

June 2022

Acetyl isogamabogic acid activates unfolded protein response and apoptosis in head and neck cancer

Mehrnoosh Ghafouri

Wayne State University School of Medicine, mehrnoosh.ghafouri@med.wayne.edu

Chester Gauss

Western Michigan University School of Medicine

Yue Xi PhD

Carman and Ann Adams Department of Pediatrics, Wayne State University School of Medicine

Thomas Jetmore MD

Department of Otolaryngology, Wayne State University School of Medicine

Jordyn Lucas MD

Department of Otolaryngology, Wayne State University School of Medicine

See next page for additional authors

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Recommended Citation

Ghafouri, Mehrnoosh; Gauss, Chester; Xi, Yue PhD; Jetmore, Thomas MD; Lucas, Jordyn MD; Callaghan, Michael U. MD; and Fribley, Andrew M. PhD, "Acetyl isogamabogic acid activates unfolded protein response and apoptosis in head and neck cancer" (2022). *Medical Student Research Symposium*. 182.
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Authors

Mehrnoosh Ghafouri, Chester Gauss, Yue Xi PhD, Thomas Jetmore MD, Jordyn Lucas MD, Michael U. Callaghan MD, and Andrew M. Fribley PhD

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Key words: HNSCC, CHOP, AIGA, unfolded protein response, ER stress, natural products

Head and neck squamous cell carcinoma (HNSCC) develops in the mucous membranes of the mouth, nose, and throat. HNSCC is the sixth most common malignancy in the world with 650,000 new diagnosis and 350,000 death every year. Current treatments are chemotherapy and radiation however, the 5-year survival rate for patients at stage 3 or 4 is less than 50%. There is an urgent unmet clinical need to investigate novel treatments for these patients. HNSCC is characterized by dysregulated cell growth rate and aberrant protein synthesis which leads to increased protein folding demand and the need for chaperones. This high protein demand leads to accumulation of misfolded proteins in endoplasmic reticulum that causes ER stress and results in Unfolded Protein Response (UPR). To address the shortcoming of the current treatments for HNSCC, we attempted a high-throughput screen on a compound library of 2400 compounds in order to identify compounds that could induce ER stress and enforce a terminal (apoptotic) UPR in HNSCC. Acetyl-IsoGambogic Acid (AIGA) emerged as a hit; AIGA strongly showed activation of UPR and apoptotic pathways. Further cell proliferation assays, gene expression, protein immunoblot profiles, DNA fragmentation assay, and fluorescence-activated cell sorting (FACS) were consistent with activation of UPR and apoptosis in a panel of HNSCC cell lines. Considered together these data confirmed that our HTS approach could successfully identify novel inducers of terminal unfolded protein response. Natural compounds such as AIGA might be able to provide a new therapeutic approach for treating patients with HNSCC.