment of some other tumors.[34,35] The benefit of somatostatin analogues in the treatment of uveal melanomas should be investigated in randomized controlled studies including the multivariable Cox regression test.

Vapreotide, the second compound used has as affinity with SSR2 that is similar to that of octreotide, but a much higher affinity with SSR5 and less with SSR3.[3] There was no statistical difference between octreotide and vapreotide in the level of inhibition of uveal melanoma cell proliferation, which may indicate that the inhibitory function on proliferation of these cells is mediated through SSR2. This notion is further supported by the fact that only expression of SSR2 in the tumors correlated significantly with a prolonged ad vitam prognosis. Our observation is supported by previous studies showing that the amount of SSR2 mRNA expressed in neuroblastomas correlates with the ad vitam prognoses of the patients.[36–38] A significant correlation of SSR3 and -5 expressed in uveal melanomas and the ad vitam prognosis was not found. However, our data are limited by the small number of cases. Studies of larger samples are necessary to investigate the prognostic value of SSR expression in uveal melanomas, especially that of SSR2B.

To investigate the diagnostic value of SSR expression on uveal melanoma cells, octreotide scintigraphy was performed in eyes of four patients with uveal melanomas. The octreoscan showed pathologic uptake in the eye, with the uveal melanomas of two patients demonstrating SSR activity. However the sensitivity of octreotide scintigraphy may be limited by the tumor size, because only those melanomas with a height of 15 mm were detectable. The two smaller tumors with sizes of 6 and 8 mm could not be imaged. These findings are supported by the fact that the smallest cutaneous melanoma detected by octreotide scintigraphy had a size of 15 mm.[30]

In summary, we have found that uveal melanomas express SSRs, especially SSR2 and patients with a high amount of SSR2 have a better ad vitam prognosis. Because proliferation of cells in several melanoma lines was inhibited by octreotide or vapreotide, treatment with a somatostatin analogue may be beneficial in the treatment of uveal melanomas and extend the ad vitam prognosis.

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