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Editorial

Sigma-2 Receptor: Biomarker for Solid Tumor Diagnosis and Target for Tumor Treatment

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Sigma receptors are a distinct class of receptors that are found in many tumors and normal tissues and have been associated with many cellular and organ processes, including motor function, endocrine function, proliferation, immunoregulation and ion channel modulation [1]. There are two types of sigma receptors, sigma-1 and sigma-2. Sigma-1 receptor has been cloned from many species [2] and its involvement in pathologies such as anxiety, depression, schizophrenia and drug addiction, Parkinson's and Alzheimer's disease has been demonstrated [3]. Sigma-2 receptor has not yet been cloned. Attempts to isolate these receptors led to the hypothesis that they could be related to histone proteins [4,5], but recent studies led to identify sigma-2 receptor protein as the progesterone receptor membrane component 1 (PGRMC1) [6]. A great impulse in sigma-2 receptor research has been given by the evidence that the sigma-2 subtype is overexpressed in a variety of peripheral and brain human tumors. Moreover, activation of sigma-2 receptors with sigma-2 ligands induces antiproliferative and cytotoxic effects in tumor cells *in vitro* as well as in *in vivo* preclinical models [7]. Therefore, sigma-2 receptors are promising targets for tumor diagnosis and treatment.

Sigma-2 receptor as a biomarker of solid tumors

Sigma-2 receptor was first identified by Hellewell and Bowen through receptor binding studies in rat PC12 adrenal pheochromocytoma cells [8]. Vilner et al. , demonstrated that the density of sigma-2 receptors in a wide variety of human and murine tumor cell lines was higher than that of sigma-1 receptors [9]. Moreover, sigma-2 receptors are expressed in higher density in human cancer cells as compared to most normal tissues [10]. This observation suggested that sigma-2 receptor may be a potential biomarker for cancer imaging with noninvasive techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT).

Every solid tumor contains two cell populations: proliferative cells (P) and quiescent cells (Q) [11]. The proliferative status (PS) is the measure of solid tumor proliferation, and is defined as the ratio of P cells to Q cells. A similar measure of cell proliferation is the growth fraction (GF), defined as the ratio of the number of P cells in a tumor to the total number of P and Q cells. The number of P and Q cells in a tumor, changes from one patient to another, and knowledge of the PS and GF of a tumor can provide useful information to determining an appropriate chemotherapy or radiation therapy for treating cancer patients [12].

Sigma-2 receptor is a useful biomarker for determining the PS and GF of solid tumors using PET and SPECT, as reported in many studies. Mach and colleagues demonstrated that the density of sigma-2 receptors in proliferating cells was 10-fold greater than the density observed in quiescent cells [13,14]. In addition, the upregulation and downregulation of sigma-2 receptors was observed in the transition between the P and Q states of mammary mouse cells [15]. Since the same P/Q ratio of sigma-2 receptor density was observed in solid tumors and cell culture conditions, the results obtained from cell culture conditions may be translated to solid tumors xenografts of these breast cancer cell lines [15]. These data demonstrate that the sigma-2 receptor is a biomarker of cell proliferation in breast tumors, and this approach can be extended to evaluate the proliferative status of other human tumors which have high sigma-2 receptors density [9]. Therefore, radiotracers having a high sigma-2 receptors affinity can be an useful tools to evaluate the PS and GF of human tumors using PET and SPECT techniques, as demonstrated in a clinical study (NCT00968656A) just completed with fluorine-18 radiolabeled sigma-2 ligand [16].

Sigma-2 receptor ligands as antitumor agents

Since, several sigma-2 ligands have been shown to induce *in vitro* and *in vivo*, cancer cell death, therapies that have sigma-2 receptor target, might play a role against a wide spectrum of cancer types [17-19]. Multiple are the pathways activated by sigma-2 receptor ligands to induce cell death such as caspases involvement, reactive oxygen species (ROS) generation, lysosomal leakage, autophagy and modulation of Ca^{2+} release by intracellular stores [20-22]. Apparently, activation of the pathways depends on tumor cell type and on the structure of the sigma-2 ligands used [20]. Some sigma-2 ligands have been shown to induce caspase-dependent apoptosis in pancreas tumor [17,18], but not in breast tumor [21]. Several ligands induce calcium release in different tumors, such as breast, prostate, colon, and neuroblastoma [19,22] but this effect is not always associated with tumor death [1,23]. Different degrees of caspase activation, inhibition of the mTOR pathway, and intracellular cytoskeletal abnormalities resulting in autophagy was found for some sigma-2 ligands [25]. The important role of sigma-2

receptor ligands in cancer therapy is supported by an increase of number of review articles [1,24,25].

Recent *in vivo* studies combining gemcitabine chemotherapy with the sigma-2 selective ligands demonstrate an additive effect in the blocking of tumor growth [18,26]. Furthermore, the same effect is observed by combining doxorubicin with sigma-2 ligands in several *in vitro* cancer cell lines [27-30]. Therefore, combination of sigma-2 ligands with traditional anticancer drugs seems to be a very promising research area.

In addition, two new different approaches using sigma-2 ligands as delivery agents have been reported. One approach has been the synthesis of conjugate compounds that link a sigma-2 ligand to small molecule therapeutics that are selectively internalized by cancer cells [29]. The second approach has been the synthesis of sigma-2 ligand conjugated to gold nanocages demonstrating the feasibility of sigma-2 ligand in targeted delivery of nanoparticles in human cancer cell lines *in vitro* [31].

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