The NFκB pathway and endocrine-resistant breast cancer

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Abstract

Endocrine therapy with an estrogen receptor (ER)-targeted antiestrogen, such as tamoxifen, or estrogen ablation by aromatase inhibitors is clinically indicated for the management of all forms of ER-positive breast cancer. However, 30–50% of ER-positive breast cancer cases fail to benefit clinically from endocrine therapy alone, and recent molecular evidence suggests that ‘crosstalk’ pathways originating from activated receptor tyrosine kinases and/or other proliferative and survival signals may be contributing to this endocrine resistance. Molecular identification and validation of candidate ER crosstalking pathways will likely lead to clinically important prognostic markers and targets for the application of novel therapeutics in combination with standard endocrine agents. This review focuses on a critical survival and proliferation pathway involving activation of nuclear factor-κB (NFκB), a family of ubiquitously expressed transcription factors that for nearly two decades have been known to be critical regulators of mammalian immune and inflammatory responses, and more recently have been associated with chemotherapy resistance. With the demonstration that activation of NFκB is absolutely required for normal mammary gland development, NFκB involvement in human breast cancers was initially explored and linked to the development of hormone-independent (ER-negative) breast cancer. Newer clinical evidence now implicates NFκB activation, particularly DNA-binding by the p50 subunit of NFκB, as a potential prognostic marker capable of identifying a high-risk subset of ER-positive, primary breast cancers destined for early relapse despite adjuvant endocrine therapy with tamoxifen. Furthermore, initial preclinical studies suggest that treatment strategies designed to prevent or interrupt activation of NFκB in cell-line models of these more aggressive, ER-positive breast cancers can restore their sensitivity to such standard endocrine agents as tamoxifen.

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Receptor crosstalk and endocrine resistance

Levels of estrogen receptor (ER) (alpha isoform) overexpression, as well as the coexpression of ER-associated gene products (e.g. PR, pS2), have long been recognized as markers of breast cancer prognosis and, more importantly, predictors of response to endocrine therapy and clinical outcome. In fact, the clinical responsiveness of ER-positive breast cancers to the antiestrogen tamoxifen correlates positively with the absolute expression level (fmol/mg protein) of tumor ER (McGuire 1980, Elledge & Fuqua 2000). Gene microarray and other studies now indicate that ER-positive breast cancers can be divided into clinical subsets with extremely different outcomes, ranging from tumors with good prognosis and endocrine responsiveness to others with de novo or acquired endocrine resistance and risk of early relapse (Gruvberger et al. 2001, Sorlie et al. 2001, Benz 2004a). Additionally, a growing body of preclinical and clinical reports link antiestrogen resistance with tumor overexpression
of one or more members of the ErbB/HER family of receptor tyrosine kinases (reviewed in Benz 2004a,b). In particular, up to 15% of newly arising breast cancers are not only ER-positive but also overexpress the ErbB2 receptor as a result of oncogene amplification. Several clinical studies have shown that ErbB2-positive breast cancers that are also ER-positive have significantly lower ER and PR content than ER-positive breast cancers that are ErbB2-negative (Eppenberger-Castori et al. 2001, Konecny et al. 2003). Supporting these clinical observations, ER-positive breast cancer cell lines engineered to overexpress ErbB2 retain their ER positivity but show marked reductions in their ER content (Konecny et al. 2003, Benz et al. 1992). While this downregulation of ER and PR expression may partially explain the reduced antitumor activity of antiestrogens against ER-positive/ErbB2-positive breast cancers relative to ER-positive/ErbB2-negative cancers, how ErbB2 activation downregulates ER and PR expression remains a mechanistic mystery.

Recent studies are beginning to elucidate how signaling pathways activated by ErbB-related membrane receptor tyrosine kinases (RTK) crosstalk with ER pathways (reviewed in Benz 2004a,b). Membrane receptor-initiated signaling through the mitogen-activated protein kinase (MAPK) pathway and the phosphatidylinositol-3-kinase (PI3K)-Akt pathway results in phosphorylation of ER on its various serine (S167, S118, S104, S106) residues and leads to both ligand-dependent and ligand-independent ER-mediated gene activation via 'classical' (direct ER DNA-binding at promoters containing estrogen-response elements) and 'non-classical' (ER tethering and coactivation of other DNA-bound transcription factor complexes such as AP-1, Sp1, C/EBPβ and CREB) gene induction. Importantly, the net transcriptional effect of crosstalk that phosphorylates ER and its many transcriptional coregulators includes the functional conversion of an ER-binding antiestrogen such as tamoxifen into an ER agonist, capable of driving ER-positive cancer growth almost as efficiently as the potent estrogen, estradiol (Benz et al. 1992). Promising preclinical results from our well-characterized MCF-7/HER2 model of ER-positive/ErbB2-positive breast cancer are now fueling clinical studies involving patients with endocrine-resistant, ER-positive breast cancers, in which ErbB RTK inhibitors are being administered in combination with tamoxifen (Benz et al. 1992, Kurokawa et al. 2000, Shou et al. 2004, Schiff et al. 2004).

Alterations in ER crosstalk pathways clinically linked with tamoxifen resistance but not necessarily originating from ErbB2 amplification and overexpression have also been described; these include enhanced activation of the gene-regulating transcription factor complex, AP-1 (Johnston et al. 1999, Schiff et al. 2000), dysregulated PI3/Akt (Campbell et al. 2001), protein kinase Ca (Chisamore et al. 2001), and the insulin-like growth factor I (Pariset et al. 1999) signaling pathways. Notably, all of these signaling pathways leading to tamoxifen resistance share a common mechanistic link with activation of another gene-regulating complex, nuclear factor-κB (NFκB) (Vertegaal et al. 2000, Zhou et al. 2000, Bhat-Nakshatri et al. 2002, DeGraffenried et al. 2004).

NFκB in organ development and disease

The NFκB complex is composed of a family of inducible transcription factors found in almost all cells (Baeuerle & Baltimore 1996, Ghosh et al. 1998, Allen & Tresini 2000); and this complex is generally recognized as an essential cell mediator acting 'at the crossroads of life and death' (Karin & Lin 2002). Activation of NFκB occurs in response to extra- and intracellular chemical stresses, various cytokines and growth stimuli, resulting in the direct induction of hundreds of genes whose cellular influences extend well beyond those of the immune system, where its essential role was first appreciated nearly two decades ago (Pahl 1999). In fact, the antiapoptotic, proliferation-, motility- and invasion-promoting roles of NFκB appear to be critical for normal organ development, including the mammary gland (reviewed in Cao & Karin 2003). NFκB activation can become abnormal during organ aging, with development and progression of various chronic inflammatory disorders, and in malignancies such as B and T cell lymphoma and leukemia, and thyroid, head and neck, gastrointestinal, and breast carcinoma (Baldwin 2001, Giardina & Hubbard 2002, Feinman et al. 2004, Veiby & Read 2004).

The NFκB family consists of five mammalian members: p50 (NFκB1), p52 (NFκB2), p65 (relA), c-rel and relB. These all share a conserved 300-amino-acid N-terminal Rel homology domain (homologous to that encoded by the avian oncogene, v-Rel) that is responsible for dimerization, nuclear translocation, DNA binding, and association with IκB inhibitory proteins (Dixit & Mak 2002, Ghosh & Karin 2002). These Rel family members exist as homo- or heterodimers, although the most abundant form of intracellular NFκB is generally thought to be the p50/p65 heterodimer. In resting cells, NFκB is cytoplasmically sequestered as a latent complex bound to one or more members of the IκB protein family (IκBα, IκBβ, IκBε, IκBγ, Bcl-3), and the precursor Rel proteins
p100 and p105). Diverse cell stimuli (e.g. tumor necrosis factor (TNF)α, CD40 ligand, interleukin (IL)-1, TRANCE, epidermal growth factor (EGF), phorbol esters, peroxides, ionizing radiation) induce phosphorylation (via activation of the IκB kinase complex, IKK) and subsequent proteasomal degradation of IκB inhibitory proteins, activating NFκB for nuclear translocation, where it binds promoter-specific κB consensus DNA elements that direct transcription of over 180 known NFκB target genes. While phosphorylation and degradation of IκB inhibitory proteins are considered the rate-limiting if not obligate mechanisms by which NFκB is activated, novel NFκB phosphorylating kinases and IKK-independent pathways leading to IκB proteosomal degradation have recently been described. Most activated forms of NFκB induce gene transcription, although specific NFκB subunits lack transactivation domains; thus, activation and nuclear translocation of p50/p50 and p52/p52 homodimers can result in repression of NFκB-dependent genes (Ghosh & Karin 2002). However, when either NFκB p50 or p52 products of the p105 and p100 Rel precursor proteins are bound to the oncogenic and noninhibitory IκB family member, Bcl-3, they become transcriptionally competent and stimulate expression of NFκB-dependent genes (Cogswell et al. 2000, Ghosh & Karin 2002).

Since NFκB regulates so many known survival and proliferation genes, it is not surprising that NFκB activation has generally been implicated in cancer chemotherapy resistance mechanisms (Wang et al. 1999). When first studied in human breast cancer cell lines and breast cancer samples, however, constitutive activation of NFκB was associated only with hormone-independent (ER-negative) breast cancers, and this was thought to be due to its known inhibitory effects on almost all steroid receptors, including ER (Nakshatri et al. 1997).

Importance of NFκB in hormone-dependent breast cancer

Less than a decade ago, NFκB activation was initially linked with the etiology and progression of hormone-independent breast cancers, where it was shown transcriptionally to induce genes mediating cell proliferation and invasion, such as cyclin D1 and urokinase-type plasminogen activator (uPA). Measured by DNA-binding, transactivation and immunoblot assays, NFκB activation was first evaluated in several samples and cell lines, where it was found to be minimal in ER-positive breast cancers and cell lines but constitutively elevated in ER-negative breast cancers and cell lines (Nakshatri et al. 1997, Sovak et al. 1997). A subsequent study compared a small number of breast cancers with normal adjacent breast tissue (and also a few breast cancer cell lines) by measuring total NFκB DNA-binding activity and subunit (p65, c-rel, p52 and p50) protein and transcript expression levels (Cogswell et al. 2000). The breast cancer samples all showed greater total NFκB DNA-binding activity than the normal mammary gland tissue, but the increased tumor activity did not correlate with tumor ER status. In contrast, the cell line results again confirmed low NFκB activation in ER-positive cell lines and high NFκB activation in ER-negative breast cancer cells; moreover, these breast cancer cell lines showed predominantly increased p65 subunit expression and p65/p50 NFκB DNA-binding activity, while the breast tumor samples showed selective upregulation of p50, p52 and c-rel expression (as well as Bcl-3) and increased DNA-binding by complexes composed mostly of these subunits and with relatively little p65 (Cogsell et al. 2000).

We recently performed the most extensive evaluation to date of NFκB activation in primary human breast tumor samples in order to clarify the extent and clinical importance of NFκB activation in hormone-dependent breast cancer (Zhou et al. 2005). With a new ELISA-based method to quantitate specific p65 and p50 NFκB DNA-binding subunits, these subunit activities were independently measured in 81 ER-positive, primary breast cancer sample extracts with a wide range of ER content (group A samples: >100 fmol/mg protein; group B samples: 21–87 fmol/mg protein). NFκB p50 and p65 subunit DNA-binding activities were also evaluated for their prognostic association with clinical outcome in the subset of 59 group B cases that were comparably staged, characterized for a number of other prognostic biomarkers (Quong et al. 2002), uniformly treated with adjuvant tamoxifen, and clinically followed until metastatic relapse to determine disease-free patient survival (Zhou et al. 2005). Among the entire collection of 81 breast cancer samples (groups A+B), DNA-binding complexes with the p50 NFκB subunit were almost twofold more abundant than those with the p65 NFκB subunit, although these two independently measured parameters were tightly correlated (rs = 0.86, P < 0.0001). As illustrated in Fig. 1 (panel A), the group B breast cancers with a median under 0.5-fold lower ER content showed significantly higher NFκB DNA-binding than the group A tumors with higher ER content, indicating that hormone-dependent breast cancers might be subset according to NFκB activity and ER content.
Metastatic relapse rates and disease-free survival (DFS) status were available only for the group B cases; despite uniform adjuvant treatment with tamoxifen, the 13/59 primary breast tumors destined for later relapse possessed significantly higher NFκB p50 DNA-binding than the 46/59 similarly staged, ER-positive cases not destined for relapse. The generally lower NFκB p65 DNA-binding activities followed a similar trend that did not reach statistical significance.

Regression tree analyses were performed on both the p50 and p65 DNA-binding values to establish statistical cutpoints (0.95 and 0.75 respectively) that would optimally separate the Kaplan–Meier DFS curves for high versus low NFκB subsets within the group B cases. As shown in Fig. 1 (panel B), the higher NFκB p50 DNA-binding values were associated with significantly reduced DFS ($P=0.04$). Likewise, the p65 DNA-binding DFS curves showed a similar trend, but their separation did not achieve statistical significance ($P=0.09$).

Among the numerous other biomarkers previously determined in the group B tumors, only AP-1 DNA-binding and uPA expression also showed significant prognostic associations with patient outcome assessed by Kaplan–Meier DFS plots ($P=0.009$ and $P=0.001$ respectively). Furthermore, we found that tumor ErbB2 and uPA protein levels, as well as AP-1 DNA-binding activities, correlated significantly with both NFκB p50 and p65 DNA-binding values (Zhou et al. 2005). Mechanistically, the observed NFκB correlation with ErbB2 expression could have resulted from the reported activation of the NFκB pathway by ErbB2 RTK signaling (Romieu-Mourez et al. 2002, Biswas et al. 2004). Likewise, the NFκB correlations with uPA expression and AP-1 DNA-binding probably reflect the fact that the uPA gene is known to be transcriptionally activated by both NFκB and AP-1 transcription factor complexes working in concert (Hansen et al. 1992, Sliva et al. 2002). Given these mechanistic links and the fact that large clinical trials have consistently demonstrated that uPA expression independently identifies a high-risk subset of early-stage breast cancers (Eppenberger et al. 1998), it is tempting to conclude that tumor cell invasiveness and motility mediated by increased uPA expression and induced by activated NFκB and AP-1 complexes contributed to the relapse rate and reduced DFS survival observed in our group B, ER-positive primary breast cancer cases that failed to benefit from adjuvant tamoxifen.

**NFκB inhibition can reverse endocrine resistance**

NFκB p50 and p65 subunit DNA-binding activities were also assessed in a panel of breast cancer cell lines representing four different clinical phenotypes (ER-positive/ErbB2-negative, ER-positive/ErbB2-positive,
ER-negative/ErbB2-positive, and ER-negative/ErbB2-negative). As shown in Fig. 2 (panel A), the ER-negative breast cancer cell lines SkBr3 and MDA231 exhibited significantly greater NFκB p50 subunit DNA-binding than the ER-positive and tamoxifen-sensitive MCF7 and T47D breast cancer cell lines. Interestingly, the ER-positive/ErbB2-positive and tamoxifen-resistant BT474 and MCF7/HER2 cell lines exhibited intermediate NFκB p50 DNA-binding activities. Among experimental and medicinal strategies to inhibit constitutively active NFκB are drugs that target upstream NFκB activating signals or downstream IkB degradative mechanisms (Yamamoto & Gaynor 2001), including the potent and specific antioxidant pyrrolidine dithiocarbamate (Schreck et al. 1992), proteasome inhibitors such as MG-132 and PS-341 (bortezomib/Velcade) (Cordoso et al. 2004), and sesquiterpene lactones found in antiphlogistic plant extracts such as the specific IKK inhibitor, parthenolide (PA) (Hehner et al. 1999). To explore the endocrine-modulating role of NFκB and attempt to restore tamoxifen sensitivity to our cell line models of high-risk, ER-positive breast cancers, we treated BT474 and MCF7/HER2 cell lines with tamoxifen, NFκB-inhibiting doses of either PA or PS-341, or a combination of tamoxifen with PA or PS-341 (Zhou et al. 2005). For comparison, tamoxifen-sensitive MCF-7 cells were also subjected to these same treatments. Doses of PA and PS-341 that fully inhibit NFκB activation in all three cell lines (Zhou et al. 2005) produced comparable growth inhibition of all these cells, as seen in Fig. 2 (panels B and C). While PA and PS-341 failed to enhance tamoxifen inhibition of MCF-7 growth, these same PA and PS-341 doses significantly enhanced tamoxifen growth inhibition of the resistant MCF7/HER2 and BT474 cells. These
findings support the interpretation that ErbB2 RTK induction of NFκB in MCF7/HER2 and BT474 cells renders them resistant to the antiestrogenic effects of tamoxifen, and this antiestrogenic effect is restored when the ErbB2-activated NFκB pathway is inhibited by either the IKK inhibitor PA or the proteasome inhibitor PS-341. These findings are also consistent with a recent report demonstrating that inhibition of NFκB by cotreatment with PA overcomes endocrine resistance induced in MCF7 cells by the constitutive overexpression of Akt (DeGraffenried et al. 2004).

In vivo preclinical evaluation of the ability of PA and PS-341 to restore tamoxifen sensitivity is planned with nude mice implanted with MCF7/HER2 or BT474 breast tumor xenografts.

**Targeting the NFκB pathway in hormone-dependent breast cancer**

The constitutive activation of NFκB documented in various pathophysiologic disorders has been a major impetus for commercial development of new agents capable of inactivating the NFκB pathway (Yamamoto & Gaynor 2001, Ghosh & Karin 2002, Feinman et al. 2004, Karin et al. 2004, Veiby & Read 2004). Much of this effort initially focused on blocking dysregulated NFκB function in leukocytes to treat chronic inflammatory disorders and originated with the isolation of many different NFκB-inhibiting, anti-inflammatory compounds from traditional medicines. However, with recent clinical approval of the proteasome inhibitor, bortezomib (PS-341), used at NFκB-inhibiting doses to treat multiple myeloma, and with promising activity against assorted other malignancies (Cardoso et al. 2004), has come renewed enthusiasm for the preclinical development and evaluation of more specific, NFκB pathway-inhibiting anticancer agents. A number of endogenous molecules have been identified as inhibitors of NFκB, and these were recently proposed as new opportunities for the control of cancer (Chen 2004). Table 1 lists a number of structurally diverse, commercially available, natural and synthetic compounds with known NFκB-inhibiting activity. Some of these have established anticancer activity (e.g. acrolein) or are functionally related to an

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**Table 1 Natural and synthetic compounds with NFκB inhibiting activity**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Description</th>
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<tr>
<td>A77-1726</td>
<td>Active metabolite of the immunsuppressant leflunomide that inhibits NFκB</td>
</tr>
<tr>
<td>Acrolein</td>
<td>Reactive metabolite of cyclophosphamide, environmental agent and smoke component that conjugates and inactivates NFκB</td>
</tr>
<tr>
<td>Aspirin and Mesalamine</td>
<td>Anti-inflammatory agents that inhibit IκB phosphorylation</td>
</tr>
<tr>
<td>BAY11-7082 and BAY11-7085</td>
<td>Inhibitors of IκB phosphorylation</td>
</tr>
<tr>
<td>Betulonic acid</td>
<td>Plane tree isolate that suppresses NFκB and induces mitochondrial-mediated apoptosis</td>
</tr>
<tr>
<td>Octylcaffeate and CAPE</td>
<td>Isolates from honeybee hives that are antioxidants, and inhibit MAPK and nuclear translocation of NFκB</td>
</tr>
<tr>
<td>Dithiocarbamates</td>
<td>Family of antioxidants, NOS inhibitors, thiol and metal chelators that prevent NFκB activation</td>
</tr>
<tr>
<td>Diethylmaleate</td>
<td>Conjugates and inactivates NFκB</td>
</tr>
<tr>
<td>Epoxomicin</td>
<td>Fungal isolate and proteasome inhibitor that prevents activation of NFκB</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>Lipid-lowering agent that inhibits NOS and NFκB</td>
</tr>
<tr>
<td>Helenalin</td>
<td>Sesquiterpene lactone plant isolate that alkylates p65 subunit of NFκB</td>
</tr>
<tr>
<td>10Z-hymenialdisine</td>
<td>Marine sponge isolate that inhibits MEK1/2, MAPK and NFκB</td>
</tr>
<tr>
<td>Lactacystin</td>
<td>Bacterial isolate and proteasome inhibitor that prevents NFκB activation</td>
</tr>
<tr>
<td>MG-132</td>
<td>Tripeptide aldehyde proteasome inhibitor that prevents NFκB activation</td>
</tr>
<tr>
<td>NBD</td>
<td>Cell-permeable peptide that blocks IKK and prevents NFκB activation</td>
</tr>
<tr>
<td>N-Oleoyldopamine</td>
<td>Capsaicin-like lipid that inhibits 5-lipoxygenase and NFκB activation</td>
</tr>
<tr>
<td>Panepoxydone</td>
<td>Fungal isolate that inhibits NFκB activation</td>
</tr>
<tr>
<td>Parthenolide A,</td>
<td>Sesquiterpene lactone from feverfew leaves that specifically inhibits IKK</td>
</tr>
<tr>
<td>Prostaglandin A,</td>
<td>Inhibits phosphorylation/degradation of IκB</td>
</tr>
<tr>
<td>Rocaglamide</td>
<td>Isolate from Chinese perfume tree that is potent inhibitor of NFκB activation</td>
</tr>
<tr>
<td>Sauchinone</td>
<td>Lignan isolate from Chinese lizard tail flower that inhibits NOS, suppresses IKK activity and inhibits NFκB, AP-1 and C/EBP transactivation</td>
</tr>
<tr>
<td>SNS0</td>
<td>Peptide that inhibits nuclear translocation of NFκB</td>
</tr>
<tr>
<td>Trimethyl-D-sphingosine</td>
<td>Membrane-inserting sphingolipid that inhibits oxidative burst, PKC and NFκB activation</td>
</tr>
<tr>
<td>Sulindac sulfide</td>
<td>Anti-inflammatory inhibitor of Ras, COX, and NFκB signals</td>
</tr>
<tr>
<td>Trichodion</td>
<td>Fungal isolate and anti-inflammatory pyrone that inhibits AP-1, NFκB, and STAT1 gene induction</td>
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approved anticancer agent (e.g. MG-132, lactacystin, epoxomicin); others have known cancer prevention properties (e.g. aspirin, sulindac), or are being investigated either for their ability to enhance cancer chemotherapy activity (e.g. parthenolide) or for their own intrinsic antineoplastic activity (e.g. betulinic acid, rocaglamide, trimethyl-D-sphingosine). However, most of these compounds are not so specifically targeted to the NF\(_k\)B pathway as are the IKK inhibitors (e.g. parthenolide, BAY11-7085), and this specificity may ultimately prove important if some measure of increased tumor NF\(_k\)B activity is used to select breast or other cancers for treatment with NF\(_k\)B inhibitors.

While an interspecies comparison of mammary cancer gene expression profiles recently identified the NF\(_k\)B pathway as one of the few proliferation and survival pathways commonly dysregulated in mouse and human mammary cancers (Hu et al. 2004), our recent study indicates that hormone-dependent, human breast cancers can be subset into those with and without dysregulated NF\(_k\)B, suggesting the need for a predictive biomarker, such as increased NF\(_k\)B p50 subunit DNA binding, to identify breast cancer patients most likely to benefit from a specific NF\(_k\)B inhibitor (Zhou et al. 2005). If \textit{in vivo} studies confirm that NF\(_k\)B pathway inhibition improves the efficacy of endocrine treatment against ER-positive breast cancers with increased NF\(_k\)B p50 subunit DNA binding, then clinical trials can be designed to test this strategy even in the absence of specific NF\(_k\)B-inhibiting investigational drugs. The pathway schematic shown in Fig. 3 identifies known investigational agents potentially capable of interrupting intracellular signals immediately upstream and downstream of NF\(_k\)B activation, preventing its crosstalk and interference with the ER mechanism targeted by our standard endocrine agents.

\textbf{Figure 3} Pathway schematic depicting known intracellular signaling mechanisms upstream and downstream of the NF\(_k\)B activation proposed to mediate tumor cell survival and proliferation as well as endocrine resistance. Also identified are a number of investigational agents that specifically inhibit these mechanisms and thus potentially prevent NF\(_k\)B interference with the ER mechanism targeted by endocrine therapeutics such as antiestrogens and aromatase inhibitors. Thus, clinical strategies combining NF\(_k\)B pathway inhibitors with standard endocrine agents may additively increase apoptosis and growth arrest in some high-risk, hormone-dependent breast cancers.
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