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PUMA pathway is a weak link in breast cancer metastasis

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Substantial advancements have improved the success of chemotherapy, radiation, and surgical treatments for primary breast cancers. However, breast cancer that has spread, or metastasized, to other parts of the body remains a challenge to cure. It is difficult to predict whether a tumor will recur and metastasize, and uncertainty can lead to inadequate or overaggressive treatment.

The cells that initiate metastasis often resemble mammary stem cells, a population of healthy cells that enable mammary gland development during adulthood. During pregnancy, hormonal signaling activates healthy stem cells, which initiate mammary gland remodeling that supports breast milk production. Now, a new study from Jay Desgrosellier's lab at UCSD has used the activation signature of mammary stem cells to identify vulnerabilities in stem-like metastasis-initiating cells.

In a study published this week in the *JCI*, Sun et al. report that low-level expression of a protein called PUMA (p53-upregulated modulator of apoptosis) distinguishes stem-like cells in cancer patients who experienced tumor recurrence during a 10-year follow-up period. The cells' ability to suppress PUMA levels was critical to their survival-enhancing PUMA expression selectively depleted stem-like properties and reduced metastasis, whereas reducing PUMA restored metastasis in cultured cells.

Together, these findings expose a possible Achilles heel in aggressive

breast cancers that may enable earlier identification and better targeting of metastases. Present limitations in the ability to predict and eliminate aggressive cancer cells likely contribute to the majority of deaths from metastatic breast cancer, but the development of adjuvant approaches that exploit their weaknesses may greatly improve disease outcomes.

More information: Qi Sun et al, Proapoptotic PUMA targets stem-like breast cancer cells to suppress metastasis, *Journal of Clinical Investigation* (2017). DOI: 10.1172/JCI93707