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The composition of mammary gland stroma regulates tumour cell invasion

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Keywords

invasion, involution, mammary, stroma, tumour cell

Introduction

In vitro studies have suggested that epithelial-stromal interactions may be important in tumour progression. However, the exact nature of the changes that take place in the stroma to facilitate tumour cell invasion *in vivo* have yet to be determined.

Aims

To compare the effects of ECM isolated from nulliparous and postlactational involuting rat mammary glands on human tumour cell motility and invasion *in vitro*.

Comments

The concept that the unit of function with respect to the normal and malignant mammary gland should include both the epithelial and stromal components is a good one. The authors propose here that tissue remodeling causes a break in the stromal barriers that suppress tumour cell invasion. However, the situation is complex with not just matrix degrading enzymes and breakdown products of the extracellular matrix (ECM) to consider but a whole array of both stromal and epithelial growth factors. Since the protein concentration in the involuting mammary gland (MG) extract was five times higher than in the nulliparous MG ECM it is possible that it is the difference in the concentration and not the composition of active components that stimulates increased cell motility. Further experiments using a variety of candidate chemoattractant growth factors as well as their specific neutralising antibodies in Boyden chamber assays could prove interesting.

Methods

ECM was isolated by high salt extraction from six frozen MG pairs per group of rats. Effects of extracted ECM were tested on three human breast cancer cell lines, MCF-7 (the highly metastic MDA-MB-435 derived line), C-100 and H1-177 (MDA-MB-435 cells transfected with the metastasis supressor gene, *nm23-H1*). Cell motility was measured in Boyden chambers containing filters precoated with MG extract, Engelbroth-Holm-Swarm (EHS) murine tumour matrix or fibronectin. For invasion assays the 8 μm filter pores were occluded with 200 μl of each matrix. Cells were also plated on to a thick matrix composed of 1:2 MG extract to EHS matrix for 3-dimensional structure analysis. Zymography, immunoblotting and RNase protection assays were also carried out on MG extracts.

Results

MCF-7 and H1-177 cells showed low levels of motility. The highly metastatic C-100 cells displayed low motility through filters coated with ECM from nulliparous rats but their motility was enhanced 10-fold through ECM from involuting MG as well as EHS. Similar results were obtained using invasion assay. In 3-dimensional culture assays, C-100 cells overlaid on EHS and involuting MG ECM formed 'organoids' and duct-like structures with growth cones of cells disseminating into the matrix, whereas those grown on nulliparous MG ECM formed 2-dimensional sheets. Zymography showed elevated levels of gelatinase activity in involuting MG matrix compared with nulliparous and mid-pregnant rat MG extracts. The MMP inhibitor GW9471 inhibited C-100 cell invasion. Western blotting demonstrated lower levels of fibronectin in involuting ECM with a high degree of fragmentation. Similarly, lower RNA levels showed that less fibronectin was being synthesised in the postlactational state. C-100 cell motility and invasion were also found to be inhibited by intact fibronectin but enhanced by fibronectin fragments.

Discussion

It has been shown that certain physiological changes that take place in the mammary gland stroma during involution are similar to those that occur during malignancy. These include enzyme degradation of the ECM, loss of cell adhesion, breakdown of the basement membrane and release of growth factors. Unlike normal cells, malignant cells appear to be resistant to the apoptosis which occurs during tissue remodeling and thus these conditions may facilitate tumour cell dissemination and invasion. However, results with the MCF-7 cell line which did not exhibit significant invasive potential with any of the matrices tested, suggests that this altered environment may be permissive but not instructive. A dual effect of pregnancy on breast cancer risk was therefore considered.

References

1. Bemis LT, Schedin P: Reproductive state of rat mammary gland stroma modulates human breast cancer cell migration and invasion. Cancer Res. 2000, 60: 3414-3418.