27

GROWTH FACTORS IN NORMAL AND MALIGNANT MAMMARY EPITHELIAL PROLIFERATION

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Growth factors are important components of the secretions of the normal lactating breast epithelium. In addition, they may play fundamental roles in regulating cyclic growth, development and regression of the mammary gland. We have examined the roles of three growth factors found in milk, TGFα, MDGF-1, and TGFβ, on proliferation and differentiation of normal human mammary epithelial cells. TGFα begins to be produced in high concentrations by normal mammary epithelial cells as they adapt from non-proliferating organoids to rapidly proliferating primary cultures. TGFα appears to be an autocrine growth factor in high density culture since an antibody directed against the EGF receptor reversibly blocks cellular proliferation. MDGF-1 is also produced by normal, proliferating human mammary epithelial cells. This 60 kDa growth factor does not seem to be structurally related to any other known growth factor; it binds to a 120-140 kDa high affinity binding site. MDGF-1 stimulates proliferation, collagen production and tyrosine phosphorylation when added to cultures of normal breast epithelial cells or some human breast cancer cell lines. Finally, TGFβ is also produced at high levels by normal human mammary epithelial cells. When added to these cells it causes reversible growth arrest, increased cellular adhesion, cell elongation, and induction of milk fat globule antigen and PDGF B chain mRNA. The ability of stepwise malignant transformation by benzo[a]pyrene, a single activated oncogene (v-ras^H, v-mos, SV40T) or a combination of two of these oncogenes to modulate either growth factor production or response was also studied. Data with this model suggest that growth factor production does not specifically characterize breast cancer; rather, changed growth factor responses mark the transformed phenotype. Benzo[a]pyrene immortalization of mammary epithelial cells does not markedly compromise function of any of these growth factors, nor does it modulate their production. SV40T compromises MDGF-1 function but sensitizes cells to TGFα and β. v-ras^H compromises growth modulatory functions of TGFα and MDGF-1. Finally, combinations of v-ras^H with v-mos or SV40T interfere with growth modulation of cells by all three growth factors; however, TGFβ can still induce differentiation unabated in these cells. Transformation of the cells with combinations of two oncogenes is associated with acquisition of tumorigenic potential in the nude mouse.

26

CATHEPSIN D IN BREAST CANCER.

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Cathepsin D is an acidic lysosomal protease present in all cells. In estrogen receptor positive and negative breast cancer cell lines, the mRNA coding for pro-cathepsin D is over-expressed and sorting and maturation of the pro-enzyme are altered, leading to accumulation of the active proteinase in large endosomes and to secretion of the precursor (52K protein). In MCF7 cells, the cathepsin D mRNA is induced directly and transcriptionally by estrogens and indirectly by growth factors. In vitro, pro-cathepsin D is an autocrine mitogen on breast cancer cells and can be auto-activated to degrade extra-cellular matrix and proteoglycans and to activate other proteinases in acidic microenvironments. In patients, there is a significant correlation between high cathepsin D concentrations in the cytosol of primary breast cancer and development of metastasis (F. Spyratos et al, The Lancet ii, 8672, 1115, 1989 ; S. Thorpe et al, Cancer Res. 49, 6008, 1989). This prognostic marker is independent of others and appears to be particularly useful in lymph node-negative tumors. These results suggest that overexpression and possible derouting of cathepsin D plays an important role in invasion and metastasis of breast cancer.

28

REGULATION OF BREAST CANCER GROWTH BY INSULIN-LIKE GROWTH FACTORS (IGFs)

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The IGFs may be important autocrine, paracrine, or endocrine growth factors for human breast cancer. IGF-I and II stimulate growth of cultured human breast cancer cells. IGF-I is slightly more potent, paralleling its higher affinity for the IGF-I receptor. Antibody blockade of the IGF-I receptor inhibits growth stimulation induced by both IGFs, suggesting that this receptor mediates the growth effects of both peptides. However, IGF-I receptor blockade does not inhibit estrogen (E_2)-induced growth suggesting that secreted IGFs are not the major mediators of E_2 action. Several breast cancer cell lines express IGF-II mRNA by both Northern analysis and RNase protection assay. IGF-II activity is found in conditioned medium by radioimmuno and radioreceptor assay, after removal of somatomedin binding proteins (BP) which are secreted in abundance. IGF-I is undetectable. BPs of ≈ 25K and 40K predominate in ER-negative cell lines while BPs of 36K predominate in ER-positive cells. Blockade of the IGF-I receptor inhibits anchorage-independent and monolayer growth in serum of a panel of breast cancer cell lines. Growth of one line (MDA-231) was also inhibited in vivo by receptor antibody treatment of nude mice. The antibody had no effect on growth of MCF-7 tumors. These data suggest that IGFs are important regulators of breast cancer cell proliferation and that antagonism of this pathway may offer a new treatment strategy.