UNMC Department of Ob/Gyn
Laboratory of Ovarian Cancer

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Current Research Projects

Project 1. Membrane estrogen receptor(s) in ovarian physiology and pathology.

Ovarian cancer is, after breast cancer, the second most common gynecological cancer in terms of incidence but the first one in terms of morbidity. Ovarian carcinogenesis mechanisms have not yet been elucidated. Although 40 – 60% of ovarian cancers express classic estrogen receptors, only a minor proportion of patients (ranging from 7–18%) respond clinically to anti-estrogen treatment, suggesting that molecules other than classic estrogen receptors also mediated estrogen actions in the ovarian cells. Our previous data show that GPR30/GPER is expressed in the ovarian cells and is able to mediate estrogen action on follicle formation and development (Endocrinology, 2007, 148:4853-486; Endocrinology, 2008, 149: 4452-4461). The function of GPR30-mediated estrogen action on early folliculogenesis implies the possibility that membrane estrogen receptors may play important roles on the resistance of anti-estrogen therapy. Currently, one of the major project in our laboratory is to explore the function and mechanism of GPR30 mediated estrogen action on the initiation, progression and metastasis of ovarian cancer.

Project 2. Development of novel chemotherapy drugs for ovarian cancer

Chemotherapy is currently the major intervention therapy for the ovarian cancer. However, the severe toxicity and the common drug resistance significantly reduced the patient survival rate. Therefore, development of novel chemotherapy drugs with high anti-cancer efficacy and low toxicity is essential for the effective treatment of ovarian cancer. Recently, we surprisingly found that the putative GPER agonist G-1 was able to suppress ovarian cancer cell growth and induce cancer cell death. Our study also showed that G-1 suppressed cancer cell proliferation and induced cancer cell apoptosis in a GPER-independent manner. Most importantly, we found that G-1 exerts its function by targeting microtubules of cancer cells, a mechanism similar to the widely used chemotherapy drugs paclitaxel (American Journal of Translational Research, 2012, 4: 390-402; Cell Death & Dis. 2013, 4:e869]. Experiments are ongoing to uncover the molecular mechanisms underlying G-1 suppression of ovarian cancer cell proliferation. The goal of this project is to identify G-1 as a novel chemotherapeutic drug and push this potential chemotherapy drug to the clinical trial.

Project 3. Hippo signaling pathway and ovarian cancer

Biomarker for early diagnosis is the key for rescue the life of ovarian cancer patients. Predictive and prognostic biomarkers help to tailor medication use in individual patients with the goals of enhancing efficacy and minimizing toxicity. One of the major interests in our laboratory is to identify the
biomarkers for early diagnosis of ovarian cancer and for the outcome prediction of cancer patients. Yes-associated protein (YAP), the central component of the Hippo signaling cascade, functions as an oncogene in several malignancies. Our recent data showed that in the compared with age-matched normal human ovaries, ovarian tissues from the granulosa cell tumor (GCT) patients exhibited higher levels of YAP expression. YAP protein was predominantly expressed in the nucleus of GCT tumor cells, whereas the non-tumor ovarian stromal cells expressed very low levels of YAP. Knockdown of YAP resulted in a significant reduction in GCT cell proliferation and migration. Conversely, overexpression of wild-type YAP or a constitutively active YAP mutant resulted in a significant increase in KGN cell proliferation and migration [Endocrine-Related Cancer, 2014, doi:10.1530/ERC-13-0339]. These results demonstrate that YAP plays an important role in regulating ovarian GCT cell proliferation and migration and may be a promising prognostic marker for GCT. Targeting the Hippo/YAP pathway may provide a novel therapeutic approach for GCT. Another ongoing project in our laboratory is exploring the function and mechanism of Hippo signaling pathway in the initiation and progression of epithelial ovarian cancer (EOC).

Project 4. Fertility preservation in cancer patients (Oncofertility)

Thanks to the significant improvement in diagnostic and therapeutic technology, the survival rate of the cancer patients are drastically increased in recent years. Chemotherapy and radiation treatments for cancer damage ovarian cells lead to infertility of the cancer survivors. The elimination of the chance for cancer survivors to have children becomes significant health issue and a big social problem. This project aims to identify the molecules or pathways underlying the physiological or pathological regulation of ovarian function so that novel therapies could be developed to improve the fertility of cancer survivors. The Hippo signaling pathway has been implicated as a conserved regulator of cell proliferation and organ size in both Drosophila and mammals. Our recent data showed that components of the hippo signaling cascade are expressed in the ovarian cells. Knockdown of YAP, the effector of the hippo pathway, significantly reduced FSH-induced aromatase (CYP19A1) expression and estrogen production in KGN cells, suggesting that the Hippo pathway may be involved in the regulation of ovarian function [Endocrine-Related Cancer, 2014, doi:10.1530/ERC-13-0339]. We are currently exploring functions of the Hippo signaling pathway in the ovarian physiology and pathophysiology using both in vivo and in vitro models, aiming to discover molecular target(s) and develop novel drugs to improve the fertility of the post-chemotherapy patients, and rapidly translate these new technologies to the clinic.

Selected Publications ( * Corresponding author; § Equal Contribution)

David Fu§, Xiangmin Lv§, Guohua Hua, Chunbo He, Jixin Dong, Subodh M Lele, David WC Li, Qiongli Zhai, John S Davis, and Cheng Wang*. The Hippo-Signaling Pathway Is Involved in the Regulation of Cell Proliferation in Granulosa Cell Tumors. Endocrine-Related Cancer, first published on 3 January 2014, doi:10.1530/ERC-13-0339. (Cover article)
Cheng Wang*§, Xiangmin Lv§, Ming-Ying Tsai and John S Davis*. The putative G-protein coupled estrogen receptor agonist G-1 suppresses proliferation of ovarian cancer cells via blocking tubulin polymerization. 
*Cell Death & Dis. 2013, 4:e869


Cheng Wang*, Xiangmin Lv, Chao Jiang, Crystal Cordes, and John S Davis*. Transforming growth factor alpha (TGFα), via a possible autocrine/paracrine mechanism, regulates granulosa cell tumor (GCT) cell proliferation and migration through activation of multiple pathways. *PLoS ONE*, 2012, 7 (11) e48299.


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