POTENTIAL ROLE OF GROWTH FACTORS IN OVARIAN CANCER

Jasonni VM\textsuperscript{1}, Amadori A\textsuperscript{2}, Gentile G\textsuperscript{2}, Alesi L\textsuperscript{2}

\textsuperscript{1}Department of Obstetric and Gynecology, University of Messina. \textsuperscript{2}Department of Obstetric and Gynecology, University of Bologna.

TABLE OF CONTENTS

1. Abstract
2. Introduction
   2.1 epidermal growth factor (EGF).
   2.2 Transforming growth factor alpha (TGF alpha).
   2.3 Transforming growth factor beta (TGF beta).
   2.4 Insulin-like growth factors (IGFs).
   2.5 Fibroblast growth factors (FGFs).
   2.6 Macrophage colony stimulating factor (MCSF).
4. Oncogenes and ovarian cancer.
5. Conclusion.
6. References.

1. ABSTRACT

As with many other tumors, the origin and development of ovarian cancer is constituted by several molecular mechanisms, many of which are still unknown. Furthermore, data in the literature are incomplete and often contradictory, and they are mainly founded on results obtained on cell lines and not on observations based on the \textit{in vivo} study of ovarian cancer. Despite this situation, the study of control mechanisms of proliferation and differentiation in normal ovarian functioning has enabled clinicians to identify certain growth factors and oncogenes which seem to have an important role in the neoplastic transformation of ovarian tissue.

In this review, our aim is to summarise the most important data regarding function of growth factors and oncogene in normal and neoplastic epithelial ovarian cells.

2. INTRODUCTION

The growth factors that mainly are involved in the neoplastic transformation of human epithelial ovarian cells are first described in the following paragraphs, where their functions in normal ovarian tissue are summarised.

2.1 Epidermal growth factor (EGF)

This polypeptide, by binding to its receptor, epidermal growth factor receptor (EGFr), exerts a mitogenic action on the target cells. In the ovaries, greater concentrations of EGF are present in the fluid of immature follicles. Its action has been studied ‘\textit{in vitro}’ on ovarian epithelial cell lines. Proliferation of normal ovarian epithelial cells stimulated by EGF is potentiated from two-to fivefold. This action is amplified when EGF and Insulin-like growth factor I (IGF-I) are administered together.

However, at concentrations which are higher than physiological ones, EGF increases Follicle stimulating hormone (FSH) receptor, modulates steroid ovarian synthesis, leads to the maturation of ovocytes and stimulates the proliferation of granulosa cells. Despite all this data, the origin of EGF in follicular fluid is not yet fully understood. Similarly, the type of ovarian cell which is capable of synthesising this growth factor has yet to be identified. On the contrary, EGFr has been observed in the following cells: theca interna, granulosa cells, corpus luteum and stroma (1).

2.2 Transforming growth factor alpha (TGF alpha)

TGF alpha has the same effect to that of the aforementioned growth factor. Moreover, it binds to EGFr with an affinity which is similar to that of EGF itself. TGF alpha has a mitogenic action on the ovary, inducing the proliferation and differentiation of granulosa cells. TGF alpha is also contained in
Pathogenesis of ovarian carcinoma

follicular fluid. Like EGF, its origin in the ovary is not yet fully understood.

2.3 Transforming growth factor beta (TGF beta)

Despite its name, the main action of this growth factor is that of inhibiting cell proliferation of target cells while its transforming effect is limited only to some cells. Theca and granulosa cells in rodent ovaries produce TGF beta. Of the three forms of TGF beta (TGF beta 1, 2, 3), ovarian epithelial cells produce the first two. This growth factor is produced in an inactive form. It only becomes active under the influence of certain enzymes produced by the same cells which synthesise it or by neighbouring ones. TGF beta acts on target cells via autocrine mechanisms, at the same time regulating cell proliferation and granulosa cell response to gonadotropin hormones. For this reason, it is thought that the physiological role of TGF beta on ovarian epithelial cells is inhibiting excessive cell proliferation. The action of this growth factor would thus appear to be similar to that of EGF and TGF alpha. Following ovulation, the release of this growth factor could be inhibited in order to stimulate the proliferation of ovarian epithelial cells and to promote the ovarian surface repairing. It is thought that the production and action of TGF beta in the ovary, similarly to breast epithelial cells, could also be independent of the effect of sex hormones (2).

2.4 Insulin-like growth factors (IGFs)

In ovarian regulation, the most important growth factor in this group is the insulin-like growth factor (IGF-1). IGF-1 exerts a double action on the ovary: it stimulates ovarian epithelial cell proliferation and modulates granulosa cell steroidogenesis during follicular development by acting together with gonadotropins (3). IGF-I or IGF-II alone have no effect on proliferation of normal ovarian epithelial cells. On the contrary, used in combination with EGF, it is possible to observe cell proliferation (Fig. 1). A high IGF-I concentration in dominant follicular fluid seem to be closely related to follicular fluid concentrations of estradiol (E2) and progesterone (P) (4).

2.5 Fibroblast growth factors (FGFs)

These powerful mitogens exert their action on granulosa cells. Furthermore, FGFs are present in follicular fluid, and their action might be important in stimulating neovascularization of the corpus luteum after ovulation (5).

2.6 Macrophage Colony Stimulating factor (MCSF)

Originally observed in macrophages, MCSF is also expressed in other types of cells, like ovarian epithelial cells and trophoblasts. This growth factor is important mainly because its receptor is encoded by an oncogene, the c-fms. In normal ovary, MCSF is often expressed while high c-fms concentrations are rarely present. MCSF might be considered a complementary marker of CA-125, because its plasma levels are elevated in patients with ovarian cancer who have normal CA-125 levels (6).

---

**Figure 1:** Role of insulin-like growth factors (IGFs) and epidermal growth factor (EGF) in ovarian cell proliferation.
3. PATHOGENESIS OF OVARIAN CANCER.

Fig 2 shows that the risk of ovarian epithelial tumor is reduced in patients with a history of parity, delayed menarche, and use of hormonal contraceptive. Regarding the origin of ovarian epithelial tumor and the significance of these protective factors, Fathalla’s (7) hypothesis is of particular interest. According to this author, the incessant ovulation, which is common in women at high risk of developing ovarian cancer, might promote the development of epithelial ovarian cancer. The higher risk of epithelial ovarian transformation might be due to recurrent trauma in the surface epithelium of the ovary during ovulation. After this event, proliferation of epithelial cells repairs defects in the ovarian surface. Moreover, it was observed that most ovarian cancers may arise from the epithelial inclusion cysts which occur after ovulation and from the surface epithelium (8). After ovulation it is possible that many growth factors in the follicular fluid, like EGF, TGF alpha, IGF I and FGF, may stimulate proliferation of perilesional ovarian epithelium, while TGF beta may be inhibited in order to allow proliferation of epithelial cells and repair the defect of the ovarian surface (2).

After neoplastic transformation, it was shown that malignant ovarian epithelial cells are less responsive to growth factor stimulation. Regarding EGF, Interleukin-1 (IL-1), Interleukin-6 (IL-6) and TGF beta, ovarian cell lines are often less responsive to their action than normal epithelial cells (9,1,6).

These results suggest that neoplastic transformation of ovarian epithelial cells makes them increasingly independent from external mitogenic stimuli. Moreover, conflicting results exist concerning production of growth factor (EGF, TGF alpha, PDGF, FGF) by neoplastic epithelial cell lines. In fact many authors (10, 11) found that EGF and TGF alpha are produced by ovarian cancer, while others (5) were not able to validate these findings.

4. ONCOGENES AND OVARIAN CANCER.

Naturally, pathogenesis of ovarian epithelial carcinoma is not fully explained by the action of growth factors. Presence of other cofactors may be essential to the neoplastic epithelial cell transformation. For example, a large number of protooncogenes was shown to be expressed by epithelial ovarian cancers (12). These cofactor are DNA sequences which encode proteins that normally contribute to regulate physiological epithelial cell proliferation. During tumorigenesis, proto-oncogenes may be amplified by virtue of molecular mutation. Protooncogene transformation might lead either to an overexpression of mitogenic molecules or an inactivation of those with inhibitory action, thus contributing to neoplastic transformation and development. The most important protooncogenes of the first group are undoubtedly constituted by fms and
Pathogenesis of ovarian carcinoma

Figure 3: Role of Colony stimulating factor 1 (CSF-1) and cfms in pathogenesis of ovarian cancer.

**Figure. 3:** Role of Colony stimulating factor 1 (CSF-1) and cfms in pathogenesis of ovarian cancer.

**Figure. 4:** HER-2/neu can be considered an independent prognostic factor in ovarian cancer.

HER-2/neu. The first one encodes a transmembrane tyrosine kinase receptor which binds MCSF. It is possible that fms-MCSF both stimulates epithelial cell proliferation and induces a chemical attraction for macrophages which, in turn, can produce mitogenic stimulating factor previously described (6) (Fig 3). Elevated plasma concentrations of fms are present in the sera of 70% of patients with ovarian cancer (13).

The second protooncogenes, HER-2/neu, encodes another tyrosine kinase which is similar to the EGFr. Its action may consist on amplification of EGF mitogenic action in target cells; this oncogene is overexpressed in 30-35% of ovarian cancer which are associated with a poor prognosis (14) (Fig 4). Among the onco-suppressor genes, p53 is mutated and overexpressed in one half of ovarian cancers. The mutation of this genes leads to the loss of tumor suppression function. The results of these events yields a higher likelihood of ovarian cell transformation. Unlike HER-2/neu, mutation of p53
Gonadotropin

GR

GPT >> GDP

α > ras mutation

β γ

G proteins

Adenylate Cyclase

Transduction of Hormonal Signal

Figure legend: GR = Gonadotropin receptor; GTP= Guanosin triphosphate; GDP = Guanosin diphosphate.

Figure. 5: Role of G protein in transducing intracellular signal in target cell nucleus.

is not correlated with a poorer prognosis (15). Apart from these oncogenes, other factors are able to induce epithelial cell transformation. One of these molecules is G protein. As shown in Fig. 5, protein G is composed of three subunits: alpha, beta and gamma. Hormone-receptor complex formation induces a dissociation of alpha subunit. This subunit transduces the intracellular signal (which often consists of proliferation induction) in the target cell nucleus. In normal epithelial cell, its action is limited by enzymatic degradation. On the contrary, Ras oncogenes encode G proteins that stimulates target cell nucleus without enzyme regulation. Sometimes, in some ovarian cancers, Ki-RAS oncogene is overexpressed (5).

5. CONCLUSION

Pathogenesis of ovarian cancer is not completely understood. Nevertheless, it is now well known that epithelial ovarian cell transformation is due to the action of host of molecules. All these events together participate in the formation and development of ovarian cancer. Other studies are necessary in order to investigate oncogenic molecular mechanisms in vivo.

6. REFERENCES


