

NF-KB: AT THE CROSSROADS OF LIFE AND DEATH IN HUMAN BREAST CANCER

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Breast cancer is a disease of aging-- both its incidence and its biology are age-dependent (Benz et al., *Int. J. Biochem. Cell Biol.*, 2002). In particular, since up to 75% of breast cancers overexpress estrogen receptor (ER, alpha isoform), these ER-positive breast cancers represent one of the most prevalent and life-threatening diseases of aging (Benz et al., *Breast Cancer Res. Treat.*, 2002). While ER-positive breast cancers are expected to respond clinically to ER-targeted endocrine therapeutics like the antiestrogen tamoxifen (TAM), 30-50% of these cases exhibit clinical resistance to these agents. This major medical problem can be addressed by identifying the clinical importance of known intracellular pathways capable of enhancing breast cancer cell survival, proliferation and/or metastatic potential. Many of the pathways known to be clinically associated with TAM resistance share a common mechanistic link with activation of the pivotal gene-regulating transcription factor complex, Nuclear Factor- κ B (NF- κ B). Activated NF- κ B complexes regulate cell survival and proliferation as well as organ development; and these complexes are also critically involved in inflammation, oxidative stress, immunity and tumorigenesis. NF- κ B function was recently found to be absolutely essential for normal mammary gland development (Cao and Karin, *J. Mammary Gland Biol. Neoplasia*, 2003), perhaps in part due to its interaction with ER. When first studied in human breast cancer cell lines and breast cancer samples, however, constitutive upregulation of NF- κ B was associated only with the development of hormone-independent (ER-negative) breast cancers (Sovak et al., *J. Clin. Invest.*, 1997; Nakshatri et al., *Mol. Cell. Biol.*, 1997; Cogswell et al., *Oncogene*, 2000). Our more recent studies employing a broader panel of breast cancer cell lines and the largest collection of primary human breast cancers analyzed to date for NF- κ B activation indicate that tumor level of NF- κ B activation at the time of diagnosis can potentially identify a high-risk subset of ER-positive breast cancers destined for metastatic relapse (and reduced disease-free patient survival, DFS) despite the use of adjuvant TAM therapy. Interestingly, these outcome analyses show that increased NF- κ B p50 subunit DNA-binding activity, but not p65 subunit DNA-binding activity, associates significantly with clinical relapse and reduced DFS despite adjuvant TAM. Moreover, our panel of breast cancer cell lines suggest that tumor treatment specifically directed at inhibiting elevated NF- κ B activity by such drugs as parthenolide or the proteasome inhibitor PS-341/Velcade, can fully restore the sensitivity of endocrine-resistant ER-positive breast cancers to standard agents like TAM. Thus, as new NF- κ B inhibiting therapeutics are currently under development, additional studies are needed to direct their application to ER-positive breast cancer and to better understand what specific components of the NF- κ B pathways should be therapeutically targeted.