Sigma ligands as potential novel 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] [1] and in multiple peripheral tissues [2]. They are divided into two subtypes, sigma-1 (s1R) and sigma-2 (s2R) receptor [3] that are distinguished based on their different ligand selectivity patterns and molecular weights [1]. Selective sigma ligands (agonists and antagonists) have been shown to specifically label tumor sites, induce cancer cells to undergo apoptosis and inhibit tumor growth [4]. However the mechanisms of action underlying the anticancer activity of sigma ligands and their signaling pathways are reported to be highly dependent both on the type of the ligand and the type of the tumor [5] they target even though they may share similarities in their receptor binding properties. Aim of this work is to study the expression of sigma ligands and their relation to pancreatic cancer development, their potential as drugs against this cancer using patient derived animal cancer models and to detect common features of the mechanism of action that ligands of the same selectivity may share.
Methods: The expression of the sigma receptors was examined in:

- Pairs of cancer and normal tissue derived from different patients with pancreatic or colorectal cancer
- Pancreatic cancer cell lines ($AsPC_1$, $BxPC_3$, MiaPaca)
- Primary pancreatic cancer cell lines (021013 Attached, 021013 Floating)

Furthermore, pancreatic cell lines ($AsPC_1$, $BxPC_3$) 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: Expression of sigma 1 and sigma 2 receptors was observed in all cancer cell lines and tumor tissues. 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 and Siramesine found to exhibit the best anticancer activity. 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:

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