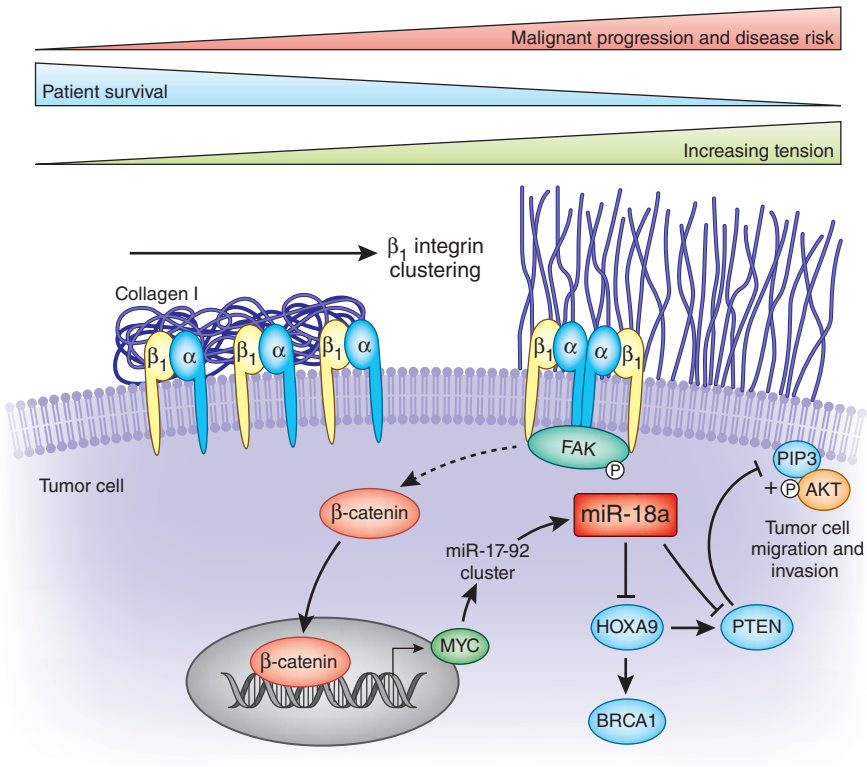

Katie Vicari

Figure 1 ECM-generated mechanical force drives an miRNA circuit that promotes malignancy in preclinical models and predicts distal relapse-free survival (DRFS) in luminal breast cancer. Increased ECM stiffness promotes β1 integrin clustering, transcriptionally activates MYC and induces the polycistronic miR-17-92 cluster. This results in the upregulation of a particular miRNA, miR-18a, which, in turn, reduces expression of PTEN and HOXA9. Low PTEN increases signaling through the phosphoinositide 3-kinase (PIP3)–AKT pathway, promoting invasion and metastasis. Increased ECM-generated mechanical force can therefore regulate the expression of PTEN, HOXA9 and also BRCA1 via a miR-18a–dependent signaling network. FAK, focal adhesion kinase.

is prevented[6], this suggests functional links between miRNA expression and ECM mechanosignaling during cancer progression. The authors now delineated how miR-18a fosters tumor progression by showing that its induction by increased matrix stiffness upon integrin engagement results in reduced amounts of the tumor suppressor PTEN (protein and mRNA). Because PTEN is frequently lost in aggressive breast cancers[14], these studies identify how ECM collagen stiffness can trigger the aggressive biology of breast cancers.

Using human mammary epithelial cells grown on a stiff substrate and in stiff mouse mammary gland tissue, Mouw *et al.*[7] found that miR-18a expression decreases expression of PTEN both directly and indirectly through the targeting of the homeobox-A gene *HOXA9* (**Fig. 1**). HOXA9, a known regulator of mammary gland homeostasis and mammary tissue regeneration during the menstrual cycle and pregnancy, is frequently lost in aggressive breast cancers[14]. The authors further demonstrated that direct binding of the HOXA9 DNA-binding domain to the *PTEN* promoter is required for gene expression, which is relevant, as lack of *HOXA9* expression has been shown to also lead to loss of *BRCA1* expression[14]. These data provide a molecular link between ECM mechanosignaling and the epigenetic loss of *BRCA1* expression.

Because loss of PTEN and HOXA9 predicts aggressive biology, the mechanosignaling-regulating expression of miR-18a and downstream PTEN and HOXA9 suggests expression of miR-18 could stratify human breast cancers for risk. The clinical relevance of ECM stiffness–induced miR-18a and PTEN repression was investigated by assessing abundance of HOXA9 and PTEN in breast cancer subtypes and in normal tissue[7]. Basal-type breast cancer is the clinically most aggressive subtype of breast cancer; accordingly, ECM stiffness and miR-18a expression was the highest in these cancers, and PTEN and HOXA9 mRNA expression lowest. Mouw *et al.*[7] used publicly available gene expression data sets to test for associations between miR-18a and clinical outcome in all breast cancer subtypes. High miR-18a expression at initial diagnosis was associated with shorter time to distant relapse-free survival, and miR-18a expression was significantly predictive of future disease progression for women with luminal breast cancers (but not basal-type breast cancers).

This study has some limitations and uncovers important future directions. Biomarkers are needed to predict risk for all cancers; the finding that miR-18a can stratify luminal breast cancer risk provides the groundwork to identify women who may need aggressive chemotherapy regimens and, conversely, spare those with relatively indolent disease from unnecessary chemotherapy. The investigators found that miR-18a expression predicted prognosis in luminal breast cancers but not in the basal-like subtype of triple-negative breast cancers[7]. Dysregulation of PTEN and HOXA9 signaling seems to be crucial in the pathogenesis of basal-like breast cancers[13,14]; thus, it would be expected that as miR-18a caused the loss of these two proteins, its expression would predict disease outcome in women with this type of tumor. However, this may not have been observed because the overall prognosis for established basal-like breast cancer, in which miR-18a expression was highest, is poor. The potential of this work may lie in testing whether miR-18a expression can serve as an early-detection and early-risk marker for basal-type breast cancer. Future studies may provide a more precise tool to assess the complex contribution of ECM collagen to the molecular circuitry governing breast cancer risk and aggressive biology.

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The author declares no competing financial interests.

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Erratum: ECM stiffness paves the way for tumor cells

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In the version of this article initially published, the figure showed blocking arrows from HOXA9 to BRCA1 and PTEN, but these should have been regular arrows. PIP3 and AKT should have been located close to the membrane, instead of the cytoplasm. Integrin proteins should have been heterodimers rather than homodimers, and the protein β-catenin should not have had a phosphorylated residue. The errors have been corrected in the HTML and PDF versions of the article.