The Novel Sphingosine Kinase-2 Inhibitor ABC294640 Blocks Survival and Tumorigenesis in Chemo- And Endocrine- Resistant Breast Cancer.


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Resistance to chemotherapy is a major cause of breast cancer treatment failure today. The sphingolipid metabolizing enzyme, sphingosine kinase, converts pro-apoptotic ceramide into pro-survival sphingosine-1-phosphate (S1P). Sphingosine kinase-1 (Sphk1) has been shown to be involved in breast cancer endocrine- and chemo-resistance and is a proposed key regulator of proliferation. There is, however, conflicting data on the role of sphingosine kinase-2 (Sphk2) in cancer biology and drug resistance, with some suggesting that Sphk2 has an opposing role to that of Sphk1. Here, we studied the effects of the novel selective Sphk2 inhibitor, ABC294640 (3-(4-chlorophenyl)- adamantane-1-carboxylic acid (pyridin-4-ylmethyl) amide), on human breast cancer and compared to its parent compound, SKI-II (4-[[4-(4-Chlorophenyl)-2-thiazolyl]amino]phenol). Treatment with ABC294640 increased levels of endogenous long chain ceramides while simultaneously reducing levels of S1P in vitro. ABC294640 blocked both viability and survival at low micromolar IC50 concentrations in the endocrine therapy resistant - MDA-MB-231, MDA-MB-468 and MDA-MB-361 cell lines, as well as the chemotherapy resistant MCF-7TN-R cell line. Furthermore, treatment with the inhibitor significantly reduced proliferation, as seen in immunofluorescence staining of Ki-67 in vitro. Interestingly, ABC294640 can induce apoptosis and release caspase-9, possibly through modulation of activity of the transcription factor NF-kappaB. Treatment with 10μM of the inhibitor blocked transcription of genes known to be mediated by the NF-κB, such as at IAP1, IAP2, and SOD1. Xenograft immunocompromised mouse models were utilized to validate the biological relevance of our sphingosine kinase inhibitors. In fact, ABC294640 significantly reduced breast cancer tumorigenesis of MDA-MB-468 and MCF-7TN-R in vivo. Treatment with 50 mg/kg of the inhibitor for 14 days decreased MDA-MB-468 tumor volume by 37.3% (n=10) compared to vector control. Similarly, there was a 67.4% decrease in tumor volume following 18 days of treatment in the chemoresistant MCF-7TN-R xenograft mice (n=10). These results indicate that pharmacological inhibition of Sphk2 with an orally bioavailable selective inhibitor, ABC294640, has therapeutic potential in the treatment of chemo- and endocrine therapy- resistant breast cancer.