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Identification of a new prognostic signatures and therapeutic targets for HER2+ and triple negative breast cancer using subtype-specific mouse models

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HER2$^+$ and Triple-Negative Breast Cancers (TNBC) represent highly aggressive subtypes. HER2+ BC is commonly treated with chemotherapy plus anti-HER2 drugs, such as Herceptin. Drug resistance, high cost and side effects limit the use and benefits of anti-HER2-therapy worldwide. There is therefore great interest in an effective prognostic predictor and novel therapeutic targets for HER2$^+$ breast cancer. We identified MMTV-Her2/Neu mammary tumor-initiating cells (TICs) and showed that non-adherent tumorspheres can be used as surrogate for TICs (Can Res. 2007, Clin Can Res. 2009). Using improved conditions, we have further enriched Her2/Neu TICs to a frequency of 1/20-1/40. A 17-gene TIC-specific signature derived from differentially expressed genes in TICs versus non-TICs predicts survival in multiple human HER2$^+$ BC cohorts with hazard ratios of over 8, and can be used to stratify HER2$^+$ patients for anti-HER2 therapy (submitted). Using a lentiviral shRNA screen, we also identified several kinases required for Her2/Neu tumorsphere growth, for which no previous requirement for their function in HER2$^+$ BC has been described (in progress).

TNBCs often contain loss-of-function mutations/alterations in the tumor suppressors RB1, p53 and Pten. We showed that conditional deletion of Rb in mammary stem cells/bipotent progenitors led to tumors that clustered with luminal-B or TNBC. The latter contained mutations in p53. Combined deletions of Rb and p53 led exclusively to TNBC (J. Clin Invest. 2010, Cell Cycle, 2011). Similarly, inactivation of Pten in mammary epithelium induced diverse tumor types, whereas combined deletion of Pten and p53 led to TNBC-like tumors (in progress). Drug and shRNA screens have identified several agents/targets that specifically kill Rb/p53, Pten/p53 mutant TNBC as well as human TNBC lines but not immortalized mammary epithelial cells (in progress).

Biography

Dr. Eldad Zacksenhaus earned his PhD at the University of Toronto in Molecular Genetics on the cloning of UBE1, and postdoctoral training at the Hospital for Sick Children on the tumor suppressor RB. He is senior scientist at University Health Network and Associate Professor of Medicine, University of Toronto. His research is focused on tumor suppressors, in particularly Rb, breast cancer, cancer stem cells and targeted therapy for HER2 and TNBC (JCI, 2010, JCB, 2010, Cancer Res. 2010, Autophagy, 2011, PLoS One, 2011, Cell Cycle 2011). He's a co-organized of the "International RB Symposium" Nov. 17-18, 2011, Toronto, Canada.