

Endocrinotherapy resistance of prostate and breast cancer: Importance of the NF- κ B pathway (Review)

XIUMEI WANG^{1,2*}, YAO FANG^{1,2*}, WENBO SUN¹, ZHI XU³, YANYAN ZHANG¹,
XIAOWEI WEI⁴, XUANSHEG DING² and YONG XU^{1,3}

¹Jiangsu Cancer Hospital and Jiangsu Institute of Cancer Research, and Nanjing Medical University Affiliated Cancer Hospital, Nanjing, Jiangsu 210009; ²School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, Nanjing, Jiangsu 211198; ³Jiangsu Key Lab of Cancer Biomarkers, Prevention and Treatment, Nanjing Medical University, Nanjing, Jiangsu 211166;

⁴Department of Oncology, Nanjing First Hospital, Nanjing Medical University, Nanjing, Jiangsu 210006, P.R. China

Received October 7, 2019; Accepted January 24, 2020

DOI: 10.3892/ijo.2020.4990

Abstract. Prostate cancer (PCa) and breast cancer (BCa) are two common sex hormone-related cancer types with high rates of morbidity, and are leading causes of cancer death globally in men and women, respectively. The biological function of androgen or estrogen is a key factor for PCa or BCa tumorigenesis, respectively. Nevertheless, after hormone deprivation therapy, the majority of patients ultimately develop hormone-independent malignancies that are resistant to endocrinotherapy. It is widely recognized, therefore, that understanding of the mechanisms underlying the process from hormone dependence towards hormone independence is critical to discover molecular targets for the control of advanced PCa and BCa. This review aimed to dissect the important mechanisms involved in the therapeutic resistance of PCa and BCa. It was concluded that activation of the NF- κ B pathway is an important common mechanism for metastasis and therapeutic resistance of the two types of cancer; in particular, the RelB-activated noncanonical NF- κ B pathway appears to be able to lengthen and strengthen NF- κ B activity, which has been a focus of recent investigations.

Contents

1. Introduction
2. Key ligand receptors in PCa and BCa tumorigenesis
3. Mechanistic switch from AR/ER to NF- κ B in PCa and BCa progression
4. NF- κ B activation in endocrinotherapy resistance
5. Main NF- κ B-regulated proteins in endocrinotherapy resistance
6. NF- κ B as a target in PCa and BCa treatments
7. Conclusions and perspectives

1. Introduction

Prostate cancer (PCa) and breast cancer (BCa) are two common types of malignant tumor with high mortality rates. According to recent statistical data, the number of new cases of PCa and BCa accounts for 7.1 and 11.6% of the total cancer cases worldwide, and the numbers of deaths from PCa and BCa account for 3.8 and 6.6% of all cancer deaths, respectively (1). Particularly in Asian countries like China, the incidences of PCa and BCa have been constantly increasing over the last two decades (2). Owing to the improved early diagnosis and advanced therapeutic strategies, the mortality rates of PCa and BCa have appreciably decreased. Unfortunately, the majority of patients eventually develop more aggressive malignant forms that are resistant to the most common treatments, leading to a poor prognosis (3,4). Thus, therapeutic resistance still poses a major challenge on the path to conquer PCa and BCa.

As sex hormone-related cancer types, PCa and BCa share a common feature; namely, that the interaction between sex hormones and hormone receptors is required to initiate tumorigenesis (5,6). In PCa, the androgen response is thought to be essential for tumorigenesis. Blockage of the interaction between androgen and the androgen receptor (AR) has been implicated in the induction of caspase-mediated apoptosis, as well as the inhibition of cell proliferation by altering cell cycling (7,8). Like androgen, estrogen is also essential for cell survival and proliferation, and estrogen receptor (ER) activation is recognized to play a pivotal role in BCa

Correspondence to: Professor Yong Xu, Jiangsu Cancer Hospital and Jiangsu Institute of Cancer Research, and Nanjing Medical University Affiliated Cancer Hospital, 42 Baiziting, Nanjing, Jiangsu 210009, P.R. China
E-mail: yxu4696@njmu.edu.cn

Professor Xuansheng Ding, School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, 639 Longmian Road, Nanjing, Jiangsu 211198, P.R. China
E-mail: xsding2013@163.com

*Contributed equally

Key words: NF- κ B, androgen receptor, estrogen receptor, endocrinotherapy resistance, prostate cancer, breast cancer

progression (9-11). Overall, heightened AR and ER activities are thought to contribute to the development of PCa and BCa through AR/ER-mediated signal transduction.

Since sex hormone responses are a key factor for the initiation of tumorigenesis in both PCa and BCa, hormone deprivation has become a common therapeutic option for the treatment of these two types of cancer. However, although most patients can gain certain therapeutic benefits from hormone therapies in the early stages, a large number of patients eventually acquire therapeutic resistance, leading to tumor recurrence and metastasis in hormone-free conditions (3,12). Overall, the therapeutic strategies for PCa and BCa are quite similar (Table I).

For patients with low- and intermediate-risk localized PCa, local treatment such as prostatectomy and radiotherapy are efficient to prevent distant organ metastasis (13-15). Additionally, radiotherapy plus hormone therapy has been applied to treat patients with high-risk locally advanced PCa, metastatic PCa that is unsuitable for surgery, or tumor recurrence after prostatectomy (13,15,16). Finally, chemotherapy with serious side-effects is still required to treat malignant PCa when hormone therapy is no longer effective (13,15). Notably, recent advanced targeted therapy and immunotherapy for inhibiting malignancy-associated molecules, as well as specific signaling pathways, have been successfully used to control hormone-refractory states (17,18). In BCa treatment, for patients with the early stages of BCa, after breast-conserving surgery or mastectomy, radiotherapy is essential to reduce the risk of recurrence (19,20). Generally, endocrinotherapy is the first-line treatment for ER-positive BCa (21). Ultimately, chemotherapy is essential in treating patients with metastatic BCa, including human epidermal growth factor receptor 2 (HER2)-positive BCa, high-risk luminal HER2-negative BCa and triple-negative BCa (TNBC) (22-24). Likewise, targeted therapy for inhibiting HER2 appears to efficiently treat malignant BCa (25). Immunotherapy also has also become a potent therapeutic approach to controlling BCa progression and reversing drug resistance (26).

Overall, hormone therapy is a powerful tool for the treatment of the early stages of AR-positive PCa or ER-positive BCa. Nevertheless, chemotherapy is necessary for treating late-stage disease that is resistant to hormone therapy. Unfortunately, advanced disease with a metastatic phenotype remains incurable, particularly life-threatening metastases to the bones or brain (27-30). Thus, more efficient targeted therapy and immunotherapy are needed to more effectively treat advanced PCa/BCa. To that end, the aim of the present review was to integrate research on the mechanism by which PCa or BCa gradually progresses to the AR/ER-negative genotype. Activation of the NF- κ B pathway appears to play a central role in the progression of hormone-independent malignancies and in endocrinotherapy resistance; in particular, RelB is a key factor in sustaining NF- κ B activity to replace the function of AR/ER.

2. Key ligand receptors in PCa and BCa tumorigenesis

The interaction between ligands and receptors is thought to be essential for normal physiological development, but also to be involved in cancer progression. Abnormal activation of

AR/ER signaling uniquely contributes toward the tumorigenesis of PCa/BCa. Nevertheless, unlike PCa with AR alone, the progesterone receptor (PR) and HER2 are also important receptors, along with ER, in BCa.

Biological functions of AR and ER in PCa and BCa. As major sex hormone receptors, AR and ER belong to the nuclear receptor superfamily, which can be activated by multiple ligands including steroids, thyroid hormones and retinoic acid (31-33). AR and ER function as transcription factors in the regulation of downstream gene expression (8,34). The mechanisms of AR/ER-mediated transcriptional regulation are illustrated in Fig. 1. AR is expressed in both androgen-dependent and -independent PCa (5,33); it can be activated by various steroid hormones, particularly androgenic hormones including testosterone and dihydrotestosterone (35,36). Similar to AR, there exist both ER α and ER β , which are responsive to estrogen activation (6). In general, AR/ER form heterodimers with heat shock proteins (HSPs) to remain in an inactive state in the cytosol. HSP is released when hormone ligands bind to AR/ER, and subsequently the hormone ligand-receptor complexes transfer into the nuclei as a dimer, and bind to androgen/estrogen response elements located in the enhancer regions of the downstream regulated genes (3,8,37). Additionally, many co-factors also participate in AR/ER-mediated transcriptional regulation by interacting with AR/ER (3,6,8,33,37). Accordingly, multiple endocrine therapeutic approaches focusing on the suppression of AR/ER activation have been frequently used to treat PCa and BCa. However, after the initial benefits received from the AR/ER-targeted treatment, the therapeutic efficacies are inevitably declined when patients develop more aggressive AR/ER-independent malignancies (7,33,34,38).

PR and HER2 in BCa. In addition to ER, PR is another important sex steroid hormone receptor for sexual maturation and gestation, whose function is also relevant to BCa progression (39-42). Notably, HER2, a typical proto-oncogene, has been recognized as a key factor for promoting high risk BCa through a steroid-independent signaling pathway (43-45). Thus, HER2 has become an important biomarker for BCa progression as well as a therapeutic target for ~30% of patients with BCa (44-46). Increasing evidence has demonstrated that downregulation of PR and/or upregulation of HER2 in BCa leads to the acquisition of endocrinotherapy resistance (41,43,44,47).

3. Mechanistic switch from AR/ER to NF- κ B in PCa and BCa progression

The functional consequences of cell signaling modulation are mainly ascribed to gene transcriptional regulation in PCa and BCa progression (48,49). AR/ER-mediated transcriptional regulation is thought to be critical for the development of the early stages of PCa/BCa. Nevertheless, AR/ER function eventually declines in the late stages of malignant PCa/BCa, particularly as a consequences of hormone deprivation therapy (50,51). Notably, other transcription factors like NF- κ B functionally take over AR/ER to substantially reprogram the cell transcriptome, sustaining PCa/BCa progression under hormone-free conditions (52-54).

Table I. Comprehensive therapeutic strategies for PCa and BCa.

A, PCa	
Type/stage	Treatment
Primary/localized	Prostatectomy; radiotherapy
Advanced/metastatic	Radiotherapy plus hormone therapy; hormone therapy; chemotherapy; targeted therapy; immunotherapy
B, BCa	
Type/stage	Treatment
Primary/localized	Breast-conserving surgery; mastectomy; radiotherapy
Advanced/metastatic	Radiotherapy plus hormone therapy; hormone therapy; chemotherapy; targeted therapy; immunotherapy

PCa, prostate cancer; BCa, breast cancer.

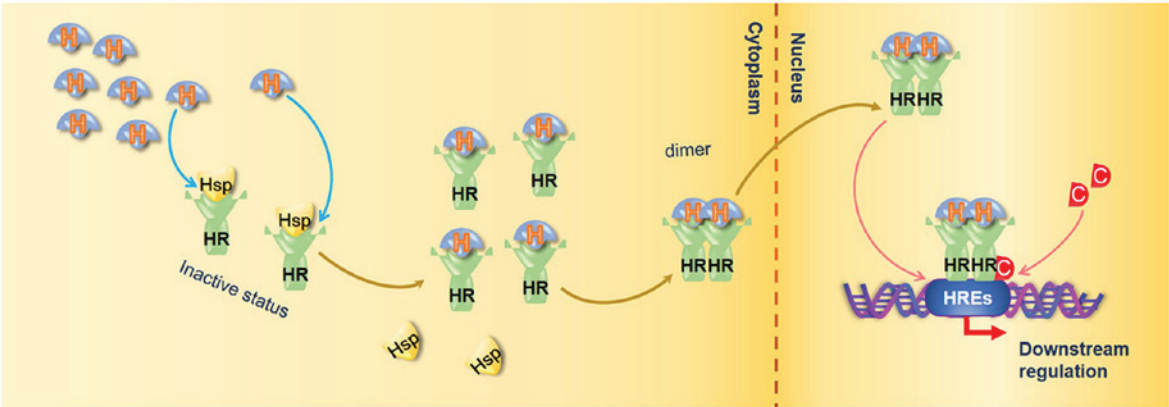


Figure 1. AR/ER, a ligand-activated transcription factor. The AR/ER is usually bound by Hsp and remains inactive in the cytoplasm. When a steroid hormone signal appears, Hsp is shed to free the corresponding receptor for androgen/estrogen binding, followed by the translocation of the ligand-receptor complexes into the nuclei to mediate the transcriptional activation of the downstream regulatory genes. AR, androgen receptor; ER, estrogen receptor; H, androgen/estrogen; HR, AR/ER; HREs, androgen/estrogen response elements; Hsp, heat shock protein; C, transcription co-factor.

NF-κB functional substitution of AR/ER. It is thought that NF-κB negatively regulates AR function by competing for transcriptional regulation (55). Previous studies have demonstrated that androgen-independent PCa exhibits higher constitutive NF-κB binding activity than its androgen-dependent counterpart. Tumor necrosis factor (TNF)α induces NF-κB activation via stimulation of inhibitor of NF-κB (IKK), which is inhibited as an androgen analogue (56). For example, prostate-specific antigen (PSA), a common PCa biomarker, is regulated by AR (57). However, NF-κB is also able to regulate PSA through binding to a κB response element located in the promoter region (52). Consistently, inhibition of NF-κB results in the suppression of castration-resistant prostate cancer (CRPC) xenograft tumor growth (58). Nevertheless, NF-κB also appears to positively regulate androgen receptor splicing variant (ARV) transactivation (59,60). Additionally, AR-negative PCa stem cells with high constitutive NF-κB activity promote tumor growth during androgen deprivation therapy, suggesting that NF-κB gradually substitutes AR

during CRPC progression (61). Notably, AR activation results in the suppression of the canonical NF-κB pathway, but leads to upregulation of the noncanonical NF-κB pathway (61). Likewise, NF-κB plays a key role in the promotion of estrogen-independent growth in both ER-positive and -negative BCa (62). In particular, the evidence of low NF-κB activation in ER-positive BCa cells and high NF-κB activation in ER-negative BCa cells indicates an inverse relationship between ER and NF-κB in BCa progression (53), suggesting that constitutive NF-κB activity is consistently increased during ER-independent BCa progression (63,64). Blockage of NF-κB activation efficiently inhibits proliferation and reverses therapeutic resistance in ER-negative cells (54). Mechanistically, NF-κB represses ER expression, and high levels of NF-κB can cause downregulation of ER (65). In particular, it has been noted that levels of RelB are inversely correlated with the status of ER in BCa cells (66). RelB can stimulate PR/SET domain 1, which represses ER expression by binding to the ER promoter (67). However, in some

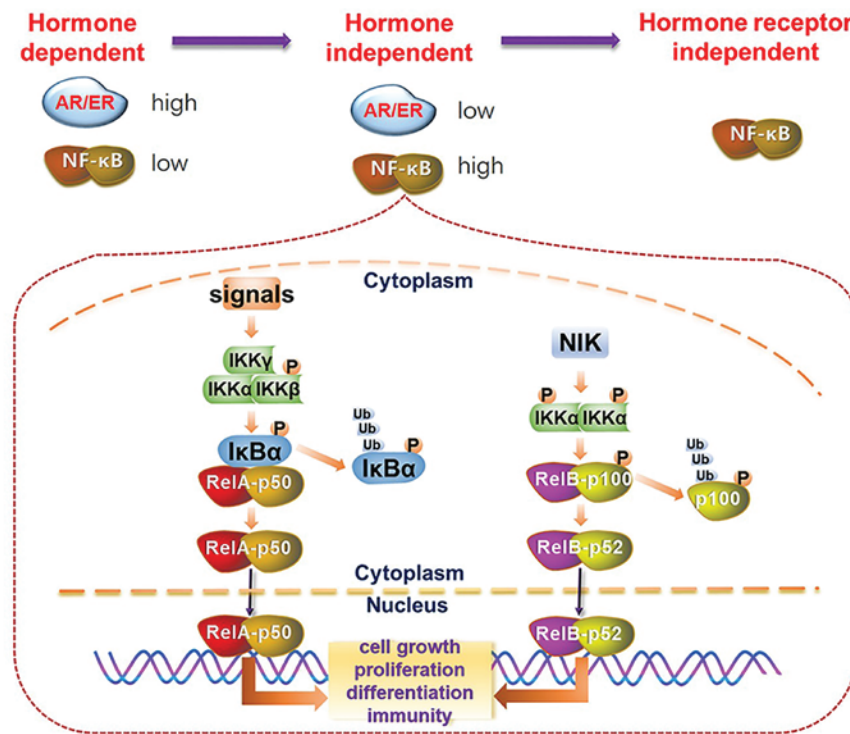


Figure 2. NF- κ B functional substitution of AR/ER for sustaining PCa/BCa progression. The interaction between androgen-AR in PCa or estrogen-ER in BCa is essential for the transcriptional regulation of hormone responsive gene expression and the initiation of PCa/BCa tumorigenesis. Along with malignant progression, AR and ER functions decline and tumors start to metastasize the nearby organs. NF- κ B dominantly activates metastasis-related gene transcription as a hormone-independent response. In general, the IKK-I κ B α -p50:RelA signaling axis is responsible for canonical NF- κ B pathway activation, while the NIK-IKK-p100:RelB-p52:RelB signaling axis is required for noncanonical NF- κ B pathway activation. AR, androgen receptor; ER, estrogen receptor; IKK, inhibitor of NF- κ B; PCa, prostate cancer; BCa, breast cancer; I κ B α , inhibitor of NF- κ B kinase subunit- α ; Ub, ubiquitin; P, phosphoric acid.

early-stage ER-positive BCa cells, NF- κ B activation has been shown to recruit ER to p53/estrogen response element motifs, resulting in increased ER transcriptional responses (68,69). Taken together, these findings predict that NF- κ B gradually replaces ER, from transcriptional cooperation in inflammatory BCa states to functional substitution in hormone refractory states. The activation of the NF- κ B pathway in the progression of hormone-deprived aggressive PCa and BCa is depicted in Fig. 2.

NF- κ B activation mechanism. NF- κ B is involved in various biological processes, such as cell survival, proliferation, differentiation and the immune response (70). Members of the NF- κ B family have a conserved Rel homology domain at their N-terminus, including RelA (p65), RelB, c-Rel, NF- κ B1 (p50) and NF- κ B2 (p52) (71,72). NF- κ B activation is divided into the canonical NF- κ B pathway and the noncanonical NF- κ B pathway. In the canonical NF- κ B pathway, stimulating ligands including the Toll-like superfamily, interleukin (IL)-1, TNF and other antigens interact with their receptors to recruit adaptors, such as TNF receptor associated factor (TRAF)2, TRAF3 and nuclear receptor subfamily 2 group C member 2, which activate the I κ B kinase complex (IKK α , IKK β and IKK γ /NEMO) to phosphorylate and then ubiquitinate I κ B α , leading to p50:RelA dimer nuclear translocation (73,74). By contrast, in the activation of the noncanonical NF- κ B pathway, NF- κ B-induced kinase stimulates IKK α to phosphorylate p100, resulting in the release of p52 and promoting p52:RelB nuclear translocation (75,76). However, evidence has shown

that p50 can also dimerize with RelB to activate the noncanonical NF- κ B pathway (76).

Role of the NF- κ B pathway in malignant PCa development. The activation of NF- κ B plays a crucial role in PCa progression. Ras (GTP binding protein) cooperates with NF- κ B and acts as a signal scaffold for metastatic promotion in PCa (77). In this context, it is well documented that NF- κ B-activated inflammation, including cytokines/chemokines, contributes to CRPC (61). For instance, androgen ablation results in regression of androgen-dependent PCa, in which IKK α -activated NF- κ B increases cytokine production leading to androgen-free proliferation (78). Importantly, constitutive activation of NF- κ B is highly associated with PCa resistance to both chemotherapy and radiotherapy (79).

Role of the NF- κ B pathway in advanced BCa development. Mounting evidence highlights that NF- κ B promotes BCa metastasis by activating the epithelial-mesenchymal transition (EMT) process, partially by upregulating IL-1 β and IL-6 (80). In malignant BCa, epidermal growth factor receptor is integrated with NF- κ B in the activation of IL-1, which promotes the invasive capacity of BCa cells (81). Additionally, IL-8 stimulates the PI3K-AKT-NF- κ B signaling axis, which in turn upregulates integrin β 1/ β 3 expression, leading to increased motility as well as enhanced chemoresistance and radioresistance in BCa cells (63). Furthermore, a previous study demonstrated that the NF- κ B-controlled proinflammatory cytokine network is important for the maintenance of

cancer stem cells in the regulation of BCa plasticity, suggesting that NF- κ B-mediated cytokine activation is critical for the recurrence of BCa after hormone therapy (82).

4. NF- κ B activation in endocrinotherapy resistance

Although most patients with PCa and BCa are responsive to endocrinotherapy initially, treatment resistance and tumor relapse remains a salient question in clinical supervision. Indeed, clinical outcomes indicate that hormone deprivation treatment somehow promotes the development of hormone-independent malignant tumor types (83,84). Accordingly, multiple mechanisms have been reported to be relevant to endocrinotherapy resistance, including activation of the NF- κ B pathway (47,83-87). Notably, the TNF- α , WNT5A, PI3K-AKT, Ras-Raf-ERK and transforming growth factor (TGF)- β 1-mitogen activated protein kinase (MAPK) signaling axes have been demonstrated to be important upstream signaling pathways of the NF- κ B pathway in both PCa and BCa (47,85,86,88-92).

As a typical redox responsible transcription factor, NF- κ B responds to stimulation with reactive oxygen species (ROS). In the regard, NADPH oxidase 4 leads to ROS production accompanied by mitochondrial respiration, thereby stimulating the NF- κ B pathway (88). Anticancer drugs such as TNF- α and adriamycin adapt to increase ROS, in turn induce antioxidant enzymes like manganese superoxide dismutase (MnSOD) through NF- κ B activation (88,89). The PI3K-AKT and Ras-Raf-ERK signaling axes have been shown to play pivotal roles in PCa/BCa progression by modulating NF- κ B in substitution for AR/ER (47,85,86,90-95). In particular, the activation of the PI3K-AKT-NF- κ B signaling axis has been well documented for the development of a hormone-independent phenotype as well as therapeutic resistance in both PCa and BCa (63,96,97). Notably, PI3K activation in PTEN-deficient PCa is a hallmark of an androgen-independent phenotype (17). The results of a previous study suggested a reciprocal feedback between the two oncogenic pathways (98). PI3K activation leads to repression of AR transcriptional output and, consistently, PI3K inhibition activates AR signaling. Conversely, AR inhibition promotes PI3K activity in PTEN-deficient PCa. Thus, combined AR and PI3K inhibition produces improved therapeutic responses (98). Since PI3K is a key upstream signaling molecule for activation of the NF- κ B pathway, this finding mechanistically elucidated the inverse association between AR and the NF- κ B pathway.

In addition, TGF- β 1-induced p38-MAPK signaling upregulates IL-6 expression due to RelA activation (99-101). RalBP1-associated Eps domain-containing protein 2 mediates RelA activation, and was also shown to promote androgen-independent growth (102). Nevertheless, NF- κ B has also been shown to cooperate with AR under androgen deprivation conditions; for instance, macrophage stimulating 1 receptor, a receptor tyrosine kinase, is able to activate NF- κ B, which is sufficient to drive AR nuclear localization under androgen deprivation condition and support CRPC growth (103).

Notably, the canonical NF- κ B pathway can actually induce the noncanonical NF- κ B pathway, thereby sustaining high NF- κ B activity (76,104). Additionally, several inducible agents have been demonstrated to directly activate the noncanonical NF- κ B pathway. WNT5A from bone stromal cells induces bone morphogenetic protein 6 (BMP-6) via RelB activation; in

turn, BMP-6 stimulates PCa cell proliferation via the interaction between Smad5 and β -catenin (28). In addition, WNT5A activates NF- κ B signaling to induce MMP7 expression, thereby contributing to the invasion of TNBC cells (105). A decrease in chicken ovalbumin upstream promoter transcription factor II results in endocrinotherapy resistance in BCa cells by activating the noncanonical NF- κ B pathway (106); whereas, fucoxanthin appears to be able to reverse BCa endocrinotherapy resistance by suppressing RelB activation (107). Overexpression of aryl hydrocarbon receptor (AhR) leads to the activation of RelB, in turn upregulating IL-8 expression in BCa cells (108,109). Ribonucleotide reductase M2 (RRM2) leads to increased RelB activity, thereby endowing tamoxifen resistance due to the upregulation of Bcl-2 in BCa cells (110). Overall, NF- κ B functions as a master switch, changing PCa/BCa from an AR/ER-positive phenotype to an AR/ER-negative phenotype (Fig. 3).

5. Main NF- κ B-regulated proteins in endocrinotherapy resistance

NF- κ B regulates a series of genes relevant to endocrinotherapy resistance. Particularly, it has been widely recognized that both canonical and noncanonical NF- κ B pathways are vital for resistance to hormone receptor-targeted treatment in PCa and BCa (52,53,58,60,111). As important NF- κ B-regulated proteins, Bcl-2, cyclin D1, IL-6 and IL-8 appeared to be critical for endocrinotherapy resistance in both PCa and BCa. The main NF- κ B regulated proteins associated with endocrinotherapy resistance are summarized in Fig. 4.

Effect of the canonical NF- κ B pathway in PCa endocrinotherapy resistance. Bcl-2, an important antiapoptotic protein, was upregulated in response to ROS-mediated NF- κ B activation, promoting therapeutic resistance (112). TNF- α -mediated RelA activation contributes to CRPC partially through upregulation of Bcl-2 (113). In addition, the activation of NF- κ B results in upregulation of IL-6, leading to castration resistance (114). Induction of IL-6 is important for hormone resistance, which is positively regulated by the canonical NF- κ B pathway, but negatively regulated by AP-1 (115). IL-8 also promotes the progression of CRPC through NF- κ B activation (116). NF- κ B-activated IL-4 has been shown to enhance AR function in PCa cells with an absence or low levels of androgen (117). Altogether, the feed-forward activation of NF- κ B-cytokines/chemokines is essential for the appearance of CRPC (118). In androgen-refractory PCa, the activation of canonical NF- κ B pathway significantly increases the disease-specific death due to AKT-mediated IKK phosphorylation (119). Furthermore, NF- κ B-enhanced EMT upregulates Twist1 in response to AR inhibition, leading to CRPC (120).

Effect of the canonical NF- κ B pathway in BCa endocrinotherapy resistance. Estrogen withdrawal leads to increased p50:RelA DNA binding activity and sustained estrogen-independent growth through upregulation of cyclin D1 and Bcl-3 (121). Moreover, NF- κ B-mediated upregulation of cyclin D1, urokinase and vascular endothelial growth factor contributes to endocrinotherapy resistance in high-risk ER-positive BCa (122). Immediate early gene X-1 expression is stimulated by tamoxifen through the binding of NF- κ B to the promoter (123). X-box binding protein 1

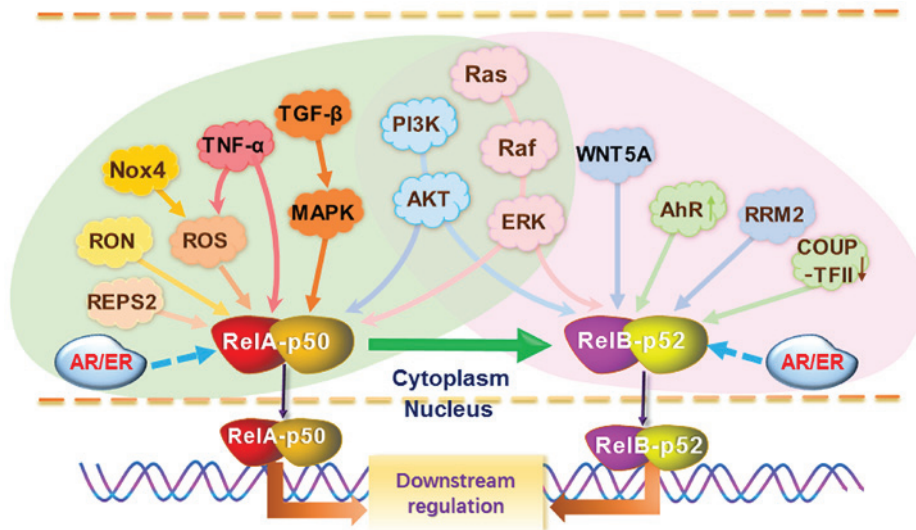


Figure 3. Upstream signaling involved in NF- κ B activation in the endocrinotherapy resistance of prostate cancer and breast cancer. The canonical NF- κ B pathway is stimulated by a cell signaling network, including TNF- α , RON, REPS2, PI3K-AKT, TGF- β -MAPK, Ras-Raf-ERK and treatment-induced ROS. While several regulators have been identified to be able to activate the noncanonical NF- κ B pathway, including WNT5A, COUP-TFII, AhR and RRM2. Particularly, PI3K-AKT and Ras-Raf-ERK function as vital upstream signals, are able to stimulate both canonical and noncanonical NF- κ B pathway. Importantly, the canonical NF- κ B pathway can further activate the noncanonical NF- κ B pathway to sustain the NF- κ B activity. TNF- α , tumor necrosis factor- α ; REPS2, RalBP1-associated Eps domain-containing protein 2; TGF- β , transforming growth factor- β ; MAPK, mitogen activated protein kinase; COUP-TFII, chicken ovalbumin upstream promoter transcription factor II; AhR, aryl hydrocarbon receptor; RRM2, ribonucleotide reductase M2; Nox4, NADPH oxidase 4; ROS, reactive oxygen species.

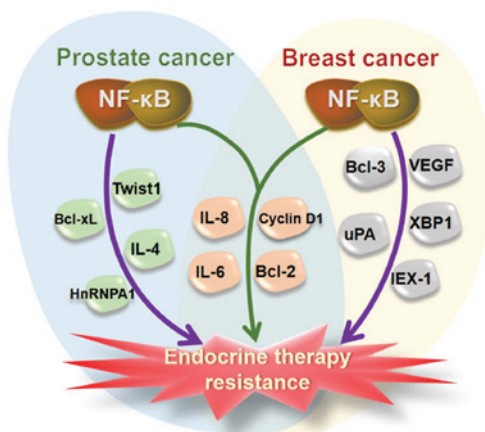


Figure 4. Downstream NF- κ B-regulated proteins involved in the endocrinotherapy resistance of PCa and BCa. Antiapoptotic protein Bcl-2, cell cycle regulator cyclin D1, cytokine IL-6 and IL-8 appear to be common factors in response to endocrinotherapy resistance in both PCa and BCa. PCa, prostate cancer; BCa, breast cancer; IL, interleukin; VEGF, vascular endothelial growth factor; HnRNPA1, c-Myc-dependent heterogeneous nuclear RNA-binding protein A1; uPA, urokinase-type plasminogen activator; XBP1, X-box binding protein 1; IEX-1, immediate early gene X-1.

is a key factor for antiestrogen resistance, the expression of which is regulated by modulating RelA (124). In tamoxifen-resistant BCa cells, NF- κ B activation results in an increase in IL-6 (125). In TNBC cells, the lipoprotein(a)-lysophosphatidic acid receptor 2-enhancer of zeste 2 polycomb repressive complex 2 subunit-NF- κ B signaling cascade is required for the coordinated autocrine effect of IL-6 and IL-8 (126). As expected, Bcl-2 is upregulated by the canonical NF- κ B pathway in response to tamoxifen (127). Similar to PCa, the activation of the PI3K-AKT-NF- κ B signaling axis is highly associated with endocrinotherapy resistance in BCa (128).

Emerging role of the noncanonical NF- κ B pathway in endocrinotherapy resistance. In contrast to the well-studied p50:RelA activation described above, the role of p52:RelB in cancer responses to treatment remains elusive. Indeed, the noncanonical NF- κ B pathway exerts even more effects in metastasis and therapeutic resistance rather than in tumorigenesis. p52:RelB can activate AR-responsive genes, such as PSA and NKX3.1 (a prostate-specific tumor suppressor) in a ligand-independent manner, suggesting that the noncanonical NF- κ B pathway also plays a supporting role in CRPC progression (129). In addition, p52:RelB activation increases PCa cell survival and proliferation by upregulating Bcl-xL and cyclin D1 (130-132). Moreover, p52:RelB activation contributes to resistance to AR-targeted therapies through regulation of multiple signaling pathways, such as by modulating AR (60), upregulating c-Myc-dependent heterogeneous nuclear RNA-binding protein A1 (133), and enhancing glucose flux to the glycolysis and pentose phosphate pathways (134). Consistent with PCa, RelB is also highly expressed in hormone therapy-resistant BCa cells (111). Fucoxanthin appears to be able to reverse hormone therapy resistance by suppressing p52:RelB (107). Overexpression of AhR and RRM2 leads to the activation of RelB, thereby endowing tamoxifen resistance due to the upregulation of Bcl-2 and IL-8 (111). MEK-mediated p52 activation is required for TNBC growth and drug resistance (135). Overexpression of HOXB13 (a homeobox protein) enhances RelB nuclear translocation and contributes to therapeutic resistance (136).

6. NF- κ B as a target in PCa and BCa treatment

Since NF- κ B contributes to endocrinotherapy resistance in PCa and BCa, NF- κ B-targeted therapy has frequently been applied to enhance endocrinotherapy. Nitric oxide donors sensitize Trail-mediated apoptosis via inhibition of Bcl-xL through

inactivation of NF- κ B (137). IL-6, a NF- κ B-regulated cytokine, contributes to androgen-independent PCa progression. Inhibition of IL-6 enhances the sensitivity of PCa to docetaxel (138). NF- κ B activation in ARVs associated with CRPC leads to anti-androgen therapy resistance. Repression of NF- κ B enhances the efficiency of hormone therapy (59). Notably, *Wedelia chinensis* herbal extract has been shown not merely to inhibit AR activity in androgen-dependent PCa, but also to suppress the expression of IKK α / β phosphorylation in hormone-independent PCa cells (139). In BCa, NSC35446, a hydrochloride salt compound, is able to inhibit anti-estrogenic tumor growth and reverse antiestrogen resistance by targeting NF- κ B (140). Additionally, ivermectin reverses chemotherapeutic resistance via suppression of NF- κ B-activated P-gp expression (141). Importantly, a number of compounds appear to efficiently treat both aggressive PCa and BCa via repression of NF- κ B-mediated transcriptional activation. Curcumin, an inhibitor of the NF- κ B canonical pathway, is able to inhibit the hormone-mediated invasion of BCa (142). The combination of curcumin and bicalutamide enhances the growth inhibition of androgen-independent PCa cells (143), while 1 α ,25-dihydroxyvitamin D3 has been reported to repress the NF- κ B noncanonical pathway, which strongly reduces the growth of drug-resistant BCa cells and enhances the radiosensitivity of PCa cells (144,145). Parthenolide, a native compound that functions as an NF- κ B repressor, has been shown to restore the sensitivity of tamoxifen to endocrine-resistant BCa cells and to enhance PCa cell radiosensitivity (146-148).

7. Conclusions and perspectives

Endocrinotherapy resistance and tumor relapse are major challenges in treating advanced PCa and BCa. The progression from hormone-dependence to hormone-independence has been widely recognized to be one of main causes of endocrinotherapy resistance. Therefore, the molecular basis for the failure of treatments targeting AR or ER has been well investigated. This review reorganized the molecular mechanisms underlining endocrinotherapy resistance and concluded that NF- κ B is the most important transcription regulator in activating the expression of a series of genes, leading to the acquisition of the endocrinotherapy resistance. In the majority of cases, NF- κ B functionally substitutes AR or ER in transcriptional regulation for sustaining tumor cell survival and proliferation, by activating a different set of genes when the efficacy of AR/ER-targeted treatments declines. It should be noted, however, the inverse association between AR/ER and NF- κ B is not persistent during the progression of PCa and BCa; in particular, a few case studies have demonstrated that RelA can cooperate with AR in transcriptional regulation when androgen deprivation treatment fails (103). Additionally, although the NF- κ B pathway is thought to serve as a key mechanism underlying endocrinotherapy resistance, other signaling pathways, such as Myc, Stat3 and Wnt, also play regulatory roles in the acquisition of therapeutic resistance. Furthermore, NF- κ B also plays a crucial role in the radioresistance of PCa and BCa through upregulation of antioxidant and antiapoptotic proteins, including MnSOD and Bcl-2 (149).

The present review also outlined that several upstream signaling pathways engage to trigger the NF- κ B pathway; in particular, PI3K-AKT upstream signaling activates the NF- κ B

pathway in response to oxidative stress and inflammatory stimulation. Importantly, the cytokine/chemokine-NF- κ B signaling feed-forward loop is indispensable for the acquisition of endocrinotherapy resistance. It was recently concluded that TGF- β , IL-6, IL-8 and TNF- α are the most important cytokines associated with multidrug resistance in BCa (150). These four cytokines are typical NF- κ B-regulated proteins, and increased levels of inflammation in turn activate the NF- κ B pathway, which promotes endocrinotherapy resistance.

Distant organ metastasis associated with multidrug resistance precludes successful treatment. A myriad of studies have demonstrated that RelA-activated canonical NF- κ B pathway is critical for cancer progression and therapeutic resistance (82,103,110,124,151-153). However, the effect of the RelB-activated noncanonical NF- κ B pathway is underestimated. Indeed, RelA can upregulate RelB, leading to sustained long-term NF- κ B activity in cancer progression (76). Since the function of RelA is essential for normal physiological development, the failure of anticancer treatment by targeting RelA may be caused by either low therapeutic efficacy or unexpected side effects. It has been demonstrated that RelB is uniquely expressed at a high level in advanced PCa, which contributes to therapeutic resistance (149,154). Accordingly, blockage of RelB nuclear translocation has the effect of reversing resistance to treatment in AR-negative PCa (155). Thus, the inactivation of the noncanonical NF- κ B pathway may provide a promising approach to the treatment of advanced PCa and BCa when AR/ER-targeted therapeutic efficiency declines.

In summary, this review emphasized the importance of NF- κ B in the acquisition of endocrinotherapy resistance in PCa and BCa, suggesting that inhibition of the NF- κ B pathway may overcome endocrinotherapy resistance and should be beneficial in developing comprehensive treatment strategies to control malignant PCa and BCa. In addition to the well-documented canonical NF- κ B pathway, the noncanonical NF- κ B pathway remains to be fully elucidated. Emerging evidence predicts that RelB may exert an even greater effect than RelA on metastasis and therapeutic resistance, based on its capacity for maintaining NF- κ B activity. Of further interest, therefore, is why and how the noncanonical NF- κ B pathway contributes to cancer progression and therapeutic resistance. To that end, this review is expected to shed light on future in-depth investigations into NF- κ B function to advance the treatment of PCa/BCa therapeutic resistance.

Acknowledgements

Not applicable.

Funding

This work was supported by National Natural Science Foundation of China Research Grants (grant no. 81572742) and National Program Project for Precision Medicine in National Research and Development Plan, China (grant no. 2016YFC0905900), and the National Natural Science Foundation of China (grant nos. 81274158 and 81873131).

Availability of data and materials

Not applicable.

Authors' contributions

XW and YX conceived and wrote the review. XW, YF, WS, ZX and YZ collected and organized the literature. XW, XD and YX supervised the work and provided administrative, technical and material support. All authors read and approved the content of the review.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 68: 394-424, 2018.
- Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ and He J: Cancer statistics in China, 2015. *CA Cancer J Clin* 66: 115-132, 2016.
- Feldman BJ and Feldman D: The development of androgen-independent prostate cancer. *Nat Rev Cancer* 1: 34-45, 2001.
- Rhodes LV, Short SP, Neel NF, Salvo VA, Zhu Y, Elliott S, Wei Y, Yu D, Sun M, Muir SE, *et al*: Cytokine receptor CXCR4 mediates estrogen-independent tumorigenesis, metastasis, and resistance to endocrine therapy in human breast cancer. *Cancer Res* 71: 603-613, 2011.
- Debes JD and Tindall DJ: The role of androgens and the androgen receptor in prostate cancer. *Cancer Lett* 187: 1-7, 2002.
- Duffy MJ: Estrogen receptors: Role in breast cancer. *Crit Rev Clin Lab Sci* 43: 325-347, 2006.
- Balk SP and Knudsen KE: AR, the cell cycle, and prostate cancer. *Nucl Recept Signal* 6: e001, 2008.
- Lamb AD, Massie CE and Neal DE: The transcriptional programme of the androgen receptor (AR) in prostate cancer. *BJU Int* 113: 358-366, 2014.
- Russo J and Russo IH: The role of estrogen in the initiation of breast cancer. *J Steroid Biochem Mol Biol* 102: 89-96, 2006.
- Yue W, Wang JP, Li Y, Fan P, Liu G, Zhang N, Conaway M, Wang H, Korach KS, Bocchinfuso W, *et al*: Effects of estrogen on breast cancer development: Role of estrogen receptor independent mechanisms. *Int J Cancer* 127: 1748-1757, 2010.
- Samavat H and Kurzer MS: Estrogen metabolism and breast cancer. *Cancer Lett* 356: 231-243, 2015.
- DeMichele A and Chodosh LA: 'Braking' the cycle of resistance in endocrine therapy for breast cancer. *Clin Cancer Res* 21: 4999-5001, 2015.
- Horwich A, Parker C, de Reijke T, Kataja V; ESMO Guidelines Working Group: Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 24 (Suppl 6): vi106-vi114, 2013.
- Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, Mason M, Matveev V, Wiegel T, Zattoni F, *et al*: European Association of Urology: EAU guidelines on prostate cancer. Part I: Screening, diagnosis, and local treatment with curative intent-update 2013. *Eur Urol* 65: 124-137, 2014.
- Mohler JL, Armstrong AJ, Bahnson RR, D'Amico AV, Davis BJ, Eastham JA, Enke CA, Farrington TA, Higano CS, Horwitz EM, *et al*: Prostate cancer, version 1.2016. *J Natl Compr Canc Netw* 14: 19-30, 2016.
- Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, Mason M, Matveev V, Wiegel T, Zattoni F, *et al*: European Association of Urology: EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol* 65: 467-479, 2014.
- Wise HM, Hermida MA and Leslie NR: Prostate cancer, PI3K, PTEN and prognosis. *Clin Sci (Lond)* 131: 197-210, 2017.
- Bilusic M, Madan RA and Gulley JL: Immunotherapy of prostate cancer: Facts and hopes. *Clin Cancer Res* 23: 6764-6770, 2017.
- Kim YJ, Jung SY and Kim K: Survival benefit of radiotherapy after surgery in de novo stage IV breast cancer: A population-based propensity-score matched analysis. *Sci Rep* 9: 8527, 2019.
- Yao Y, Chu Y, Xu B, Hu Q and Song Q: Radiotherapy after surgery has significant survival benefits for patients with triple-negative breast cancer. *Cancer Med* 8: 554-563, 2019.
- Rugo HS, Rumble RB, Macrae E, Barton DL, Connolly HK, Dickler MN, Fallowfield L, Fowble B, Ingle JN, Jahanzeb M, *et al*: Endocrine therapy for hormone receptor-positive metastatic breast cancer: American society of clinical oncology guideline. *J Clin Oncol* 34: 3069-3103, 2016.
- Alvarez López I, de la Haba Rodríguez J, Ruiz Simón A, Bellet Ezquerro M, Calvo Martínez L, García Estévez L, Rodríguez Lescure Á and Isla Casado D; SEOM (Spanish Society for Medical Oncology): SEOM clinical guidelines for the treatment of metastatic breast cancer. *Clin Transl Oncol* 12: 719-723, 2010.
- Senkus E, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rutgers E, Zackrisson S, Cardoso F and Committee EG; ESMO Guidelines Committee: Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 26 (Suppl 5): v8-v30, 2015.
- Goetz MP, Gradishar WJ, Anderson BO, Abraham J, Aft R, Allison KH, Blair SL, Burstein HJ, Dang C, Elias AD, *et al*: NCCN guidelines insights: Breast cancer, version 3.2018. *J Natl Compr Canc Netw* 17: 118-126, 2019.
- Ahmed S, Sami A and Xiang J: HER2-directed therapy: Current treatment options for HER2-positive breast cancer. *Breast Cancer* 22: 101-116, 2015.
- Esteve FJ, Hubbard-Lucey VM, Tang J and Pusztai L: Immunotherapy and targeted therapy combinations in metastatic breast cancer. *Lancet Oncol* 20: e175-e186, 2019.
- Tremont-Lukats IW, Bobustuc G, Lagos GK, Lolas K, Kyritsis AP and Puduvalli VK: Brain metastasis from prostate carcinoma: The M.D. Anderson Cancer Center experience. *Cancer* 98: 363-368, 2003.
- Lee GT, Kang DI, Ha YS, Jung YS, Chung J, Min K, Kim TH, Moon KH, Chung JM, Lee DH, *et al*: Prostate cancer bone metastases acquire resistance to androgen deprivation via WNT5A-mediated BMP-6 induction. *Br J Cancer* 110: 1634-1644, 2014.
- Bergen ES, Berghoff AS, Medjedovic M, Rudas M, Fitzal F, Bago-Horvath Z, Dieckmann K, Mader RM, Exner R, Gnant M, *et al*: Continued endocrine therapy is associated with improved survival in patients with breast cancer brain metastases. *Clin Cancer Res* 25: 2737-2744, 2019.
- Yao B, Wang J, Qu S, Liu Y, Jin Y, Lu J, Bao Q, Li L, Yuan H and Ma C: Upregulated osterix promotes invasion and bone metastasis and predicts for a poor prognosis in breast cancer. *Cell Death Dis* 10: 28, 2019.
- Mangelsdorf DJ, Thummel C, Beato M, Herrlich P, Schütz G, Umesono K, Blumberg B, Kastner P, Mark M, Chambon P, *et al*: The nuclear receptor superfamily: The second decade. *Cell* 83: 835-839, 1995.
- Girdler F and Brotherick I: The oestrogen receptors (ER alpha and ER beta) and their role in breast cancer: A review. *Breast* 9: 194-200, 2000.
- Suzuki H, Ueda T, Ichikawa T and Ito H: Androgen receptor involvement in the progression of prostate cancer. *Endocr Relat Cancer* 10: 209-216, 2003.
- Carroll JS: Mechanisms of oestrogen receptor (ER) gene regulation in breast cancer. *Eur J Endocrinol* 175: R41-R49, 2016.
- Russell DW and Wilson JD: Steroid 5 alpha-reductase: Two genes/two enzymes. *Annu Rev Biochem* 63: 25-61, 1994.
- Marcelli M and Cunningham GR: Hormonal signaling in prostatic hyperplasia and neoplasia. *J Clin Endocrinol Metab* 84: 3463-3468, 1999.
- Sommer S and Fuqua SA: Estrogen receptor and breast cancer. *Semin Cancer Biol* 11: 339-352, 2001.
- Alluri PG, Speers C and Chinnaiyan AM: Estrogen receptor mutations and their role in breast cancer progression. *Breast Cancer Res* 16: 494, 2014.
- Mc Cormack O, Chung WY, Fitzpatrick P, Cooke F, Flynn B, Harrison M, Fox E, Gallagher E, McGoldrick A, Dervan PA, *et al*: Progesterone receptor B (PRB) promoter hypermethylation in sporadic breast cancer: Progesterone receptor B hypermethylation in breast cancer. *Breast Cancer Res Treat* 111: 45-53, 2008.

40. Wang H, Lee EW, Zhou L, Leung PC, Ross DD, Unadkat JD and Mao Q: Progesterone receptor (PR) isoforms PRA and PRB differentially regulate expression of the breast cancer resistance protein in human placental choriocarcinoma BeWo cells. *Mol Pharmacol* 73: 845-854, 2008.
41. Wu X, Zhang X, Zhang H, Su P, Li W, Li L, Wang Y, Liu W, Gao P and Zhou G: Progesterone receptor downregulates breast cancer resistance protein expression via binding to the progesterone response element in breast cancer. *Cancer Sci* 103: 959-967, 2012.
42. Grimm SL, Hartig SM and Edwards DP: Progesterone receptor signaling mechanisms. *J Mol Biol* 428: 3831-3849, 2016.
43. Dowsett M: Overexpression of HER-2 as a resistance mechanism to hormonal therapy for breast cancer. *Endocr Relat Cancer* 8: 191-195, 2001.
44. Kurokawa H and Arteaga CL: ErbB (HER) receptors can abrogate antiestrogen action in human breast cancer by multiple signaling mechanisms. *Clin Cancer Res* 9: 511S-515S, 2003.
45. Hsu JL and Hung MC: The role of HER2, EGFR, and other receptor tyrosine kinases in breast cancer. *Cancer Metastasis Rev* 35: 575-588, 2016.
46. Järvinen TAH, Peltö-Huikko M, Holli K and Isola J: Estrogen receptor beta is coexpressed with ERalpha and PR and associated with nodal status, grade, and proliferation rate in breast cancer. *Am J Pathol* 156: 29-35, 2000.
47. Fan W, Chang J and Fu P: Endocrine therapy resistance in breast cancer: Current status, possible mechanisms and overcoming strategies. *Future Med Chem* 7: 1511-1519, 2015.
48. Ding J, Wang X, Zhang Y, Sang X, Yi J, Liu C, Liu Z, Wang M, Zhang N, Xue Y, *et al*: Inhibition of BTF3 sensitizes luminal breast cancer cells to PI3Kα inhibition through the transcriptional regulation of ERα. *Cancer Lett* 440-441: 54-63, 2019.
49. Blessing AM, Rajapakshe K, Reddy Bollu L, Shi Y, White MA, Pham AH, Lin C, Jonsson P, Cortes CJ, Cheung E, *et al*: Transcriptional regulation of core autophagy and lysosomal genes by the androgen receptor promotes prostate cancer progression. *Autophagy* 13: 506-521, 2017.
50. McCartan D, Bolger JC, Fagan A, Byrne C, Hao Y, Qin L, McLlroy M, Xu J, Hill AD, Gaora PO, *et al*: Global characterization of the SRC-1 transcriptome identifies ADAM22 as an ER-independent mediator of endocrine-resistant breast cancer. *Cancer Res* 72: 220-229, 2012.
51. Sahin I, Mega AE and Carneiro BA: Androgen receptor-independent prostate cancer: An emerging clinical entity. *Cancer Biol Ther* 19: 347-348, 2018.
52. Chen CD and Sawyers CL: NF-kappa B activates prostate-specific antigen expression and is upregulated in androgen-independent prostate cancer. *Mol Cell Biol* 22: 2862-2870, 2002.
53. Zhou Y, Eppenberger-Castori S, Eppenberger U and Benz CC: The NFkappaB pathway and endocrine-resistant breast cancer. *Endocr Relat Cancer* 12 (Suppl 1): S37-S46, 2005.
54. Oida K, Matsuda A, Jung K, Xia Y, Jang H, Amagai Y, Ahn G, Nishikawa S, Ishizaka S, Jensen-Jarolim E, *et al*: Nuclear factor-κB plays a critical role in both intrinsic and acquired resistance against endocrine therapy in human breast cancer cells. *Sci Rep* 4: 4057, 2014.
55. Malinen M, Niskanen EA, Kaikkonen MU and Palvimo JJ: Crosstalk between androgen and pro-inflammatory signaling remodels androgen receptor and NF-κB cistrome to reprogram the prostate cancer cell transcriptome. *Nucleic Acids Res* 45: 619-630, 2017.
56. Péant B, Diallo JS, Lessard L, Delvoye N, Le Page C, Saad F and Mes-Masson AM: Regulation of IkappaB kinase epsilon expression by the androgen receptor and the nuclear factor-kappaB transcription factor in prostate cancer. *Mol Cancer Res* 5: 87-94, 2007.
57. Yuan X, Cai C, Chen S, Chen S, Yu Z and Balk SP: Androgen receptor functions in castration-resistant prostate cancer and mechanisms of resistance to new agents targeting the androgen axis. *Oncogene* 33: 2815-2825, 2014.
58. Zhang L, Altuwajiri S, Deng F, Chen L, Lal P, Bhanot UK, Korets R, Wenske S, Lilja HG, Chang C, *et al*: NF-kappaB regulates androgen receptor expression and prostate cancer growth. *Am J Pathol* 175: 489-499, 2009.
59. Jin R, Yamashita H, Yu X, Wang J, Franco OE, Wang Y, Hayward SW and Matusik RJ: Inhibition of NF-kappa B signaling restores responsiveness of castrate-resistant prostate cancer cells to anti-androgen treatment by decreasing androgen receptor-variant expression. *Oncogene* 34: 3700-3710, 2015.
60. Nadiminty N, Tummala R, Liu C, Yang J, Lou W, Evans CP and Gao AC: NF-κB2/p52 induces resistance to enzalutamide in prostate cancer: Role of androgen receptor and its variants. *Mol Cancer Ther* 12: 1629-1637, 2013.
61. Staal J and Beyaert R: Inflammation and NF-kappaB signaling in prostate cancer: Mechanisms and clinical implications. *Cells* 7: 7, 2018.
62. Sas L, Lardon F, Vermeulen PB, Hauspy J, Van Dam P, Pauwels P, Dirix LY and Van Laere SJ: The interaction between ER and NFκB in resistance to endocrine therapy. *Breast Cancer Res* 14: 212, 2012.
63. Shao N, Lu Z, Zhang Y, Wang M, Li W, Hu Z, Wang S and Lin Y: Interleukin-8 upregulates integrin β3 expression and promotes estrogen receptor-negative breast cancer cell invasion by activating the PI3K/Akt/NF-κB pathway. *Cancer Lett* 364: 165-172, 2015.
64. Nakshatri H Jr, Bhat-Nakshatri P, Martin DA, Goulet RJ Jr and Sledge GW Jr: Constitutive activation of NF-kappaB during progression of breast cancer to hormone-independent growth. *Mol Cell Biol* 17: 3629-3639, 1997.
65. Belguise K and Sonenshein GE: PKCθ promotes c-Rel-driven mammary tumorigenesis in mice and humans by repressing estrogen receptor alpha synthesis. *J Clin Invest* 117: 4009-4021, 2007.
66. Wang X, Belguise K, Kersual N, Kirsch KH, Mineva ND, Galtier F, Chabos D and Sonenshein GE: Oestrogen signalling inhibits invasive phenotype by repressing RelB and its target BCL2. *Nat Cell Biol* 9: 470-478, 2007.
67. Wang X, Belguise K, O'Neill CF, Sánchez-Morgan N, Romagnoli M, Eddy SF, Mineva ND, Yu Z, Min C, Trinkaus-Randall V, *et al*: RelB NF-kappaB represses estrogen receptor alpha expression via induction of the zinc finger protein Blimp1. *Mol Cell Biol* 29: 3832-3844, 2009.
68. Pradhan M, Baumgarten SC, Bembinster LA and Frasor J: CBP mediates NF-κB-dependent histone acetylation and estrogen receptor recruitment to an estrogen response element in the BIRC3 promoter. *Mol Cell Biol* 32: 569-575, 2012.
69. Frasor J, El-Shennawy L, Stender JD and Kastrati I: NFκB affects estrogen receptor expression and activity in breast cancer through multiple mechanisms. *Mol Cell Endocrinol* 418: 235-239, 2015.
70. Zeligs KP, Neuman MK and Annunziata CM: Molecular pathways: The balance between cancer and the immune system challenges the therapeutic specificity of targeting nuclear factor-κB signaling for cancer treatment. *Clin Cancer Res* 22: 4302-4308, 2016.
71. Sun SC: Non-canonical NF-κB signaling pathway. *Cell Res* 21: 71-85, 2011.
72. Kastrati I, Siklos MI, Calderon-Gierszal EL, El-Shennawy L, Georgieva G, Thayer EN, Thatcher GR and Frasor J: Dimethyl fumarate inhibits the nuclear factor κB pathway in breast cancer cells by covalent modification of p65 protein. *J Biol Chem* 291: 3639-3647, 2016.
73. Vrabel D, Pour L and Ševčíková S: The impact of NF-κB signaling on pathogenesis and current treatment strategies in multiple myeloma. *Blood Rev* 34: 56-66, 2019.
74. Park MH and Hong JT: Roles of NF-κB in cancer and inflammatory diseases and their therapeutic approaches. *Cells* 5: 5, 2016.
75. Maubach G, Feige MH, Lim MCC and Naumann M: NF-kappaB-inducing kinase in cancer. *Biochim Biophys Acta Rev Cancer* 1871: 40-49, 2019.
76. Gray CM, Remouchamps C, McCorkell KA, Solt LA, Dejardin E, Orange JS and May MJ: Noncanonical NF-κB signaling is limited by classical NF-κB activity. *Sci Signal* 7: ra13, 2014.
77. Min J, Zaslavsky A, Fedele G, McLaughlin SK, Reczek EE, De Raedt T, Guney I, Strohlic DE, Macconail LE, Beroukhim R, *et al*: An oncogene-tumor suppressor cascade drives metastatic prostate cancer by coordinately activating Ras and nuclear factor-kappaB. *Nat Med* 16: 286-294, 2010.
78. Ammirante M, Luo JL, Grivnenikov S, Nedospasov S and Karin M: B-cell-derived lymphotoxin promotes castration-resistant prostate cancer. *Nature* 464: 302-305, 2010.
79. Mendonca MS, Turchan WT, Alpuche ME, Watson CN, Estabrook NC, Chin-Sinex H, Shapiro JB, Imasuen-Williams IE, Rangel G, Gilley DP, *et al*: DMAPT inhibits NF-κB activity and increases sensitivity of prostate cancer cells to X-rays in vitro and in tumor xenografts in vivo. *Free Radic Biol Med* 112: 318-326, 2017.
80. Kendellen MF, Bradford JW, Lawrence CL, Clark KS and Baldwin AS: Canonical and non-canonical NF-κB signaling promotes breast cancer tumor-initiating cells. *Oncogene* 33: 1297-1305, 2014.
81. Streicher KL, Willmarth NE, Garcia J, Boerner JL, Dewey TG and Ethier SP: Activation of a nuclear factor kappaB/interleukin-1 positive feedback loop by amphiregulin in human breast cancer cells. *Mol Cancer Res* 5: 847-861, 2007.

82. Saha S, Mukherjee S, Khan P, Kajal K, Mazumdar M, Manna A, Mukherjee S, De S, Jana D, Sarkar DK, *et al*: Aspirin suppresses the acquisition of chemoresistance in breast cancer by disrupting an NF κ B-IL6 signaling axis responsible for the generation of cancer stem cells. *Cancer Res* 76: 2000-2012, 2016.
83. Watson PA, Arora VK and Sawyers CL: Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer. *Nat Rev Cancer* 15: 701-711, 2015.
84. Stender JD, Nwachukwu JC, Kastrati I, Kim Y, Strid T, Yakir M, Srinivasan S, Nowak J, Izard T, Rangarajan ES, *et al*: Structural and molecular mechanisms of cytokine-mediated endocrine resistance in human breast cancer cells. *Mol Cell* 65: 1122-1135. e1125, 2017.
85. Osborne CK and Schiff R: Mechanisms of endocrine resistance in breast cancer. *Annu Rev Med* 62: 233-247, 2011.
86. Karantanos T, Evans CP, Tombal B, Thompson TC, Montironi R and Isaacs WB: Understanding the mechanisms of androgen deprivation resistance in prostate cancer at the molecular level. *Eur Urol* 67: 470-479, 2015.
87. Crona DJ and Whang YE: Androgen receptor-dependent and -independent mechanisms involved in prostate cancer therapy resistance. *Cancers (Basel)* 9: 9, 2017.
88. Lee JW, Kim GY and Kim JH: Androgen receptor is up-regulated by a BLT2-linked pathway to contribute to prostate cancer progression. *Biochem Biophys Res Commun* 420: 428-433, 2012.
89. Penney RB and Roy D: Thioredoxin-mediated redox regulation of resistance to endocrine therapy in breast cancer. *Biochim Biophys Acta* 1836: 60-79, 2013.
90. Bakin RE, Gioeli D, Bissonette EA and Weber MJ: Attenuation of Ras signaling restores androgen sensitivity to hormone-refractory C4-2 prostate cancer cells. *Cancer Res* 63: 1975-1980, 2003.
91. Mulholland DJ, Kobayashi N, Ruscetti M, Zhi A, Tran LM, Huang J, Gleave M and Wu H: Pten loss and RAS/MAPK activation cooperate to promote EMT and metastasis initiated from prostate cancer stem/progenitor cells. *Cancer Res* 72: 1878-1889, 2012.
92. Heckler MM, Thakor H, Schafer CC and Riggins RB: ERK/MAPK regulates ERR γ expression, transcriptional activity and receptor-mediated tamoxifen resistance in ER⁺ breast cancer. *FEBS J* 281: 2431-2442, 2014.
93. Hong SK, Jeong JH, Chan AM and Park JI: AKT upregulates B-Raf Ser445 phosphorylation and ERK1/2 activation in prostate cancer cells in response to androgen depletion. *Exp Cell Res* 319: 1732-1743, 2013.
94. Wang H, Zhang L, Fu Y, Fang F, Jiang Y, Dong Y and Zhu W: CSL regulates AKT to mediate androgen independence in prostate cancer progression. *Prostate* 76: 140-150, 2016.
95. Lu S, Ren C, Liu Y and Epper DE: PI3K-Akt signaling is involved in the regulation of p21(WAF/CIP) expression and androgen-independent growth in prostate cancer cells. *Int J Oncol* 28: 245-251, 2006.
96. Lee SO, Lou W, Nadiminty N, Lin X and Gao AC: Requirement for NF-(kappa)B in interleukin-4-induced androgen receptor activation in prostate cancer cells. *Prostate* 64: 160-167, 2005.
97. Rodriguez M, Luo W, Weng J, Zeng L, Yi Z, Siwko S and Liu M: PSGR promotes prostatic intraepithelial neoplasia and prostate cancer xenograft growth through NF- κ B. *Oncogenesis* 3: e114, 2014.
98. Carver BS, Chapinski C, Wongvipat J, Hieronymus H, Chen Y, Chandralapaty S, Arora VK, Le C, Koutcher J, Scher H, *et al*: Reciprocal feedback regulation of PI3K and androgen receptor signaling in PTEN-deficient prostate cancer. *Cancer Cell* 19: 575-586, 2011.
99. Park JI, Lee MG, Cho K, Park BJ, Chae KS, Byun DS, Ryu BK, Park YK and Chi SG: Transforming growth factor-beta1 activates interleukin-6 expression in prostate cancer cells through the synergistic collaboration of the Smad2, p38-NF-kappaB, JNK, and Ras signaling pathways. *Oncogene* 22: 4314-4332, 2003.
100. Holloway JN, Murthy S and El-Ashry D: A cytoplasmic substrate of mitogen-activated protein kinase is responsible for estrogen receptor-alpha down-regulation in breast cancer cells: The role of nuclear factor-kappaB. *Mol Endocrinol* 18: 1396-1410, 2004.
101. Tian M and Schiemann WP: TGF-beta stimulation of EMT programs elicits non-genomic ER-alpha activity and anti-estrogen resistance in breast cancer cells. *J Cancer Metastasis Treat* 3: 150-160, 2017.
102. Penninkhof F, Grootegeed JA and Blok LJ: Identification of REPS2 as a putative modulator of NF-kappaB activity in prostate cancer cells. *Oncogene* 23: 5607-5615, 2004.
103. Brown NE, Paluch AM, Nashu MA, Komurov K and Waltz SE: Tumor cell autonomous RON receptor expression promotes prostate cancer growth under conditions of androgen deprivation. *Neoplasia* 20: 917-929, 2018.
104. House CD, Jordan E, Hernandez L, Ozaki M, James JM, Kim M, Kruhlak MJ, Batchelor E, Elloumi F, Cam MC, *et al*: NFkappaB promotes ovarian tumorigenesis via classical pathways that support proliferative cancer cells and alternative pathways that support ALDH(+) cancer stem-like cells. *Cancer Res* 77: 6927-6940, 2017.
105. Han B, Zhou B, Qu Y, Gao B, Xu Y, Chung S, Tanaka H, Yang W, Giuliano AE and Cui X: FOXC1-induced non-canonical WNT5A-MMP7 signaling regulates invasiveness in triple-negative breast cancer. *Oncogene* 37: 1399-1408, 2018.
106. Litchfield LM, Appana SN, Datta S and Klinge CM: COUP-TFII inhibits NFkappaB activation in endocrine-resistant breast cancer cells. *Mol Cell Endocrinol* 382: 358-367, 2014.
107. Rwigemera A, Mamelona J and Martin LJ: Inhibitory effects of fucoxanthinol on the viability of human breast cancer cell lines MCF-7 and MDA-MB-231 are correlated with modulation of the NF-kappaB pathway. *Cell Biol Toxicol* 30: 157-167, 2014.
108. Vogel CF, Li W, Wu D, Miller JK, Sweeney C, Lazennec G, Fujisawa Y and Matsumura F: Interaction of aryl hydrocarbon receptor and NF- κ B subunit RelB in breast cancer is associated with interleukin-8 overexpression. *Arch Biochem Biophys* 512: 78-86, 2011.
109. Bekki K, Vogel H, Li W, Ito T, Sweeney C, Haarmann-Stemmann T, Matsumura F and Vogel CF: The aryl hydrocarbon receptor (AhR) mediates resistance to apoptosis induced in breast cancer cells. *Pestic Biochem Physiol* 120: 5-13, 2015.
110. Shah KN, Wilson EA, Malla R, Elford HL and Faridi JS: Targeting ribonucleotide reductase M2 and NF-kappaB activation with didox to circumvent tamoxifen resistance in breast cancer. *Mol Cancer Ther* 14: 2411-2421, 2015.
111. Yde CW, Emdal KB, Guerra B and Lykkesfeldt AE: NF κ B signaling is important for growth of antiestrogen resistant breast cancer cells. *Breast Cancer Res Treat* 135: 67-78, 2012.
112. Catz SD and Johnson JL: Transcriptional regulation of bcl-2 by nuclear factor kappa B and its significance in prostate cancer. *Oncogene* 20: 7342-7351, 2001.
113. Srinivasan S, Kumar R, Koduru S, Chandramouli A and Damodaran C: Inhibiting TNF-mediated signaling: A novel therapeutic paradigm for androgen independent prostate cancer. *Apoptosis* 15: 153-161, 2010.
114. Liu VWS, Yau WL, Tam CW, Yao KM and Shiu SY: Melatonin inhibits androgen receptor splice variant-7 (AR-V7)-induced nuclear factor-kappa B (NF-kappaB) activation and NF-kappaB activator-induced AR-V7 expression in prostate cancer cells: Potential implications for the use of melatonin in castration-resistant prostate cancer (CRPC) therapy. *Int J Mol Sci* 18: 18, 2017.
115. Zerbini LF, Wang Y, Cho JY and Libermann TA: Constitutive activation of nuclear factor kappaB p50/p65 and Fra-1 and JunD is essential for deregulated interleukin 6 expression in prostate cancer. *Cancer Res* 63: 2206-2215, 2003.
116. Araki S, Omori Y, Lyn D, Singh RK, Meinbach DM, Sandman Y, Lokeshwar VB and Lokeshwar BL: Interleukin-8 is a molecular determinant of androgen independence and progression in prostate cancer. *Cancer Res* 67: 6854-6862, 2007.
117. Lee SO, Pinder E, Chun JY, Lou W, Sun M and Gao AC: Interleukin-4 stimulates androgen-independent growth in LNCaP human prostate cancer cells. *Prostate* 68: 85-91, 2008.
118. Jeong JH, Park SJ, Dickinson SI and Luo JL: A constitutive intrinsic inflammatory signaling circuit composed of miR-196b, Meis2, PPP3CC, and p65 drives prostate cancer castration resistance. *Mol Cell* 65: 154-167, 2017.
119. McCall P, Bennett L, Ahmad I, Mackenzie LM, Forbes IW, Leung HY, Sansom OJ, Orange C, Seywright M, Underwood MA, *et al*: NF κ B signalling is upregulated in a subset of castrate-resistant prostate cancer patients and correlates with disease progression. *Br J Cancer* 107: 1554-1563, 2012.
120. Shiota M, Yokomizo A, Takeuchi A, Kashiwagi E, Dejima T, Inokuchi J, Tatsugami K, Uchiumi T and Eto M: Protein kinase C regulates Twist1 expression via NF- κ B in prostate cancer. *Endocr Relat Cancer* 24: 171-180, 2017.
121. Pratt MAC, Bishop TE, White D, Yasvinski G, Ménard M, Niu MY and Clarke R: Estrogen withdrawal-induced NF-kappaB activity and bcl-3 expression in breast cancer cells: Roles in growth and hormone independence. *Mol Cell Biol* 23: 6887-6900, 2003.

122. Zhou Y, Yau C, Gray JW, Chew K, Dairkee SH, Moore DH, Eppenberger U, Eppenberger-Castori S and Benz CC: Enhanced NF kappa B and AP-1 transcriptional activity associated with antiestrogen resistant breast cancer. *BMC Cancer* 7: 59, 2007.
123. Semlali A, Oliva J, Badia E, Pons M and Duchesne MJ: Immediate early gene X-1 (IEX-1), a hydroxytamoxifen regulated gene with increased stimulation in MCF-7 derived resistant breast cancer cells. *J Steroid Biochem Mol Biol* 88: 247-259, 2004.
124. Hu R, Warri A, Jin L, Zwart A, Riggins RB, Fang HB and Clarke R: NF- κ B signaling is required for XBP1 (unspliced and spliced)-mediated effects on antiestrogen responsiveness and cell fate decisions in breast cancer. *Mol Cell Biol* 35: 379-390, 2015.
125. Yamaguchi N, Nakayama Y and Yamaguchi N: Down-regulation of Forkhead box protein A1 (FOXA1) leads to cancer stem cell-like properties in tamoxifen-resistant breast cancer cells through induction of interleukin-6. *J Biol Chem* 292: 8136-8148, 2017.
126. Hartman ZC, Poage GM, den Hollander P, Tsimelzon A, Hill J, Panupinthu N, Zhang Y, Mazumdar A, Hilsenbeck SG, Mills GB, *et al*: Growth of triple-negative breast cancer cells relies upon coordinate autocrine expression of the proinflammatory cytokines IL-6 and IL-8. *Cancer Res* 73: 3470-3480, 2013.
127. Nehra R, Riggins RB, Shajahan AN, Zwart A, Crawford AC and Clarke R: BCL2 and CASP8 regulation by NF-kappaB differentially affect mitochondrial function and cell fate in antiestrogen-sensitive and -resistant breast cancer cells. *FASEB J* 24: 2040-2055, 2010.
128. Riggins RB, Zwart A, Nehra R and Clarke R: The nuclear factor κ B inhibitor parthenolide restores ICI 182,780 (Faslodex; fulvestrant)-induced apoptosis in antiestrogen-resistant breast cancer cells. *Mol Cancer Ther* 4: 33-41, 2005.
129. Nadiminty N, Lou W, Sun M, Chen J, Yue J, Kung HJ, Evans CP, Zhou Q and Gao AC: Aberrant activation of the androgen receptor by NF-kappaB2/p52 in prostate cancer cells. *Cancer Res* 70: 3309-3319, 2010.
130. Nadiminty N, Chun JY, Lou W, Lin X and Gao AC: NF-kappaB2/p52 enhances androgen-independent growth of human LNCaP cells via protection from apoptotic cell death and cell cycle arrest induced by androgen-deprivation. *Prostate* 68: 1725-1733, 2008.
131. Nadiminty N, Dutt S, Tepper C and Gao AC: Microarray analysis reveals potential target genes of NF-kappaB2/p52 in LNCaP prostate cancer cells. *Prostate* 70: 276-287, 2010.
132. Mehraein-Ghomi F, Church DR and Schreiber CL: M. A. Weichmann, Basu HS, Wilding G: Inhibitor of p52 NF- κ B subunit and androgen receptor (AR) interaction reduces growth of human prostate cancer cells by abrogating nuclear translocation of p52 and phosphorylated ARser81. *Genes Cancer* 6: 428-444, 2015.
133. Nadiminty N, Tummala R, Liu C, Lou W, Evans CP and Gao AC: NF-kappaB2/p52:c-Myc:hnRNPA1 pathway regulates expression of androgen receptor splice variants and enzalutamide sensitivity in prostate cancer. *Mol Cancer Ther* 14: 1884-1895, 2015.
134. Cui Y, Nadiminty N, Liu C, Lou W, Schwartz CT and Gao AC: Upregulation of glucose metabolism by NF- κ B2/p52 mediates enzalutamide resistance in castration-resistant prostate cancer cells. *Endocr Relat Cancer* 21: 435-442, 2014.
135. House CD, Grajales V, Ozaki M, Jordan E, Wubneh H, Kimble DC, James JM, Kim MK and Annunziata CM: IKK ϵ cooperates with either MEK or non-canonical NF- κ B driving growth of triple-negative breast cancer cells in different contexts. *BMC Cancer* 18: 595, 2018.
136. Kim YR, Kim IJ, Kang TW, Choi C, Kim KK, Kim MS, Nam KI and Jung C: HOXB13 downregulates intracellular zinc and increases NF- κ B signaling to promote prostate cancer metastasis. *Oncogene* 33: 4558-4567, 2014.
137. Huerta-Yepez S, Vega M, Jazirehi A, Garban H, Hongo F, Cheng G and Bonavida B: Nitric oxide sensitizes prostate carcinoma cell lines to TRAIL-mediated apoptosis via inactivation of NF-kappa B and inhibition of Bcl-xL expression. *Oncogene* 23: 4993-5003, 2004.
138. Domingo-Domenech J, Oliva C, Rovira A, Codony-Servat J, Bosch M, Filella X, Montagut C, Tapia M, Camps C, Dang L, *et al*: Interleukin 6, a nuclear factor-kappaB target, predicts resistance to docetaxel in hormone-independent prostate cancer and nuclear factor-kappaB inhibition by PS-1145 enhances docetaxel antitumor activity. *Clin Cancer Res* 12: 5578-5586, 2006.
139. Tsai CH, Tzeng SF, Hsieh SC, Yang YC, Hsiao YW, Tsai MH and Hsiao PW: A standardized herbal extract mitigates tumor inflammation and augments chemotherapy effect of docetaxel in prostate cancer. *Sci Rep* 7: 15624, 2017.
140. Nathan S, Ma Y, Tomita YA, De Oliveira E, Brown ML and Rosen EM: BRCA1-mimetic compound NSC35446.HCl inhibits IKKB expression by reducing estrogen receptor- α occupancy in the IKKB promoter and inhibits NF- κ B activity in antiestrogen-resistant human breast cancer cells. *Breast Cancer Res Treat* 166: 681-693, 2017.
141. Jiang L, Wang P, Sun YJ and Wu YJ: Ivermectin reverses the drug resistance in cancer cells through EGFR/ERK/Akt/NF- κ B pathway. *J Exp Clin Cancer Res* 38: 265, 2019.
142. Coker-Gurkan A, Celik M, Ugur M, Arisan ED, Obakan-Yerlikaya P, Durdu ZB and Palavan-Unsal N: Curcumin inhibits autocrine growth hormone-mediated invasion and metastasis by targeting NF- κ B signaling and polyamine metabolism in breast cancer cells. *Amino Acids* 50: 1045-1069, 2018.
143. Li J, Xiang S, Zhang Q, Wu J, Tang Q, Zhou J, Yang L, Chen Z and Hann SS: Combination of curcumin and bicalutamide enhanced the growth inhibition of androgen-independent prostate cancer cells through SAPK/JNK and MEK/ERK1/2-mediated targeting NF- κ B/p65 and MUC1-C. *J Exp Clin Cancer Res* 34: 46, 2015.
144. Xu Y, Fang F, St Clair DK, Jossion S, Sompol P, Spasojevic I and St Clair WH: Suppression of RelB-mediated manganese superoxide dismutase expression reveals a primary mechanism for radiosensitization effect of α ,25-dihydroxyvitamin D(3) in prostate cancer cells. *Mol Cancer Ther* 6: 2048-2056, 2007.
145. Lundqvist J, Yde CW and Lykkesfeldt AE: $1\alpha,25$ -dihydroxyvitamin D3 inhibits cell growth and NF κ B signaling in tamoxifen-resistant breast cancer cells. *Steroids* 85: 30-35, 2014.
146. deGraffenried LA, Chandrasekar B, Friedrichs WE, Donzis E, Silva J, Hidalgo M, Freeman JW and Weiss GR: NF-kappa B inhibition markedly enhances sensitivity of resistant breast cancer tumor cells to tamoxifen. *Ann Oncol* 15: 885-890, 2004.
147. Lobanova YS, Scherbakov AM, Shatskaya VA, Evteev VA and Krasil'nikov MA: NF-kappaB suppression provokes the sensitization of hormone-resistant breast cancer cells to estrogen apoptosis. *Mol Cell Biochem* 324: 65-71, 2009.
148. Xu Y, Fang F, Miriyala S, Crooks PA, Oberley TD, Chaiswing L, Noel T, Holley AK, Zhao Y, Kinningham KK, *et al*: KEAP1 is a redox sensitive target that arbitrates the opposing radiosensitive effects of parthenolide in normal and cancer cells. *Cancer Res* 73: 4406-4417, 2013.
149. Jossion S, Xu Y, Fang F, Dhar SK, St Clair DK and St Clair WH: RelB regulates manganese superoxide dismutase gene and resistance to ionizing radiation of prostate cancer cells. *Oncogene* 25: 1554-1559, 2006.
150. Tan C, Hu W, He Y, Zhang Y, Zhang G, Xu Y and Tang J: Cytokine-mediated therapeutic resistance in breast cancer. *Cytokine* 108: 151-159, 2018.
151. Khurana N and Sikka SC: Targeting crosstalk between Nrf-2, NF- κ B and androgen receptor signaling in prostate cancer. *Cancers (Basel)* 10: 10, 2018.
152. Ahmed KM, Zhang H and Park CC: NF- κ B regulates radioresistance mediated by β 1-integrin in three-dimensional culture of breast cancer cells. *Cancer Res* 73: 3737-3748, 2013.
153. Chaturvedi MM, Sung B, Yadav VR, Kannappan R and Aggarwal BB: NF- κ B addiction and its role in cancer: 'one size does not fit all'. *Oncogene* 30: 1615-1630, 2011.
154. Lessard L, B  gin LR, Gleave ME, Mes-Masson AM and Saad F: Nuclear localisation of nuclear factor-kappaB transcription factors in prostate cancer: An immunohistochemical study. *Br J Cancer* 93: 1019-1023, 2005.
155. Zhang Y, Xu Z, Ding J, Tan C, Hu W, Li Y, Huang W and Xu Y: HZ08 suppresses RelB-activated MnSOD expression and enhances radiosensitivity of prostate Cancer cells. *J Exp Clin Cancer Res* 37: 174, 2018.