B-6

The Anti-Proliferative Effects of the Mycotoxin Verrucarin A on Neuroendocrine Tumor Cells

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BACKGROUND: High throughput screening of natural compounds has identified Verrucarin A (VC-A), a mycotoxin, to have anti-proliferative effects in several cancer types. VC-A downregulates the expression of prosurvival phospho-Akt (p-Akt), NF-*k*B (p65) and p-mTOR signaling proteins in pancreatic adenocarcinoma and prostate cancer. As the overactivation of the PI3K/Akt signaling pathway has been associated with the overexpression of SSTR2 in neuroendocrine tumors (NETs), VC-A may be useful for the targeted therapy of NETs as part of an antibody-drug conjugate. However, the anti-neoplastic properties of VC-A have not been investigated in neuroendocrine (NE) cancers so far.

METHODS: To determine the anti-proliferative effects of VC-A, all cell lines were treated with VC-A for 72 hours and an MTT assay was used to determine the IC50. To assess whether cell viability was decreased by apoptotic mechanisms an Annexin V assay coupled with a western blot for apoptotic markers (XIAP, cPARP, PARP and MCL-1) were used. The effect of VC-A on NE cancer markers ASCL1 and Chromogranin A (CgA) were determined by western blot.

RESULTS: VC-A demonstrated a low nanomolar IC50 against BON (pancreatic neuroendocrine) and H727 (pulmonary neuroendocrine) cell lines. The IC50 of VC-A was 10-fold higher in pulmonary fibroblasts (WI-38) and normal thyroid cells (NThyori). Annexin V and western blot results demonstrated that VC-A increased apoptotic events in a dose-dependent manner. VC-A also induced apoptosis by decreasing anti-apoptotic proteins: Mcl1, and cyclin D1 and decreased the CDK inhibitors p21 and p27. Furthermore, VC-A altered the NE phenotype by decreasing NE cancer markers CgA and ASCL1.

CONCLUSION: The cytotoxicity of VC-A has previously been determined to depend on chemical moieties that can be maintained during antibody conjugation. Because of the structure and anticancer properties, VC-A shows promise as a potential lead compound for the generation of a potent antibody drug conjugate for the treatment of neuroendocrine tumors.

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