Hypothesis for endometrial carcinoma carcinogenesis

Preventive prospects

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Summary: Considering endometrial carcinoma as a natural experimental model for in vivo study of carcinogenesis, a hypothesis of endometrial type A carcinogenesis and some preventive prospects are advanced.

Under the name of endometrial carcinoma two different types are considered: A) hormone dependant type, and B) autonomous type.

Aging, obesity, hypertension and/or diabetes, persistent exposure to unopposed exogenous or endogenous estrogens are recognized epidemiological factors for endometrial carcinoma.

Experimental and clinical studies have shown that in pregnancy associated with clinical conditions characterized by a compromised maternal circulation in the intervillous space, a state of true or relative hypoxia stimulates syncytial hyperplasia, as adaptive process, in order to increase the exchange area of the placenta.

Vaginosonographic studies have shown in patients with endometrial thickness greater than or equal to 4 mm complex and atypical hyperplasia than endometrial carcinoma in a higher percentage than in patients with endometrial thickness less than 3 mm.

It seems that hypoxia in endometrial thickness, greater than 3 mm promoted by estrogens, would be a supplementary proliferating factor.

Immunological studies have shown, in patients with complex or atypical hyperplasia of the endometrium and/or endometrial carcinoma, a host immunological reaction (DTHS-reactivity test) to a pharmaceutical placental suspension, when injected intradermally.

An extract prepared from placental suspension is also recognized in vitro, by patients' serum (Ouchterlony's technique).

To conclude, hypoxic insult, as common pathophysiological factor in most predisposing diseases for endometrial cancer, leads to a persistent multicellular hyperplasia of the endometrium. Sometimes populations with an altered growth pattern develop. Their occurrence marks a specific change from reactive hyperplasia into a genuine preneoplastic stage that in some cases, when not disturbed in their natural evolution, will become tumor after a given time.

Genetic phenotypic instability, in the presence of hypoxic selective pressure and sequential selection of preneoplastic cells for increased growth autonomy, are essential elements for the neoplastic development.

Prevention and treatment of diseases predisposing to endometrial carcinoma and/or boosting of host immunological response against enxyme-altered cell proliferation in patients at risk, by a vacccine prepared from modified placental glycoproteins and an adjuvant, would be preventive measures.

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INTRODUCTION

In oncology the best therapy and preventive measures can be achieved only by considering the natural history of the disease. Early identification of the pro-

Clin. Exp. Obst. Gyn. - ISSN: 0390-6663
XX, n. 4, 1993

motional phase of carcinogenesis would also provide a valid indication for preventive interventions.

Endometrial carcinoma is preceded in some cases by endometrial proliferations and cellular alterations that in advanced stages may be considered precancerous lesions. These lesions, in some cases, when not disturbed in their natural evolution, may become tumor after a given time.

Under the name of endometrial carcinoma two different pathogenic types are considered: A) hormone-dependant type, and B) autonomous type.

Type A is characterized by diminished fertility, hyperplastic endometrial processes in history, obesity, hyperlipidemia, diabetes and history of exogenous estrogen administration. Other characteristics are: hyperplasia in tumor-free parts, hyperplasia of ovarian stroma, prevalence of highly differentiated adenocarcinoma (gl), superficial myometrial invasion, rare metastases in pelvic lymph nodes, high concentration of estradiol and progesterone receptors in tumor and apparent sensitivity to adjuvant progestin therapy.

Type B lacks all these signs. It is poorly differentiated on the basis of endometrial atrophy and deeply invasive in the myometrium, has a high potential for lymphogenic spread, is not sensitive to progestogens, has no or only weak progesterone receptors, and has very doubtful prognosis.

Considering endometrial carcinoma as a natural experimental model for in vivo study of carcinogenesis, a hypothesis of endometrial carcinoma type A carcinogenesis and some preventive prospects are advanced.

EXPERIMENTAL STUDIES AND CLINICAL RESULTS

1. — Vaginosonographic studies [7] have shown, in postmenopausal women with or without atypical bleeding, that the endometrial thickness in the bleeding group was 1 to 3 mm in 4% of cases and contained neither complex and atypical hyperplasia nor cancer.

In patients with endometrial thickness greater or equal to 4 mm, the Authors found an endometrial carcinoma in 23%, complex and atypical hyperplasia in 9%, and other malignancies in another 9% of cases.

Of the asymptomatic women, all having at least 4 mm thick endometrium, an endometrial carcinoma was found in 22% of cases, complex and atypical hyperplasia in 4%, and in 6% of cases other malignancies.

The low frequency of the precancerous stage (complex and atypical hyperplasia) in 7 of the 23 cases of endometrial cancer (23%) might indicate that not all these cases develop in an estrogen dependant manner.

2. — Morphologic aspects of placental function studies [1] have shown a reactivation of placental syncytial growth in late pregnancy, resulting in hyperplasia of the syncytium, in patients with hypertension, preeclampsia, prolonged pregnancy and occasional diabetes.

Studies of oxygen tension in the intervillous space in such patients have shown that the PO_2 is below normal values. Therefore, a compromised maternal circulation in the intervillous space may create a true or relative hypoxia that stimulates syncytial hyperplasia as adaptive process, in order to increase the exchange area of the placenta.

3. — Our studies [3, 4, 5] have shown in these pregnant patients and in patients with complex or atypical hyperplasia and/or endometrial carcinoma, a host immunological reaction (DTHS reactivity test) to a pharmaceutical placental suspension (PS), when injected intradermally.

In vitro studies have shown that a glycoprotein of MW 40kDa, from an extract prepared of placental suspension, is recognized also by a protein of the patients' serum, respectively (Ouctherlony's technique).

By electrophoresis studies this serum component migrates in the albumin-zone, and by gel filtration, on Sephadex G-150, together with the albumin (MW of 67000kDa).

The placental protein responsible for « in vivo » and « in vitro » reactions was not identified with the known placental or serum proteins: PP1-PP21, MP2-MP7, SP1-SP3 [5].

4. — Other experimental studies [8] have shown cultivated explants of human breast cancer, delivered in a group of proteins with a MW of 6800kDa.

CONCLUDING REMARKS

Obesity, hypertension and diabetes are recognized epidemiological risk factors for endometrial carcinoma. A number of studies have demonstrated that both exogenous and endogenous estrogens increase the risk of endometrial cancer (unopposed postmenopausal estrogen therapy).

Endogenous estrogens are elevated in states of chronic anovulation, such as polycystic ovary disease and may be identified in women with estrogen producing neoplasms, such as granulosa cell or theca tumors of the ovary.

The risk of endometrial cancer in postmenopausal women is greatly increased by obesity, which is reported to increase the formation of estrone from androstenedione.

Thus, persistent exposure to unopposed exogenous or endogenous estrogens maintains the capacity of the endometrium for extensive proliferation, resulting in endometrial hyperplasia. But when endometrial thickness exceeds 3 mm, hypoxia would be a supplementary factor for extensive proliferation. The metabolism of these reactive proliferating cells results in enzyme-altered cells and foci, which is sunpposed to be related with the origin of neoplasia, and in this sense these lesions can be considered preneoplastic (complex and atypical hyperplasia of the endometrium), for what we have found a marker, a modified glycoprotein of pharmaceutical placental suspension (PS) able to react in vivo (DTHS-reactivity test) and in vitro, and to point the specific lesions that become tumor, in some cases, after a given time.

In hypertensive or diabetic patients, endometrial hyperplasia could be explained as reactive proliferation to hypoxia, maintained by generalized vasoconstriction and/or diabetic vascularitis.

It also seems that in aging women, when sclerotic artery narrowing proceeds slowly enough, the persistent ischemia leads to the activation of a hypoxia-sensitive growth factors in endometrial cells, resulting in enzyme -altered cell proliferation.

Hypoxia when operating at a cell viability limit and for a sufficient length of time, involves genetic events, that collectively constitute the dysplastic phenotype. Many of these properties lead only to subtle differences from the normal cells of the tissue of origin.

These suggest that preneoplastic cell lines may be viewed as selected populations of enzyme-altered stem cells under the pressure of hypoxia, which retains the potential for tissue specific differentiation, when given an appropriate hormonal and/or oxygenation support (environmental control).

From a biochemical view point, alteration in carbohydrate metabolizing enzymes is a common effect in hypoxic conditions and during the early carcinogenic process of different tissues.

Generally this is linked to an increase in the activities of key glycolytic enzymes, e.g. hexokinase, phosphofructokinase and piruvatkinase. These deviations are explained by changes in the isoenzyme pattern, as adaptive process to hypoxia. In this way these cells lose the sensitivity of glycolytic pathways in nutritional and hormonal adjustment and feed-back controls.

Alteration in carbohydrate-metabolizing enzymes by the increasing of fetal isoenzymes is a common effect during early carcinogenic process of different tissues. In addition, the activities of the neoglucogenetic enzymes fructose-1,6-byphosphatase and glucose-6-phosphate dehydrogenase are reduced. The accumulated metabolites of the glycolysis (PK block) and the neoglucogenesis (FBPase block) are channelled into the pentose phosphate pathway to yield NADPH by the glucose-6-phosphate dehydrogenase reaction and ribose-5-phosphate. The aminoacids

serine and glycine are synthesized from 3-phosphoglycerate, an intermediate metabolite of the glycolytic pathway and diacylglycerol via glycerol-3-phosphate.

These alterations in carbohydrate metabolism enable preneoplastic cells to produce metabolites for cell growth in concert with a production of cell energy, conferring selective advantages of enzyme-altered cells.

It seems clear that enzyme-altered cells are less stable than other normal cells, indicating that de-differentiation during carcinogenesis may be a self-accelerated process.

From a molecular viewpoint, de-differentiation (molecular rearrangement of the nucleotidic sequences of genes, intra or interchromosomal), and/or over-expression of oncogenes, or their activation by transposomes, as mechanisms adaptive to hypoxia, could, under some conditions, be a starting point for the initiation of a carcinogenic process.

Cell membrane molecular changes, including the appearance of glycoproteins with a greater molecular weight (class A of glycoproteins, on Sephadex G-50), consequent to modified genotype in hypoxic enzyme-altered cells, disturb intercellular comunication. Cell growth escapes, in this way of intercellular comunication control, through cyto-skeleton disorganization and disturbance of signal transmissions from cell membrane surfaces. Growth factors and proteins coded by oncogenes have tyrosine-phosphate enzymatic activity, disorganizing the microtubules, microfilaments and adhesion-plaques systems.

In this continuous process, cell entropy grows and its free energy decreases, permitting cellular proliferation. The cell returns towards this stabler state any time when cell organization is disturbed.

Transformation of enzyme-altered cells takes place by the destruction of a part of the genetic material, including anti-oncogenes, which normally block the proliferative process promoted by oncogenes.

Consequently, altered control system of cell growth in promoted cells, results in:

— deficient control of cellular growth and de-differentiation;

— autocrine production of growth factors;

— lower sensitivity to growth inhibitors and increased sensitivity to growth factors secreted by other cells.

These phenomena and possibly others could lead to a selection advantage in clonal expansion for the preneoplastic and neoplastic cells. Altered proliferative potential, partial suspension of growth control, possibly in connection with intrinsic genetic instability, are prerequisites paving the way for rapid genetic, phenotypic and biological diversification during progression.

In conclusion, hypoxia results, like common physiopathological results in most predisposing diseases for endometrial cancer (aging, uncontrolled arterial hypertension, untreated diabetes and endometrial thickness due to persistent exposure to unopposed estrogens) lead to a persistent multicellular hyperplasia of the endometrium.

Within the frame of persistent multicellular hyperplasia, sometimes populations with an altered growth pattern develop. Their occurrence marks a specific change from reactive hyperplasia into a genuine preneoplastic stage.

The results of detailed studies of the sequential changes during carcinogenesis indicate that a basic shift in energy metabolism takes place during this process. Such metabolic aberrations play a crucial role in neoplastic development.

Genetic changes which occur in the presence of hypoxic selective pressure are unstable.

The initiating event in carcinogenesis results in this destabilization of the genome, allowing increased random gene-

ration of variant cells. Most of such variant cells would be eliminated by the host, but occasionally one would have a growth advantage, perhaps by developing greater autonomy.

Recent research suggests that epidermal growth factors (EGFs), insulin-like growth factors (IGFs) and their modulating proteins (IGFBPs) and other endometrial peptides play a mitogenic role in endometrial growth and differentiation.

It seems that cellular proliferation promoted by hypoxia is due to other growth factors (P40?) and soluble growth factor binding proteins (P67?). They reflect a reactivation of the fetal genes and appearance of fetal isoenzymes and a repression of the adult genes.

These changes in gene expression reflect fundamental changes in gene regulation of growing cells and may confer distinct selective advantages to these cells (e.g. replacement of an isoenzyme subject to hormonal control by one independent of such control.

Genetic phenotypic instability and sequential selection of preneoplastic cells for increased growth autonomy and other cancer characteristics are essential elements of neoplastic development.

Concerning the prophylaxis of endometrial cancer, the prevention and treatment of predisposed diseases are important measures.

Boosting host immunological response against enzyme altered cell proliferation, or the inducing of this reaction in patients at risk, by a vaccine prepared from modified placental glycoproteins and an adjuvant (BCG), would be another preventive measure.

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