Somatostatin Receptors and Their Subtypes in Human Tumors and in Peritumoral Vessels

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Somatostatin receptors are expressed by a large variety of human tumors. In vitro receptor autoradiographic studies have shown that these tumors can express more than one somatostatin receptor subtype. Whereas the majority of tumors bind octreotide with high affinity, some, ie, prostate tumors, bind octreotide with low affinity only. The discovery of five somatostatin receptor subtypes, sst_{1-5}, by gene cloning has increased our understanding of somatostatin receptor structure and function. Using in situ hybridization techniques, we found that various human tumors, identified as somatostatin receptor–positive in binding studies, expressed sst_2 mRNA in the majority of cases, whereas sst_1 and sst_3 were less frequent. Often, all three sst were expressed simultaneously. In another recent in situ hybridization study, primary prostate cancers were shown to preferentially express sst_1 rather than sst_2 or sst_3. Moreover, a high incidence of sst_5 was found in growth hormone (GH)-producing pituitary adenomas and, to a lesser extent, in active pituitary adenomas; gastroenteropancreatic (GEP) tumors showed all possible combinations, but with a predominance of sst_2. Overall, the presence of sst_2 mRNA and/or sst_5 generally correlated with the presence of octreotide-binding sites, but with exceptions. These results indicate the highly variable abundance of sst mRNAs in individual somatostatin receptor–containing tumors. Somatostatin receptors were not only found in tumoural tissue, but also in the peritumoral vascular system. This was particularly well studied in colorectal carcinomas, where the peritumoral veins were shown to express in all cases a high density of somatostatin receptors, probably of the sst_2 type, binding octreotide with high affinity. Therefore, the host peritumoral vascular system may be a possible target of somatostatin action in tumor development. Somatostatin may act locally on tumor growth through two different mechanisms dependent on local somatostatin receptor expression: through direct action on tumor cells or through action on peritumoral vessels, which may alter the hemodynamics of the tumoral blood circulation.

IN THE LAST 10 years, the presence of somatostatin receptors has been reported in a large number of human primary tumors and tumor cell lines,[1] using somatostatin receptor–binding techniques, either with in vitro homogenate binding assays or somatostatin receptor autoradiography. The autoradiographical data clearly showed that tumor cells expressed somatostatin receptors. Moreover, early studies using different iodinated somatostatin analogs made it possible to differentiate pharmacologically between somatostatin receptors with high (SS1 subtype) or low (SS2 subtype) affinity for octreotide, introducing the concept of somatostatin receptor subtypes in tumors. Whereas most tumors expressed the SS1 subtype, characterized by a high affinity for somatostatin-14, somatostatin-28, and octreotide, a number of tumors clearly had the SS2 subtype, with a high affinity for somatostatin-14 and somatostatin-28, but a low affinity for octreotide.[1] Both receptor subtypes were shown in gastroenteropancreatic (GEP) tumors to be functionally relevant, since the excess hormone released by the tumor was inhibited by somatostatin-14 and somatostatin-28, but not by octreotide in the case of SS2, and by somatostatin-14, somatostatin-28 and octreotide in the case of SS1, in vitro as well as in vivo. Some GEP tumors, a significant proportion of medullary thyroid carcinomas, ovarian tumours, and all prostate carcinomas preferentially expressed the SS2 subtype.[1,2]

The recent cloning of several somatostatin receptor genes has increased our understanding of somatostatin receptor structure and function. To date, the human somatostatin receptor subtypes sst_1, sst_2, sst_3, sst_4, and sst_5 have been cloned and partially characterized. All five receptor subtypes can functionally couple to the inhibition of adenylyl cyclase. Pharmacological studies have shown that all five human subtypes bind somatostatin-14 and somatostatin-28 with high affinity, whereas the sst_2 subtype preferentially binds the octapeptide analog octreotide with very high affinity and is identical to the former SS1 subtype. In a recent study,[3] we evaluated the somatostatin receptor gene expression of sst_1, sst_2, and sst_3 subtypes by in situ hybridization in 55 human primary tumors (meningiomas, neuroblastomas, pituitary adenomas, small-cell lung carcinomas, lymphomas, breast tumors, carcinoids, islet-cell carcinomas, medullary thyroid carcinomas, and ovarian tumors), chosen for their high density of somatostatin receptors in binding assays. We confirmed that human tumors can express various somatostatin receptor subtypes. All 55 tumors expressed at least one sst subtype. Of 55 somatostatin receptor–positive tumors, 46 had sst_2 mRNA; all 46 were characterized as having receptors with a high affinity for the synthetic analog octreotide and were therefore likely to correspond to the former SS1 subtype. Of 55 tumors, 12 expressed sst_1, and 14 expressed sst_3 mRNA. In several cases, all three sst were expressed simultaneously. The four cases having predominantly sst_1 mRNAs were identified in binding experiments with ^{125}I-labeled somatostatin-14 and somatostatin-28 analogs, rather than with ^{125}I-[Tyr^3]-octreotide.

In another recent in situ hybridization study,[2] primary

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prostate cancers were shown to express sst_1 rather than sst_2 or sst_3. These primary prostate cancers do not have somatostatin receptors identified with ^{125}I-[Tyr^3]-octreotide, but express somatostatin receptors identified with ^{125}I-[Leu^8, D-Trp^{22}, Tyr^{25}]-somatostatin-28, with a high affinity for somatostatin-14 and somatostatin-28, but low affinity for octreotide. The receptors are located on tumoral cells. Unexpectedly, primary human prostate cancers express a somatostatin receptor subtype that differs from that of benign prostate tissue, which predominantly expresses the octreotide-preferring sst_2 subtype in smooth muscles surrounding the prostate gland.[2]

Following these first demonstrations of the presence of sst_1, sst_2, and sst_3 in primary human tumors using in situ hybridization, we have performed a further study on the gene expression of sst_1, sst_2, and sst_3, as well as sst_5, in a series of 30 pituitary adenomas, 25 breast tumors, and 35 GEP tumors shown to express somatostatin receptors to variable degrees. The following conclusions could be drawn from this study. It could be confirmed that in a majority of these tumors, the sst_2 receptor subtype was abundantly expressed, even though a significant number of pituitary adenomas and breast and GEP tumors expressed sst_1 and/or sst_3 as well. Interestingly, a very high incidence of the sst_5 subtype was found in growth hormone (GH)-producing pituitary adenomas and, to a lesser extent, in inactive pituitary adenomas, whereas breast tumors seldom expressed sst_5; GEP tumors showed all possible combinations of sst expression, with, however, a predominance of sst_2 and sst_1. Overall, the presence of sst_2 mRNA and/or sst_5 mRNA generally correlated with the presence of octreotide-binding sites. A lack of octreotide-binding sites corresponded with a lack of sst_2 mRNA. However, a few tumors having octreotide binding sites had no measurable sst_2 mRNA, but sst_5 or sst_3 mRNA. Clearly, the relatively low sensitivity of in situ hybridization methodologies (compared with reverse-transcriptase polymerase chain reaction) should be taken into account. Nevertheless, these results may indicate the highly variable abundance of sst mRNAs in individual somatostatin receptor–containing tumors. The sst subtypes probably mediate distinct somatostatin actions, and it may therefore be worthwhile to search for subtype-specific analogs to use for specific treatment and diagnosis of these tumors.

SOMATOSTATIN RECEPTORS IN PERITUMORAL VESSELS

Recently, the peritumoral vascular system of the host has emerged as a possible target of somatostatin action in tumor development.[4] A vascular action of somatostatin on neoplasms may turn out to be widespread and very important indeed, since the presence of strongly somatostatin receptor–positive veins has been identified in the peritumoral zone of several types of malignant neoplasms, including colon carcinoma, carcinoma of the lung, breast cancer, renal-cell carcinoma, and malignant lymphoma.[4] In a series of human colonic carcinomas,[5] a high density of somatostatin receptors has been observed in the immediate vicinity of all the tumors (0 to 2 cm); as the distance from the carcinomas increases (5 to 10 cm), the density of vascular somatostatin receptors in the colon decreases considerably, suggesting a local phenomenon related to the presence of the tumor. The presence of vascular somatostatin receptors seems to be independent of the presence or absence of somatostatin receptors in the tumor itself. The somatostatin receptor subtype expressed by the veins is not yet established, but probably belongs to the sst_2 type, since a high affinity for octreotide could be observed.

The function of somatostatin in the peritumoral vasculature, mediated by a high density of somatostatin receptors in the venous smooth muscle cells and possibly in the endothelium, can be defined to some extent; in normal and pathological states, the vasoconstrictive effect of somatostatin, in particular in the gut, is well established. Therefore, an increased somatostatin receptor density may allow a strong and rapid vasoconstriction, possibly resulting in local hypoxia and necrosis of the tumor, or a more prolonged vasoconstriction, directed against metastatic tumor dissemination. This mechanism may explain the occasional clinical observation of a marked decrease in tumor size during octreotide therapy in some patients. Alternatively, somatostatin may regulate the extent of peritumoral inflammation, as has been suggested for substance P. Peritumoral veins, the main tumor-draining vessels, may control processes such as the extravasation of plasma, particularly of fibrin and of white blood cells associated with inflammation, tumor stromal generation, blood flow in the tumor, local thrombus formation, and tumor growth and propagation. Finally, the high expression of somatostatin receptors in peritumoral veins may be seen as a defense of the host against tumor angiogenesis, as the latter can be inhibited by somatostatin analogs in the chick chorioallantoic membrane system, possibly through somatostatin receptors similar to those identified in human peritumoral vessels.

Many peptides released by nerves, or generated by endothelium and injured tissues, are known to regulate vascular function (tone and permeability) and proliferation (angiogenesis). However, the potency of these peptides to regulate vascular functions may vary between vascular type (artery, capillary, and vein) and vascular caliber, perhaps in relation to the density of the receptors, and to different spectra of membrane-associated peptidases. This may be critical for the generation of tissue- and peptide-specific responses in specialized vascular beds. Peptides and peptide receptors may represent a novel group of substances that influence the preexisting peritumoral vasculature of the host, and perhaps also tumor angiogenesis, in addition to the large number of already defined humoral factors.

Therefore, somatostatin may act locally on tumor growth through two different mechanisms dependent on local somatostatin receptor expression: through direct action on tumor cells or through action on peritumoral vessels, which may alter the hemodynamics of the tumoral blood circulation.

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