Sigma Receptors [sRs]: Study of their role in cancer and the development of new targeted anticancer therapies

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Background

Sigma receptors [sRs] are a relatively novel group of receptors widespread in the central nervous system (CNS) and in multiple peripheral tissues. They are divided into two subtypes, sigma-1 (s1R) and sigma-2 (s2R) receptor that are distinguished based on their different ligand selectivity patterns and molecular weights. Selective sigma ligands (agonists and antagonists) have been shown to specifically label tumor sites, induce cancer cells to undergo apoptosis and inhibit tumor growth. Aim of this work is to study the expression of sigma ligands and their relation to cancer development, their potential as drugs using patient derived animal cancer models (PDX) and to detect common features of the mechanism of action that ligands of the same selectivity may share.

Materials and Methods

Development of transplantable PDX models of pancreatic cancer was performed subcutaneously (s.c.) using immunocompromised mice (NSG). For primary cell lines tumor growth characteristics were also recorded determining tumorigenicity, take rate and doubling time. The expression of sigma receptors was examined in tissue samples from patients with colorectal and pancreatic cancer and in pancreatic cell lines using Western Blot. Furthermore, pancreatic cell lines (AsPC1, BxPC3, MiaPaca) and primary cell lines (021013 Attached, 021013 Floating) were treated with known chemotherapeutic drugs and multiple sigma ligands (agonists and antagonists). The antiproliferative effect of these compounds was studied with in vitro Cancer Screen assay (SRB assay).

Results

Upon transplantation into NSG mice one specimen (021013) was cultured ex vivo giving rise to two different cell populations. These cell populations were further tested to determine their growth rates in NSG mice and a different way of growth was revealed. A differential expression of sigma receptors was also revealed among the two subpopulations. Expression of sigma 1 and sigma 2 receptors was observed in all cancer cell lines and tumor tissues that were tested. Sigma 2 receptor is highly expressed in cancer compared to adjacent normal tissue. In addition, sigma 2 receptor seems to be overexpressed in cancer compared to sigma 1 receptor. Amongst the sigma ligands that so far have been tested, PB28, Rimcazole and Siramesine found to exhibit the best anticancer activity.

Conclusions

In the present study we examined the expression of sigma receptors on human pancreatic and colorectal cell lines and how this expression affects cell proliferation against various sigma ligands. Expression of sigma receptors found not to significantly affect the chemosensitivity of cells against the tested sigma agonists and antagonists. Studies to evaluate the potency of those ligands either as single agents or in combination with established drugs in human-to-mouse models of cancer are ongoing.

References:

1. Morphological characteristics of established pancreatic PDX

Figure 1: Phase contrast photos of the different cell populations from ex vivo cultures of the xenograft 021013. From 021013 tumors two different subpopulations have been isolated: one growing as adherent cells (021013 Attached) and another one in suspension (021013 Floating).

2. Growth curve

Figure 2: After injections of 021013 cells (10³ cells/injection) in NSG mice (n=6 tumors) the average tumor size (mm²) was calculated and plotted as a function of time (days) in order to determine the growth rates of the two subpopulations. The two isolated cell populations grow in a different way with the 021013 Floating to exhibit lower doubling time.

3. Expression of Sigma Receptors

Figure 3: The expression of sigma receptors (s1R and s2R) was studied in A) pairs of cancer and normal tissue derived from different patients with colorectal cancer B) tissue samples derived from patients with pancreatic cancer and C) primary (021013 Attached, 021013 Floating) and established (AsPC1, BxPC3, MiaPaca) pancreatic cancer cell lines. s2 receptor is highly expressed in cancer and also overexpressed compared to s1.

4. Impact of Sigma Receptor expression in chemosensitivity and proliferation of cancer cells lines

Figure 4: Growth curves of cell lines treated with sigma ligands. SRB assay was used to evaluate the anticancer properties of sigma ligands against a diverse panel of cancer cell lines. Incubation period was 48h. Points represent means of at least two independent experiments. CV<20%