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Ph.D. DISSERTATION DEFENSE

Candidate:	Daniel Centeno
Degree:	Doctor of Philosophy
School/Department:	Charles V. Schaefer, Jr. School of Engineering and Science / Chemistry and Chemical Biology
Date:	Friday, August 9th, 2024
Time/Location:	11:00 am / McLean Hall 510
Title:	Modeling of Intracellular Taurine Levels in Ovarian Cancer
Chairman:	Dr. Marcin Iwanicki, Department of Chemistry and Chemical Biology, School of Engineering and Sciences
Committee Members:	Dr. Kenny Wong, Department of Chemistry and Chemical Biology, School of Engineering and Sciences Dr. Hongjun Wang, Department of Biomedical Engineering, School of Engineering and Sciences Dr. Christian Traba, Department of Chemistry, Biochemistry, and Physics, Fairleigh Dickinson University

ABSTRACT

Taurine, a non-proteogenic amino acid commonly used as a nutritional supplement, possesses numerous cytoprotective properties that support human health and cellular homeostasis. It has been shown to protect various tissues from degeneration caused by the DNA-damaging chemotherapeutic agent cisplatin. However, it is not yet understood whether and how taurine protects human ovarian cancer (OC) cells from cisplatin-induced DNA damage.

We have found that OC ascites-derived cells contained significantly more intracellular taurine than cell cultures modeling OC. In culture, elevation of intracellular taurine concentration to OC ascites-cell-associated levels suppressed the proliferation of various OC cell lines and patient-derived organoids, inhibited glycolysis, and evoked cellular protection from cisplatin. Taurine's protection was associated with a decrease in cisplatin-induced DNA damage.

A combination of RNA sequencing, reverse phase protein arrays, live-cell microscopy, flow cytometry, and biochemical validation experiments provided evidence for taurine-mediated induction of mutant- or wild-type p53 binding to DNA, and activation of p53 effectors involved in negative regulation of the cell cycle (p21), and glycolysis (TIGAR). Paradoxically, taurine's suppression of cell proliferation was associated with activation of pro-mitogenic signal transduction including ERK, mTOR, and increased mRNA expression of major DNA damage sensing molecules such as DNAPK, ATM and ATR. While inhibition of ERK or p53 did not interfere with taurine's ability to protect cells from cisplatin, suppression of mTOR with Torin2, a clinically relevant inhibitor that also targets DNAPK and ATM/ATR, broke taurine's protection from cisplatin. Our studies implicate that elevation of intracellular taurine could suppress cell growth, metabolism, and activate cell protective mechanisms involving mTOR and DNA damage sensing signal transduction.