Published in final edited form as:

Nature. 2012 October 25; 490(7421): 490–491. doi:10.1038/490490a.

Destiny from density

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Abstract

The identification of a signalling protein that regulates the accumulation of fat and connective tissue in breasts may help to explain why high mammographic density is linked to breast-cancer risk and may provide a marker for predicting this risk.

Our ability to evaluate the lifetime risk of breast cancer in women who have a family history of breast and ovarian cancer was revolutionized by the identification¹ of the breast-cancer-associated genes *BRCA1* and *BRCA2*. But although this was a landmark discovery, it has not translated into improvements in the assessment of breast-cancer risk in the general population², because more than 95% of women who develop breast cancer do not have a *BRCA*-gene mutation³. So the search for biomarkers to predict the risk in these women remains a goal for many biologists, clinicians and epidemiologists.

Over the past decade, increased mammographic density — thought to result primarily from an increased proportion of breast collagen content relative to fat-tissue content^{4,5} — has emerged as a non-genetic marker of breast-cancer risk⁶. However, the biological mechanism that relates tissue density to tumour development is poorly defined. Writing in *Cancer Discovery*, DeFilippis *et al.*⁷ now provide a link between mammographic density and cellular signalling during the initiation of breast cancer.

The human breast is composed of many cell types, including connective-tissue (stromal) cells, fat cells (adipocytes), cells that make up blood vessels (endothelial cells) and immune cells. Collectively, these cells make up the microenvironment of the breast⁸. Over the past five years, it has been increasingly recognized that this microenvironment, including the relative proportions of different types of cell and therefore the tissue density, may have a major role in the initiation and progression of breast cancer^{9,10}. One indication of this role is the epidemiological link between mammographic density and cancer risk: Caucasian women with high mammographic density have a two- to sixfold increase in life-time risk of developing breast cancer⁶. Another indication is the physical change in the breast micro environment that is seen in the initial stages of breast-tumour formation. This is described as a ‘desmoplastic’ reaction, which is characterized by the recruitment and activation of stromal cells and results in increased collagen deposition in the breast — and therefore increased mammographic density¹¹.

The increased density is measured by a general increase in X-ray absorbance and is therefore relatively inexpensive and easy to measure. But we have little understanding of what determines increased density and how this is linked to increased cancer risk and the initiation of tumour formation^{4,6}. The situation is complicated by the complex relationships between mammographic density, breast-cancer risk, ageing, obesity and race. For example, mammographic density typically declines with age¹², but, because breast cancer is an age-related disease, this means, paradoxically, that a woman’s breast-cancer risk will increase with age while her mammographic density declines.

DeFilippis and colleagues have helped to unravel this story by revealing that expression of a single molecule, CD36, is necessary and sufficient to regulate two key features of mammographic density: the number of adipocytes in the breast and the amount of collagen deposited in the breast tissue. The authors show that expression of CD36 is lower in breast-tissue cells of women with high mammographic density — in women with or without breast cancer — than in cells from breasts with normal density. CD36 is an integral membrane protein found in many cell types, and it is already known to regulate several basic cellular processes governing how cells interact and grow, including the differentiation of adipocytes, the growth of new blood vessels (angiogenesis) and immune signalling¹³. Now it seems that an influence on mammographic density can be added to this list.

To establish how CD36 expression exerts its effects on breast-tissue density, the authors modulated CD36 expression *in vitro* in cells taken from healthy human breast tissue. They found that reducing CD36 expression led to a decrease in the total number of fat cells and an increase in the amount of collagen deposited in the extracellular matrix around the cells; higher CD36 expression increased the number of fat cells. The researchers also observed lower fat accumulation and greater collagen accumulation in the mammary glands of mice lacking the *Cd36* gene. These findings indicate that inhibition of this protein is sufficient to recapitulate some of the key events that lead to higher mammographic density and initiation of breast cancer.

Not only do these findings provide a mechanistic link between cell-signalling pathways and mammographic density, they are also a convincing indication that loss of CD36 may be an early event in breast carcinogenesis. Although mammographic density is used as a surrogate marker of breast-cancer risk in the general population, it is an imprecise indicator. It gives little insight into the biology of why a woman might develop breast cancer, and it is confounded by paradoxes, such as the increase in density but decrease in risk if a woman exercises, or the decrease in density but increase in risk as a woman ages. By demonstrating that CD36 links the biology of breast density with the biology of breast-cancer initiation, DeFilippis and colleagues have identified information that may help to make density a more useful marker of risk. Finally, their results also raise the possibility that CD36 could be pharmacologically targeted in attempts to prevent breast cancer in the majority of women who (fortunately) lack a *BRCA* mutation.

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Figure 1. Regulating the breast microenvironment

The main tissue types in human breasts are adipose (fat) tissue and stromal (connective) tissue, which contains collagen. The ratio of fat to collagen determines the mammographic density of the breast, with density increasing as the relative amount of fat tissue falls. High mammographic density is a known risk factor for breast cancer, and mammographic density also increases as a breast tumour forms. DeFilippis et al.⁷ have found that expression of the cell-signalling protein CD36 is lower in several types of cell taken from breasts that have high mammographic density, both in the presence or absence of cancer. They also show that reduced CD36 expression leads to increased collagen deposition and decreased fat accumulation in the breast.