

Scientific Report of the Unit of Obstetrics and Gynaecology of the University of Siena

A. Molar pregnancies.

Transcriptional and translational levels of TIMP 1,2,3 and TIMP 4 in hydatiform mole. The invasive growth of normal trophoblast is similar to that of malignant tumors in numerous respects; however, trophoblast invasion is precisely regulated, confined spatially to the uterus and temporally to early pregnancy. In gestational trophoblastic diseases (GTD), which are characterized by abnormal proliferative trophoblast (comprise a spectrum of disorders from the benign hydatidiform mole complete and partial through to the malignant invasive mole, choriocarcinoma, and the rare placental site/epithelioid trophoblastic tumour), this control mechanism is impaired and an abnormal proliferation of the trophoblast occurs with varying propensities for local myometrial invasion and distant metastases. The process of trophoblast invasion involves the enzymatic degradation of the extracellular matrix (ECM), and among the various tissue inhibitors of metalloproteinases (TIMP) have a critical role in tumor growth.

B. Neuropeptides, growth factors and endometrial cancer.

Activins were originally isolated as factors from ovarian fluid that stimulate the secretion of FSH from pituitary cells. These factors are members of the transforming growth factor-beta family and are encoded by two closely related genes, activin- $\beta\alpha$ and activin- $\beta\beta$. They exist as homodimers ($\beta A\beta A$, $\beta B\beta B$) or a heterodimer ($\beta A\beta B$) of the gene products and have been designated as activin A, activin B, and activin AB, respectively. Recently, two new activin β -chains (activin- βC , activin βD) have been reported, and the biological activities of these remain to be determined. Recent studies demonstrated that human endometrial adenocarcinoma tissues express high levels of activin A, the pathophysiological functions of endometrial activin A remain unclear. Human endometrial cancer cells express both activin receptor and TGF-beta receptor, and TGF-beta1 utilizes the same intracellular signaling molecules as activin A. These results suggest that in endometrial adenocarcinoma cells, the intracellular signals underlying TGF-beta1-mediated inhibition of growth can themselves be inhibited by activin A. Therefore, the increased expression of activin A may be involved in carcinogenesis by reducing TGF-beta-mediated signals inhibiting cell growth in human endometrial adenocarcinoma tissues.

Activin is considered to be a potent growth regulator in most epithelial carcinoma cells. For this reason, elucidation of the regulation pathways governing the expression and the actions of activin system is likely to be critical to our understanding of oncogenesis in a variety of tissues, including endometrium.

Moreover, whether activin A induces cell-cycle arrest by modulation of Cyclin D2 and p21 in endometrial carcinoma will be evaluated.

Urocortins (urocortin I, II, and III) are neuropeptides involved in the regulation of hypothalamus-pituitary-adrenal axis response to stress stimuli, since they trigger ACTH secretion from the pituitary. The human endometrial stromal and epithelial cells express both urocortins and their receptors, and recently we found that urocortin I is able to induce the differentiation of stromal cells into decidual cells, and that is expressed and secreted in increasing amounts throughout the menstrual cycle. Urocortin I peptide and mRNA expression was significantly reduced in endometrial adenocarcinoma than in healthy age-matched controls, thus suggesting a role for urocortin I in endometrial tumoral cell growth and proliferation. The expression and roles of urocortin II and III in endometrial adenocarcinoma are currently under investigation.

C. Inhibins a putative markers of ovarian tumors

Inhibins are proteins produced by ovarian granulosa cells and are members of the transforming growth factor-beta superfamily. Since increased circulating levels of immunoreactive inhibin were detected in women with malignant ovarian tumors, they were proposed as tumor markers for ovarian carcinoma. Our studies have demonstrated that inhibin B is the major molecular form of the inhibin family proteins produced by granulosa cells cancer, and we are currently evaluating the clinical usefulness of total inhibin measurement as a marker for epithelial ovarian cancer.

D. Activin and breast cancer.

Activins and inhibins are growth factors involved in cell differentiation and proliferation. Human breast tissues such as normal mammary tissue, fibroadenoma, and breast cancer express inhibin and activin mRNA and proteins.

In the present study we are evaluating the expression of peptides belonging to the family of activin/inhibin (follistatin, FLRG, cripto, nodal), as well as the clinical utility of activin A measurement in diagnosis and short-term follow-up of breast cancer.