Role of Insulin-like Growth Factors and the Type I Insulin-like Growth Factor Receptor in the Estrogen-stimulated Proliferation of Human Breast Cancer Cells*

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Estrogen sensitizes the MCF-7 estrogen-responsive breast cancer cell line to the mitogenic effect of insulin and the insulin-like growth factors (IGFs). This sensitization is specific for estrogen and occurs at physiological concentrations of estradiol. Dose-response experiments with insulin, IGF-I, and IGF-II suggested that the sensitization is mediated through the type I IGF receptor. Binding experiments with 125I-IGF-I and hybridization of a type I IGF receptor probe to RNA showed that the levels of the type I IGF receptor and its mRNA are increased 7- and 6.5-fold, respectively, by estradiol. IGF-I and estradiol had similar synergistic effects on other estrogen-responsive breast cancer cell lines, but IGF-I alone increased the proliferation of the MDA MB-231 cell line which is not responsive to estrogens. These experiments suggest that an important mechanism by which estrogens stimulate the proliferation of hormone-dependent breast cancer cells involves sensitization to the proliferative effects of IGFs and that this may involve regulation of the type I IGF receptor.

Breast cancer is frequently estrogen-responsive (McGuire et al., 1975); however, the mechanisms underlying this responsiveness are poorly understood. Cell lines have been established from primary breast tumors and pleural effusions of patients with advanced breast cancer (Soule et al., 1973; Engel et al., 1978), and these cell lines provide experimental systems for defining growth factors that are important in regulating the proliferation of breast cancer cells. Some of these cell lines, notably the MCF-7, ZR-75, and T47D cell lines, have been widely used as models of estrogen-responsive breast cancer because they contain estrogen receptors and their growth is stimulated by estrogens (Johnson et al., 1978; Darbre et al., 1984).

Autocrine and paracrine mechanisms are thought to be involved in the estrogen stimulation of breast cancer cell proliferation. It has been reported that growth factors such as transforming growth factor α (TGF-α) (Dickson et al., 1986; Perroteau et al., 1986), transforming growth factor β (TGF-β) (Knabbe et al., 1987), and platelet-derived growth factor (Bronzert et al., 1987) are synthesized by breast cancer cells in culture. Further, some studies have suggested that the synthesis of TGF-α is increased by estrogens (Lippman et al., 1987) while the secretion of TGF-β, a negative growth factor, is inhibited (Knabbe et al., 1987).

Conflicting results have been reported for the expression of IGF-I in breast tumor cells. Initially, Huff et al. (1986 and 1988) reported that IGF-I is synthesized under estrogen control in MCF-7 cells. However, Karey and Sirbasku (1988) using an immunoblot assay to measure IGF-I in conditioned medium reported that MCF-7 cells do not produce biologically significant concentrations of IGF-I, and, subsequently, Vee et al. (1989) using a sensitive RNase protection assay could not detect IGF-I mRNA in breast cancer cell lines.

Despite the appeal of autocrine and paracrine models of growth regulation, the relative importance of the different growth factors implicated in the control of cultured breast cancer cells remains unclear (Karey and Sirbasku, 1988; Arteaga et al., 1988; Imanishi et al., 1989). In addition, measurement of some of these factors in primary breast tumors has not produced data consistent with the models of estrogen-regulated autocrine growth stimulation derived from cell culture work. For example, similar levels of TGF-α have been found in estrogen receptor-positive and -negative tumors (Bates et al., 1988).

Insulin, IGF-I, and insulin-like growth factor II (IGF-II) are structurally related molecules. Insulin is involved in the acute regulation of blood sugar levels, whereas IGF-I and IGF-II are mitogens principally involved in the control of growth and development (Froesch et al., 1985). These three peptides bind to the insulin receptor, the type I IGF receptor, and the type II IGF receptor. The insulin and type I IGF receptors have a similar heterotetrameric structure composed of two α subunits (135,000 daltons) and two β subunits (90,000 daltons) while the type II IGF receptor is a single chain molecule (250,000 daltons). The type I receptor has a high affinity for IGF-I, a somewhat lower affinity for IGF-II, and a low affinity for insulin (0.1-1% of that for IGF-I). The type II receptor has a high affinity for IGF-II and a moderate affinity for IGF-I, but does not bind insulin (Baxter, 1986).

In addition to the three receptors, IGF-I and -II bind to a number of other binding proteins (e.g. BP28 and BP53, Baxter and Martin, 1989) which are found in serum but are also produced by a wide variety of different cell types.

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The abbreviations used are: TGF, transforming growth factor; IGF, insulin-like growth factor; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; PBS, phosphate-buffered saline; DSS, di-sodium salt of 4-(2-hydroxyethyl)pyridine.

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Although insulin, IGF-I, and IGF-II bind to an array of receptors and binding proteins (Baxter, 1986), the major mitogenic effects of the insulin-like growth factors are thought to be mediated through the type I IGF receptor. Type I receptors have been identified on cultured breast cancer cells (Furlanetto and DiCarlo, 1984; De Leon et al., 1988) and in membrane fractions prepared from primary breast tumors (Pekonen et al., 1988; Foekens et al., 1989).

In this study, we have examined the involvement of insulin and the insulin-like growth factors in the stimulation of the growth of MCF-7 human breast cancer cells by estradiol. Insulin and the insulin-like growth factors were found to be potent mitogens for the stimulation of MCF-7 cell proliferation, but this stimulation was largely dependent on the presence of estrogen. Our results suggest that an important mechanism by which estrogen stimulates the proliferation of breast cancer cells involves sensitization to the proliferative effects of insulin-like growth factors. We also show that binding of IGF-I to the type I IGF receptor and type I IGF receptor mRNA levels are stimulated by estradiol which suggests that the sensitization by estradiol may be mediated by controlling type I IGF receptor levels.

**EXPERIMENTAL PROCEDURES**

**Materials—**Recombinant IGF-I and IGF-II were obtained from Bachem. Bovine insulin was obtained from Collaborative Research.

**Cell Culture—**MCF-7 cells (Soule et al., 1973) were cultured as previously described (May and Westley, 1988; Johnson et al., 1989). For growth experiments, 10,000 MCF-7 cells were plated in 0.5 ml of normal growth medium (Dulbecco's modified Eagle's medium containing 10% fetal calf serum and 1 μg/ml insulin) in 16-mm diameter wells. The cells were allowed to attach for 18 h and then progressively withdrawn from estradiol and then treated with different concentrations of estradiol as described previously (May and Westley, 1988). RNA was separated by electrophoresis on denaturing formaldehyde agarose gels and then transferred to Hybond-N membranes. The cDNA insert of plasmid pIGF-I-R5 (Ulrich et al., 1986) was labeled using [32P]dCTP by random priming and hybridized to the immobilized RNA at a concentration of 5 × 10⁶ cpm/ml for 3 days at 42 °C. The prehybridization and hybridization solutions were as described previously (Westley and May, 1984). The filter was then washed extensively at 65 °C and exposed to preflashed x-ray film at approximately 70 °C. The relative amount of type I IGF receptor mRNA was measured by densitometric scanning of the autoradiographs.

**RESULTS**

**Involvement of Insulin and Insulin-like Growth Factors in the Proliferative Response of MCF-7 Cells to Estradiol—**Estradiol stimulated the growth of MCF-7 cells most consistently when cells were withdrawn from estradiol and then treated with different concentrations of estradiol as described previously (May and Westley, 1988). Under these conditions, the proliferation of cells slowed progressively during the withdrawal period and consequently they did not proliferate significantly during the 9 days of culture in the withdrawal medium alone. Under these conditions, estradiol alone stimulated cell proliferation so that after 9 days, there were 2–2.5-fold more cells in wells containing medium supplemented with estradiol alone (examples shown in panels A, B, and C of Fig. 1).

To identify growth factors that influence the proliferation of breast cancer cells and may be involved in the stimulation of cell proliferation by estradiol, withdrawn cells were treated with estradiol and various growth factors. TGF-α, TGF-β, platelet-derived growth factor, and basic fibroblast growth factor were found to have little effect (data not shown).

In contrast, insulin and the insulin-like growth factors dramatically increased cell proliferation, but only in the presence of estradiol. Fig. 1 shows the effects of insulin (1 μg/ml), IGF-I (50 ng/ml), and IGF-II (50 ng/ml) alone and in the presence of estradiol. Nine days of treatment with insulin, IGF-I, or IGF-II alone increased cell numbers 1.3–1.5-fold. Together with estradiol, insulin, IGF-I, or IGF-II dramatically stimulated cell proliferation. This effect was clearly visible after 6 days of culture and was more marked after 9 days when cell numbers were increased approximately 10-fold in wells treated with estradiol and the growth factor.

**Insulin, IGF-I, and IGF-II Stimulate the Growth of MCF-7 Cells in the Presence of Estradiol—**The effects of insulin, IGF-I, and IGF-II could be mediated by the insulin, type I, or type II IGF receptor. To identify the receptor responsible for mediating the effects of insulin and the insulin-like growth factors on MCF-7 cell proliferation, MCF-7 cells were withdrawn and then treated with estradiol and a range of concentrations of insulin, IGF-I, and IGF-II (Fig. 2). IGF-I stimulated growth above that observed in the presence of estradiol alone at
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FIG. 1. Effects of insulin, IGF-I, IGF-II, and estradiol on the growth of MCF-7 cells. MCF-7 cells were plated in 16-mm wells and then withdrawn from estrogens present in normal growth medium as described under "Experimental Procedures." Triplicate wells were then treated for 6 and 9 days with withdrawal medium alone (○, control), estradiol, 10 nM (E2), the growth factor (●, insulin, panel A; ●, IGF-I, panel B; ●, IGF-II, panel C), or estradiol together with the growth factor (●, insulin, panel A; IGF-I, panel B; and IGF-II, panel C). The amount of DNA in each well after 6 and 9 days was measured as described under "Experimental Procedures" and expressed as a percentage of the maximum amount of DNA in one of the wells containing estradiol and the growth factor.

FIG. 2. Dose-response curves for IGF-I, IGF-II, and insulin in the presence of estradiol. MCF-7 cells were plated out and withdrawn as described under "Experimental Procedures." Triplicate wells were treated for 6 and 9 days with withdrawal medium alone (○, control), estradiol, 10 nM (E2), the growth factor (●, insulin, panel A; ●, IGF-I, panel B; ●, IGF-II, panel C), or estradiol together with the growth factor (●, insulin, panel A; IGF-I, panel B; and IGF-II, panel C). The amount of DNA in each well after 6 and 9 days was measured as described under "Experimental Procedures" and expressed as a percentage of the maximum amount of DNA in one of the wells containing estradiol and the growth factor.

FIG. 3. Concentration of estradiol required to sensitize cells to IGF-I. MCF-7 cells were plated and withdrawn as described under "Experimental Procedures." Triplicate wells were then treated for 9 days with the indicated concentration of estradiol in the presence (●) or absence (○) of IGF-I (50 ng/ml). The amount of DNA in each well was then measured and expressed as in Fig. 1.
of IGF-I. In addition, the low concentration of estradiol (approximately 0.1 nM) required to stimulate the proliferation of MCF-7 cells in the presence and absence of IGF-I suggests that both increases are mediated by the estrogen receptor.

Estradiol Increases Binding to the Type I IGF Receptor and Its mRNA in MCF-7 Cells—The binding of [125I]-IGF-I to monolayers of MCF-7 cells was measured as described under “Experimental Procedures.” In initial experiments, monolayers were incubated with [125I]-IGF-I in the presence and absence of unlabeled IGF-I. Binding was maximal after 2 h, and, under these conditions, nonspecific binding was approximately 15% of the total binding (Fig. 5A).

IGF-I may bind to the type I and type II IGF receptors as well as to the insulin receptor and a number of IGF binding proteins. The type I IGF receptor is a heterotetramer, and IGF-I binds to the 135,000-dalton α subunit to give a complex of 142,000 daltons. Type I IGF receptor can be unambiguously identified following cross-linking of [125I]-IGF-I to the α subunit by polyacrylamide gel electrophoresis. MCF-7 cells were therefore incubated with [125I]-IGF-I both alone and in the presence of various concentrations of competing nonradioactive IGF-I, IGF-II, and insulin. The complexes formed were cross-linked using DSS and analyzed by polyacrylamide gel electrophoresis as described under “Experimental Procedures.” The [125I]-IGF-I complex migrated with an apparent molecular weight of 145,000 which is in good agreement with the molecular weight of 142,000 for the LY subunit of the type-1 IGF receptor cross-linked to [125I]-IGF-I. [125I]-IGF-I unlabeled IGF-I (Fig. 6). In contrast to the cross-linked IGF-I, shows that binding was to the type I IGF receptor rather than the type II IGF or insulin receptor. The relative concentrations of IGF-I, IGF-II, and insulin required to displace [125I]-IGF-I from the receptor were similar to those required to stimulate the proliferation of MCF-7 cells in the presence of estrogen.

To determine if the type I receptor is regulated by estradiol, withdrawn and estrogen-stimulated cells were incubated with [125I]-IGF-I alone or in the presence of excess unlabeled IGF-I or insulin. Cells were subsequently exposed to DSS, and the amount of cross-linked receptor was measured as described under “Experimental Procedures.” Fig. 6 shows that in estrogen-treated cells there was a prominent band of radioactivity corresponding to the type I IGF receptor which was barely visible in withdrawn cells. Scanning densitometry showed that there is at least 7-fold more binding in estrogen-treated than control cells.

A protein of approximately 40,000 daltons was also cross-linked to the iodinated IGF-I (Fig. 6). In contrast to the type I IGF receptor, binding to this protein was not suppressed by insulin, and approximately the same amount was cross-linked in withdrawn and estrogen-treated cells.

The type I IGF receptor mRNA was then measured in withdrawn MCF-7 cells and cells treated with a range of concentrations of estradiol. The type I IGF receptor cDNA hybridized to a mRNA of approximately 11 kilobases which corresponds to the higher molecular weight mRNA identified by Ullrich et al. (1986) in human RNA samples. Type I IGF receptor mRNA was increased at concentrations of 10^{-12} M estradiol and above and was maximal at 10^{-9} when there was 6.5-fold more RNA than in withdrawn cells (Fig. 7).
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FIG. 6. Polyacrylamide gel of 125I-IGF-I cross-linked to MCF-7 cells using disuccinimidyl suberate. MCF-7 cells were plated out and withdrawn as described under "Experimental Procedures" for 5 days. They were then cultured for 2 days in withdrawal medium alone (C) or withdrawal medium supplemented with estradiol (10 nM, E2). Cells were incubated with 125I-IGF-I alone (T) or in the presence of unlabeled IGF-I (+IGF-I, 100 nM) or insulin (+Ins, 30 μM) for 2.5 h, washed to remove unbound 125I-IGF-I, and then incubated with 0.2 mM DSS for 45 min at 4°C. The cells were then dissolved in sample buffer and analyzed by polyacrylamide gel electrophoresis as described under "Experimental Procedures." The distance migrated by the molecular weight markers (myosin, 200,000; phosphorylase b, 97,000; albumin, 68,000; and ovalbumin, 43,000) are shown on the left.

FIG. 7. Regulation of type I IGF receptor mRNA by estradiol. Total RNA was extracted from MCF-7 cells that had been withdrawn (C) or treated with the indicated concentration of estradiol. RNA (10 μg) was separated by gel electrophoresis and transferred to a nylon membrane. The filter was hybridized with 32P-labeled IGF-I-R8 cDNA corresponding to the N terminus of the α subunit as described under "Experimental Procedures." A, autoradiograph of filter. B, amount of 32P-labeled cDNA hybridized quantified by densitometry of the x-ray film.

Involvement of IGF-I in the Stimulation of MCF-7 Cells by Estradiol in the Absence of Added IGF-I—The small increase in cell growth following the treatment of MCF-7 cells with estradiol alone appears to be a specific estrogenic effect as it occurs at 0.1 nM estradiol and was not observed when MCF-7 cells were treated with other hormones (Figs. 2 and 3). This increase could involve sensitization of cells by estradiol to the mitogenic effects of low concentrations of IGFs either present in the newborn calf serum or elaborated by the MCF-7 cells.

A neutralizing monoclonal antibody (Sm 1.2) raised against IGF-I has been used to investigate the contribution of serum IGF-I to the proliferation of fibroblasts in culture (Russell et al., 1984; Clemens and Van Wyk, 1985) and the autocrine stimulation of small cell lung carcinoma cells by IGF-I (Minuto et al., 1988). MCF-7 cells were withdrawn and then cultured in the presence and absence of Sm 1.2 during treatment with estradiol (10 nM) alone or estradiol together with IGF-I. Fig. 8 shows that the antibody had no effect on untreated cells but that it significantly reduced the stimulation by estradiol alone (p < 0.01). The growth stimulation of MCF-7 cells by estradiol in combination with IGF-I (10 ng/ml) was also largely inhibited by Sm 1.2.

Effects of Estradiol and IGF-I on Other Human Breast Cancer Cell Lines—The relative contribution of estradiol and IGF-I to the proliferation of other breast cancer cell lines was assessed. The ZR-75 and T47D estrogen receptor-positive cell lines and the MDA MB-231 estrogen receptor-negative cell line were withdrawn as described under "Experimental Procedures" and then treated with IGF-I and estradiol alone and in combination. For the ZR-75 and T47D cell lines, estradiol and IGF-I had a synergistic effect similar to that found with the MCF-7 cells although the effect was not so dramatic (data not shown). The results with the MDA MB-231 cell line are shown in Fig. 9. In contrast to the MCF-7 cells, MDA MB-231 cells proliferated in the withdrawal medium alone, and
FIG. 9. Effect of estradiol and IGF-I on the proliferation of MDA MB-231 cells. MDA MB-231 cells were plated out and withdrawn as described under "Experimental Procedures." Cells were then treated for 6 or 9 days with withdrawal medium alone (Control), estradiol alone (E2, 10 nM), IGF-I alone (50 ng/ml), or IGF-I and estradiol together (E2 + IGF-I, 10 nM and 50 ng/ml, respectively). The relative number of cells in each well after 6 and 9 days was then determined as in Fig. 1.

TABLE I
Effect of estradiol on binding of 125I-IGF-I to estrogen-treated and withdrawn MDA MB 231 and MCF-7 cells

<table>
<thead>
<tr>
<th>Cells</th>
<th>125I-IGF-I bound to type I IGF receptor</th>
<th>( \text{cpm} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA MB 231</td>
<td>Withdrawn</td>
<td>6862</td>
</tr>
<tr>
<td>MCF-7</td>
<td>Estrogen-treated</td>
<td>7685</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1268</td>
</tr>
</tbody>
</table>

estradiol did not increase this proliferation. IGF-I, in the presence or absence of estradiol, increased cell proliferation approximately 2-fold. Thus, MDA MB-231 cells respond to IGF-I, but this responsiveness is not influenced by estradiol.

The effect of estradiol treatment on the type I receptor in MDA MB-231 cells and MCF-7 cells is compared in Table I. Withdrawn and estrogen-treated cells were incubated with 125I-IGF-I alone and in the presence of excess nonradioactive insulin (to measure binding to the type I IGF receptor). In MDA MB-231 cells, there was no statistically significant difference between the amount of 125I-IGF-I bound to the type I IGF receptor in withdrawn and estrogen-treated cells. In MCF-7 cells, insulin-suppressible binding was detected in estradiol-treated cells but not withdrawn cells showing that type I IGF receptor could be identified in estrogen-treated but not withdrawn cells in agreement with the data shown in Fig. 6. MDA MB-231 cells bound approximately 6-fold more 125I-IGF-I than estrogen-stimulated MCF-7 cells. This suggests, therefore, that the MDA MB-231 cell line expresses high levels of the type I IGF receptor but that the amount of this receptor is not influenced by estradiol.

DISCUSSION

In this study, we have shown that insulin or insulin-like growth factors are involved in the stimulation of the proliferation of breast cancer cells by estradiol. These experiments suggest a direct sensitization of breast cancer cells by estradiol to the effects of growth factors that act through the type I IGF receptor. Other growth factors do not substitute for insulin or the IGFs, and growth factors that have been reported to be synthesized in response to estradiol treatment in breast cancer cells do not have a synergistic effect with insulin and the IGFs on cell proliferation.

In this study, IGF-I alone was found to have a very small effect on MCF-7 cell proliferation. This is in contrast to other studies (Huff et al., 1986; Karey and Sirbasku, 1988) which reported much larger effects. It is possible that the larger effects obtained in these studies were at least in part due to low levels of estrogens in the culture medium. Residual estrogen would act synergistically with exogenous insulin or IGFs to give an apparently large effect for the growth factors alone. Although the source of residual estrogen is not known, it is noteworthy that our study differs from those of Huff et al. (1986) and Karey and Sirbasku (1988) in that medium lacking phenol red (a weak estrogen) was used, the serum was more severely stripped, and the cells were withdrawn from estragen for 4 days before the start of the experiment. In agreement with our findings, van der Burg et al. (1988) found that IGF-I and estradiol act synergistically in phenol red-free medium supplemented with serum which had been depleted of estradiol and endogenous growth factor activities.

Huff et al. (1986 and 1988) reported that breast cancer cells produce IGF-I and that estrogens regulate IGF-I synthesis. These authors suggested that estrogens stimulate breast cancer cell growth by increasing their production of IGF-I which would then act as an autocrine growth factor.

Our data are not consistent with an autocrine model of estrogen-regulated growth involving IGF-I. This is because IGF-I alone has very little effect on cell proliferation and is unable to substitute for estradiol. The results of other studies are also not consistent with an autocrine model. Yee et al. (1989) were unable to detect IGF-I mRNA in breast tumor cells using a sensitive RNase protection assay, and Karey and Sirbasku (1988) were unable to detect biologically significant concentrations of IGF-I in medium conditioned by breast cancer cell lines.

Overall, our data emphasize the importance of the influence of estradiol on the sensitivity of breast cancer cells to IGFs. As the magnitude of this effect is large, we suggest that the sensitization to IGFs is more important than the regulation of growth factors such as IGF-I, TGF-α, and TGF-β (Lippman et al., 1987) in the stimulation of breast cancer growth by estrogen.

Treatment of MCF-7 cells with estradiol alone resulted in a small increase in proliferation. This increase by estradiol alone probably also involves a sensitization to IGF-I as Sm 1.2 significantly reduced the stimulation of cell proliferation by estradiol alone. In this case, the source of IGF-I was presumably the serum present in the culture medium as bovine IGF-I is identical with human IGF-I (Honegger and Humbel, 1986). The inability to totally abolish the growth stimulation by estradiol alone may have resulted from the difficulty in immunoneutralization of serum IGFs due to their A. J. Stewart, B. R. Westley, and F. E. B. May, unpublished data.
association with serum binding proteins (Russell et al., 1984) or because some of the sensitization may be due to insulin or IGF-II (acting through the type I receptor) present in calf serum which would not be neutralized by Sn-1-2. Insulin and the IGFs are thought to exert their mitogenic effects principally through the type I IGF receptor. We therefore measured binding of 125I-IGF-I to monolayers of MCF-7 cells. In agreement with other studies (Furlanetto and DiCarlo, 1984; De Leon et al., 1988), binding of iodinated IGF-I was detected which was suppressed by excess unlabeled IGF-I and -II. In cells growing in normal culture medium, however, only about one-third of bound 125I-IGF-I was associated with the type I IGF receptor, the remainder being associated with other binding proteins or receptors. A low molecular weight IGF-I binding protein was identified which did not bind insulin and this may correspond to one of the IGF-I binding proteins of 46,000, 36,000, and 29,000 that are secreted by MCF-7 cells (De Leon et al., 1988).

The binding of IGF-I to multiple proteins complicated the analysis of the effects of estradiol on the type I IGF receptor. Using chemical cross linking, type I receptor was detected on estrogen-stimulated but not withdrawn cells. The observation that estradiol also increases type I IGF receptor mRNA levels to a similar extent suggests that estradiol exerts its control principally by regulating mRNA levels, and this may result from regulation of the transcription of the type I IGF receptor gene. This is the first demonstration of regulation of the type I IGF receptor by estradiol in breast cancer cells and provides an attractive explanation for the sensitization of breast cancer cells to IGFs by estradiol.

A synergistic effect of estradiol and IGF-I was also found in the estrogen-responsive ZR-75 and T47D cell lines suggesting that regulation of the response to IGF-I is a general phenomenon and not restricted to MCF-7 cells. In addition, type I IGF receptor was identified on MDA MB-231 cells, and its levels were not affected by estradiol. The binding data were in agreement with the proliferation experiments which showed that IGF-I stimulated the proliferation of MDA MB-231 cells but estradiol had no effect. These results are consistent with a model in which the IGFs are able to stimulate cells to IGFs by estradiol. Regulation of the response to IGF-I is a general feature of the IGF-I binding proteins and suggests that regulation of the type I IGF receptor while in estrogen receptor-positive cells, responsiveness to IGF-I may be regulated principally by regulating mRNA levels, and this may result from regulation of the transcription of the type I IGF receptor gene. This is the first demonstration of regulation of the type I IGF receptor by estradiol in breast cancer cells and provides an attractive explanation for the sensitization of breast cancer cells to IGFs by estradiol.
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