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Expression of the c-erbB-2-encoded oncoprotein p185 (HER-2/neu) in pregnancy as a model for oncogene-induced carcinogenesis

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Abstract — Although oncogenes are involved in tumor development and progression, their activation during human ontogenesis is inseparably associated with normal fetal development. The c-erbB-2-encoded oncoprotein p185 (HER-2/neu) is overexpressed on fetal epithelial cells, in the placenta, and in several human carcinomas. In patients with p185-overexpressing tumors and in pregnant women at term, increased serum levels of a 105 kDa proteolytic breakdown product corresponding to the extracellular domain of oncoprotein p185 are detectable. Estrogens have been described to be potent inhibitors of p185 expression in human breast cancer cells and to influence also p105 serum levels in females. Regarding the significantly poorer prognosis of patients with c-erbB-2-positive tumors, we discuss common features and differences between c-erbB-2 oncoprotein overexpression in pregnancy and in carcinogenesis.

Introduction

Proto-oncogenes (c-onc) and their oncoproteins first attracted attention after the discovery that viral oncogenes (v-onc) originate from evolutionarily conserved cellular genes (1). Their expression products (tyrosine kinases, growth factors, GTP-binding or DNA-binding proteins) influence cellular proliferation and differentiation processes during ontogenesis (1,2). All of the proto-oncoproteins that have been identified so far are expressed in the placenta, coinciding with the invasive and tumor-like growth of the trophoblast (2,3).

The cellular oncogene c-erbB-2 encodes a 185 kDa receptor tyrosine kinase (p185, HER-2/neu), which transmits growth-stimulatory signals after binding of a yet-unidentified ligand (Figure) (4–6). While only small amounts of p185 are present on normal epithelial cells, overexpression occurs in fetal epithelium, placental tissue and human epithelial cancer (7–11). After proteolytic cleavage the 105 kDa extracellular domain of oncoprotein p185 is detectable in serum (Figure) (12,13). In cancer patients the p185 overexpression in the tumor tissue was described to be associated with a poorer prognosis and to correlate with p105 serum concentrations (10,11,14). Investigations on the course of p105 serum levels in normal pregnancies yielded a significant decrease of p105 in the 1st and 2nd trimester, followed by a significant

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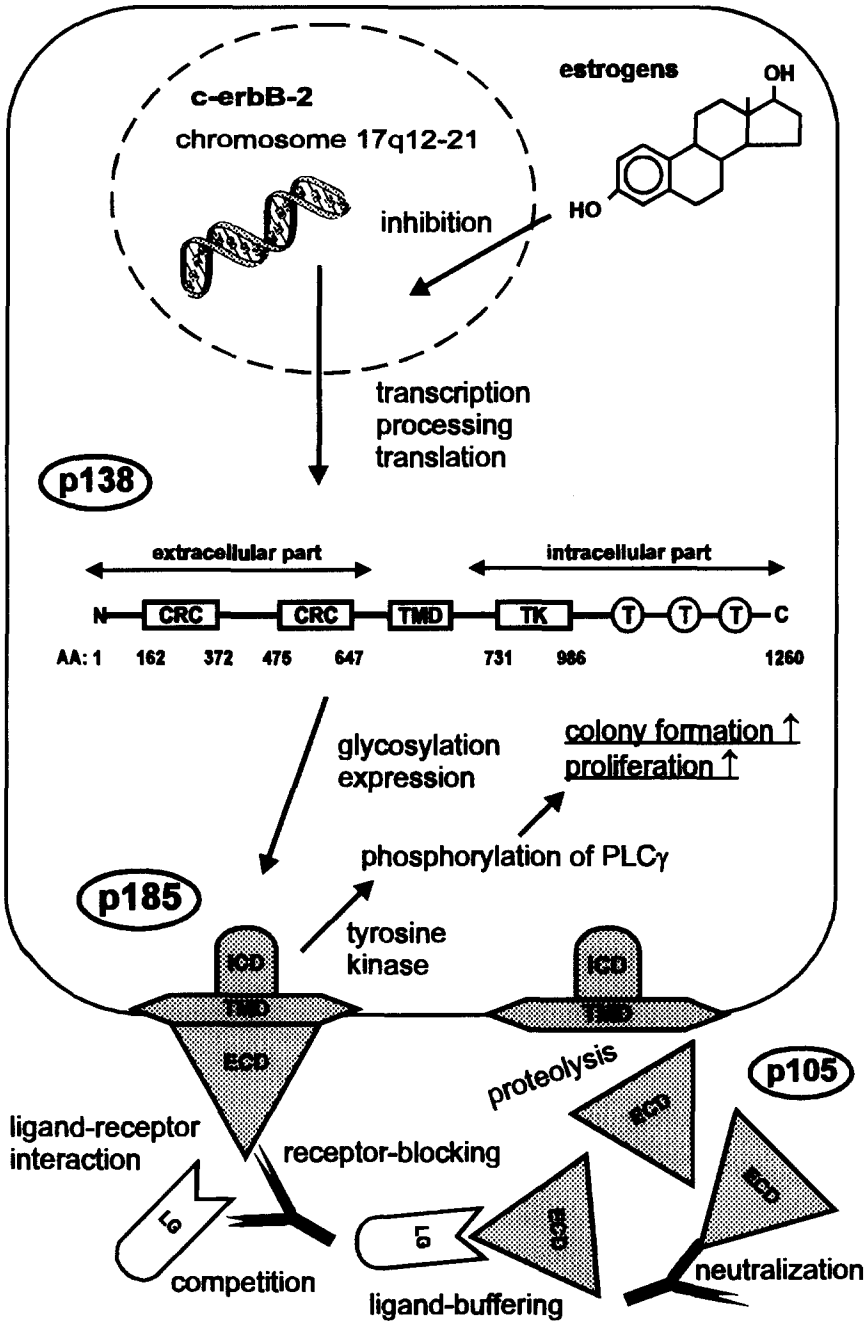

Figure Schematic diagram of expression, function and detection of c-erbB-2-encoded oncoprotein p185 (TK: tyrosine kinase; CRC: cysteine-rich cluster; T: tyrosine residue; AA: amino acid; ICD: intracellular domain; TMD: transmembrane domain; ECD = p105: extracellular domain; LG: ligand).

increase in the 3rd trimester, whereas postpartum serum values returned to the level in non-pregnant women (15,16). Estradiol was found to be a potent in-vitro inhibitor of p185 expression in human breast cancer cells. In addition it was shown that p105 serum levels in female controls are also under the control of sex steroids, so that women with oral contraception or hormonal replacement therapy had reduced p105 serum values compared with those without application of estrogens (17–19).

Discussion

As the activation of cellular oncogenes during ontogenesis presupposes regulatory mechanisms, it was our purpose to compare the controlled increase of c-erbB-2 expression in pregnancy with the uncontrolled c-erbB-2 overexpression in carcinogenesis.

Common features

1. The in-vitro inhibitory effect of estrogens on the c-erbB-2 expression of breast cancer cells is confirmed by in-vivo findings that both hormonal contraception and increasing concentrations of estrogens in early pregnancy are associated with reduced p105 serum levels (16–19).
2. Considering the opposite effects of the growing, p185-overexpressing fetoplacental unit and steep elevating serum levels of c-erbB-2-inhibiting estrogens in the course of pregnancy, an increased proteolytic deactivation of p185 in the last period of pregnancy gives a possible explanation for the high p105 levels in the 3rd trimester (13,15,16). As both the placenta and several malignancies are known to produce proteases, it seems to be probable that in cancer patients also small c-erbB-2-positive tumors could increase p105 serum concentrations by means of general and unspecific proteolysis (3). The presence of spreading factors – such as proteolysis – may decrease a cancer patient's survival by promoting metastasis and tumor growth (1,3,10). In addition this could explain the prognostic value of increased preoperative p105 serum levels as found in patients with ovarian cancer (20).
3. In-vitro examinations have shown that a proteolysis-mediated loss of the extracellular domain interrupts the interaction of ligand and receptor, and induces differentiation of initial proliferating breast cancer cells (21). This would explain why p185 is expressed in proliferative inactive areas of the placenta and would also coincide with the elevation of p105 serum levels in the last trimester of pregnancy (9,15,16).

Differences

1. The placenta – in which p185 expression exceeds several times that in postnatal epithelial cells – contains about fifty-fold less c-erbB-2 protein per microgram of total protein than do p185-expressing breast tumor cells, indicating the existence of a regulated overexpression in pregnancy (7,8).
2. The majority of studies dealing with the association of p185 expression and p105 serum levels in cancer patients found p105 serum values to be increased and to correlate with p185 overexpression in the tumor tissue (14). In contrast, the results in pregnancy show that not the level of p185 expression but rather the total amount of p185 – provided by fetus and placenta – seems to be responsible for the elevation of serum p105 in the course of pregnancy (16).
3. As the activation of the p185 receptor in tumor cells usually induces proliferative activities, it is surprising that p185 is strongly expressed in advanced stages of trophoblast differentiation and in proliferative inactive (Ki-67 negative) areas of the placenta (5,6,9).

Conclusions

The activation of c-erbB-2 oncogene expression in pregnancy enables the study of the physiological functions of oncoprotein p185. With regard to the increasing employment of c-erbB-2 serum analyses as a diagnostic tool in oncology it is necessary to understand the in-vivo development of elevated p105 serum levels in order to reach correct clinical decisions such as the choice of an effective therapy. Results obtained with in-vitro examinations never can replace the in-vivo situation of a multifunctional biological system and therefore must be interpreted with caution. Considering the differences between the growth of the p185-overexpressing fetoplacental unit and a c-erbB-2-positive tumor – as discussed above – we think that pregnancy represents a useful in-vivo model for oncogene-induced carcinogenesis.

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