# Scientists identify 'gatekeepers' of breast cancer transition to invasive disease

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Scientists have made a significant discovery that clarifies a previously poorly understood key event in the progression of breast cancer. The research, published by Cell Press in the May issue of the journal *Cancer Cell*, highlights the importance of the microenvironment in regulating breast tumor progression and suggests that it may be highly beneficial to consider therapies that do not focus solely on the tumor cells but are also targeted to the surrounding tissues.

Progression of breast cancer begins with abnormal epithelial proliferation that progresses into localized carcinoma, called ductal carcinoma in situ (DCIS); invasive carcinoma; and eventually, metastatic disease.

DCIS is believed to be a precursor to invasive ductal carcinoma, but comprehensive molecular profiling studies comparing DCIS and invasive ductal carcinomas have not yielded tumor-stage-specific genetic signatures. “These studies have focused mainly on the tumor epithelial cells and have not explored the role of the microenvironment in tumor expression,” says lead study author Dr. Kornelia Polyak from the Dana-Farber Cancer Institute in Boston.

Dr. Polyak and colleagues explored the involvement of the microenvironment in tumor progression by examining myoepithelial cells, which are known to play a critical role in mammary gland development and to have negative effects on tumor cell growth and invasion. To study the interactions between breast cancer cells and

myoepithelial cells, the researchers used a human model of breast tumor progression called MCFDCIS, which forms DCIS-like lesions that spontaneously progress to invasive tumors, a pathology that closely resembles human disease.

Using this model, the researchers observed that normal myoepithelial cells suppress tumor growth and invasion in the absence of detectable genetic changes in the tumor epithelial cells. They went on to identify an intricate network involving TGFb, Hedgehog, cell adhesion, and p63 that appears to play a critical role in myoepithelial cell differentiation. Perturbation of key mediators of these signaling pathways led to a loss of myoepithelial cells and a progression to invasion.

“Here, we show that a key event of tumor progression is the disappearance of the myoepithelial cell layer due to defective myoepithelial cell differentiation regulated by intrinsic and microenvironment signals. Thus, myoepithelial cells can be considered gatekeepers of the in situ to invasive carcinoma transition; understanding the pathways that regulate their differentiation may open new venues for cancer therapy and prevention,” offers Dr. Polyak.

Source: Cell Press