Effects of Chemotherapeutic Agents on Expression of Somatostatin Receptors in Pancreatic Tumor Cells

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Specific tumors express high amounts of receptors for somatostatin (SST), providing the basis for imaging and treatment using radiolabeled SST analogs. However, little is known about the potential influence of cytotoxic drugs on SST receptor (SSTR) expression in malignant cells. Methods: To study the interaction between cytotoxic drugs and SSTR expression, the pancreatic cancer–derived tumor cell lines BxPC-3, Panc-1, Capan-1, and ASPC-1 were exposed to a range of cytotoxic drugs in vitro: Gemcitabine, 5-fluorouracil, cisplatin (cis-diaminedichloroplatinum [II]), camptothecin, mitomycin C, and doxorubicin were checked for changes in binding characteristics of the SSTR ligand 

Results: Cells were treated with gemcitabine (1.0 or 2.0 μg/mL), 5-fluorouracil (65–520 μg/mL), camptothecin (1.5 or 3 μg/mL), mitomycin C (0.1 or 0.2 μg/mL), and doxorubicin (1.0 or 2.0 μg/mL). Each of the chemotherapeutic agents induced a loss of high-affinity receptors. In addition, gemcitabine caused a reduction of low-affinity receptors in BxPC-3, Panc-1, and ASPC-1 cells. Mitomycin C, camptothecin, and 5-fluorouracil also induced an overexpression of low-affinity receptors. In cells pretreated with cisplatin (2–10 μg/mL), binding of DOTA-LAN was increased. Excluding gemcitabine, the increase in low-affinity binding sites exhibits a weak correlation with apoptosis (r² = 0.62). For gemcitabine, these effects were reversed after 4 d of recovery of the cell lines, eventually revealing overexpression of low- and high-affinity sites for BxPC-3 and Panc-1 cells and low-affinity sites for ASPC-1 cells.

Conclusion: Our results clearly show that the pancreatic tumor lines reduce the expression of high-affinity DOTA-LAN binding sites during application of chemotherapeutic drugs, which is accompanied by variable overexpression of low-affinity binding sites. In the case of gemcitabine, SSTRs are overexpressed during recovery from drug exposure within 4 d. These findings may have implications on the interpretation of scintigraphic results obtained by receptor ligands.

Key Words: somatostatin receptors; DOTA-lanreotide; chemotherapy; gemcitabine


Somatostatin (SST) is a 14-amino-acid polypeptide synthesized in neural and endocrine cells that binds to 5 distinct SST receptors (SSTR1–SSTR5) in various target tissues (1–5). All 5 human SST (hSSTR) subtypes bind SST-14 as well as SST-28 with high affinity and belong to the superfamily of guanine nucleotide binding protein–coupled receptors (6,7). In comparison with normal tissue, tumor cells express a significantly higher amount of receptors for SST and its analogs (8). This observation provided the basis for the development of various radiolabeled SST peptide analogs as imaging agents and therapeutics in nuclear medicine (9–14).

Pancreatic cancer is among the leading causes of cancer-related death worldwide (15). The diagnosis is established at an advanced stage in most patients who are, therefore, beyond the scope of curative intervention (16,17). Recent data have indicated the expression of SSTR subtypes on pancreatic tumor cells; however, 

In-diethylenetriamine-pentaacetic acid-o-Phe¹-octreotide, which is widely applied for detection and staging of neuroendocrine tumors, is not useful in pancreatic cancer patients (9,18). In contrast, the novel SST analog 

In-diestereazacyclododecane-N,N',N"-tetraacetic acid-lanreotide (DOTA-LAN) is a promising substance for visualizing pancreatic cancer and its metastases (11,19). A large number of pancreatic cancer patients undergo chemotherapy, and data regarding the effects of chemotherapeutic treatment on the expression of SSTR are largely lacking.

This study was performed to characterize the expression of SSTR on pancreatic tumor cells (BxPC-3, Panc-1, ASPC-1, and Capan-1) and the possible influence of cytotoxic or cytostatic agents on binding characteristics of the radioligand 

In-DOTA-LAN. The cytotoxic or cytostatic
agents used in this study—gemcitabine, 5-fluorouracil, cisplatin (cis-diaminedichloroplatinum [II]), camptothecin, mitomycin C, and doxorubicin—are of clinical relevance for the treatment of pancreatic cancer and represent different mechanisms of cytotoxic activity.

MATERIALS AND METHODS

Cell Lines and Tissue Culture

All cell lines were purchased from the American Type Culture Collection (Rockville, MD); BxPC-3, Panc-1, ASPC-1, and CaPan-1 are pancreatic adenocarcinoma cell lines. Cells were cultured in RPMI 1640 medium (Seromed, Berlin, Germany) supplemented with 10% fetal calf serum, 4 mmol/L l-glutamine, and antibiotics in 5% CO₂ at 37°C. The fetal calf serum was heat inactivated for 30 min at 56°C.

Cells were grown in 162-cm² culture flasks (Costar, Cambridge, MA) for 2–3 d. At that point the cells were subconfluent, and the chemotherapeutic agents were added in their respective concentration and cells were grown for another 4 d. Cells were gently harvested with a solution of 0.05% trypsin and 0.02% ethylenediaminetetraacetic acid (GIBCO Laboratories, Grand Island, NY) and counted in a cell counter (Sysmex Toa, Tokyo, Japan).

Synthesis and Radiolabeling of DOTA-LAN

DOTA-LAN was synthesized in a 3-step reaction using the commercially available LAN (Somatuline [Ipsen, Maidenhead, U.K.]; d-Nal-Cys-Tyr-d-Trp-Lys-Val-Cys-Thr-NH₂) and DOTA as starting materials. The terminal amino group of LAN was blocked using 10% fetal calf serum, 4 mmol/L l-glutamine, and 4 mmol/L diethylenetriaminepentaacetic acid before sterilization and cells were grown for another 4 d. Cells were gently harvested with a solution of 0.05% trypsin and 0.02% ethylenediaminetetraacetic acid (GIBCO Laboratories, Grand Island, NY) and counted in a cell counter (Sysmex Toa, Tokyo, Japan).

Effects of Chemotherapeutic Agents on Cell Growth and Cell Cycle

To evaluate the effects of the chemotherapeutic agents on cell growth and survival, we determined the reduction in cell number after treatment with the chemotherapeutic agents, the percentage of cells in the different phases of the cell cycle before and after treatment, and the percentage of apoptotic cells before and after treatment with the chemotherapeutic agents. Cells of the control group were treated with medium alone. Cells were seeded at an initial cell density of 10⁵ cells per milliliter in 162-cm² tissue culture flasks (Costar) and incubated for 72 h under tissue culture conditions. For all experiments the cells were kept in RPMI 1640 medium supplemented with 10% fetal calf serum and 4 mmol/L l-glutamine, and cell numbers in controls and treated cultures were counted in triplicate in a microcell counter (Sysmex Toa).

For staining of the DNA and cell cycle analysis, 4 × 10⁶ cells were washed in phosphate-buffered saline (PBS; Sigma, St. Louis, MO), resuspended in 100 μL PBS, and added to 4 mL 70% ethanol (precooled at −20°C) under continuous mixing. The cells were fixed for 30 min on ice, washed again with PBS, resuspended in 200 μL 0.1% Triton X-100 and PBS supplemented with 2 μg/mL ribonuclease A (type XII-A; Sigma) and 50 μg/mL propidium iodide, and incubated overnight at room temperature. Cells were analyzed using an Epics XL-MLC (Coulter, Miami, FL) flow cytometer (10,000 cells), and the resulting histograms were processed using MulticycleAV software (Phoenix Flow Systems, San Diego, CA). Data are presented as percentage of cells (mean ± SD; n = 3) in G1/0, G2M, or S phase. Apoptotic cells were calculated as the percentage of cells appearing as a subG1 (subG1/0 cell DNA content) peak in cell cycle histograms.

Northern Blot Analysis of SSTRs

Plasmids containing the receptor complementary DNAs (cDNAs) for the hSSTRs (hSSTR1–hSSTR4) were kindly provided by Prof. Dr. G. Bell (Howard Hughes Medical Institute, Chicago, IL). The plasmid carrying hSSTR5 was kindly provided by Dr. A.M. O’Carroll (National Institutes of Health, Bethesda, MD). The precision of each receptor clone was confirmed by agarose gel analysis of restriction fragments and a complete sequence analysis. Isolation of plasmid DNA was performed with the Qiagen plasmid purification kit (Qiagen, Hilden, Germany).

Northern blot analysis was performed using 32P-labeled DNA probes. The probes were purified using the Redivue random prime labeling kit (Amersham, Buckinghamshire, U.K.) and 32P-deoxyctydine 5’-triphosphate (Amersham). Hybridization was performed as described (20,21). Briefly, the membranes were prehybridized at 42°C in a hybridization solution containing 50% formamide, 5 × Denhardt’s solution, 5 × saline sodium citrate (SSC), 0.2% sodium dodecyl sulfate (SDS), and 100 μg/mL salmon sperm DNA.
After 4 h of prehybridization, the labeled probe was added in fresh hybridization buffer and hybridization was performed overnight. Thereafter, blots were rinsed twice at room temperature with 2 × SSC buffer containing 0.1% SDS, then rinsed twice at 42°C with 0.2 × SSC buffer containing 0.1% SDS, and finally used to expose an x-ray film (Hyperfilm; Amersham).

**Radioligand Binding of 111In-DOTA-LAN In Vitro**

To evaluate ligand binding to SSTRs expressed on various tumor cells, direct binding experiments were performed (22). All experiments were performed at least in triplicate and consisted of 2 incubation series: total binding and nonspecific binding. Specific binding was expressed as the difference of total and nonspecific binding. Before cells were used in binding experiments, they were washed twice in assay buffer (0.15 mol/L NaCl, 20 mmol/L Hepes-KOH, pH 7.4) containing 0.1% bovine serum albumin. In saturation studies, 2 × 10⁵ cells were incubated with increasing concentrations of ¹¹¹In-DOTA-LAN (0.1–30 nmol/L) in the absence (total binding) or the presence (nonspecific binding) of 0.01–50 nmol/L unlabeled DOTA-LAN under equilibrium conditions (90 min at room temperature). The final assay volume was 0.2 mL. Displacement studies were performed by incubating 2 × 10⁵ cells with 0.05 nmol/L ¹¹¹In-DOTA-LAN in the absence (total binding) or the presence (nonspecific binding) of increasing concentrations (0.01–1,000 nmol/L) of unlabeled DOTA-LAN. The reactions were terminated by addition of 1 mL ice-cold 20 mmol/L Hepes-KOH buffer containing 0.1% bovine serum albumin followed by rapid centrifugation (4,000 rpm, 10 min, 4°C) and 2 buffer washes. Radioactivity associated with the pellet was counted in a γ-counter for 1 min. The saturation binding data were evaluated according to Scatchard (23).

**Statistical Analysis**

Statistical calculations were done with the Texasoft program (Kwikstat, Cedar Hill, TX) using the Mann–Whitney test with a threshold for significance at P < 0.05.

**RESULTS**

**Expression of SSTR1–SSTR5 in Pancreatic Adenocarcinoma Cell Lines**

The expression of SSTR subtypes in BxPC-3, Panc-1, ASPC-1, and Capan-1 cells was tested using subtype-specific cDNA clones and Northern blot analysis. Figure 1A shows the relative mean signal intensities of densitometric measurements of the resulting hybridizations. SSTR3 is predominantly expressed in the cell lines investigated here, with low levels of SSTR4 and SSTR5 and no significant expression of SSTR1 and SSTR2 subtypes.

**Binding of DOTA-LAN to Pancreatic Adenocarcinoma Cell Lines**

To study the binding properties of radiolabeled DOTA-LAN with established human pancreatic tumor cell lines, saturation studies were performed with intact tumor cells. All cell lines bound ¹¹¹In-DOTA-LAN in a specific manner. For cell lines BxPC-3, Panc-1, and ASPC-1 the binding could be subdivided into 2 binding classes—namely, high-affinity and low-affinity binding sites (dissociation constants Kd1 = 0.1–5 nmol/L vs. Kd2 = 7.5–28 nmol/L). The Capan-1 cell line expressed only 1 class of binding sites.

**Effects of Chemotherapeutics on Growth of Pancreatic Cancer Lines**

The tumor cell lines were treated with appropriate concentrations of the chemotherapeutic agent in tissue culture flasks, and cell numbers of medium controls and treated cultures were counted after exposure to 0.05% trypsin and
0.02% ethylenediaminetetraacetic acid. The result of these measurements is shown in Figure 2A for BxPC-3 cells. Exposure of the cells to 1.0 or 2.0 μg/mL gemcitabine, 2.5 or 5 μg/mL cisplatin, 1.5 or 3 μg/mL camptothecin, 0.1–0.2 μg/mL mitomycin C, and 1.0 or 2.0 μg/mL doxorubicin resulted in reductions in cell numbers ranging from 6% for cisplatin to 75% for camptothecin. For Panc-1 cells, the reduction is 30.2% ± 3.1% and 28.8% ± 1.6% for 1.0 and 2.0 μg/mL gemcitabine, respectively. When Panc-1 cells were treated with 5 μg/mL cisplatin, the cell number reduction was 6% ± 5.25% and 10 μg/mL cisplatin gave a reduction of 4.7% ± 2.3%. ASPC-1 cells, when treated with 65 μg/mL 5-fluorouracil, revealed a reduction of the cell number of 49.7% ± 2.5% and, after treatment with 130 μg/mL 5-fluorouracil, a reduction of 47.6% ± 2%. The reduction of the cell number of Capan-1 cells was 18.6% ± 1.4% when cells were treated with 65 μg/mL 5-fluorouracil and 26.7% ± 0.9% when treated with 130 μg/mL 5-fluorouracil.

Induction of Apoptosis in Response to Chemotherapeutic Agents

The human pancreatic adenocarcinoma tumor cell lines BxPC-3, Panc-1, ASPC-1, and Capan-1 showed a percentage of 1.7%–10.35% of apoptotic cells in medium controls (Fig. 2A). Apoptotic cells were detected as a fraction of subG1 cells on cell cycle histograms. All chemotherapeutics induced the appearance of apoptotic cells, with gemcitabine showing highest activity, followed by mitomycin C, camptothecin, doxorubicin, and cisplatin.

Again, similar results were found for Panc-1 cells, with approximately 50% apoptotic cells for gemcitabine pretreatment and approximately 5% apoptotic cells for cisplatin. When ASPC-1 and Capan-1 cells were treated with 5-fluorouracil, the percentage of apoptotic cells was also increased, ranging from 35% to 57% apoptotic cells (data not shown).

Cell Cycle Distribution

Cell cycle distribution was measured by analysis of histograms obtained with propidium iodide–stained fixed cells in flow cytometry (Fig. 2B for BxPC-3 cells). Under these experimental conditions, gemcitabine, cisplatin, and camptothecin induced an accumulation of cells in S phase and at the higher concentration in G2M phase, whereas mitomycin C arrested cells primarily in G1/0 phase and treatment with doxorubicin in G2M phase. Alterations in S-phase distribution are significantly different from controls for all treatments except 1 μg/mL doxorubicin and in G2M-phase distribution for all treatments except 2.5 μg/mL cisplatin, 0.2 μg/mL mitomycin C, and 1 μg/mL doxorubicin.

Similar results were found for Panc-1 cells, with accumulation in S or G2M phase for gemcitabine treatment and S phase for cisplatin. 5-Fluorouracil induced high S-phase accumulation of ASPC-1 and Capan-1 cells (data not shown).

Effects of Chemotherapeutics on Binding of 111In-DOTA-LAN to Pancreatic Cancer Cells

After treating BxPC-3 cells with gemcitabine, the high-affinity binding sites were diminished and the low-affinity binding sites were reduced dose dependently (Fig. 3). In contrast, cisplatin in concentrations of 2.5 and 5 μg/mL increased the expression of the high-affinity and low-affinity receptors of pancreatic tumor BxPC-3 cells significantly. After treatment with camptothecin in concentrations of 1.5 and 3 μg/mL, the high-affinity binding sites of the BxPC-3 cells were diminished, with increased expression of low-affinity sites for 1.5 μg/mL camptothecin. Treatment with
mitomycin C (0.1 and 0.2 μg/mL) as well as doxorubicin resulted in disappearance of high-affinity sites and increased expression of low-affinity sites. The differences in expression of high-affinity sites are statistically significant for all treatments (Bmax and number of sites) and for all binding tests except those involving doxorubicin. 5-Fluorouracil reduced the amount of high-affinity DOTA-LAN binding in ASPC-1 cells, without induction of low-affinity binding sites, and binding of the tracer was not affected in Capan-1 cells. Regression analysis revealed a weak correlation of the number of low-affinity binding sites per cell for high- and low-affinity sites (1 and 2), respectively, in BxPC-3 cells (n = 3; mean ± SEM). gemca = gemcitabine (1 and 2 μg/mL); cisPt = cisplatin (2.5 and 5 μg/mL); cpt = camptothecin (1.5 and 3 μg/mL); mito = mitomycin C (0.1 and 0.2 μg/mL); doxo = doxorubicin (1 and 2 μg/mL).

**FIGURE 3.** Effects of chemotherapeutic agents on binding of DOTA-LAN and number of binding sites per cell for high- and low-affinity sites (1 and 2), respectively, in BxPC-3 cells (n = 3; mean ± SEM). gemca = gemcitabine (1 and 2 μg/mL); cisPt = cisplatin (2.5 and 5 μg/mL); cpt = camptothecin (1.5 and 3 μg/mL); mito = mitomycin C (0.1 and 0.2 μg/mL); doxo = doxorubicin (1 and 2 μg/mL).

**DISCUSSION**

Various findings have led to a general interest in the possible oncologic usefulness of SST analogs: the discovery of an antiproliferative action of SST-14 on HeLa and gerbil fibroma tumor cells in vitro (24), the shrinkage of pituitary and carcinoid tumors in response to octreotide treatment (25,26), and the detection of various SSTR-positive human tumors. So far, the 3 commercially available cyclic octapeptide analogs octreotide (SMS 201–995, Sandostatin; Novartis, Basel, Switzerland) (26), vapreotide (RC-160, Octastatin; Debiopharm, Lausanne, Switzerland) (27), and LAN (Somatuline) have been shown to be effective in controlling the growth of some human tumors (28). At the University of Vienna, our laboratory has recently developed a novel LAN-based tracer for tumor diagnosis and treatment (10,19). The tracer is a conjugate of DOTA coupled directly to the amino terminus of LAN (19). The substance can be stably labeled with a variety of radionuclides. 111In- or 90Y-DOTA-LAN binds with high affinity (Kd = 1–12 nmol/L) to several primary human tumors, such as intestinal adenocarcinomas, breast cancer, and also neuroendocrine tumors. Recently, we have shown that pancreatic cancer cells express clinically relevant amounts of SSTR3 in vitro and in vivo as reflected by successful tumor imaging using the novel compound 111In-DOTA-LAN, which binds hSSTR2–hSSTR5 with high affinity (18).

Few studies of the potential interaction between cytotoxic chemotherapy and expression of SSTR have been reported. LAN seems to be a potentially useful modulating agent for enhancing 5-fluorouracil and mitomycin C activity in human colon cancer cell lines (29). Octreotide has been shown to potentiate the effect of various chemotherapeutic agents in a synergistic or additive manner (30). Because such interplay might have potential consequences for clinical application of SST analogs, we have investigated whether cytotoxic pretreatment affects SSTR expression and binding

**FIGURE 4.** Reexpression of SSTR in pancreatic cancer cells after pretreatment with gemcitabine at 1 μg/mL (gemca1) and further incubation for 4 d (reexp; n = 3; mean ± SEM). Low-affinity binding of ASPC-1 cell reexpression exceeds scale used here (636.5 ± 11.5 fmol/10^6 cells). con = control.
behavior of DOTA-LAN in pancreatic adenocarcinoma. Such interactions can be shown for other peptide or receptor systems: We recently reported for a cohort of 450 patients with intestinal adenocarcinoma, including pancreatic cancers, using \(^{123}\)I-vasoactive intestinal peptide (VIP) that this peptide scintigraphy has a very high diagnostic sensitivity for previously untreated patients; however, for patients undergoing chemotherapy, the sensitivity of VIP scintigraphy was <30% for primary tumors (31).

Pancreatic adenocarcinoma cell lines BxPC-3, Panc-1 (poorly differentiated), ASPC-1 (isolated from ascitic fluid), and Capan-1 (metastasis to liver, well differentiated) were found to express all 5 hSSTRs, although in different quantities (18). The chemotherapeutic agents were selected to present a spectrum of different cellular targets. Gemcitabine (\(2',2''\)-difluoro-\(2'-\)deoxycytidine) is a new pyrimidine antimetabolite (32). Its cytotoxic effect is based on the incorporation of \(2',2''\)-difluoro-\(2'-\)deoxycytidine triphosphate instead of cytosine into the DNA, leading to irreversible inhibition of its synthesis blocking the cells at the S phase and late G1/0 phase (masked chain termination). Gemcitabine has replaced 5-fluorouracil because of its more favorable clinical profile. Cisplatin is an inorganic metal complex, which damages cells in all stages of the cell cycle, inhibits DNA biosynthesis, and binds DNA through the formation of interstrand crosslinks (33). Camptothecin is a natural product that interferes with the activity of topoisomerase I, the enzyme responsible for cutting and religating single DNA strands. Mitomycin C is a bioreductive alkylating agent that undergoes metabolic reductive activation through an enzyme-mediated reduction to generate an alkylating agent that crosslinks DNA, and doxorubicin blocks the synthesis of DNA and RNA through effects on topoisomerase II (33). The concentrations of the drugs for these in vitro experiments were chosen to have a significant effect in terms of antiproliferative and cytotoxic activity in these highly chemoresistant cell lines and to be comparable with clinical peak plasma concentrations. In vivo, the peak plasma concentration for gemcitabine is 15 \(\mu\)mol/L, for 5-fluorouracil is 0.6 \(\mu\)mol/L, for cisplatin is 1.9 \(\mu\)g/mL, for mitomycin C is 0.34 \(\mu\)g/mL, for doxorubicin is 0.4 \(\mu\)g/mL, and for camptothecin is approximately 70 nmol/L (as calculated for the camptothecin analog topotecan (34–39)). All chemotherapeutic drugs were found to have an antiproliferative effect with >20% inhibition compared with controls, and exposure to gemcitabine resulted in the appearance of a high number of apoptotic cells (>40% of cells). The growth-inhibitory effect of the respective drugs correlated well with accumulation in G2/M phase to S phase, with the exception of mitomycin C, which was associated with an almost complete G1/0-phase arrest.

After treatment with gemcitabine we found that the high-affinity binding sites on BxPC-3, Panc-1, and ASPC-1 cells were diminished and that the low-affinity binding sites were reduced dose dependently. Further incubation, after removing the chemotherapeutic drug, led to reexpression of high- and low-affinity binding sites at high levels. Treating Capan-1 and ASPC-1 cells with 5-fluorouracil led to a dose-dependent reduction of the receptors on Capan-1 cells but had no effect on ASPC-1 cells. With the exception of gemcitabine (reduction of binding for both receptor types) and cisplatin (induction of both kind of receptors), the other chemotherapeutics resulted in disappearance of high-affinity binding sites and increased expression of low-affinity sites. Therefore, a high rate of apoptotic cell death, as seen for gemcitabine, seems to be necessary to induce a loss of high- and low-affinity binding sites. G1/0 arrest, detected in response to treatment with mitomycin C, results in overexpression of low-affinity SSTR binding sites, partial growth inhibition, and absence of apoptosis, as shown for cisplatin in overexpression of both receptor classes and for camptothecin and doxorubicin with high inhibitory effects and intermediate percentages of apoptotic cells in a loss of high-affinity sites and reduction in low-affinity sites in higher concentrations. It remains to be investigated whether a general correlation exists between induction of apoptosis, cell cycle perturbations, growth inhibition, and expression of low- and high-affinity SSTR binding sites or whether these correlations are unique for the respective drugs.

Further investigation is needed to determine whether the loss of high-affinity sites can be made up by the increased expression of low-affinity sites in clinical imaging. At least for gemcitabine, the SSTRs seem to be reexpressed shortly after chemotherapeutic treatment. Therefore, our in vitro data provide evidence that assessment of response should be possible for the most frequently used drug in pancreatic cancer imaging by DOTA-LAN, especially because assessment of the clinical response is made with at least a 1-wk break after chemotherapy.

**CONCLUSION**

Our results clearly show that the pancreatic tumor lines reduce the expression of high-affinity DOTA-LAN binding sites in response to application of gemcitabine, camptothecin, mitomycin C, and doxorubicin, accompanied by variable overexpression of low-affinity binding sites. Regulation of expression of SSTRs seems to be related to the extent of growth inhibition, induction of apoptosis, and arrest, confined to specific cell cycle phases. In the case of gemcitabine, SSTRs are overexpressed during recovery from drug exposure within 4 d, indicating that assessment of response to chemotherapy may be possible within a short break after termination of drug application.

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