

## **Gonadotropins and ovarian cancer growth and invasion**

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**Introduction:** There is substantial epidemiological evidence that gonadotropins, i.e., follicle-stimulating hormone (FSH) and luteinizing hormone (LH), may be involved in the etiology of epithelial ovarian cancer. According to the incessant ovulation theory, repeated ovulations contribute to (pre)neoplastic changes of the ovarian surface epithelium (OSE), and the wound healing process of ruptured OSE promotes the development of ovarian carcinomas in women. Normal OSE and ovarian tumors express FSH receptors (FSHR) and LH receptors (LHR). **Methodology:** We and others have demonstrated that treatments with FSH and LH resulted in growth stimulation in normal OSE, immortalized OSE and ovarian cancer cells in a dose- and time-dependent manner *in vitro*. **Results and Discussion:** Our results indicate that gonadotropins may be involved in the transformation and progression of normal OSE to neoplastic OSE. In pre-neoplastic OSE cells, the over-expression of FSHR activated ERK1/2 and increased the expression of EGFR, *c-myc*, and HER-2/neu, all of which are generally over-expressed in ovarian cancer. In addition, the over-expression of FSHR accelerated cell proliferation, thus supporting a role for FSHR in ovarian cancer development, especially in terms of neoplastic conversion and growth potential. As well, there appears to be a potent cross-talk between gonadotropins and growth factors such as EGF in the control of ovarian cancer progression. Treatment with FSH and LH increased EGFR levels, and pre-treatment with inhibitors of PI3K or ERK1/2 partially blocked the gonadotropin-induced up-regulation of EGFR expression. Furthermore, gonadotropins may contribute to ovarian cancer metastasis via activation of proteolysis and increase invasion through the PKA and PI3K pathways. We observed that FSH or LH increased the invasiveness of ovarian cancer cells, and enhanced the levels and activation of MMP-2 and MMP-9, while decreasing the levels of TIMP-1, TIMP-2 and PAI-1. **Conclusions:** These results strongly support a role for gonadotropins in ovarian cancer progression. **Acknowledgement:** This research was supported by the Canadian Institutes of Health Research.