Integrin alpha V beta 3 expression in luminal breast cancer cells promotes their reversion to acinar-like structure in conjunction with their relevant microenvironment.

[1]Hanan Abu-Tayeh, [1]Keren Weidenfeld, [1]Alisa Zhilin-Roth, [1]Sagi Schif-Zuck, [2]Sonja Thaler, [3]Cristina Cotarelo, [4]Tuan Zea Tan, [5,6] Jean Paul Thiery, [7]Jeffrey E. Green, [8]Geula Klorin, [8]Edmond Sabo [2,9] Jonathan P. Sleeman and [1]Dalit Barkan.

[1]Department of Human Biology, University of Haifa. Haifa, Israel. [2]Karlsruhe Institute of Technology (KIT), Campus Nord, Institut für Toxikologie und Genetik, Karlsruhe, Germany.[3]Department of Pathology, University Medical Center Mainz, Langenbeckstr, Mainz, Germany.[4]Cancer Science Institute of Singapore, National University of Singapore.[5]Department of Biochemistry, Yong Loo Lin School of Medicine, National University of Singapore.[6]Institute of Molecular and Cell Biology, A*STAR, Singapore.[7]Laboratory of Cancer Biology and Genetics, National Cancer Institute, Bethesda, MD, USA. [8]Department of Pathology, Rambam Medical Center, Israel.[9]Medical Faculty Mannheim, Centre for Biomedicine and Medical Technology Mannheim (CBTM), University of Heidelberg, Mannheim, Germany.

Re-establishing tissue organization of breast cancer cells into acini was shown previously to override their malignant phenotype. Here we demonstrate that expression of Integrin αvβ3 (Int- αvβ3) in luminal A breast cancer cell lines can revert them back to a normal-like acini when cultured in their relevant physiological microenvironment. This reversion promoted their growth arrest and was mediated by Int-αvβ3 expression and activation on cancer luminal progenitor like cells (CLPC). Furthermore, this reversion was mediated by donwregulation of NOTCH-4 expression and downstream signaling. Intriguingly, the reverted acini resembled pre-neoplastic stage of breast tissue; likewise Int-αvβ3 expression was mostly detected in a benign stage of the human breast tissues.

Hence, all together these data propose a novel strategy to normalize the malignant phenotype by reprogramming CLPC to differentiate via the expression of Int-αVβ3.

Significance: Recurrence beyond 10-year survival is the principal cause of mortality of luminal A breast cancer patients that no longer respond well to conventional therapies. Given that these cancers are enriched with CLPC makes them good candidates for differentiation therapy by which reprogramming of CLPC to differentiate to a more benign state may be achieved by promoting downstream signaling that emanate from Int-αVβ3. Therefore, promoting such differentiation may be utilized to combat recurring breast cancers thus keeping them on halt.