THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

Samrita Dogra

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE
GRADUATE COLLEGE
Department of Graduate Pharmaceutical Sciences

Wednesday, November 20, 2019 | 12:00 Noon
College of Pharmacy Building, Room 101

Apelin/APJ Pathway: Functional Characterization in Drug Resistance and Metastasis in Ovarian Cancer

COMMITTEE IN CHARGE: Sukyung Woo, PhD, Chair; Youngjae You, PhD; Jessie L. Au, PharmD, PhD; Randle Gallucci, PhD; Resham Bhattacharya, PhD

ABSTRACT: High grade serous ovarian cancer (HGSOC) is the most common and lethal histology, which accounts for 80% of ovarian cancer death. Its high mortality is due to the extensive metastasis at diagnosis, and the emergence of drug resistance. Thus, developing effective treatments that overcome resistance to standard-of-care treatments and/or disrupt metastatic processes are urgently needed. We identified APJ, a novel target that is significantly overexpressed in HGSOC patient tumors than in normal tissues, to a higher extent in metastatic than primary tumors. High expression of APJ correlated with decreased median overall survival by 14.7 months in patients with HGSOC. The objective of this dissertation was to functionally validate the role of a novel apelin/APJ pathway in mediating drug resistance and metastasis in ovarian cancer. APJ is a G-protein coupled receptor activated by the specific endogenous ligand apelin, an adipokine secreted by adipocytes. To determine the functional significance of APJ in HGSOC, we used multiple cell lines with APJ

expression (low, moderate, and high), molecular manipulation (overexpression and inhibition), and pharmacological inhibitors. Using various in vitro model systems, we demonstrated that APJ expression in cancer cells is both necessary and sufficient to increase pro-metastatic phenotypes, including proliferation, cell adhesion, anoikis resistance, migration, and invasion. In vivo, high expression of APJ promotes extensive peritoneal seeding and metastatic growth in orthotopic models of HGSOC. Mechanistically, APJ activation results in phosphorylation of STAT3 in addition to the well-studied ERK and AKT pathways which together contributed to the aggressive phenotypes observed both in vitro and in vivo.

In addition, we examined the role of apelinergic signaling in modulating cross-talk between the cancer cells and adipocytes in the tumor microenvironment. Using ex vivo omental metastasis model and in vivo approaches, we demonstrated that adipocyte-derived apelin promotes homing-in of the tumor cells to the omentum. We found that APJ activation promotes lipid accumulation in tumor cells via CD36 upregulation and cancer cells efficiently utilize these fatty acids via oxidation to generate energy by activation of the AMPK-CPT1a axis. This 'lipolytic phenotype' of the APJ high expression cells could potentially help the cancer cells to survive at the metastatic site.

This dissertation work contributes to understanding the roles of multifunctional apelin/APJ signaling pathway in drug resistance and metastasis in ovarian cancer. Our findings highlight that targeting the APJ pathway could potentially modulate the cross talk between cancer cells and two key components of the ovarian tumor microenvironment i.e., endothelial cells and adipocytes. Thus, inhibiting apelin/APJ signaling could lead to reduced metastasis by modulation of angiogenesis and tumor metabolism.