The Canonical NF-κB 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-κB in tumor progression *in vivo* is unknown, as murine NF-κB components and kinases either are required for murine survival or interfere with normal mammary gland development. As NF-κB inhibitors block both tumor-associated macrophages (TAM) and MEC NF-κB, the importance of MEC NF-κB to tumor progression *in vivo* remained to be determined. Herein, an MEC-targeted inducible transgenic inhibitor of NF-κB (IκBαSR) was developed in ErbB2 mammary oncomice. Inducible suppression of NF-κB 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-κB enhanced TAM recruitment. Genome-wide expression and proteomic analysis showed that IκBαSR inhibited tumor stem cell pathways. IκBαSR 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-κB contributes to mammary tumorigenesis. As we show that NF-κB contributes to expansion of breast tumor stem cells and heterotypic signals that enhance TAM and vasculogenesis, these processes may contribute to NF-κB–dependent mammary tumorigenesis. *Cancer Res; 70(24); 10464–73. ©2010 AACR.*