TARGETED THERAPIES

Pim kinase inhibition and chemoresistance

The Pim kinase family of serine/threonine kinases is composed of three isoforms, Pim-1, Pim-2 and Pim-3, which have an important role in tumor progression. Pim kinases suppress apoptosis and regulate cell-cycle progression and have been suggested to function synergistically with c-Myc as well as serving a putative oncogenic function. Elevated levels of Pim kinases have been reported in solid tumors such as prostate cancer and pancreatic cancer. Pim-1 was initially discovered in murine leukemia and several independent studies have shown this kinase to be upregulated in human prostate cancer.

A study by Mumenthaler *et al.* has revealed that inhibition of Pim-1 when combined with chemotherapy could be an important strategy for combating chemoresistance in prostate cancer. A common feature of aggressive, hormone-refractory prostate cancer is chemoresistance and Pim-1 kinase has been linked with chemoresistance in prostate cancer cells. It has been suggested that Pim kinases contribute to tumorigenesis and promote drug resistance in prostate cancer. Inhibitors that target this kinase might therefore be used as potential therapy for prostate cancer.

Mumenthaler and colleagues used prostate cancer models to determine if the novel, small-molecule Pim kinase inhibitor, SGI-1776, was efficacious alone or in combination with a taxane-based chemotherapeutic regimen for the treatment of prostate cancer.

Radiometric assays were used to measure kinase inhibition and quantitative real-time reverse transcription polymerase chain reaction was used to confirm Pim-1, Pim-2 and Pim-3 expression in the human prostate cancer cell lines. Using an ATP viability assay the authors confirmed that SGI-1776 reduced prostate cancer cell viability in the examined lines and this reduction in viability was dose-dependent. It has previously been shown that in the presence of

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chemotherapeutic agents, Pim-1 acts as a survival factor and the investigators were keen to investigate whether SGI-1776 could sensitize prostate cancer cells to chemotherapy using paclitaxel. They noted an additional cytotoxic effect when SGI-1776 was combined with paclitaxel. Androgen-independent cell lines, 22Rv1, PC3 and C4-2B were most sensitive to SGI-1776. Both the 22Rv1 and C4-2B cell lines are hormone refractory and express the androgen receptor. SGI-1776 caused cell-cycle arrest and caspase-dependent apoptosis in the studied cell lines.

The 22Rv1 cell line was the most sensitive to SGI-1776 treatment, so the researchers overexpressed recombinant Pim-1 in this cell line to validate the specificity of SGI-1776 and this resulted in increased SGI-1776 sensitivity. The researchers also found that SGI-1776 sensitizes prostate cancer cell to taxane-based therapeutics. They created a taxane-resistant form of the 22Rv1 cell line to examine the effects of Pim kinase inhibition on resistance to paclitaxel and found that taxane-resistant cells are sensitive to SGI-1776 and that this agent was capable of inducing apoptosis in this model. The taxane-resistant cell line was also resistant to increasing doses of docetaxel, the current standard treatment for hormone-refractory prostate cancer.

The results of this study also confirmed the ability of SGI-1776 to resensitize multidrug-resistant prostate cancer cells to taxanes and the authors proposed that the likely mechanism of reversing resistance was inhibition of multidrug resistance 1 gene activity and triggering apoptosis.

Taxane-based chemotherapy is currently a standard treatment for patients with advanced or hormone-refractory prostate cancer. It is important to understand the mechanism of chemoresistance in prostate cancer cells and targeting candidate markers to sensitize these cells to a chemotherapy regimen in order to effectively treat prostate cancer patients.

“These findings suggest that Pim kinase inhibition may prove to be a beneficial strategy for treating prostate cancer and in particular those that are nonresponsive to taxane-based chemotherapy” comment the researchers.

SGI-1776 is currently being investigated in human clinical trials for hormone-refractory and docetaxel-refractory prostate cancer.

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Original article Mumenthaler, S. M. *et al.* Pharmacologic inhibition of Pim kinases alters prostate cancer cell growth and resensitizes chemoresistant cells to taxanes. *Mol. Cancer Ther.* 8, 2882–2893 (2009)