MICROENVIRONMENT

A dense danger

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The stromal microenvironment of a tumour shows characteristic alterations, such as desmoplasia (increased deposition of extracellular matrix (ECM)) and decreased lipid storage. Similar changes are also seen in mammographically dense normal breast tissue, which is a risk factor for future breast cancer development. Thus, these stromal alterations may have a role in both the initiation and the progression of breast cancer. A new study has shown that CD36 is causally involved in suppressing the stromal remodelling that accompanies tumorigenesis.

Thea Tlsty and colleagues derived stromal fibroblasts from invasive breast carcinoma samples and from normal breast tissue of high or low mammographic density. The differential ECM deposition and lipid accumulation between tumour and normal stroma — and between normal tissues of high and low mammographic density — was partially recapitulated in culture. This provided an experimentally tractable system for investigating the molecular changes.

Gene expression analysis in these cultured fibroblasts and in cancerous versus normal breast tissue samples identified downregulation of the cell surface molecule CD36 as the most significant change associated with stromal remodelling. Furthermore, immunohistochemical analyses of breast tissue sections showed that CD36 was downregulated in various cell types in cancer stroma and in high-mammographic-density stroma compared with normal, low-mammographic-density stroma. The stromal cells with reduced CD36 expression included adipocytes, endothelial cells and macrophages, which is consistent with multiple putative functions for

CD36, such as in lipid metabolism, cell migration, angiogenesis and phagocytosis.

In normal breast fibroblasts, knockdown and overexpression of CD36 affected ECM deposition and lipid accumulation. Furthermore, these processes were also modified in the normal mammary stroma of *Cd36*-knockout mice relative to wild-type controls. The authors also mined clinically annotated human gene expression data sets, and discovered that stromal CD36 downregulation in breast cancer samples correlated with increased tumour size and grade.

In addition to the specific molecular phenotypes described in this study, a detailed characterization of the effect of CD36 manipulation on tumour incidence and progression in animal models is required to better understand the function of CD36 in the stroma. Finally, it will be interesting to see whether enhancing stromal CD36 expression could be a preventive or therapeutic strategy in breast cancer, and whether CD36 expression levels provide superior diagnostic information to that of the macroscopic detection of stromal remodelling.

Darren J. Burgess

ORIGINAL RESEARCH PAPER Defilippis, R. A. *et al.* CD36 repression activates a multicellular stromal program shared by high mammographic density and tumor tissues. *Cancer Discov.* 9 Jul 2012 (doi:10.1158/2159-8290.CD-12-0107)