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

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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-κB pathway is an important common mechanism for metastasis and therapeutic resistance of the two types of cancer; in particular, the RelB-activated noncanonical NF-κB pathway appears to be able to lengthen and strengthen NF-κB activity, which has been a focus of recent investigations.

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

Contents

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

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-κB 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-κB 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 ERα and Erβ, 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-κB 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-κB 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.

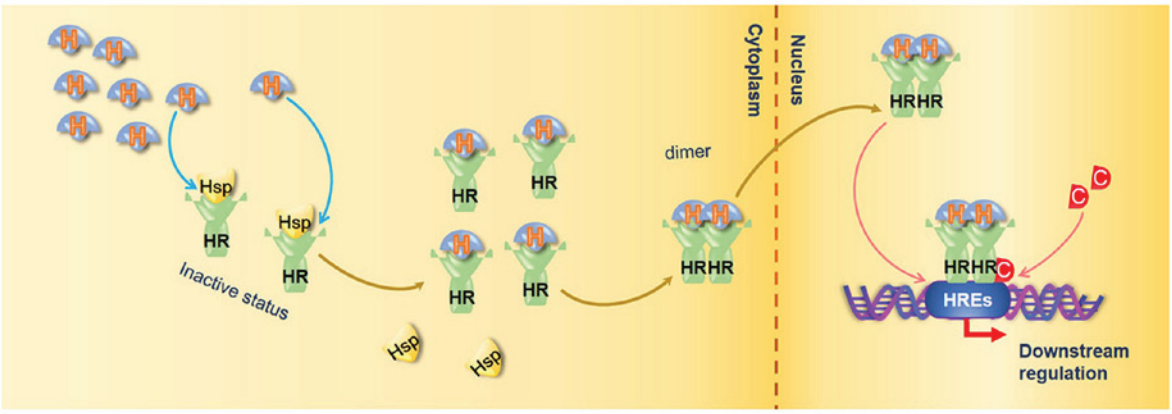

Figure 1. AR/ER, a ligand-activated transcription factor. The AR/ER is usually bound by Hsp and remains inactive in the cytoplasm. When a steroid hormone signal appears, Hsp is shed to free the corresponding receptor for androgen/estrogen binding, followed by the translocation of the ligand-receptor 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

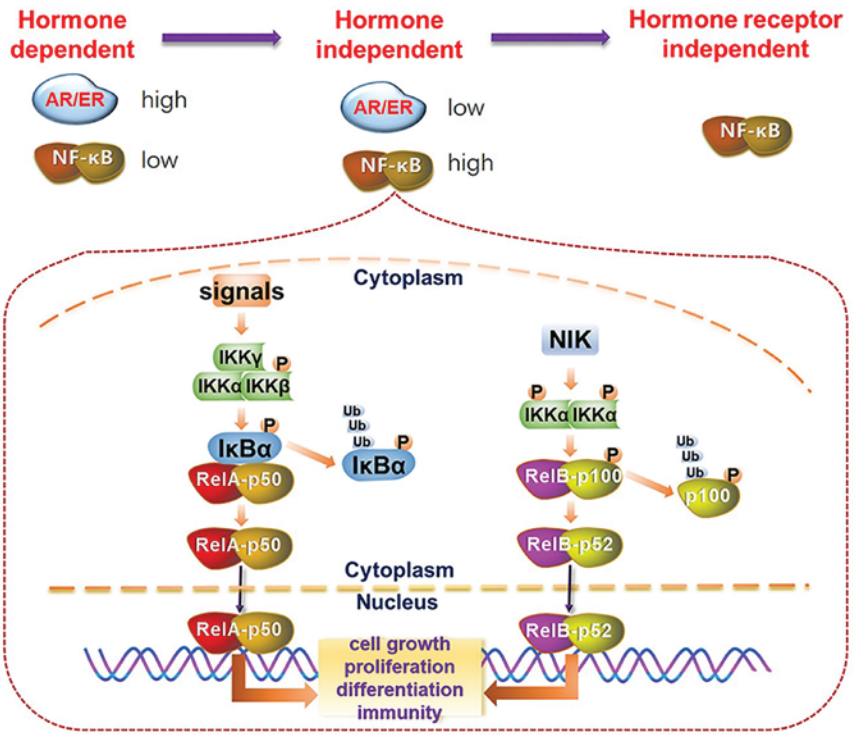

Figure 2. NF-κB functional substitution of AR/ER for sustaining PCa/BCa progression. The interaction between androgen-AR in PCa or estrogen-ER in BCa is essential for the transcriptional regulation of hormone responsive gene expression and the initiation of PCa/BCa tumorigenesis. Along with malignant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

early-stage ER-positive BCa cells, NF-κB activation has been shown to recruit ER to p65/estrogen response element motifs, resulting in increased ER transcriptional responses (68,69). Taken together, these findings predict that NF-κB gradually replaces ER, from transcriptional cooperation in inflammatory BCa states to functional substitution in hormone refractory states. The activation of the NF-κB pathway in the progression of hormone-deprived aggressive PCa and BCa is depicted in Fig. 2.

NF-κB activation mechanism. NF-κB is involved in various biological processes, such as cell survival, proliferation, differentiation and the immune response (70). Members of the NF-κB family have a conserved Rel homology domain at their N-terminus, including RelA (p65), RelB, c-Rel, NF-κB1 (p50) and NF-κB2 (p52) (71,72). NF-κB activation is divided into the canonical NF-κB pathway and the noncanonical NF-κB pathway. In the canonical NF-κB 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 IκB kinase complex (IKKα, IKKβ and IKKγ/NEMO) to phosphorylate and then ubiquitinate IκBα, leading to p50:RelA dimer nuclear translocation (73,74). By contrast, in the activation of the noncanonical NF-κB pathway, NF-κB-induced kinase stimulates IKKα 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-κB pathway (76).

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

Role of the NF-κB pathway in advanced BCa development. Mounting evidence highlights that NF-κB promotes BCa metastasis by activating the epithelial-mesenchymal transition (EMT) process, partially by upregulating IL-1β and IL-6 (80). In malignant BCa, epidermal growth factor receptor is integrated with NF-κB in the activation of IL-1, which promotes the invasive capacity of BCa cells (81). Additionally, IL-8 stimulates the PI3K-AKT-NF-κB signaling axis, which in turn upregulates integrin β1/β3 expression, leading to increased motility as well as enhanced chemoresistance and radioresistance in BCa cells (63). Furthermore, a previous study demonstrated that the NF-κB-controlled proinflammatory cytokine network is important for the maintenance of

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

4. NF-κB 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-κB pathway (47,83-87). Notably, the TNF-α, WNT5A, PI3K-AKT, Ras-Raf-ERK and transforming growth factor (TGF)-β1-mitogen activated protein kinase (MAPK) signaling axes have been demonstrated to be important upstream signaling pathways of the NF-κB pathway in both PCa and BCa (47,85,86,88-92).

As a typical redox responsible transcription factor, NF-κB 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-κB 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-κB 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-κB in substitution for AR/ER (47,85,86,90-95). In particular, the activation of the PI3K-AKT-NF-κB 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-κB pathway, this finding mechanistically elucidated the inverse association between AR and the NF-κB pathway.

In addition, TGF-β1-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-κB 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-κB, which is sufficient to drive AR nuclear localization under androgen deprivation condition and support CRPC growth (103).

Notably, the canonical NF-κB pathway can actually induce the noncanonical NF-κB pathway, thereby sustaining high NF-κB activity (76,104). Additionally, several inducible agents have been demonstrated to directly activate the noncanonical NF-κB 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-κB 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-κB 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-κB 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-κB-regulated proteins in endocrinotherapy resistance

NF-κB regulates a series of genes relevant to endocrinotherapy resistance. Particularly, it has been widely recognized that both canonical and noncanonical NF-κB pathways are vital for resistance to hormone receptor-targeted treatment in PCa and BCa (52,53,58,60,111). As important NF-κB-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-κB regulated proteins associated with endocrinotherapy resistance are summarized in Fig. 4.

Effect of the canonical NF-κB pathway in PCa endocrinotherapy resistance. Bcl-2, an important antiapoptotic protein, was upregulated in response to ROS-mediated NF-κB 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-κB 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-κB pathway, but negatively regulated by AP-1 (115). IL-8 also promotes the progression of CRPC through NF-κB activation (116). NF-κB-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-κB-cytokines/chemokines is essential for the appearance of CRPC (118). In androgen-refractory PCa, the activation of canonical NF-κB pathway significantly increases the disease-specific death due to AKT-mediated IKK phosphorylation (119). Furthermore, NF-κB-enhanced EMT upregulates Twist1 in response to AR inhibition, leading to CRPC (120).

Effect of the canonical NF-κB 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-κB-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-κB to the promoter (123). X-box binding protein 1

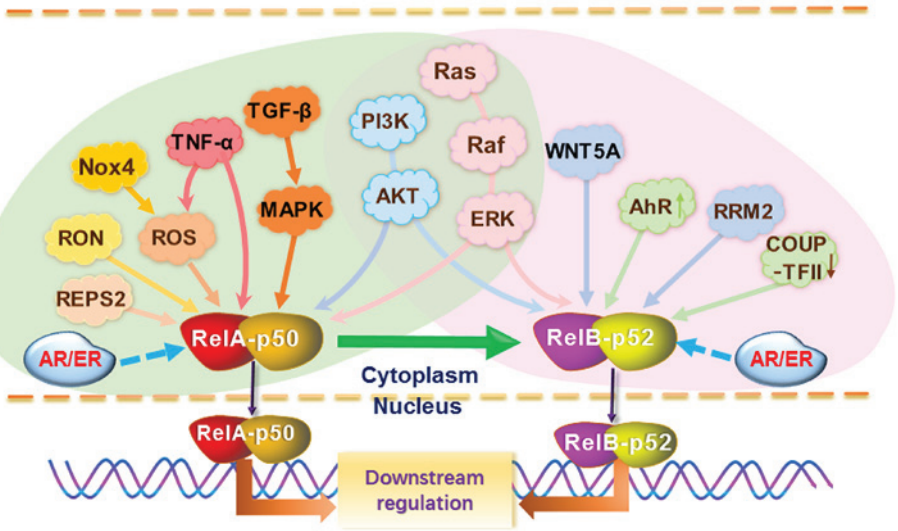

Figure 3. Upstream signaling involved in NF-κB activation in the endocrinotherapy resistance of prostate cancer and breast cancer. The canonical NF-κB pathway is stimulated by a cell signaling network, including TNF-α, RON, REPS2, PI3K-AKT, TGF-β-MAPK, Ras-Raf-ERK and treatment-induced ROS. While several regulators have been identified to be able to activate the noncanonical NF-κB 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-κB pathway. Importantly, the canonical NF-κB pathway can further activate the noncanonical NF-κB pathway to sustain the NF-κB 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.

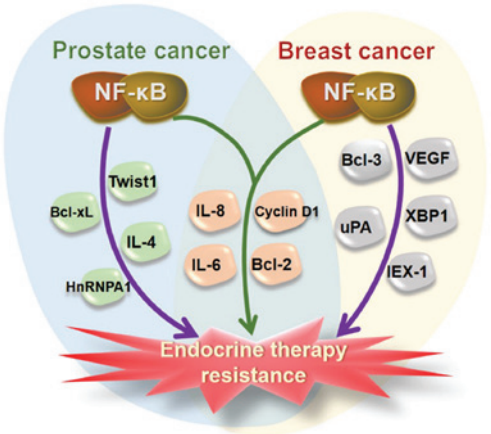

Figure 4. Downstream NF-κB-regulated proteins involved in the endocrinotherapy resistance of PCa and BCa. Antiapoptotic protein Bcl-2, cell cycle regulator cyclin D1, cytokine IL-6 and IL-8 appear to be common factors in response to endocrinotherapy resistance in both PCa and BCa. PCa, prostate cancer; 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-κB 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-κB 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-κB pathway in response to tamoxifen (127). Similar to PCa, the activation of the PI3K-AKT-NF-κB signaling axis is highly associated with endocrinotherapy resistance in BCa (128).

Emerging role of the noncanonical NF-κB 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-κB 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-κB 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-κB as a target in PCa and BCa treatment

Since NF-κB contributes to endocrinotherapy resistance in PCa and BCa, NF-κB-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-κB (137). IL-6, a NF-κB-regulated cytokine, contributes to androgen-independent PCa progression. Inhibition of IL-6 enhances the sensitivity of PCa to docetaxel (138). NF-κB activation in ARVs associated with CRPC leads to anti-androgen therapy resistance. Repression of NF-κB 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 IKKα/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-κB (140). Additionally, ivermectin reverses chemotherapeutic resistance via suppression of NF-κB-activated P-gp expression (141). Importantly, a number of compounds appear to efficiently treat both aggressive PCa and BCa via repression of NF-κB-mediated transcriptional activation. Curcumin, an inhibitor of the NF-κB 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 1α,25-dihydroxyvitamin D3 has been reported to repress the NF-κB 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-κB 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-κB 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-κB 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-κB 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-κB 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-κB 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-κB pathway; in particular, PI3K-AKT upstream signaling activates the NF-κB pathway in response to oxidative stress and inflammatory stimulation. Importantly, the cytokine/chemokine-NF-κB 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-κB-regulated proteins, and increased levels of inflammation in turn activate the NF-κB 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-κB pathway is critical for cancer progression and therapeutic resistance (82,103,110,124,151-153). However, the effect of the RelB-activated noncanonical NF-κB pathway is underestimated. Indeed, RelA can upregulate RelB, leading to sustained long-term NF-κB 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-κB 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-κB in the acquisition of endocrinotherapy resistance in PCa and BCa, suggesting that inhibition of the NF-κB 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-κB pathway, the noncanonical NF-κB 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-κB activity. Of further interest, therefore, is why and how the noncanonical NF-κB 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-κB 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.

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