Abstract SY08-02: Gene regulatory network models identify targets for mammary tumor normalization

Amy Brock¹

Author Affiliations
Proceedings: AACR 103rd Annual Meeting 2012-- Mar 31-Apr 4, 2012; Chicago, IL

Abstract

The majority of breast cancer therapeutics aim at slowing tumor expansion through selective killing of tumor cells. Given the enormous plasticity of cells (highlighted by recent advances in the iPS field), we have instead sought to induce a cell state transition from a mammary tumor cell phenotype to a normal mammary epithelial cell state. We have tackled the critical problem of identifying target genes for the normalization or differentiation of mammary tumor cells by employing a systems biology approach that integrates computational modeling with in vivo and in vitro studies. In vivo gene expression data of mammary tumor progression in the FVB C3(1) SV40Tag transgenic mouse model were collected at multiple time points as the disease progressed from normal gland to DCIS-like lesions to invasive carcinoma. Gene regulatory network models predicted novel transcription factor targets that appeared critical to the rise of the tumor phenotype. These putative gene targets were then assessed in a 3D spheroid assay. RNAi inhibition of two computationally predicted transcription factors reverted mammary tumor cells to a normalized mammary epithelial cell phenotype, with appropriate apical/basal polarization, lumen formation and reduced proliferative index. Validated targets were then tested in vivo. This integrated strategy has pinpointed transcription factors for RNAi therapeutic targeting in vivo but importantly, the method is not limited to breast cancer and may be useful for many different tumor types. In summary, our major advance has been the demonstration that a gene regulatory network reverse engineering approach can identify genes that are causatively involved in cancer progression and that represent viable therapeutic differentiation targets.

Citation Format: (Authors). (Abstract title) [abstract]. In: Proceedings of the 103rd Annual Meeting of the American Association for Cancer Research; 2012 Mar 31-Apr 4; Chicago, IL. Philadelphia (PA): AACR; Cancer Res 2012;72(8 Suppl):Abstract nr SY08-02. doi:1538-7445.AM2012-SY08-02

©2012 American Association for Cancer Research