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Investigating the Functional Significance of Aberrant αvβ6 and Fibronectin Expression in Myoepithelial Cells: Role in the Progression of DCIS?

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Background

Ductal carcinoma *in-situ* (DCIS) is a direct precursor of many invasive breast cancers, however, it is estimated that DCIS will progress in only 50% of cases, which has led to concerns regarding over-treatment. Thus, there is an urgent clinical need to determine which cases will progress and better stratify management.

Genomic studies have indicated that DCIS tumour cells are as genetically advanced as invasive disease, with no specific stepwise changes identified. However, these studies ignored the breast microenvironment, which is complex, comprising the myoepithelial cell (MEC) population and the stroma. In the normal breast MECs exert tumour suppressive functions. In DCIS, MECs are altered, and this may compromise MEC function and contribute to progression.

We previously have shown de-novo expression of αvβ6 in DCIS-associated MECs and up-regulation of Fibronectin. This study aims to evaluate the functional relevance of these changes.

Methods

Established MEC cell lines positive and negative for αvβ6, and primary MECs were used to assess the relationship between αvβ6 and FN expression, and the role of FN in αvβ6-mediated TGF-β signalling using 2D and 3D model systems, invasion assays and siRNA.

Results

β6-positive MECs exhibit higher levels of FN expression at mRNA and protein level compared to β6-negative MECs. Knockdown of either β6-integrin or FN in β6-positive MECs significantly reduced TGF-β signalling, TGF-β-mediated MMP-9 expression and invasion.

Conclusion

Expression of both αvβ6 and FN by MECs is required to generate enhanced TGF-β signalling, which mediates MMP-9 dependent tumour cell invasion. These changes could contribute to a progression signature to facilitate improved stratification of DCIS patients.

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