Keynote Lecture VIII

Endocrine Signaling in Ovarian Cancer

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Dr Leung received his BSc and MSc degrees from the University of British Columbia, and a PhD from the University of Western Ontario. Following postdoctoral training at the UCLA and Laval University, he returned to the University of British Columbia, where he is at present Professor of Obstetrics and Gynaecology. He is Director of the Graduate Program in Reproductive and Developmental Sciences, and also directs a new CIHR Interdisciplinary Women's Reproductive Health Research Training Program, at the Child and Family Research Institute.

Dr Leung's honours and awards include: MRC Scholar and MRC Scientist Awards from the Medical Research Council of Canada, a Career Investigator Award from the BC Health Research Institute for Children's and Women's Health, and a Distinguished Scholar Award from the Michael Smith Foundation for Health Research. He has served as President of the Canadian Fertility and Andrology Society, Director of the Society for the Study of Reproduction, Director of the Ovarian Workshops in the USA, Temporary Advisor to the World Health Organization, Honorary Professor of the Institute of Zoology in Chinese Academy of Science in Beijing, Honorary Member of the Taiwan Society for Reproductive Medicine, and Institute Advisory Board member of the CIHR Institute of Gender and Health.

The ovarian surface epithelium (OSE) is the modified pelvic mesothelium that covers the ovary. It is composed of a single layer of flat-to-cuboidal epithelial cells. Approximately 90% of human ovarian cancers, viz. the epithelial ovarian carcinomas, arise from the OSE. This group of cancers is the most lethal among ovarian neoplasms and is the prime cause of death from gynecological malignancies in the Western world. Normal OSE and ovarian carcinomas secrete and have specific receptors for hormones and growth factors, indicating the role of these factors in OSE physiology and in the transformation and progression of ovarian cancers. The direct effects of several key reproductive hormones (GnRH, E2 and gonadotropins) on normal OSE and ovarian cancer cell growth have been investigated in our laboratory and summarized below.

GnRH: GnRH receptor (GnRH-R) is expressed in 80% of human ovarian epithelial tumors. We have demonstrated a direct growth inhibitory effect following treatment with GnRH in different ovarian cancer cell lines. The recent cloning of a novel isoform of GnRH (GnRH-II) in the primate brain has prompted a re-evaluation of the role of GnRHs in reproductive functions. We have demonstrated that in addition to GnRH-I, GnRH-II is expressed in normal OSE, immortalized OSE cells, primary ovarian tumors and ovarian cancer cell lines. Although a putative GnRH type II receptor has been identified in the human genome, a full-length functional GnRH type II receptor has yet to be reported. Thus, at present, it is assumed that both GnRH-I and GnRH-II exert their biological effects by binding to a common GnRH receptor (i.e. the type I GnRH-R), but via alternative intracellular signaling pathways. Our findings to date indicate that both GnRH-I and GnRH-II are potent inhibitors of ovarian cancer cell growth.

E2: Treatment with exogenous E2 resulted in growth stimulation of several ER-positive ovarian carcinoma cell lines, but not in normal OSE. The mechanism by which E2 contributes to ovarian carcinogenesis may, in part

at least, be indirect and involve an attenuation of the anti-proliferative effect of GnRH. We have observed that GnRH-R mRNAs were down-regulated by E2 pretreatment in ovarian cancer cells, which may partially explain the antagonistic effects between E2 and GnRH-I on ovarian cancer cell growth. Our results indicate that E2 represses GnRH-R gene expression at the transcriptional level via an ERα-dependent mechanism in ovarian tumors. This novel molecular mechanism underscores the potential interaction between E2 (a stimulatory regulator) and GnRH (inhibitory regulator) in ovarian cancer cell growth.

Gonadotropins: Normal OSE and ovarian tumors express FSH and LH receptors. We have shown that treatment of immortalized OSE cells with FSH resulted in cell proliferation and an activation of MAPK (ERK-1/ERK-2) and Elk-1 transcriptional factor. Cross-talks with growth factors have been implicated in gonadotropic actions on OSE cell growth. Over-expression of the FSH-R in a pre-neoplastic OSE cell line is associated with increased levels of EGFR, HER-2/neu and c-Myc, constitutive activation of ERK-1/2 and increased cell proliferation. The potential interaction between the gonadotropins and GnRH system in ovarian cell growth has also been investigated. Pretreatment of ovarian cancer cells with either FSH or LH for 24 h significantly attenuated the growth inhibitory effect of both GnRH-I and GnRH-II. This effect could, in part at least, be explained by a down-regulation of the GnRHR mRNA level by the gonadotropins in the ovarian cells.

Taken together, our findings support the hypothesis that reproductive hormones such as GnRH-I, GnRH-II, E2 and gonadotropins, are important components of the complex regulatory mechanisms that control the growth and differentiation of OSE cells to ovarian cancer.

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