Overexpression of insulin-like growth factor II in human breast cancer cells.

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Growth regulation of breast cancer cells involves a complex interaction between steroid hormones and growth factors, of which oestrogen and insulin-like growth factor II (IGFII) appear to be major components (1). Studies using oestrogen-sensitive human breast cancer cells have shown that not only can oestrogen regulate growth factor pathways in these cells (1) but also that growth factors can alter expression of genes regulated by oestrogen response elements (2). Thus, alteration of any one of these mitogenic pathways can affect cell response to the other pathways. Recent work has focused on examination of the effects on oestrogen sensitivity of cells following upregulation of endogenous growth factor gene expression by gene transfection (3-6).

Loss of steroid sensitive growth is a common feature in progression of breast cancer cells which presents a major clinical problem in the endocrine therapy of breast cancer and for which molecular mechanisms have yet to be elucidated. Cell culture models show that loss of steroid sensitive growth does not always result from loss of steroid receptor (7,8) but rather may result from increased constitutive cell growth (8,9) which has been suggested to arise from altered growth factor production. We, and others, have shown previously that upregulation of IGFII gene expression from a transfected IGFII gene can reduce estrogen sensitivity of growth and increase transformed characteristics in MCF7 human breast cancer cells (3,4). These studies have now been extended to another oestrogen-dependent human breast cancer cell line, ZR-75-1.

Our previous work used stable transfection of an inducible expression vector containing the metal response elements of the human metallothionein IIA promoter linked to the coding portion of human prepro-IGFII. Stably transfected MCF7 cells (designated MI7 cells) produced zinc-inducible IGFII mRNA (3) and protein (10). Cell growth was increased by treatment with zinc which could be blocked by the aIR3 antibody to the IGFIR indicating that the increased cell growth was via an autocrine pathway (3). Parallel transfections have now been performed into another estrogen-dependent human breast cancer cell line, ZR-75-1. Three clones of transfected ZR-75-1 cells produced levels of zinc-inducible IGFII mRNA and secreted mature IGFII protein at levels similar to that found in the MI7 cells. However, unlike the MI7 cells, no resulting effects were found with zinc on cell growth in the ZR-75-1 clones. The ZR-75-1 cells possess receptors capable of binding 125I-IGFII and show a growth response to exogenously added recombinant IGFII protein. Whilst the reason for lack of growth response in the ZR-75-1 clones may reside in other subtle differences in IGFII sensitivity from MCF7 cells, it was interesting to note that the ZR-75-1 clones all secreted high levels of prepro- and pro-forms of IGFII compared with the MI7 cells. This demonstrates that levels of overexpression of IGFII mRNA and secreted mature IGFII protein are not the only factors of consideration in deregulation of breast cancer cell growth and loss of oestrogen sensitivity.

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References: