

We have recently shown that oestrogen can increase insulin receptor substrate (IRS) expression, a key component of IGF action. We hypothesised that loss of ER would result in reduced IGF signalling and growth. To test this hypothesis we examined the IGF system in a series of MCF-7 breast cancer cells that have been selected for loss of ER (C4 cells low to moderate levels of ER and C4-12 cells ER-negative). MCF-7 cells had high levels of IGFR1 and IRS-1 protein expression that was inducible by oestrogen. C4 and C4-12 cells had reduced IGFR1 and IRS-1 expression that was no longer inducible by oestrogen both at the protein and mRNA levels. However, C4 and C4-12 cells showed no decrease in IRS-1 (1.1 Kb) or IGFR1 (1.5 Kb) promoter activity. We next examined whether the loss of IGFR1 and IRS-1 resulted in a reduced response to IGF in these cells. IGF-I stimulation of MCF-7 cells resulted in tyrosine phosphorylation of IRS-1 and activation of the extracellular signal-regulated kinase (ERK1/2). C4 and C4-12 cells stimulated with IGF-I showed reduced IRS-1 phosphorylation and dramatically reduced ERK1/2 activation. MCF-7 cells were growth stimulated to the same extent by both IGF-I and oestrogen, and addition of both mitogens resulted in growth that was greater than either ligand alone. C4 and C4-12 cells failed to show any growth response to either IGF or oestrogen. Re-expression of ER in C4-12 cells, by stable transfection of an HA-tagged ER construct, resulted in restoration of oestrogen-induction of IGFR1 and IRS-1 expression. Furthermore, the ER-positive C4-12 cells now responded mitotically to both IGF-I and oestradiol. We summarise that ER is a critical component for IGF action in breast cancer, and that loss of ER results in the loss of expression of key IGF signalling molecules that results in reduced IGF signalling and failure to respond mitotically to IGFs.

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A *BRCA*-negative breast and ovarian cancer lineage with unexplained reversible repetitive spontaneous abortion

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1. Case report

A lineage is described in which a grandfather, an only child, survived breast cancer at age 59 years and died 6 years later of a 'generalised abdominal cancer'. His only daughter had breast cancer at 48 years of age and thyroid cancer at 63 years of age. She previously had 11 consecutive spontaneous miscarriages, one of which was in the second trimester. During the twelfth pregnancy (G12), this lady was then prescribed prophylactic ethinöestrol 500 mg/day and allylestrenol, starting in the fourth week. She gained 25 kg during the pregnancy and gave birth to a daughter of 2.5 kg, 1 month before term. Another daughter was born 2 years later after an unmedicated thirteenth and last pregnancy. Both daughters developed ovarian carcinoma, the oldest at age 33 years and the youngest at 15 years. The deceased daughter had two healthy boys. The *BRCA1* and *BRCA2* mutation screening in this family was negative. Out of a total of 5 persons in 3 generations in the mother's lineage, there were 5 (possibly 6) reported cancers in 4 persons. The paternal family of the ovarian cancer cases was unremarkable in this respect. No information on abortion frequency among other members of both families is available.

2. Discussion

In the absence of *BRCA* gene mutation, another breast and ovarian cancer oncogenic abnormality must be suspected. The multiple spontaneous abortions of the mother and possibly the consistently small sizes of the families in her lineage raise the possibility that the genetic abnormality is in fact onco-developmental. This would be consistent with the observation of both fetal wastage and cancer as the phenotypical behaviour of *BRCA* mutations in experimental animals. The successful outcome of the twelfth pregnancy raises the possibility that sex hormone treatment palliated some abortigenic defect. If so, one would additionally have to postulate that this palliation lasted into the unmedicated next pregnancy.

The authors invite colleagues to contact them if they have unpublished observations compatible with a spontaneous abortion-cancer syndrome and/or apparent efficacy of antenatal sex steroids to prevent spontaneous abortion.

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