IN THE SPOTLIGHT

# Desmoplasia: A Response or a Niche?

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**Summary:** Desmoplasia—the presence of a rich stroma around a tumor—has long been associated with a poor clinical outcome in patients with cancer. It is considered to be a response to the presence of invasive tumor cells. There is now evidence that desmoplasia is the result of coordinated changes in several stromal cells under the control of a single gene product, CD36, whose repression leads to a decrease in fat accumulation and an increase in matrix deposition. The presence of these changes in tumor-free human breast tissue strongly suggests that desmoplasia may precede and not always follow the presence of malignant cells. This concept has an important clinical implication for women at high risk of developing breast carcinoma, considering that the presence of desmoplasia in normal breast tissue detected in the form of mammographic density is one of the strongest risk factors. *Cancer Discov; 2(9); 772–4. ©2012 AACR.*

*Commentary on DeFilippis et al., p. 826 (7).*

The term desmoplasia (from the Greek word desmos, *to fetter or restrain*; and plasis, *formation*), has been used by pathologists for more than a century in reference to the formation of excessive connective tissue around invasive carcinoma, primarily but not exclusively of the breast (1). Desmoplastic tissues are characterized by alterations of the tumor stroma that can range from an abundance of cellular elements such as fibroblasts, vascular cells, and immune cells with little extracellular matrix (ECM) to the presence of an abundant collagen-rich ECM with a minimum of cells, mainly fibroblasts and myofibroblasts. Initially considered to represent a condensation of preexisting collagen fibers, desmoplasia in fact is the result of an increased synthesis of ECM proteins and collagen by stromal cells such as myofibroblasts (2). The presence of desmoplasia in aggressive tumors was counterintuitive, in view of the fact that a dense ECM represents a barrier against cancer invasion and metastasis. It was therefore considered to be a reaction and response of the host tissue against invasive cancer cells, and accordingly designated "desmoplastic response or reaction."

This idea, however, was challenged in the late 1980s, when the presence of desmoplastic tissue in normal breast became noticeable on mammography studies carried out on women screened for risk of breast cancer. Desmoplastic tissues were radiographically detected as areas denser than the fat and designated mammographic densities (3–5). High mammographic density is one of the strongest risk factors for breast cancer development and is associated with common breast cancer susceptibility variants (6).

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The discovery that desmoplastic lesions can be present in the absence of tumor cells suggests that desmoplasia may not be—as initially thought—a reaction to invasive malignant cells, but a preexisting condition favoring the development of a malignancy. However, there has not been any solid explanation in support of this possibility.

In this issue of *Cancer Discovery*, DeFilippis and colleagues (7) provide some clues to this interesting question. Having isolated and propagated fibroblasts from disease-free breast biopsies conducted in women with low (25%–50%) mammographic density and high (>75%) mammographic density, these investigators initially observed that when these cells were grown *in vitro* in conditions that promoted adipocytic differentiation, fibroblasts from biopsies with high mammographic density accumulated significantly less fat than fibroblasts from biopsies with low mammographic density. This observation led them to examine the expression of CD36 (also known as fatty acid translocase), a membrane protein involved in the transport of long-chain fatty acids (8). Not unexpectedly, they found a decreased expression of CD36 in fibroblasts from breast biopsies with high mammographic density. Alterations in lipid transport, however, were not the only changes observed in these CD36 low fibroblasts. They synthesized a greater amount of interstitial collagen (type 1), fibronectin, and osteopontin. Interestingly enough, they found that fibroblasts isolated from invasive cancer tissues (carcinoma-associated fibroblasts) had the same metabolic phenotype as fibroblasts isolated from normal breast with high mammographic density characterized by a low expression of CD36, a deficiency in fat accumulation, and an increase in ECM synthesis. Supporting the relevance of these *in vitro* observations to human breast cancer, the authors mined 6 independent public gene expression data sets and found a decrease in CD36 mRNA expression in invasive ductal carcinoma tissues compared with normal tissue. The data were then confirmed by showing a decrease in CD36 protein expression in biopsies of cancer-free breast with high mammographic density and in tumor sections from women with triple-negative breast cancer. Importantly, they observed that

suppression of CD36 expression was not restricted to fibroblasts but included adipocytes, macrophages, and endothelial cells. Correlation, however, does not mean cause–effect. To address this aspect, the authors went on using gain and loss of function in cultured cells and studies in CD36 KO mice to show that this single gene product controls adipogenesis and ECM deposition and is sufficient and necessary to produce in the stroma of the mammary gland the 2 phenotypic changes characteristic of mammographic density. For example, they report a significant decrease in fat accumulation and increase in collagen and fibronectin deposition in the mammary glands of CD36 KO mice when compared with WT mice.

There are 2 novel and intriguing observations in this article. First is the observation that repression of CD36 was seen not only in the stroma adjacent to and associated with an invasive ductal carcinoma but also in the stroma of breast tissue with high percentage of mammographic density in the absence of any detectable malignant cells. This suggests that the development of a desmoplastic stroma by suppression of CD36 may not be a reactive response to the presence of tumor cells but may represent a change that predates the development of a malignancy. The concept that phenotypic changes in the microenvironment can influence and even dominate genotypic changes in malignant cells was first proposed by Weaver and Bissell (9) when they showed reversion of the malignant phenotype of human breast cancer cells in 3-dimensional culture and *in vivo* by integrin-blocking antibodies. This concept was later expanded by Kaplan, Rafii, and Lyden (10), who showed that phenotypic changes in the lungs of mice characterized by an increase in fibronectin deposition and clustering of bone marrow–derived cells precede and are indispensable for the initial stages of metastasis, in the process of premetastatic niche formation. Here the authors bring the concept further by providing data suggesting that phenotypic changes in the microenvironment can precede malignant transformation. The critical question that is, however, still not answered is whether such changes are actively involved in tumor initiation and progression. There is evidence that this may in fact be the case. Other investigators have shown that transgenic mice prone to develop mammary tumors (MMTV-PyMT) crossed with mice overexpressing collagen (Col1a1) have an increased incidence of tumor formation and develop more aggressive tumors with increased angiogenesis and metastasis (11) and that mice deficient in adiponectin synthesis (*Apn* null) have tumors that grow more aggressively (12). Whether the loss of CD36 expression in mice crossed with breast cancer–prone transgenic mice will have a similar effect is presently not known. It is also not known whether CD36 KO mice would develop mammary tumors over time in the absence of any other event.

A second novel finding in the report of DeFilippis and colleagues (7) is that repression of CD36 in desmoplastic tissue was not restricted to fibroblasts but was also observed in other stromal cells of mesenchymal (adipocytes) and hematopoietic (endothelial, macrophages) origin. This suggests that the origin of this repressive event is in poorly differentiated or multipotent stem cells present in the mammary tissue. What triggers such change in these cells can only be speculated at the present time.

Finally, the observations made by DeFilippis and colleagues (7) raise interesting questions on the mechanism by which a desmoplastic stroma would promote cancer formation. The increase in collagen and fibronectin accumulation is logical in the context of the work of Levental and Weaver and colleagues (13) who have shown that the presence of a "stiff" collagen-rich matrix initiates signals through mechanosensors that affect the expression of genes involved in differentiation and malignancy. It is also consistent in the context of the premetastatic niche in which fibronectin deposition has been shown to precede the homing of circulating tumor cells. The decrease in fat accumulation may be counterintuitive, however, considering the recent evidence that adipocytes can have protumorigenic activity and that obesity is a factor of poor prognosis in cancer (14). This aspect deserves further investigation.

The last aspect that DeFilippis and colleagues (7) raise is whether our ability to control and reexpress CD36 in the breast stroma could prevent the occurrence of cancer. We could envision that such ability would be of benefit for cancer-free women with a high percentage of mammographic density. As pointed out by the authors, the expression of CD36 can be increased by agents such as aspirin, dexamethasone, statins, or the fully human anti–TNF-α antibody adalimumab *in vitro* and by tamoxifen *in vivo*. The testing of one (or several) of these agents in clinical studies would be of interest, but would require the identification of an agent devoid of significant toxicity when chronically administered over years, and the availability of a reliable model to test such a hypothesis in a preclinical setting. CD36 KO mice may provide such a tool.

In summary, the paper by DeFilippis and colleagues (7) brings the concept that the microenvironment can play a dominant role in cancer to the next level by showing that phenotypic changes in multiple stromal cells under a single regulatory protein can precede the appearance of tumor cells. Clearly, desmoplasia is not just a response to the presence of invasive tumor cells. It also creates a niche for cancer cells.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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