



Case Report

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# The IGF Pathway in Gynecology Oncology- Current Knowledge and Possible Therapeutic Implementations



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## Abstract

Over the last 20 years, accumulating evidence has identified the IGF axis as an important player in the carcinogenesis of several human malignancies including endometrial and serous ovarian carcinomas.

The IGF system comprises the ligands (IGF-1, IGF-2), cell surface receptors (IGF1R, IGF2R) and at least six IGF binding proteins (IGFBPs) and is coupled to several intracellular messenger pathways including the RAS-RAF-MAPK and PI3K. The IGF1R expression and activation was shown to be a fundamental prerequisite for acquisition of a malignant cell phenotype. IGF1R expression was shown to be significantly higher in endometrial carcinoma than in normal endometrium. Furthermore, several factors appear to negotiate their effect on endometrial growth and proliferation through the effect on IGF1R expression, including steroid hormones, hyper insulinemia and tumor suppressor genes such as p53 and BRCA. Interestingly, treatment with metformin (an oral anti hyperglycemic agent) was recently shown to prevent endometrial cancer through down regulation of the IGF axis. In the ovary, the IGF1R has been shown to be responsible for surface epithelial proliferation and administration of IGF1 was shown to stimulate ovarian carcinoma cell growth. IGF1R expression was found to be significantly higher in malignant than benign tumors and several IGFBPs levels were consistently different in patients with malignant tumors compared to controls. In addition, numerous studies demonstrated that hyperactivation of the IGF1R signaling pathway is important in ovarian cancer cell resistance to chemotherapy. IGF axis targeted treatment such as anti-IGF1R antibodies have shown significant promise in in-vitro studies and are being investigated in clinical studies.

**Keywords:** IGF; Ovarian carcinoma; Endometrial carcinoma; Cell growth; Therapies; Chemotherapies

**Abbreviations:** IGF: Insulin-Like Growth Factor; IGFBPs: IGF Binding Proteins; IGF1R: IGF 1 Receptor; MAPK: Mitogen-Activated Protein Kinases; PCOS: Polycystic Ovary Syndrome; TKIs: Tyrosine Kinase Inhibitors; EOC: Epithelial Ovarian Cancer; siRNA: Small Interfering RNA

## Introduction

The IGF system has a regulatory effect on many cellular pathways and physiological processes including metabolic, nutritional, endocrine, growth and aging events. Accumulated evidence in the last 20 years identified the IGF axis as an important player in the carcinogenesis of several human malignancies including gynecologic malignancies, primary the endometrial and serous ovarian carcinomas [1]. The IGF system comprises the ligands (IGF-1, IGF-2), cell surface receptors (IGF1R, IGF2R) and at least six IGF binding proteins (IGFBPs) [2], serving as IGF's serum carrier and regulating the tissue effects of the IGFs by binding and preventing their access to the cell surface receptors

[3]. The IGFs exert their activities primarily through the IGF1R which is coupled to several intracellular messenger pathways including the RAS-RAF-MAPK and PI3K signaling cascades and signals mitogenic, antiapoptotic and transforming activities. In fact, several studies have shown that IGF1R expression and activation is a fundamental prerequisite for acquisition of a malignant phenotype, as cells with a disrupted IGF1R cannot be transformed by a number of oncogenes and on the other hand exogenous overexpression of IGF1R in cells results in tumor progression [1].

## IGF Axis in Carcinogenesis

### IGF axis in endometrial carcinoma

In normal endometrium cyclic changes in IGF-1 expression and signaling play key role in regulating the transition of the premenopausal endometrium through the proliferative, secretory and menstrual cycles and it has been identified as a major mediator of the effects of estradiol on uterine growth [4]. The IGF1R expression is significantly higher in endometrial carcinoma than in normal endometrium [5]. However, the association between serum IGF1 levels and endometrial cancer and its diagnostic or prognostic value is unclear, perhaps due to involvement of additional factors that can positively or negatively impinge upon IGF axis components [6-9].

Several risk factors for the development of endometrial hyperplasia and carcinoma such as unopposed estrogen, obesity, hyperinsulinemia, diabetes and PCOS, actually mediate their effects, at least partially, through the IGF system [10,11]. IGF1 and IGFBP1 gene expression were found to be significantly up-regulated in the endometrium of PCOS and endometrial carcinoma compared to controls [12] and the degree of IGF1R over-expression in endometrial carcinoma cells increased as BMI increased [13]. Estrogen has been shown to stimulate the proliferation of uterine endometrium via activation of the IGF1R, while downstream activation of the IGF mediated pathway could play a major role in the progression to ER-independent tumors [14]. Increased androgens, a mainstay in PCOS, induce IGF1R up-regulation [15] and hyperinsulinemia down regulates hepatic IGFBP-1, resulting in elevated free IGF-1 in the circulation [16]. Moreover, higher phosphorylated IGF1R were observed in diabetic vs non diabetic postmenopausal women [17]. Thus IGF axis seems to have an important part in the linkage of metabolic syndrome and endometrial cancer.

p53, a known tumor suppressor gene involved in carcinogenesis of several tissues including uterine cancer, has been linked to the IGF axis as well. It has been shown that p53 regulates IGF1R gene expression in endometrial cancer via repression of the IGF1R promoter. Pathologic deregulation of IGF1R gene expression as a result of tumor-specific, loss-of-function p53 mutations may lead to increased cell surface IGF1R concentrations and enhanced IGF1R phosphorylation by IGFs [18]. BRCA1, another important tumor suppressor gene, was shown to inhibit IGF1R transcription in endometrial carcinoma as well [19-21].

The IGF axis was recently implemented in the mechanism of anticancer activity of metformin on endometrium. Metformin demonstrates significant antiproliferative activity on endometrial cancer cells and enhance the sensitivity of those cells to chemotherapy [22-24] and several studies have shown that its action is mediated through down-regulation of the IGF1R and IGF1 expression [25-27].

### The IGF axis in ovarian carcinoma

In the ovary, the IGF1R has been shown to be responsible for surface epithelial proliferation and ovarian epithelial carcinogenesis [28] and administration of IGF1 was shown to stimulate ovarian carcinoma cell growth [29]. A majority of human studies revealed high IGF and IGF1R expression in ovarian carcinoma cells compared to borderline and benign tumors and normal ovarian tissue and a positive correlation between their expression levels and ovarian cancer cell proliferation and invasiveness in vitro [1,30-32]. Some of these studies showed a correlation between IGF1R over expression with more advanced disease and worse clinical prognosis [33-35].

The clinical correlation between the serum levels of IGFs and cancer risk or prognostic factors, as in endometrial carcinoma, is inconclusive. Several studies have found high circulating IGF1 levels to be a risk factor for developing ovarian cancer; some have found an inverse correlation and some haven't found any correlation at all [36-43]. In a recent systematic review and meta-analysis, a significantly lower serum IGF1 levels were seen in ovarian cancer patients than in controls [44]. In addition, numerous studies demonstrated that hyperactivation of the IGF1R signaling pathway is an essential event in ovarian cancer cell resistance to chemotherapy [45-48].

As mentioned previously, the IGFBPs play an important role in the IGF signaling pathway. IGFBP-2 has been consistently shown to be over-expressed in malignant ovarian cancer and has a possible role in the aggressive and invasive behavior of these tumors. High IGFBP-2 tissue expression correlates positively with serum levels, clinical features and prognosis [49-56]. The information concerning IGFBP-3 is less conclusive. Tissue IGFBP-3 levels were shown to be higher in less aggressive tumors and low tissue IGFBP-3 levels were associated with unfavorable prognostic feature. Serum IGFBP-3 levels were shown to be decreased in patients with ovarian cancer compared to those of patients with benign tumors and controls and high serum IGFBP-3 was usually associated with better prognosis [57-59]. The logical explanation for this is that IGFBP-3 is the major IGF1-binding protein in the serum, thus causing a reduction in free IGF1 levels. Hence, IGFBP-3 is considered anti-proliferative and pro-apoptotic.

### Anti-IGF treatments in gynecologic malignancies

Based on accumulating preclinical and clinical data implicating the IGF axis in cancer biology multiple studies have evaluated more than 30 drugs targeting the IGF1R pathway, including anti-IGF1R antibodies, tyrosine-kinase inhibitors (TKIs) and antibodies against IGF1 and IGF2 ligands and IGF1R inhibitors showed the highest activity [5]. More than ten IGF/IGF1R inhibitors have entered clinical studies and showed sustained response in a small number of patients with select tumor types but many large clinical trials involving patients

with adult tumors, including non-small cell lung, breast and pancreatic cancers failed to show clinical benefit in the overall patient population [60,61]. In ovarian cell lines these treatments caused significant inhibition of tumor growth and proliferation, induced apoptosis and sensitized cells to chemotherapeutic agents [18,24,56-60,62]. A similar effect was shown in regard to endometrial cancer [63-65]. Several clinical trials involving IGF1R targeted therapies are currently under way.

### Discussion and Conclusion

The IGF network has an important role in normal physiology of endometrium and ovary and has been shown to participate in ovarian epithelial and endometrial cell proliferation. Over expression of IGF axis components was consistently identified in ovarian and endometrial cancer tissues and in vitro studies have shown a causative linkage between dis-regulated expression and activation of the IGF axis and cancer cell proliferation and other hormonal and genetic factors have been shown to negotiate their effects on cancer risk through regulation the IGF axis. Some of the treatments that have shown anticancerous activity as metformin seem to work by regulating the IGF system. Multiple in vitro studies in endometrial and ovarian cancer have shown a positive effect of the IGF targeted therapies on cancer cells including decreased proliferation and tumor growth, increased apoptosis and increased sensitivity to chemotherapies. The clinical effect of these substances in the gynecologic malignancies is still to be proven since studies in other malignancies showed a low clinical effect of IGF axis inhibitors.

### Conflict of Interest

His study was not supported by external funding.

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