FEATURES

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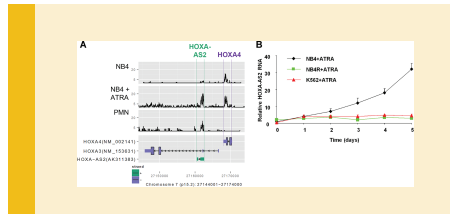
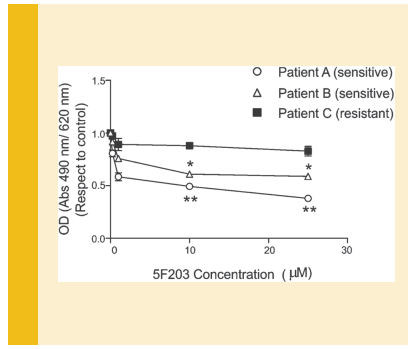


HOXA cluster antisense RNA 2 (HOXA-AS2) is a long non-coding RNA located between the HOXA3 and HOXA4 genes in the HOXA cluster. Its transcript is expressed in NB4 promyelocytic leukemia cells and human peripheral blood neutrophils, and expression is increased in NB4 cells treated with all *trans* retinoic acid (ATRA). Knockdown of HOXA-AS2 expression by transduced shRNA decreases the number of viable cells and increases the proportion of apoptotic cells, measured by annexin V binding and by activity and cleavage of caspases-3, -8, and -9. The increase in death of HOXA-AS2 knockdown cells was accompanied by an elevated TNF-related apoptosis-inducing ligand (TRAIL) levels, but ATRA-induced NB4 cells treated with TRAIL did show an increase in HOXA-AS2 expression. These results demonstrate that ATRA induction of HOXA-AS2 suppresses ATRA-induced apoptosis, possibly through a TRAIL-mediated pathway. HOXA-AS2-mediated negative regulation thus contributes to the fine-tuning of apoptosis during ATRA-induced myeloid differentiation in NB4 cells

ACCEPTED MANUSCRIPT ONLINE 20 MAY 2013



2-(4-Amino-3-methylphenyl)-5-fluorobenzothiazole (5F203, NSC 703786) lysylamide belongs to a novel mechanistic class of antitumor agents. It elicits activity against ovarian, breast, kidney and colorectal cancer models. In sensitive breast cancer cells, 5F203 activates aryl hydrocarbon receptor (AhR) signaling. Herein, the role of AhR in 5F203 activity in two ovarian cancer cell lines: IGROV-1 (sensitive to 5F203), SKOV-3 (resistant to this agent) is evaluated. In addition, cancer cells have been isolated from ascites fluid of ovarian cancer patients; sensitivity to 5F203 and concurrent AhR signal transduction has been examined in ascites-isolated ovarian cancer patients' cells. 5F203 induced enhanced CYP1A1 expression, AhR translocation and ROS formation in IGROV-1 cells and ascites-isolated ovarian cancer cells that were sensitive to 5F203. In IGROV-1 cells 5F203-induced ROS formation was accompanied by JNK, ERK and P38MAPK phosphorylation, DNA damage and cell cycle arrest prior to apoptosis. In contrast, 5F203 failed to induce CYP1A1 expression, AhR translocation or oxidative stress in 5F203-resistant SKOV-3 cells, or in ovarian cancer ascites cells inherently resistant to this agent. It is proposed that AhR may represent a new molecular target in the treatment of ovarian tumors and 5F203 may exemplify a potential novel treatment. Furthermore, putative biomarkers of sensitivity to this agent have been Identified.