

The Canonical NF- κ B Pathway Governs Mammary Tumorigenesis in Transgenic Mice and Tumor Stem Cell Expansion ↗

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Abstract

The role of mammary epithelial cell (MEC) NF- κ B in tumor progression *in vivo* is unknown, as murine NF- κ B components and kinases either are required for murine survival or interfere with normal mammary gland development. As NF- κ B inhibitors block both tumor-associated macrophages (TAM) and MEC NF- κ B, the importance of MEC NF- κ B to tumor progression *in vivo* remained to be determined. Herein, an MEC-targeted inducible transgenic inhibitor of NF- κ B (I κ B α SR) was developed in ErbB2 mammary oncomice. Inducible suppression of NF- κ B in the adult mammary epithelium delayed the onset and number of new tumors. Within similar sized breast tumors, TAM and tumor neoangiogenesis was reduced. Coculture experiments demonstrated MEC NF- κ B enhanced TAM recruitment. Genome-wide expression and proteomic analysis showed that I κ B α SR inhibited tumor stem cell pathways. I κ B α SR inhibited breast tumor stem cell markers in transgenic tumors, reduced stem cell expansion *in vitro*, and repressed expression of Nanog and Sox2 *in vivo* and *in vitro*. MEC NF- κ B contributes to mammary tumorigenesis. As we show that NF- κ B contributes to expansion of breast tumor stem cells and heterotypic signals that enhance TAM and vasculogenesis, these processes may contribute to NF- κ B-dependent mammary tumorigenesis. *Cancer Res*; 70(24); 10464–73. ©2010 AACR.