**Role of Follicular Fluid RTK Growth Factors in the Oncogenesis of High-Grade Serous Carcinoma 卵泡液中 RTK 生長因子促進高漿液性卵巢癌發展的作用機制**

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**Abstract**

High-grade serous carcinoma (HGSC) is the most lethal subtype of epithelial ovarian cancer and primarily originates from the fallopian tube epithelium (FTE) through the development of serous tubal intraepithelial carcinoma (STIC), which is characterized by mutations in the TP53 gene. HGSC is typically diagnosed at advanced stages, resulting in a poor prognosis. Our laboratory has long investigated the etiology of HGSC, hypothesizing that ovulatory follicular fluid (FF) plays a pivotal role in early oncogenesis. Epidemiological studies linking reduced ovulatory frequency, such as through oral contraceptive use or parity, to a lower risk of ovarian cancer prompted our investigation into the potential carcinogenicity of FF.

In 2015, we first demonstrated that FF contains reactive oxygen species (ROS) capable of inducing DNA damage in FTE cells, and more recently confirmed that FF-derived ROS contribute to TP53 mutations. Subsequent growth factor array analysis revealed that FF is enriched with receptor tyrosine kinase (RTK) ligands, including IGF, HGF, and EGF-like proteins, which activate downstream signaling pathways that promote cell transformation. Specifically, IGF2 enhances anchorage-independent growth (AIG) and clonogenicity through activation of the AKT/mTOR and AKT/NANOG pathways. HGF and EGF-like ligands, such as amphiregulin, further stimulate AIG, migration, and invasion through activation of their corresponding receptors. Notably, repeated co-injection of IGF2 and HGF at FF-equivalent doses into the inguinal fat pad of TP53-null mice induced lymphoma, underscoring the tumorigenic potential of these growth factors. Our recent findings further indicate that FF-derived exosomes are the primary carriers of RTK growth factors and the main mediators of transformation activity; removal of these exosomes markedly reduces the cell-transforming potential of FF.

Collectively, these discoveries elucidate the oncogenic mechanisms embedded in FF and underscore its critical role in linking ovulation to the carcinogenesis of HGSC. The identification of exosome-encapsulated transforming agents in FF provides new insights into early detection strategies, biomarker discovery, and the broader relevance of ovulatory microenvironments in cancer biology.

**Keywords:** High-grade serous carcinoma (HGSC), serous tubal intraepithelial carcinoma (STIC), ovulatory follicular fluid (FF), receptor tyrosine kinase (RTK), exosome.