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Therapeutic targeting of pancreatic cancer utilizing sigma-2 ligands

John R Hornick, MD[a], **Dirk Spitzer, PhD**[b], **Peter Goedegebuure, PhD**[b], **Robert H Mach, PhD**[c], and **William G Hawkins, MD**[b,d]

[a]Department of Surgery, Harvard Medical School, Boston, MA, USA

[b]Department of Surgery, Washington University School of Medicine, St. Louis, MO, USA

[c]Division of Radiology, Washington University School of Medicine, St. Louis, MO, USA

[d]Alvin J. Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO, USA

Abstract

One major barrier in the development of pancreas cancer therapeutics is the selective delivery of the drugs to their cellular targets. We have developed previously several sigma-2 ligands and reported the discovery of a component of the receptor for these ligands. Several sigma-2 ligands have been shown to trigger apoptosis in pancreas cancer cells. More importantly sigma-2 ligands are internalized rapidly by the cancer cells, and are capable of delivering other small molecule therapeutics. Here we review sigma-2 ligands and conjugates as a potential novel therapy suitable for investigation in patients with pancreatic cancer.

Introduction

Pancreatic cancer is a devastating disease and represents the fourth highest mortality overall amongst all cancers (1). The overall 5-year survival is 6% in the United States (2), and the total cost of pancreatic cancer in the United States was last estimated to be 4.9 billion dollars per year and will only increase as the population ages (3). Thus, there is a need for earlier detection and treatment strategies. Because less than 20% of patients present with localized disease amendable to resection, the majority of patients are offered systemic chemotherapy.

Standard chemotherapies including gemcitabine do improve short term quality of life, but long term survival has not been appreciated (4). Oxaliplatin-based regimens are now acceptable first line agents in high performance patients and acceptable second line agents, but the benefit is limited to a short extension in median survival (5). Chemotherapeutic treatment of pancreatic cancer has been of limited success due to drug resistance and associated toxicities. To combat these limitations, tremendous efforts have been put forth to identify modes of cellular resistance to current chemotherapies. Additionally, the off-site toxicity which is a limiting factor to the tolerated dosage has prompted efforts to identify tumor selective markers for the specific targeting of pancreatic cancer. Protein markers of pancreatic cancer that have been identified previously include but are not limited to members of the S100 family, prostate stem cell antigen, and mesothelin (6). These markers have been evaluated in strategies of antitumor vaccines, with the most promising being mesothelin (7). Therapies using monoclonal antibodies have the advantage of specificity but

Correspondence: William G. Hawkins, MD Associate Professor of Surgery Washington University School of Medicine 660 S. Euclid Avenue Campus Box 8109 St. Louis, MO 63110 Office: (314) 362-7046 Fax: (314) 367-1943 hawkinsw@wustl.edu.

are limited by poor availability in the local tumor environment and are restricted to antigens expressed on the cell surface.

We have identified the sigma-2 receptor as a novel molecule that is overexpressed in human pancreatic cancer (and other cancers as well). The sigma-2 receptor can induce selectively apoptosis in pancreatic cancer and augments the effects of standard therapies. We have found further that synthetic sigma-2 ligands offer sustained bioavailability in the tumor as evidenced by PET imaging and are internalized rapidly (8-10). As such, sigma-2 ligands may represent a novel platform for molecular therapeutics of pancreatic and other cancers.

Sigma receptor background

Sigma receptors were identified initially as a subclass opioid receptors, however, they had low binding affinity to the active stereoisomer of naloxone (11), a potent morphine antagonist, and were, thus, placed subsequently in their own family consisting of sigma-1 and sigma-2 receptors. Due to the nature of compounds that bind these receptors, early research focused on neuropharmacology. Sigma-1 and -2 receptors were distinguished classically based on their binding affinity for [^{3}H]-(+)-pentazocine and [^{3}H]-1,3-di(2-tolyl)guanidine ([^{3}H]-DTG). Both sigma receptor bind pentazocine, while only the sigma-2 receptor binds DTG (12). While the sigma-1 receptor is a well-characterized protein, the sigma-2 receptor protein has remained elusive until recently.

Sigma receptor binding sites were first identified on tumor cells with (+)-[^{3}H]-N-allynormetazocine (SKF 10,047) and (+)-[^{3}H]3-(3-hydroxyphenyl)-N-(1-propyl)piperidine (3-PPP) in the early eighties during attempted characterization of these proteins in NCD20 cells (13), which led to the development of compounds used to characterize the binding sites in tumor cells (14, 15). Shortly thereafter, sigma-2 receptors were identified as potential markers of cellular proliferation in solid tumors (16). Human breast cancer cell lines grown *in vitro* were assessed for proliferation directly with BrdU staining, while cells grown in nude mice were evaluated indirectly to determine the ratio of proliferating to quiescent cells, reported as the P:Q ratio. Sigma-2 receptor density was estimated by binding of [^{3}H]-DTG to cell membrane homogenates, with (+)-pentazocine to mask sigma-1 sites. Using this model, it was determined that sigma-2 receptor density was up to 10 times greater in proliferating versus quiescent cells. The findings that sigma-2 receptor ligands accumulate in malignancies and that they have increased densities in proliferating malignancies, provided the rationale for multiple labs to continue studying this class of molecules for the application of imaging cancers by PET/SPECT, reviewed in (17). Adding to the attractiveness of targeting sigma-2 receptor is our recent evidence for the involvement of the human progesterone receptor membrane binding component 1 (PGRMC1) in the sigma-2 receptor binding complex (18).

PGRMC1/Sigma-2 receptor in cancer

Identification and cloning of the sigma-2 receptor had remained elusive for many years despite over a decade of investigation into this protein. Recently, PGRMC1 was identified as the putative sigma-2 receptor binding site by photoaffinity binding with a novel ligand WC-21 as compared with the known PGRMC1 ligand AG-205 (18, 19). This important finding set the stage for validation studies on overexpression of the PGRMC1/sigma-2 receptor and its function in pancreatic cancer, because PGRMC1 has been shown previously to be targetable with small molecule inhibitors (19). In the same manner, we have targeted the sigma-2 receptor with small molecule inhibitors in pancreatic cancer (20, 21). Traditionally, PGRMC1 has been investigated for overexpression in progesterone-sensitive cancers, such as ovarian (22) and breast cancer (23). Progesterone exhibits antiapoptotic

activity in ovarian cancer, however, PGRMC1-depleted cells exhibited apoptosis when treated with progesterone (24). Most recently, this complex was found to be overexpressed in the serum and the neoplasms of patients with squamous cell lung carcinoma and lung adenocarcinoma (15). Importantly, PGRMC1 expression has been found to modulate the sensitivity of ovarian cancer to chemotherapy (25, 26) and correlates with estrogen receptor alpha and hypoxia in breast cancer (27). Initial studies of human pancreatic adenocarcinoma tumors in our lab have shown overexpression in at least half of the samples by immunohistochemistry (unpublished data). Further work will be performed to validate this finding.

PGRMC1 is part of a sterol-binding protein complex known to bind progesterone as well as other sterols and pharmaceuticals (28). This protein lacks traditional nuclear hormone receptor activity, however, and instead shares homology with cytochrome b5 (29), binds heme (30), and interacts with multiple p450 enzymes (28, 31). The p450 enzyme system is involved typically in drug metabolism as well as sterol synthesis, and PGRMC-1 directly inhibits the drug metabolizing effects of P450 enzymes (32). Additionally, PGRMC-1 activates sterol 14 alpha-demethylase (CYP51) (33) and binds with Insig-1 (insulin-induced gene) and SCAP-1 (SREBP cleavage activating protein (34). SREBP (sterol response element binding protein) is a membrane cholesterol sensing transcription factor (35, 36) that is released to the nucleus when cleaved by SCAP when cellular cholesterol is decreased (37). Thus, the sensitivity of proliferating cells to growth inhibition by PGRMC1/sigma-2 receptor ligands likely involves inhibition of cellular cholesterol balance and energy homeostasis. Indeed, cholesterol inhibition by HMG-CoA-reductase inhibitors or statins has been shown to decrease the risk of pancreatic cancer and remains an active area of research (38, 39).

The role of PGRMC1 activity and modulation after treatment with sigma-2 receptor ligands is an active area of research. Identification of all interacting proteins in this multimeric complex have yet to be fully completed. The known roles of this protein in regulation of metabolizing enzyme systems and cholesterol synthesis indicate that binding with sigma-2 receptor ligands likely modulates the energy metabolism of cancer cells on treatment. Indeed, early studies of the ligands showed that the antiproliferative effects of sigma ligands involved inhibition of cholesterol synthesis (40). Additionally, we have observed that cellular ATP content decreases quickly in pancreatic cancer cells in a dose-dependent manner when treated with SW43 (unpublished finding). Maintenance of the integrity of the cytoplasmic cell membrane is dependent on cholesterol content, which may account for the early morphologic rounding of cells after treatment that has been observed with other studies in addition to our own findings (41). Findings that PGRMC1 modulate microtubule stability during mitosis (42) may lead to other hypotheses regarding morphologic changes. Overall, PGRMC1 is involved in regulation of cellular metabolism and apoptosis in cancer cells (28, 43).

Specific uptake in pancreatic cancer cells

Sigma-2 receptor ligands are internalized preferentially by proliferating cancer cells, a characteristic that may limit systemic toxicity. Sigma-2 receptor ligands conjugated with the chromophore 4-chloro-7-nitrobenzo-2-oxa-1,3-diazole (NDB) were first utilized to show subcellular uptake into proliferating breast cancer cells (10). This study was the first to reveal uptake of these compounds by receptor-mediated endocytosis. Further studies in pancreatic cancer cells with SW120, another fluorescent derivative of the highly cytotoxic sigma-2 ligand SW43, confirmed localization to membrane components of the cells. In addition to showing decreased uptake by the receptor-mediated endocytosis inhibitor phenylarsine oxide, disruption of lipid rafts showed that uptake was also dependent on

caveolin-mediated endocytosis (44). Caveolin is a protein responsible for internalization of cholesterol enriched lipid rafts, the location of the well-studied death-receptor pathway (45). Whether sigma-2 receptor ligands are internalized actively at these sites or are more readily internalized passively due to favorable stoichiometric constraints remains to be elucidated. Interestingly though, caveolin-1 has been presented recently to be overexpressed in poorly differentiated cancers with its expression related directly to a short time to progression (46, 47).

Evidence for sigma-2 ligands as therapy for pancreatic cancer

We first became interested in sigma-2 receptors for pancreatic cancer when it was identified that agents selective for sigma-2 receptor are taken up specifically in tumor cells on PET imaging (17, 48) and induce apoptosis (49). Because pancreatic cancer is poorly detected prior to advanced stage and has a poor overall response to chemotherapy, promising agents such as this deserve attention, this rationale for evaluating selective sigma-2 ligands as a therapeutic targeting strategy is justified. Another compound, K0-135, with high selectivity to sigma-2 receptor was used initially to show subcellular uptake into pancreatic cancer cells with *in vivo* confirmation with RHM-4 (^{18}F-labled sigma-2 ligand) for selective uptake in implanted pancreas adenocarcinoma (Panc02) in C57BL/6 mice (9). Therapeutic treatments have shown repeatedly induction of apoptosis and increased survival in mice bearing pancreatic tumors after treatment with the sigma-2 receptor ligands SV119 and SW43, an effect augmented by concurrent treatment with traditional chemotherapy with gemcitabine (20, 21).

Sigma-2 ligands augment apoptosis in pancreatic cancer

Drug resistance in pancreatic cancer occurs rapidly by both natural and acquired resistance. Resistance pathways to therapies such as gemcitabine are multiple and include adaptations to cell influx/efflux, nuclear translocation, nucleoside analog conversion by dUTPase, introduction into the DNA strand, DNA editing, cell checkpoint proteins, or further down-stream apoptotic pathways (50, 51). Despite this, in our studies on cellular death by sigma-2 ligands in pancreatic cancer, we have identified significant induction of caspase-3, ion disturbances, ROS generation, and autophagy (52). These processes are global forces promoting cancer cells into apoptosis. Importantly, we failed to generate cell lines resistant to this treatment despite extended subtherapeutic exposure for up to three months in *in vitro* grown cell lines, such as Panc02, CFPAC, Aspc1, Bxpc3, and Panc1 cells (unpublished finding). Pre- and post- treatment with either traditional chemotherapy or radiation have been found to augment apoptosis in these cell lines as well. Evidence of cellular internalization of sigma-2 ligand compounds despite conjugation with small molecule tracers or inhibitors of apoptosis further provides rationale for further investigation of these compounds. The utilization of sigma-2 ligands to deliver small molecule therapeutics has been reported recently in animal models of pancreatic cancer (53). Given that this treatment is selective for pancreatic cancer cells and induces apoptosis, this observation provides compelling support for clinical development of this novel strategy.

Conclusions

Sigma-2 receptor ligands localize preferentially to pancreatic cancer and induce apoptosis with limited off-site toxicity in preclinical models. These ligands are internalized by both receptor-mediated endocytosis and transport across the cytoplasmic membrane through cholesterol-rich lipid rafts, providing the opportunity to utilize sigma-2 receptors as targeting “homing beacons” to deliver small molecules. By interfering with metabolic pathways altered specifically in cancer cells, sigma-2 receptor ligands may provide yet

another angle to induce apoptosis when resistance is developed to traditional chemotherapies. Additionally, neoadjuvant treatment may allow down-staging in patients not appropriate for operative management.

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