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Review

The role of NF-κB in breast cancer initiation, growth, metastasis, and resistance to chemotherapy

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ABSTRACT

Breast cancer (BC) is the second most fatal disease and is the prime cause of cancer allied female deaths. BC is caused by aberrant tumor suppressor genes and oncogenes regulated by transcription factors (TFs) like NF-κB. NF-κB is a pro-inflammatory TF that crucially alters the expressions of various genes associated with inflammation, cell progression, metastasis, and apoptosis and modulates a network of genes that underlie tumorigenesis. Herein, we focus on NF-κB signaling pathways, its regulators, and the rationale for targeting NF-κB. This review also includes TFs that maintain NF-κB crosstalk and their roles in promoting angiogenesis and metastasis. In addition, we discuss the importance of combination therapies, resistance to treatment, and potential novel therapeutic strategies including nanomedicine that targets NF-κB.

Abbreviations: ABCG2, ATP binding cassette subfamily G member; ADAMTS18, A disintegrin and metalloproteinase with thrombospondin motifs; ATP, Adenosine triphosphate; ATM, Ataxia telangiectasia mutated check point kinase; AKT, A serine/threonine protein kinase B (PKB); Bax, Bcl-2 associated X protein; Bcl-2, B-cell lymphoma 2; BRCA1, Breast cancer gene; BRCP, Breast cancer resistant protein; CAIX, Carbonic anhydrase IX; CCL2, Chemokine (C-C motif) ligand 2; CCR7, C-C motif chemokine receptor 7; CD40, Cluster of differentiation 40; CDK6, Cyclin-dependent kinase 6; CFTR, Cystic fibrosis transmembrane regulator; c-FLIP, Cellular FLICE-inhibitory protein; COX2, Cyclooxygenase-2; CSC, Cancer stem cells; CXCL12, Chemokine (C-X-C motif) ligand 12; CYLD, Cylindromatosis; EGF, Epidermal growth factor; EGFR, Epidermal growth factor receptor; EMT, Epithelial to mesenchymal transition; ER, Estrogen receptor; ERK, Extracellular signal-regulated kinase; FOXC1, Fork head box C1; GADD45B, Growth arrest and DNA-damage-inducible β; GPR120, G protein-coupled receptor 120; GPER, G protein-coupled estrogen receptor 1; hTERT, Human telomerase reverse transcriptase; HIF-1α, Hypoxia inducible factor-1 α; IAP, Inhibitors of apoptosis protein; IFN, Interferon; IGF-1, Insulin-like growth factor 1; IκB, Inhibitor of κ-B; IKK, IκB kinase; IL, Interleukin; iNOS, Inducible nitric oxide synthase; IRF-1, Interferon regulatory factor-1; JAG1, Jagged 1; LPS, Lipopolysaccharide; LINC00472, Long intergenic non-protein coding RNA 472; MCSF, Macrophage colony stimulating factor; MDSC, Myeloid derived suppressor cells; MDR1, Multidrug resistance 1; MMP-2, Matrix metallopeptidase 2; MnSOD, Manganese dependent superoxide dismutase; MUC1, Mucin 1; NAP, Novel angiogenic protein; NEMO, NF-κ-B essential modulator; NF-κB, Nuclear factor κ-B; PAK5, p21-activated kinase 5; P13K, Phosphatidylinositol-3-kinase; RANK, Receptor activator of NF-κB; RIP, Receptor interacting protein; ROS, Reactive oxygen species; SERM, Selective estrogen receptor modulator; STAT, Signal transducer and activator of transcription; SMYD2, SET and MYND domain-containing protein 2; TACE, Tumor necrosis α converting enzyme; TAM, Tumor associated macrophage; TEL, Tumor associated leukocytes; TF, Transcription factor; TGF, Transcription growth factor; TLRs, Toll-like receptors; TNBC, Triple negative breast cancer; TNFα, Tumor necrosis factor alpha; TNFRSF1A, Tumor necrosis factor receptor superfamily member 1A; TNFR1, Tumor necrosis factor receptor 1; TRAIL, Tumor necrosis factor related apoptosis inducing ligand; TRAF2, TNF receptor associated factor 2; TRADD, TNFR1-associated death domain protein; uPA, Urokinase type plasminogen activator; VCAM1, Vascular cell adhesion protein 1; VEGF, Vascular endothelial growth factor; XIAP, X-linked inhibitor of apoptosis; ZBTB7A, Zinc finger and BTB domain containing 7A; ZEB, Zinc-finger E-box binding homeobox.

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1. Introduction

At present, cancer is the leading cause of death everywhere. The GLOBOCAN 2020 report found that 19.3 million new cases led to 9.9 million deaths [1]. Breast cancer (BC) is a typical form of the disease and the second leading cause of global cancer-related mortality among women [2–4]. The high mortality and morbidity rates of BC are due to distant metastasis to brain, bone, liver, lungs and other organs [5]. In 2020, over 2.3 million BC cases (in both sexes) and 685,000 deaths were recorded among women [6].

BC is most commonly encountered in female with a first-degree relative diagnosed with the disease [7]. The chief risk factors associated with BC are contraceptive pills (hormones), physical inactivity, lack of nutrition, obesity, hormone replacement therapy, alcohol consumption, and smoking. Hereditary and genetic factors plays a vital role in the etiology of BC, and studies have revealed that mutations in the BRCA1 and BRCA2 genes account for 5–10% of cases and that promoting breastfeeding and physical activity might reduce risk [8]. The development of treatment regimens like radio- and chemotherapy have improved prognosis and reduced mortality rates, but the onset of BC is unpredictable due to aberrant genes that promote progression and induce resistance to treatment. Aberrantly expressed transcription factors (TF) attach to DNA loci and regulate gene expressions [9,10], and oncogenic TFs enhance the expressions of oncogenic genes that activate signaling cascades, mediate BC cell survival, and ultimately lead to tumorigenesis [11]. The major dysregulated signaling pathways are the Hedgehog (Hh), Wnt, Notch, and Nuclear factor κ-B (NF-κB) [12–15]. These pathways play a central role in the differentiation, proliferation, and evasion of apoptosis. Studies have shown the importance of these pathways in the breast cancer tumor microenvironment (TME). The breast cancer TME has high inflammation strengthened by the infiltrated immune cells, growth factors (GFs) and cytokines. Regulatory T-cells with negative immune feature associated with both ER-positive and ER-negative breast tumors and confess an immunosuppressive environment [13]. This characteristic feature has an importance in the immune TME of breast cancer.

NF-κB is a key TF that links inflammation with cancer. It has been demonstrated as being involved in the tumorigenesis in breast cancer and resistance to the endocrine therapy. NF-κB plays an essential role in the management of inflammation, proliferation, and survival of cell lines [16–20]. NF-κB is a superfamily of TFs discovered in 1986 which includes NF-κB 1 (p50) NF-κB (p52), ReIA (p65), ReIB, and C-ReI [21–23]. The N-terminal have ReI, which is responsible for the binding of specific DNA, while the C-terminal is responsible for binding with other TFs [24,25]. NF-κB is present in the cytoplasm as an inactive form by complexing with inhibitor subunits IKB-α, -β and -ϒ [26–28]. The dissociation of inhibitory subunits (IκB s) results in the activation and rapid translocation of NF-κB heterodimer into the nucleus to bind with DNA [29]. The subunit p65 then displays its transcriptional activity and induces the expressions of NF-κB target genes that inhibit apoptosis, and form a network that regulates the cell cycle, and promotes cell invasiveness, inflammation, tumorigenesis, metastasis, and eventually causing resistance to radio- and chemotherapy. NF-κB is regulated by canonical signaling (CS) pathways (activated by IL-1, TNF-α, ROS and LPS) and noncanonical signaling (NCS) pathways, which are activated by inflammatory stimuli through IKKα [30]. However, the dysregulation of NF-κB results in tumor evolvement, and thus activated NF-κB is detected in various cancers including BC [31]. Studies denote that NF-κB can significantly upregulate the expressions of 60 related genes, including REL, RELA, GADD45B, TRAILR2, CD40, CCL2, IL15, CCND, CXCL12, VCAM1, COX2, and CXCL1 in inflammatory BC. Furthermore, COX2 along with CXCL1 are upregulated in metastatic BC [32]. The increased expression of NF-κB genes results in tumor progression and metastasis [33,34].

The role of NF-κB in tumor growth with reference to TME is very complex because of its various functions. The stimulation of NF-κB in solid tumors results in the development of inflammatory TME [35,36]. The inflammatory response involved in the enhanced expression of cytokine genes and the release of cytokines thereby activation of the canonical NF-κB signaling pathway resulting into the apoptosis of transformed cells [37–39]. The leukocytes infiltrating result in the increase of malignancies in breast epithelial cells and involves NF-κB signaling [40,41]. Therefore, it can be utilized as the potential marker and therapeutic target for the prognosis and therapy of BC. Despite cytotoxic effect of drugs in eradicating tumors, they have some limitations including side effects in different organs, because they are not specific to cancer cells and target all proliferative and fast growing cells including both normal and tumor cells [42]. The efficacy of endocrine therapy like chemotherapy, comes down in targeting metastatic BC due to development of drug resistance. Because of the high incidence rate and limitations of conventional therapy for BC, it is important to look for a new and effective target in cancer cells for targeted therapy. However, the molecular mechanisms of NF-κB contribution towards the endocrine therapy resistance are still not known. Although many reviews available on NF-κB and breast cancer, this review provides current understanding of the NF-κB mediated signaling pathways during breast carcinogenesis and metastasis as well as pathways involved and therapeutic targets of NF-κB. This article also elucidates NF-κB as a potential novel target for overcoming chemo-resistance.

2. Methods of data collection

A bibliographic search of the scientific literature published till March 2023 was carried out independently of different scientific databases and search engines such as Scopus, Google Scholar, PubMed, and the libraries for original researchers. We also searched the results of various investigations on the effects of NF-κB towards chemotherapy resistance in BC. Adequate papers data indicating the results of clinical and preclinical studies were extracted independently using the standard method of data extraction [43].

3. NF-κB mediated signaling pathways during the initiation, development, and metastasis

3.1. CS and NCS pathways of NF-κB

The NF-κB mediated CS and NCS pathways are summarized in Fig. 1. The CS pathway is initiated by IκB proteins (IκBα, IκBβ, IκBε, or IκBγ) and stimulated by TNF-α, which responds to UV radiation, cytokines, growth factors, bacteria, and mitogens [44]. The pathway starts with the interaction of TNFα with its receptor TNFR1, which recruits a sequential protein including TRAF2, TRADD, and RIP. Among these adaptor proteins the TRAF2 protein recruits the complex IKKα, IKKβ, and NEMO to bind with TNFR1 and it activates IKKβ, causing the phosphorylation of IκBα [45,46]. The resulting ubiquitination of IκBα frees NF-κB (p50-p65 heterodimer) in cytoplasm and facilitates its migration to the nucleus, where it attaches to NF-κB sites of DNA and induces the expressions of IL-6 and also chemokines. On the other hand, the NCS pathway is initiated by growth factors, viruses, stress, and lipopolysaccharides. CD40, a TNF receptor, participates in the activation of RelB/ NF-κB 2, which then recruits TRAF2-TRAF3, links c-IAP to NIK, and induces the phosphorylation of NIK followed by degradation through c-IAP. NIK activates IKKα and degrades p100, thus releasing p52 along with RelB, which migrate towards the nucleus and induce the expressions of chemokine genes [47,48]. Moreover, in BC cells, the activations of CD40 and CD40L, mediated by an overactive oncogenic NF-κB signaling pathway, result in neoplastic growth [49]. Interestingly, the expressions of the adaptor proteins, including cIAP1, TRAF2, FLIP, TRADD, and XIAP, in BC cells can be attenuated by the TNF-α and IFN-γ-induced activation of IRF-1 (interferon regulatory factor-1), which eventually reduces nuclear NF-κB p65 levels in BC cells [50].

During tumorigenesis many other pathways activate NF-κB, such as

the ATM kinase pathway, which causes NEMO ubiquitination under genotoxic stress [51], the EGFR-dependent NF-κB transcription pathway [52], H_2O_2-mediated NF-κB activation that induces the IκB phosphorylation by c-Src at Tyr42 [53], and the UV-facilitated NF-κB activation via casein kinase 2 independently of IKK [54]. The activations of these pathways eventually result in the translocations of various NF-κB into the nucleus to activate its target genes. In the case of BC, it is initiated by the steroidal hormone estrogens, as reflected by the number of estrogen receptors in BC cells [55]. However, BC development can change from being hormone-reliant and estrogen-attentive to a hormone-independent, invasive, and chemo-resistant phenotype, in which cancer progression is promoted by ER^- tumor cells [56,57]. These BC types include inflammatory BC types, such as $Her2^+$ and ER^- [58,59], which exhibit NF-κB overexpression and TNBC, which is highly metastatic and does not express Her2 or progesterone or estrogen receptors. TNBC results from a mutation in p53, that causes crosstalk among p53 and NF-κB [60]. NF-κB interacts with many distinct signaling pathways, and the maintenance of crosstalk modulates its transcriptional activity.

3.2. Cross talk among NF-κB and EGFR

Reports show that EGFR and its family members are widely circulated in BC and are associated with the downstream NF-κB activation, predominantly in ER^-BC cells [61]. When overexpressed, Her2 activates NF-κB via activating PI3K/Akt signaling pathways in BC cells. Moreover, mutated p53 also contributes to the activations of EGFR, PDGF-1 (platelet derived growth factor 1), and NF-κB induces the expression of TGFβ, which together facilitate angiogenesis [62]. FOXC1 is a transcription factor and a reported prognostic biomarker of basal like BC and is overexpressed in many other cancers. It was shown that EGFR motivation upregulates the FOXC1 manifestation via PI3K/Akt, Ras/ERK, and other pathways [63]. Furthermore, it was found that NF-κB acts as a pivotal mediatory by attached to the promoter region of FOXC1 and controlling its expression via the EGF-dependent signaling pathway [64]. Hence, blocking the pathway of EGFR-NF-κB might offer a means of treating various cancers including BC.

3.3. Cross talk among NF-κB and STAT3

TFs couple to each other and bind to promoter sites essential for transcription to mutually ensure their activities and binding to DNA, though later they may promote or inhibit each other. Research indicates that STAT3 is inappropriately stimulated in 70% of BC cells, especially in TNBC, in which it contributes to pathogenesis [65]. The mechanism of crosstalk among NF-κB and some other TFs during BC development, proliferation, and metastasis is summarized in Fig. 2. STAT3 and NF-κB regulate the functions of various genes responsible for chemokine and cytokine production, anti-apoptosis, and cell cycle regulation [66,67]. They remain transcriptionally active for minutes to 1 h under cytokine stimulation during which they constitutively drive gene expression.

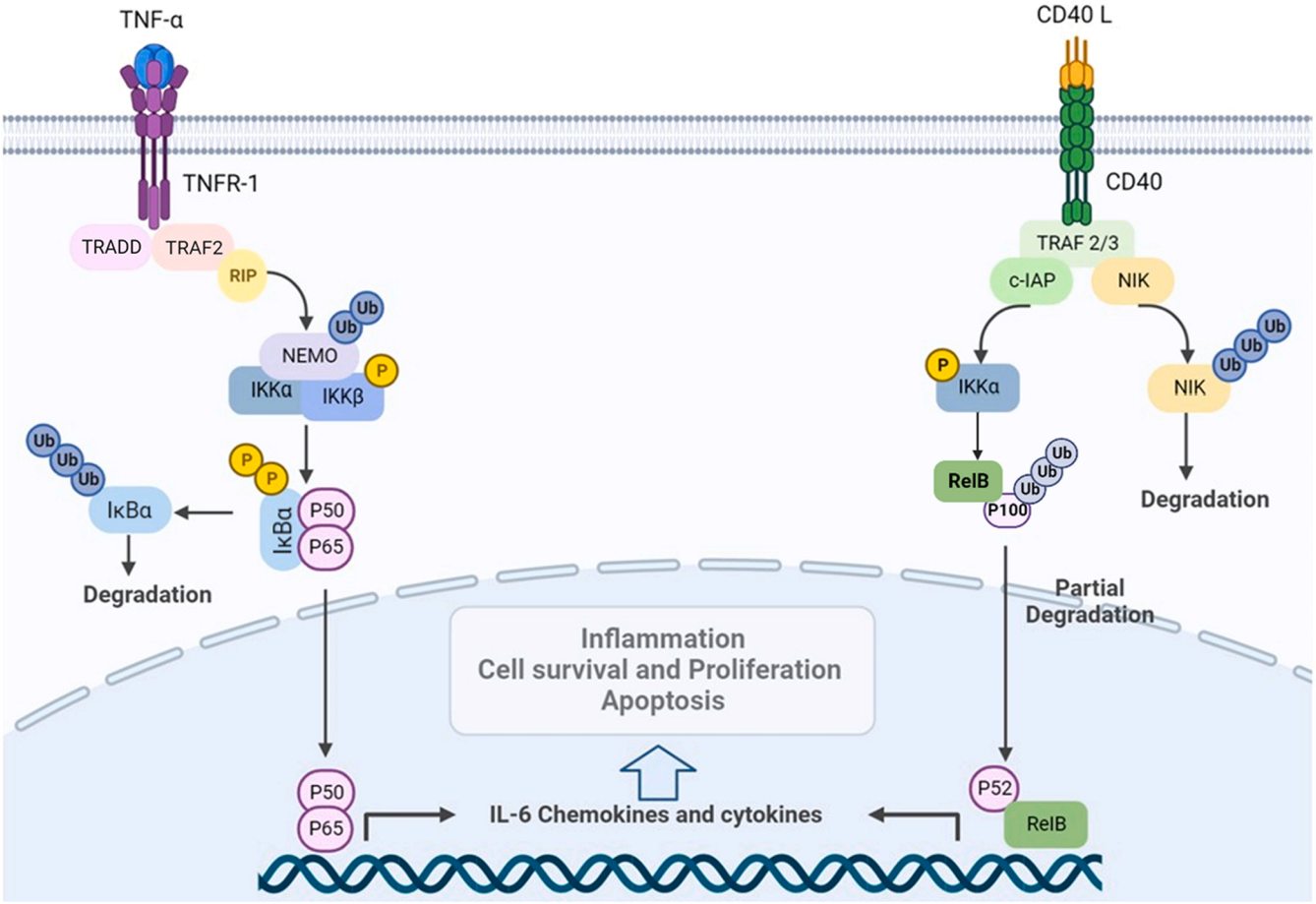

Fig. 1. NF-κB mediated pathways. NF-κB operates via canonical and noncanonical signaling pathways. The canonical pathway starts with TNFα binding to its receptor TNFR-1, which recruits TRADD, TRAF2, and RIP to form a complex. TRAF2 further recruits IKKα/IKKβ/NEMO complex. This activates IKKβ, which induces the phosphorylation, ubiquitination, and proteasome degradation of IκBα. The liberated p65-p50 complex is then translocated to the nucleus, which binds to DNA and activates NF-κB specific genes. On the other hand, the non-canonical pathway is activated by ligand binding to the CD40 receptor and the recruitments TRAF2 and TRAF3 which facilitates c-IAP to NIK bonding, leading to the phosphorylation of NIK. Phosphorylated NIK then activates IKKα and partially degrades p100 to p52. Thus, free p52-RelB then translocates to the nucleus and transcribes NF-κB targeted specific genes.

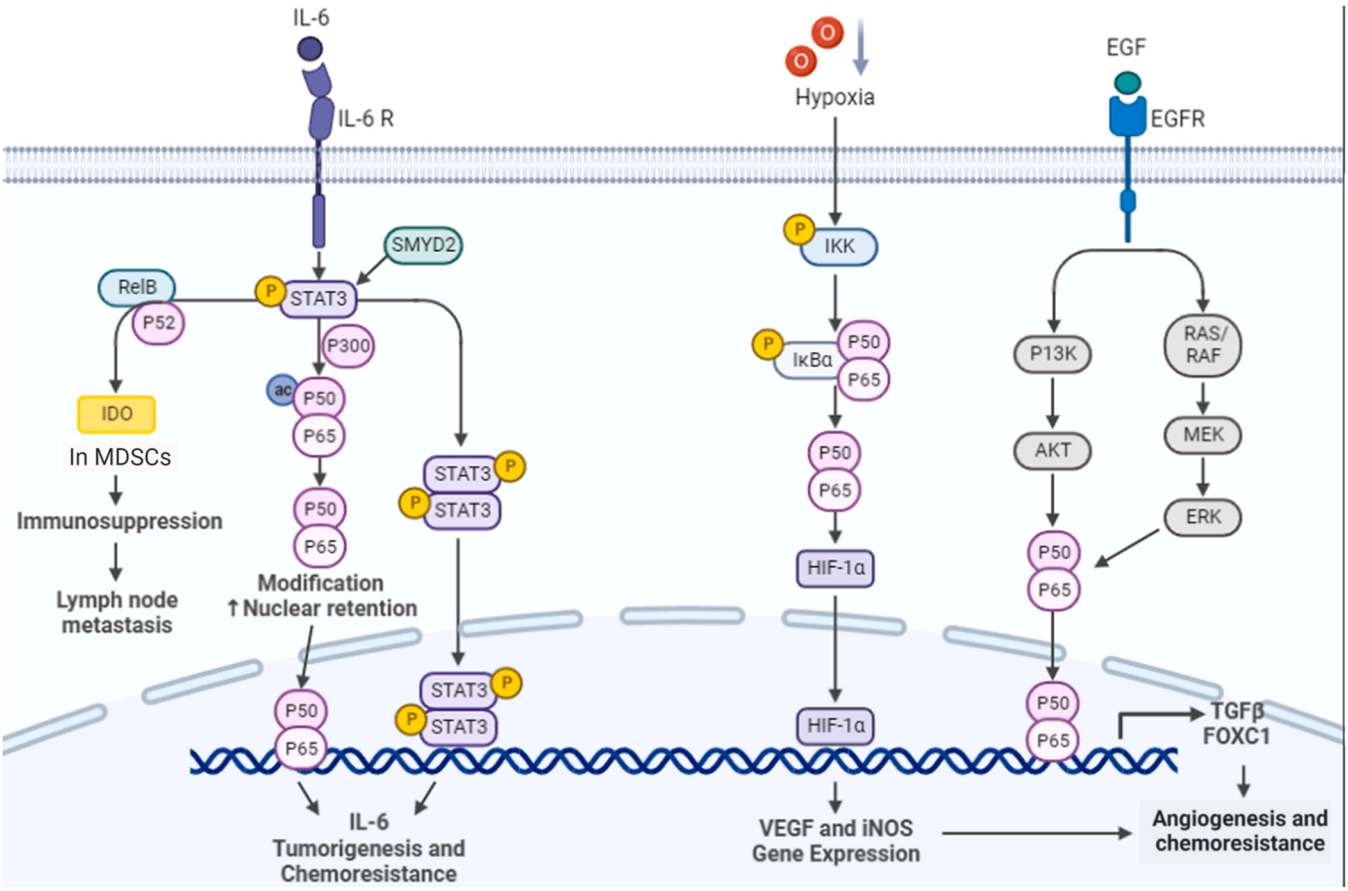

Fig. 2. Mechanism of crosstalk between NF-κB and transcription factors (A) STAT3, (B) HIF-1α, and (C) EFGR-dependent TGFβ and FOXC1. (a) Activated STAT3 mediates the acetylation of the p50/p65 heterodimer complex by p300 and increases its nuclear retention. In MDSCs, the RelB/P52 heterodimer complex regulates STAT3 by the non-canonical pathway by upregulating IDO (indoleamine 2,3-dioxygenase) and causing immunosuppression and lymph node metastasis. In TNBC, SMYD2 also activates STAT3, which results in the expressions of STAT3-specific genes. (b) Under hypoxic conditions, the p50/p65 heterodimer complex induces the transcription of HIF-1α, which activates VEGF and iNOS genes that contribute to angiogenesis and chemoresistance. (c) Overexpressed EFGR activates via PI3K/Akt and Mek/Erk pathway induces the expressions of p50/p65 heterodimer complex. The p50/p65 complex further expresses TGFβ, and FOXC1, contributing to angiogenesis and chemoresistance.

These two transcription factors interact with each other in multiple situations, and these interactions control their functions and binding to their respective promoters. Moreover, STAT3-mediated acetylation of NF-κB initiated by the acetyl transferase p300, promotes the modification of RelA and enhances the nuclear retention of NF-κB, which promotes tumorigenesis. Similarly, NF-κB regulates STAT3 in BC via its non-canonical pathway involving the MDSC-induced upregulation of indoleamine 2,3-dioxygenase [68]. MDSCs are immunosuppressors and induce lymph node metastasis in BC. In the CSC (cancer stem cell) of BC, STAT3 allies with CD44 and NF-κB to activate hTERT, whose expression is correlated with poor prognosis [62,69,70]. There are certain genes that promote the simultaneous activations of both STAT3 and NF-κB. For instance, TNFRSF1A is a STAT3-dependent gene induced by cytokine activation, and also TNFRSF1A is a receptor for TNF-α, that induces NF-κB activation when it binds with TNF-α. Thus, TNFRSF1A belongs to STAT3 target gene which controls NF-κB, promotes TNBC, and is a potential biomarker [71]. Moreover, targeting genes that functions as a node between two oncogenic pathways could provide a novel therapeutic strategy. Li et al. [72] determined that SMYD2 can methylate p53 and thus prevent it from tying to its facilitators and inhibit apoptosis. Moreover, SMYD2 was found to promote TNBC through the methylation of its non-histone substrates, including STAT3 & NF-κB, to regulate the expressions of genes contributing to tumor progression. Furthermore, synergistic cross-talk was identified between SMYD2, NF-κB and STAT3 in TNBC cells, and positive response loops between SMYD2-TNFα-NF-κB-SMYD2 and SMYD2-IL-6-STAT3-SMYD2 with epigenetic regulatory effects were found to promote TNBC. However, silencing SMYD2 or SMYD2 inhibitors (like AZ505) could reduce TNBC growth.

3.4. Cross talk among NF-κB and HIF

Hypoxia inhibits tumor cell proliferation, but tumor cells develop resistance against drugs under hypoxic conditions and become phenotypically metastatic. This process is maintained by inducible factors like HIF-1α (hypoxia inducible factor 1) and CAIX (carbonic anhydrase IX) and modulates target genes like VEGF and iNOS [73] that promote oxygen production or allow the cells to adapt to hypoxia metabolically [74]. On the other hand, HIF-1α can also respond to certain factors, including ROS, IGF-1, and TNF-α, under normoxic conditions. NF-κB (the downstream target of TNF-α) controls HIF-1α transcription and specifically binds to the HIF-1α promoter site, which also contains p65 binding sites for the guidance of oxidative stress and inflammation induced tumor cell progression [75,76]. Thus, a crosstalk exists among HIF-1α and NF-κB. Similarly, NF-κB activation via IκB phosphorylation is allied with mRNA and protein levels of HIF-1α [77,78]. Crosstalk between these two TFs, regulates and moderates the transcriptions of various genes with crucial roles in cellular processes, like cell programing to adapt to hypoxic conditions and promote EMT. Proteins, like MUC1 are regulated via both NF-κB and HIF-1α. MUC1 is a glycoprotein

involved in cell signaling and apoptosis inhibition [79], and its expression in BC cells was reported to degrade IκBα (the inhibitor of NF-κB), and thus to promote the nuclear translocation of NF-κB, induce cell survival, and inhibit apoptosis. Furthermore, in $MUC1^{+}$ BC cells, NF-κB was overexpressed and p53 inactivated [80], and HIF-1α modulated VEGF expression and allowed cells to adapt to hypoxic conditions [80]. Thus, it appears that HIF-1α and NF-κB are initiated in MUC^{+} BC cells [81]. Also, the molecular evidence indicates NF-κB is essential for IL-6 expression in BC cell lines, and the activation of IL-6 stimulates its downstream signaling transducers including HIF-1α and STAT3 [82]. Thus, the interaction among NF-κB with STAT3 and the potentiation of tumor progression by HIF-1α suggests targeting IL-6 or NF-κB might inhibit the tumor progression. Moreover, recent studies revealed that GPER (G protein-coupled estrogen receptor) actively inhibits the expressions of IL-6 and VEGF. However, during tumorigenesis GPER loses its tumor suppressive activity. Liang et al. [83] showed that combining G-1 agonist to GPER potentiates the GPER-mediated inhibition of IL-6/NF-κB, further inactivating HIF-1α and STAT3 and inhibiting angiogenesis and metastasis in TNBC. IL-1β was also found to upregulate the countenance of HIF-1α in various cancers through NF-κB dependent pathways [84]. IL-1β enhanced cell migration and proliferation under hypoxic conditions in MDAMB231 cells by upregulating NF-κB, HIF-1α, and CXCL8, but inhibiting HIF-1α did not suppress IL-1β induced tumor migration because HIF-1α action was preserved via the activation of NF-κB [85]. Thus, the novel therapeutic strategies should be developed to target inflammatory components differentially in the microenvironment of BC.

4. Role of NF-κB in different cellular functions

4.1. NF-κB as an anti-apoptotic

NF-κB regulates apoptosis but its role is tricky. The effect of NF-κB on apoptosis is determined by the balance between genes which promotes cell survival and apoptosis [86]. NF-κB expression is widely observed during mammary gland development. Moreover TRAIL, which encourages apoptosis, is upregulated when NF-κB is inhibited in BC cells [87]. However, during tumorigenesis, TRAIL expression reflects drug resistance. Woo et al. [88] observed that YM155, a survivin inhibitor, sensitizes TRAIL and induces apoptosis. The collective treatment by YM155 and TRAIL enhanced the apoptosis of several cancer cells, including renal, breast, and glioma cancer cells. Subsequently, YM155 was found to potentiate TRAIL-mediated apoptosis through cathepsin S by downregulating the actions of Mcl-1, c-FLIP, and NF-κB. Furthermore, combined treatment with Ebselen and γ-radiation upregulated the actions of TRAIL at its mRNA level and downregulated NF-κB protein levels, and significant reductions were detected in TNF-α, TGF-β, IL-2, and INF-γ [89]. Earlier studies reported that Bcl-2 overexpression in human BC cells had an anti-apoptotic effect and enhanced NF-κB activity-related metastatic potential [90,91]. The Bcl-2 family, which is made of anti-apoptotic proteins, that bind to Bax and prevent it from oligomerizing and penetrating the mitochondrial membrane to prompt the activities of caspase 3 by inducing cytochrome c release, which further inhibits apoptosis. In BC cells, Bcl-2 is overexpressed and plays very important role in the progress of chemoresistance, and Bcl-2 is activated

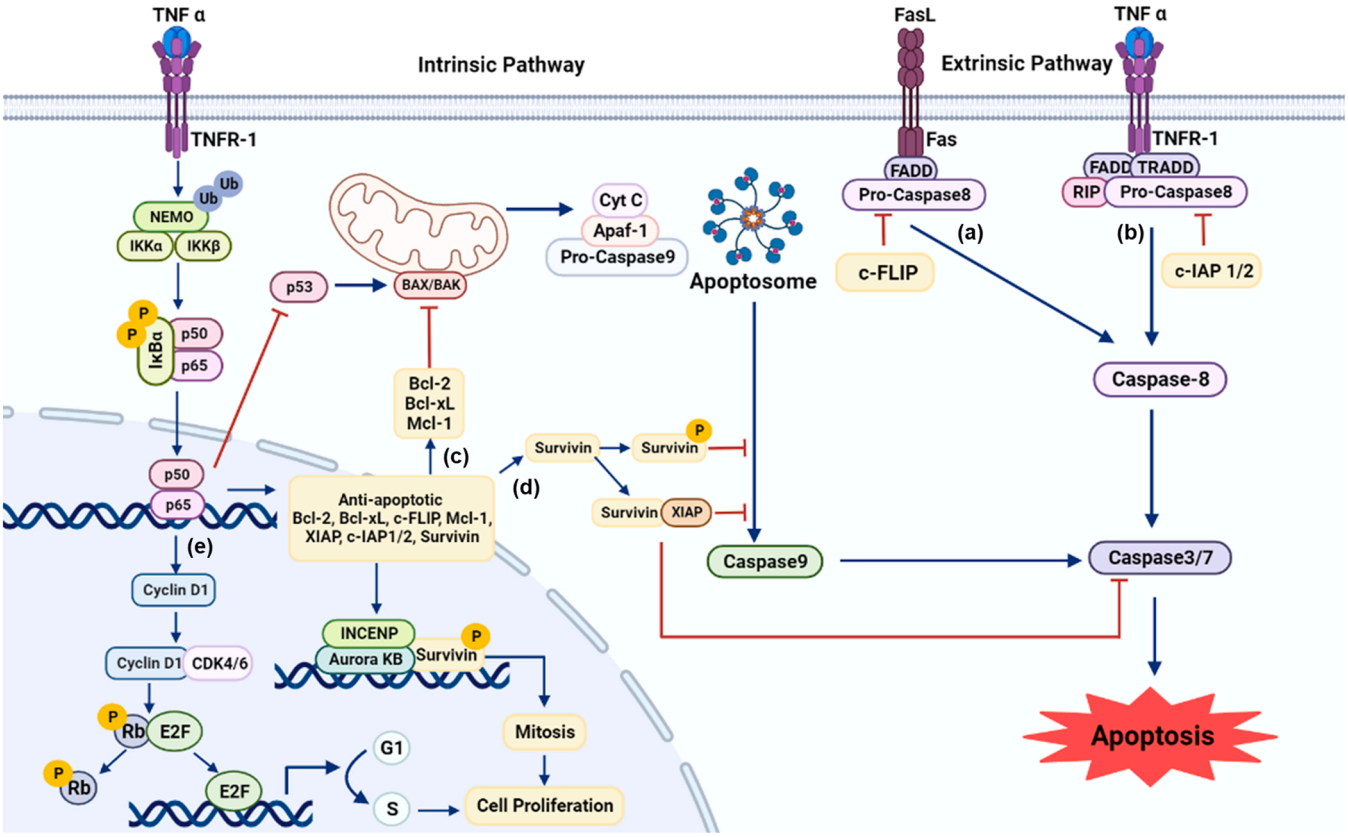

Fig. 3. NF-κB-mediated antiapoptotic pathways and the development and regulation of BC. NF-κB activation leads expression of various anti-apoptotic and cell survival proteins. Apoptosis is controlled by these proteins at various levels. These are A) Fas-mediated extrinsic apoptotic pathways are downregulated by c-FLIP via inhibiting activation of caspase-8. B) c-IAP1/2 regulates TNF-α induced apoptotic signals by suppressing the activation of caspase-8. C) Upregulation of anti-apoptotic proteins like Bcl-2, Bcl-xL, and Mcl-1 inhibits BAX/BAK thus preventing cytochrome C release from mitochondria and subsequent apoptosome formation. D) Caspase-9 activation is downregulated by survivin-XIAP complex or phosphorylated survivin. Survivin-XIAP complex also prevents caspase 3 activation. Hence apoptosis is downregulated. Also, survivin binds to Aurora kinase B and INCENP (inner centromere protein) forming a complex that regulates cell mitosis. E) Cyclin-D1-CDK4/6 complex phosphorylates Rb (retinoblastoma) protein releasing free activated E2F which binds to DNA activating S-phase genes, thus causing cell cycle progression.

by NF-κB [92]. Ren et al. [93] postulated that chrysophanol might inhibit BC cell progression by suppressing the phosphorylation of NF-κB and the corresponding downstream pathways, such as the cyclin D1 and Bcl-2 pathways. These findings show NF-κB plays an important role in BC development and the inhibition of apoptosis. NF-κB-mediated anti-apoptotic pathways during BC development are summarized in Fig. 3.

4.2. Function of NF-κB: A cell cycle regulator and metastatic promoter

Cyclins and CDK play a central role in governing the mammalian cell cycle. The cyclin D1 and Cyclin D, and CDK4 and CDK6 are overexpressed in BC. Guttridge et al. [94] determined the essence of the association between NF-κB and cyclin D, whereby NF-κB regulates growth and progression via cyclin D1 (Fig. 4). It was also shown that RANK (receptor activator of NF-κB) induced the NF-κB activation in mammary epithelial cells, where cyclin D1 appearance is significantly upregulated [95]. Recently, Zhang et al. [96] evaluated the relation between PAK5 ($P21^{cdc42/rac1}$ -activated kinase 5) and p65 in BC tissue, and Wang et al. [97] reported how to inhibit cell cycle arrest at G0/G1 phase and upregulated cyclin D1 in BC cells. They also characterized that PAK induces the phosphorylation of p65 and promotes the nuclear migration of NF-κB, which eventually attaches to the promoter region of cyclin D1. These observations show PAK upregulation increases cyclin D1 expression via NF-κB in vitro and in vivo and that cell cycle movement is governed by CDKs and their inhibitors as coordinated by cyclins. Shen et al. [98] proposed that NF-κB upregulates CDKs and cyclin D1 and determined that simvastatin (an antitumor drug) restricts the cell cycle progress and encourages apoptosis via downregulating the expression of CDKs, MMP-2, and cyclin D1 via inhibiting the NF-κB activation. Although multiple experimental models have been used to investigate interactions between cyclins and NF-κB, this topic remains controversial. Therefore, future research is necessary to establish the role of cyclins in BC cell cycle development and NF-κB activation.

During tumorigenesis, aberrant activity of PI3K induces the activation of AKT and the expression of p65, and eventually promotes the expressions of EMT regulatory proteins like N-cadherin and vimentin and downregulates E-cadherin causing metastasis via EMT. Twist1 is a helix-loop-helix that contains TFs, and mutated Twist1 has been etiologically associated with various diseases like cancer and Saethre-Chotzen syndrome. Furthermore, Twist1 activates STAT3, HIF-1α, NF-κB and integrin-linked kinase in several cancers like liver, breast, and prostate, and also induces EMT by upregulating E-cadherin thus promoting metastasis, invasion, and treatment resistance in cancer cells [99]. In addition, as discussed earlier, TNF-α promotes EMT and can induce cancer cell stemness by upregulating Twist1 in breast epithelial and BC cells, as demonstrated by Chia et al. [100]. Although the role of NF-κB in the promotion of EMT has been elucidated, the role played by TNF-α remains unknown. Findings suggest that NF-κB is operated by TNF-α in BC cell lines, and this results in the upregulation of Twist1 and nuclear migration of p65 via the activation of IKKβ through the CS pathway. This further promotes the expression of the Twist1 gene, which suggests that the Twist1 promoter region is essential for mediating EMT-induced inflammation and metastasis. Similarly, CFTR (cystic fibrosis transmembrane conductance regulator), which is widely described in epithelial cells, possesses a Cl(-) and HCO3(-) conduction anion channel, and inhibits invasion, migration, and metastasis by downregulating EMT markers and thus suppressing EMT [101,102]. In addition, CFTR can also impede NF-κB, which triggers uPA (urokinase type plasminogen activator) and plays a vital role in governing EMT. However, the expression of CFTR is downregulated in BC samples, which results in aberrant NF-κB activity and is allied with deficient

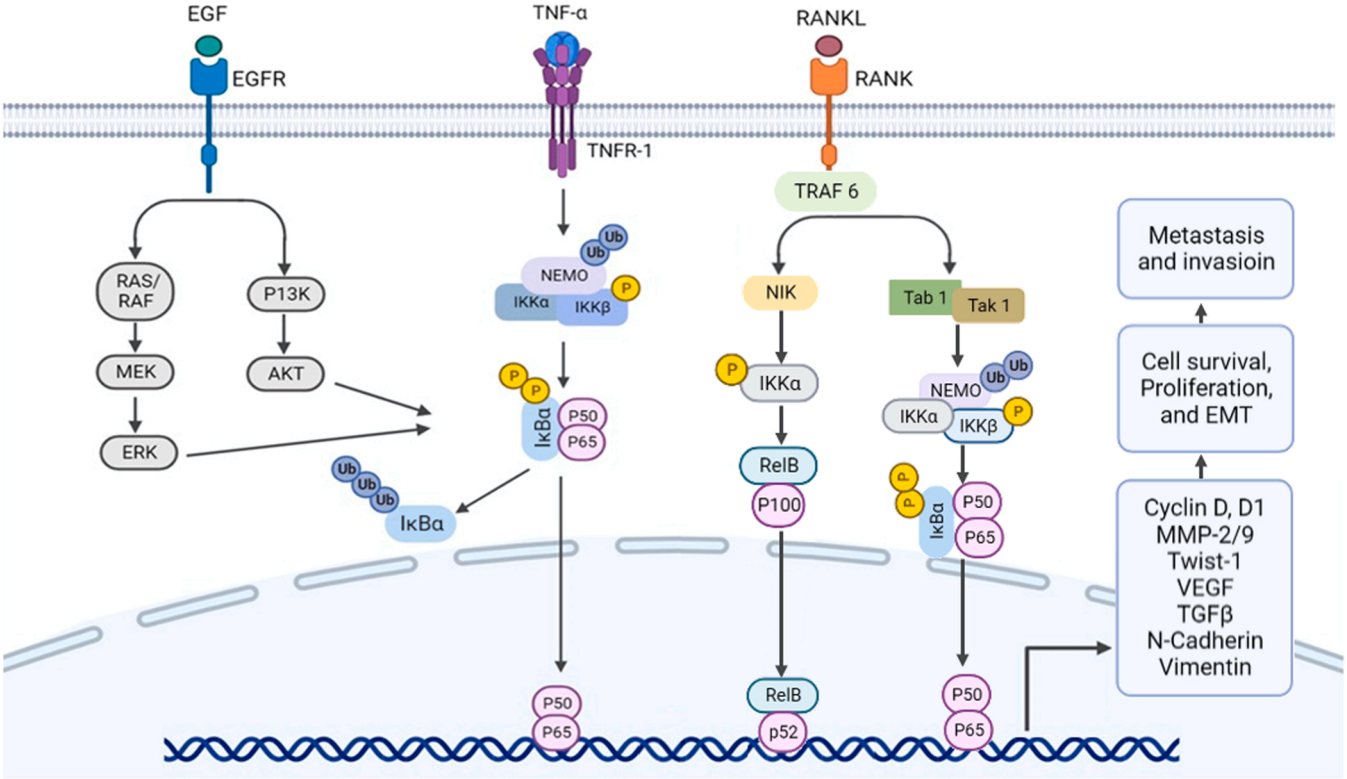

Fig. 4. NF-κB and its downstream pathways in breast cancer progression and metastasis. TNF-α activated p50/p65 complex upregulates MMP2, cyclin D, and D1. The RANKL binds to its receptor, activating TRAF 6 which activates Table1/Tak1 and NIK. The Table1/Tak1 complex activates the p50/p65 dimer and NIK activates RelB/p52 dimer via canonical and non-canonical pathways respectively. The activated p50/p65 and RelB/p52 dimer upregulate the expression of cyclin D1. These cyclins maintain the progression of cell cycle. EFGR-mediated PI3K/Akt and Mek/Erk pathways activate the transcriptions of the N-cadherin, vimentin, Twist1, TGF-β, MMP-2/9, and VEGF genes. These contribute to EMT (epithelial-to-mesenchymal transition) and distant metastasis.

prognosis [103]. Moreover, NF-κB activation also induces Ras and TGFβ dependent EMT and regulates EMT phenotype by binding to E-cadherin repressor promoter and ZEB-1/2 [104,105].

MiR655 is an oncogenic miRNA that elevates the production of stem-like cells, and significantly upregulates COX-2 expression in human BC cells in an EP4-dependent manner[106]. Thus, the ectopic over-expression of miR655 is dependent on EP4 activity and downstream pathways of EP4 along with NF-κB and PI3K/AKT/ ERK pathways that eventually promote progression and EMT in BC cells [107]. Recently, a novel biomarker ZBTB7A (zinc finger and BTB domain containing 7A) was identified and detected its involvment in the development of various cancers including BC. A new insight also revealed that ZBTB7A is expressed actively in BC metastasis and prmotes EMT. Additionally, ZBTB7A activity was regulated by NF-κB p65 in BC cells, indicating that ZBTB7A is involved in EMT promotion and that metastasis was induced via the NF-κB pathway [108]. Lymph node metastasis is the most common metastatic complication in BC, and the expressions of surface markers $CD44^{high}/CD24^{-/low}$ are widely considered to be responsible for metastasis in BC [109–111]. Furthermore, it has been reported that the activations of TALs (tumor associated leukocytes) have an important role in mediating metastasis [112]. El-Ghonaimy et al. [113] performed cytokine profiling using an antibody array on leukocytes isolated from tumor microenvironment and on positive and negative lymph nodes obtained surgically from a BC patient and detected $CD45^{+}$ cell infiltration in positive but not in negative lymph nodes. Additionally, they observed improved NF-κB /p65 signaling and increased secretions of IL-1α, TNF-β, IL-5, and IL-3 in the TALs of positive lymph nodes isolated from BC samples. Moreover, the upregulation of of CCR7 (C-C chemokine receptor 7) has been discovered in MCF-7 cells and found to play a crucial part in metastasis.

The oncogene ErbB2 is overexpressed in human BC, and recent research has determined that ErbB2 can induce tumorigenesis in immunocompetent mouse that showed NF-κB activation and thus boosted VEGF expression and angiogenesis. Under hypoxic conditions, VEGF levels are increased, and binds to integrin αvβ5, which is actively found in newly developed blood vessels and facilitates interactions between extracellular matrix and endothelial cells. Besides, NF-κB in tumor cells cannot regulate the integrin expression that mediates angiogenesis. Moreover, the prevention of NF-κB may stimulate the resistant ErbB2 cells to anti-ErbB2 monoclonal antibodies [114]. Nataraj et al. [115] identified crosstalk among VEGF and NAP (novel angiogenic protein), which promotes the expressions of VEGF and Flt-1. They found that tube formation of NAP is connected with invasion and migration. Also, they determined the existence of NAP in the tumor cytosol using anti-NAP-mAb. Furthermore, NAP promoted the NF-κB activation in BC cells through activating the JNK and MAPK pathways, as NAP is phosphorylated by VEGF and has a vital role in motivating its downstream target NF-κB. Thus, VEGF is an angiogenic factor that plays an important role in inducing angiogenesis.

Tumor-associated macrophages (TAMs) observed in the microenvironment of the tumor are generally activated by MCSF (macrophage colony stimulating factor) and CCL2 (chemokine ligand 2 with C-C motifs) [116,117]. A vital role was played by TAM in carcinogenesis via promoting cancer progression and angiogenesis and secreting angiogenic factors like VEGF [118–120]. In tumor cells, the activities of MCSF & CCL2 mediate NF-κB activation in macrophages, which increases VEGF release [121]. It has also been shown that TACE (tumor necrosis alpha converting enzyme) facilitates the release of soluble factors like MCSF [122], EGFR [123], and TNF [124] from the ectodomain, and that the expressions of these factors in BC cells are associated with poor survival of patient [125]. Rego et al. [126] detected an interaction of TACE shed MCSF and CCL2 in vitro in mammary cell lines and in vivo using BALB mice and showed tube formation by endothelial cell. These findings indicate TACE stimulates macrophage pro-angiogenic activity via NF-κB and VEGF expression. Recently, the CCL2-CCR2 axis was anticipated as a novel therapeutic strategy in hormone-dependent BC. In this study, the exposure of BC cells to estradiol significantly regulated CCL2 synthesis in estrogen-positive BC cells and upregulated the TWIST expression via activating the P3K/AKT/NF-κB pathway. Thus, TWIST was found to promote EMT, induce angiogenesis and contribute to metastasis in BC [127]. Similarly, progesterone, which targets receptors in mammary epithelial cells, also induces cell proliferation in a cyclin 1-dependent manner [128]. Progesterone also promotes the synthesis and release of RANKL from progesterone-positive luminal cells, which interacts with and expands RANK receptors in the progesterone-negative luminal cells of mouse mammary glands by activating NF-κB [129–131]. Thus, this pathway induces the transcriptions of various genes that are implicated in BC cell proliferations.

MT-2A (Metallothionein-2A) is another protein often detected in invasive BC tumors. MT-2A expression upregulated MMP-9 and AP-1 proteins and the transcription of NF-κB. Furthermore, the silencing of MT-2A featured to prevent the invasiveness of BC cells. Hence, MT-2A is a promising therapeutic marker for regulating the activation of NF-κB [132]. Additionally, Farina et al. [133] determined that AP-1, SP1, and NF-κB play crucial roles in augmenting MMP-9 through Trx-1 (thioredoxin 1), where Trx-1 is known as a redox protein usually detected in BC cells. Trx-1 dysregulates the balance among MMP-9 and TIMP-1, and is involved in the invasiveness of BC cells and strengthens MMP-9 expression at the transcription level by altering the DNA bound NF-κB activity and mediating the transcription of MMP. Thus, the overexpressed Trx-1 and NF-κB may be used as druggable targets that enable the regulation of MMP-9 in BC.

TNFα is a pro-inflammatory cytokine that enables tumor and metastatic progression by promoting angiogenesis and EMT. Rivas et al. [134] found that TNF-α is mitogenic and can promote the overexpression of ErbB2 in BC cells, which causes its phosphorylation at Tyr877 in mouse and human BC cell lines. Additionally, it can induce the Akt and NF-κB activation, whereas knock-down or prevention of ErbB2 by siRNA or AG825 (an EGFR inhibitor), respectively, blocks the activation of TNF-α, and thus regulates the NF-κB expression. Recently, Yvonne et al. [135] demonstrated that, WBP2 (WW-domain-binding protein 2) potentiates TNF-α induced cell migration and invasion by activating NF-κB in TNBC cells. Here, WBP2 elevates ubiquitin-mediated proteasomal degradation of IκBα (an upstream inhibitor of NF-κB) by enhancing mRNA stability of BTRC (beta-transducin repeat-containing E3 ubiquitin protein ligase) to promote TNBC cells aggressiveness. Likewise, Meiling et al. [136] found that CECR2 (cat eye syndrome chromosome region candidate 2) plays a key role as an epigenetic driver in promoting BC metastasis and thus by targeting CECR2 bromodomain, the expression of prometastasis genes and NF-κB-mediated immune suppression can be reduced at the metastatic sites of BC. In another study, Rahma et al. [137] demonstrated that, the NF-κB transcriptional activity and its phosphorylation was inhibited by Russelioside A which leads to the reduced metastatic capacity in 4T1 BC cells. These observations indicate that NF-κB portrayed a vital role in inducing angiogenesis and promoting metastasis in BC.

4.3. NF-κB and tumor suppressor genes

Tumorigenesis results from aberrant intracellular signaling resulting in the NF-κB activation, which rescues tumor cells from apoptosis and elevates uncontrolled mammary epithelial cell growth. BRCA1 is one of the tumor suppressor gene that responsible for hereditary BC protein which aids to the homology-directed DNA repair of double-strand breaks [138]. Besides, its absence due to mutation or knock-down in mammary cells leads to replication fork stalling resulting in genetic instability and double-strand breaks [139]. Hence, the absence of BRCA1 results in the stimulation of ATM (ataxia telangiectasia mutated check point kinase) and H2AX phosphorylation, which further contributes to genomic instability resulting from DNA damage. During this process, ATM induces the recruitment of various proteins including NF-κB, via NEMO phosphorylation (the inhibitor of IκB kinase) for DNA damage repair

[140–142]. Thus, activated NF-κB promotes anti-apoptotic cascades. In addition, when activated, NF-κB utilizes various other cascades to enhance recombination by stimulating the interaction of CtIP-BRCA1 complex [143]. Likewise, the NF-κB activated during DNA damage and replication stress induces the acetylation and phosphorylation of p53 [144]. This posttranslational modification stabilizes p53 and induces the activation of various genes which monitor the cell cycle, progression, and apoptosis [144–146]. However, when mutated p53 becomes oncogenic and positively regulates the pro-tumorigenic activity of NF-κB. As evidenced by earlier studies, absolute crosstalk occurs among p53 and NF-κB, and p53 behaves as a license element for the activities of NF-κB and its target genes [147–149]. The interaction depends on the chromatin attached p53/NF-κB p65 complex under stress and cytokine-dependent conditions. Moreover, HDACs (histone deacetylases) are connected with the epigenetic modifications of p53 and NF-κB [147,150]. HDAC inhibitors are widely used as anti-tumor agents and can induce cross talk among p53 and NF-κB and thus block the activity by class I HDAC along with the chemotherapeutic agents like hydroxyurea [151]. Weisz et al. [152] also determined that mutated p53 amplifies the activation of NF-κB via the TNF-α induced upregulation of the NF-κB 2 gene.

ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) forms catalytically active oligomers that are also dysregulated in many cancer types. ADAMTS18 is one of the most often hypermethylated tumor suppressor gene in several cancers, including BC, and this hypermethylation causes ADAMTS18 to lose its tumor-suppressing function [153]. However, demethylation restores the activity of ADAMTS18 in BC cells. Furthermore, the ectopic behavior of ADAMTS18 in BC cell lines suppresses tumor cell migration, invasion, and metastasis by deregulating NF-κB and AKT signaling [154]. These findings could result in the novel therapeutic strategies for BC.

4.4. NF-κB -mediated signaling pathways and carcinogenesis

Among the NF-κB subunits, p100 has been widely detected at elevated levels in BC tissues, and acts as a precursor for NF-κB affiliated proteins in cytoplasm. Previous studies have reported that ~90% of BCs are caused by dysregulated expressions of the subunits p50, p52, and c-Rel [155]. However, very limited information is acknowledged about the activity of RelB in BC cells. Mineva et al. [156] established that ectopic c-Rel induces the expression of RelB and an inverse relationship among RelB and ERα expressions in BC cells. They determined that the activation of RelB improved the survival rate of BC cells by upregulating Bcl-2, survivin, and MnSOD (manganese-dependent superoxide dismutase) and promoting resistance to γ-radiation and doxorubicin in ERα negative breast cells. Moreover, they also observed that $1,25(OH)_2$ D_3 reduces the activation of RelB and BC cell survival. IκBα is the most commonly studied inhibitor of NF-κB which also regulates the activation of NF-κB. However, its dysregulation causes NF-κB overactivation in various cancers, including BC. IκB kinase ε (IκKε; another IκK family member) activates the NF-κB and interferon by the NCS pathway. IKKε is a ser/thr kinase that portrays an essential role towards viral infection-induced inflammation and a breast oncogene responsible for 30% of BC cases when amplified and overexpressed [157]. CYLD is a tumor suppressor which regulates the activity of NF-κB. However, the overexpression of IKKε deactivates CYLD by phosphorylating it at ser418, which leads to NF-κB activation and tumorigenesis. Similarly, IKKε was also reported to phosphorylate TRAF factor at ser11, which induces the ubiquination of TRAF at lys63 required for the activation of NF-κB, and has been correlated with primary breast carcinoma [158].

Previous studies have determined NF-κB is expressed in BC cells and that various oncoproteins mediate its expression. For instance, dysregulation of L1CAM (L1 cell adhesion molecule) is associated with insufficient prognosis in various cancers, including ovarian cancer, PDAC, and BC. Kiefel et al. [159] reported that L1CAM also mediates the signaling of NF-κB by activating the integrin-FAK-Src-Akt signaling cascade when RGD-integrin is intact with L1CAM molecule enhancing IL-1β production in TGF-β1 treated cells, and were the first to report a L1CAM dependent signaling cascade involving the ligation of L1CAM by integrin and eventual promotion of the NF-κB activation. Kendellen et al. [160] found that NF-κB is actively expressed in tumor-initiating cells endowed with the potential to self-renewal in various cancers through both CS and NCS pathways, as was observed in derived basal-like and claudin-low subtypes of BC cell lines. NF-κB was also detected to elevate EMT and upregulate the expressions of IL-6 and IL-1β in tumor-initiating BC cell lines. Furthermore, CSC activation by the Notch-1 pathway in BC cells was discovered to be NF-κB dependent [161]. CSCs such as fibroblasts, macrophages, and non-CSC associated with NF-κB activation via Notch-1 signaling are associated with the production of JAG1 (jagged 1), a Notch pathway ligand, that plays an important role in self-renewal of CSCs in basal type BC cells. Besides, the NF-κB dependent paracrine activation of Notch signalling to induce JAG1 expression was detected during B-cell activation [162]. Furthermore, the Notch-1 signalling pathway activates the NF-κB and promotes the upregulations of its downstream target genes like VEGF, cyclin D1, MMP-2/9, Bcl-xL and Survivin, which promote BC progression [163].

Receptors also have an important role in facilitating the expressions of transcription factors. TLRs (toll like receptors) promote BC progression and are related to poor prognosis [164,165]. Stimulation of TLRs in BC drive tumor cells towards the CSC phenotype, and is boosted by the activations of the NF-κB and β-catenin but not by NF-κB alone [166]. RIP2 (receptor-interacting protein kinase 2) is a TNF receptor that directly activates NF-κB, JNK, MAPK, and ERK [167,168] and has a vital role in developing immunity and inflammation [169–171]. Moreover, the TNF receptor is overexpressed in triple negative BC (ER, PR, and Her2) which is correlated with poor survival, and has been demonstrated to facilitate metastasis, knock-down RIP2, and sensitize BC cells. Thus this receptor could be used as a prognostic marker for BC management [172]. Since NF-κB is the prime source for the development of resistance to endocrine therapy, inhibiting ER expression and NF-κB activity might desensitize cells to ER antagonists, which suggests the possibility of combinational therapy with anti-inflammatory drugs like dimethyl fumarate.

5. Role of NF-κB in the resistance to therapy

5.1. Role of NF-κB in BC resistance to chemotherapy

The activation of NF-κB potentiates the transcriptions of various pro-survival factors, including cyclin D1, Bcl-xL, and IAPs, and thus promotes anti-apoptotic signalling in BC [173–175]. This activation eventually contributes to resistance against radio-, chemo-, and endocrine therapies [176].

About 75% of BC cases are attributed to ER, which is commonly used as a biomarker of disease progression as well as for guiding endocrine therapies based on SERM (a selective estrogen receptor modulator), tamoxifen,and aromatase inhibitors. The interaction between NF-κB and ERα shows an inverse correlation [177–179] in case of expression and a reciprocal inhibition is detected between them as it supress inflammation and blocks the nuclear migration of NF-κB and its bond with DNA. NF-κB activation causes tumor progression mostly in ER^- tumors [180–182] and not in ER^+ tumors, which tend to respond to tamoxifen. However, 40–50% of ER^+ tumors do not respond to the therapy because they develop resistance to tamoxifen and express NF-κB at high levels [183,184]. Thus, the endocrine therapy that should suppress ER and inhibit NF-κB, however leads to the NF-κB activation as a marker of developing endocrine resistance. In tumor cells, the endocrine resistance induces an assertive phenotype involving various genes expression associated with EMT, stemness, and disease recurrence [177]. Furthermore, the expressions of IAP, Bcl-xL, and resistance proteins (BRCP and ABCG2) are widely detected markers of resistance [185]. Moreover, the presence of the BRCP polymorphism can serve as a prognostic aspect for

the development of tamoxifen resistance and NF-κB activation. LINC00472 (long intergenic non-coding RNA) in BC inhibits the progression of tumor, and its lower expression is associated with low survival [186,187]. It was found that ERα promotes the expression of LINC00472 and suppresses the activation of NF-κB. Upon tamoxifen treatment, LINC00472 expression was reduced, coupled with the upregulation of NF-κB expression in ER^+ breast tumor as a marker of developing resistance [188].

Moreover, in ER^- BC cells, low LINC00472 expression was detected and correlated with poor prognosis. Thus, continuous tamoxifen administration might prevent the limitation of NF-κB activation by LINC00472. However, the use of combined regimen might potentiate endocrine therapy by inhibiting ER as well NF-κB expression. Kastrati et al. [189] developed a hybrid drug with reduced side effects and an efficient pharmacokinetic profile capable of targeting multiple sites. They used the raloxifene (an SERM) as an ER inhibitor along with anti-inflammatory drug fumarate to inhibit the NF-κB pathway. Results showed raloxifene-fumarate combinatorial treatments offer a potential means of improving the anti-inflammatory effects of ER-targeted BC therapy.

5.1.1. NF-κB targeting to overcome chemoresistance in BC

Chemotherapy is an adjuvant therapy of cancer, however chemoresistance and recurrence are the most common obstacles to successful treatment. Chemoresistance might be due to various factors, such as changes in the tumor microenvironment, apoptotic pathway, and increased efflux of drug with impaired intake of drug [190,191]. Various drugs induce NF-κB activation and/or resistance in BC tumor cells. For instance, ABC (ATP binding cassette) proteins are widely expressed in cancer cells, and MRP1 and MDR1, which are the members of this transporters superfamily, are mostly accountable for the emergence of chemoresistance [192,193]. It was determined that NF-κB maintains cross talk with drug efflux proteins and is associated with their expression. This results in the upregulations of NF-κB, p65, Bcl-2, and the downregulation of Bax in doxorubicin-treated BC cells [194]. However, inhibiting the expression of NF-κB, p65 or its siRNA silencing could block the translocation as well as reduce the expressions of MDR1 and MRP1. Wang et al. [195] determined that BC cells developed resistance against epirubicin due to the Akt/NF-κB induced over expression of GPR120, which mediates the ABC transporter proteins over expression and the accumulation of epirubicin. However, sensitizing GPR120 with an antagonist like AH7614 or GPR120 siRNA was found to decrease the expressions of ABC proteins and enhance the epirubicin efficacy in MCF-7 cell lines. Thus, the authors suggested that GPR120 possibly a potential therapeutic target to overcome the chemoresistance. As documented earlier, RIP2 overexpression is allied with an inadequate prognosis and cancer recurrence in TNBC. It was recently demonstrated that RIP2 also offers resistance to paclitaxel and apoptosis caused by ceramide via NF-κB pathway activation in TNBC cells. Moreover, blocking RIP2 expression could repress NF-κB and sensitized tumor cells to paclitaxel [196]. As regards immunotherapy, trastuzumab treatment of PTEN-silenced BC cells results in the advancement of CSC populations via the activation of a NF-κB-IL-6 feedback loop [197]. In addition, certain drugs including platinum compounds, such as paclitaxel, and vinca alkaloids, which are involved in disrupting microtubule formation and can activate NF-κB induced treatment resistance [198]. CSCs have the ability to develop resistance and are prone to recurrence [199–201], whereas NF-κB-IL-6 signalling can promote self-renewal and chemoresistance following chemotherapy [202]. Saha et al. [203] exposed breast CSC cells to aspirin to disturb the NF-κB and IL-6 signalling pathways and prevent the nuclear translocation. Aspirin treatment sensitized CSCs to combinatorial treatments with 5-FU, cyclophosphamide, and doxorubicin. Thus, it appears combining antagonists with conventional combinational therapy might provide a means of improving recurrence-free survival in BC. A list of the drugs tested for clinical trials is provided in Table 1.

5.2. Role of NF-κB in BC resistance to radiotherapy

Radiation is another conventional therapy used for cancer treatment. As discussed, resistance development in the tumor cells is a major hurdle, and radio-resistance and tumor relapse are due to the activations of TFs like NF-κB [204]. Earlier studies showed that radio-resistance develops irrespective of dose (whether taken in low or heavy concentrations) [205–210]. In addition, it has been reported that the clinical doses trigger inter- and intra-cellular signaling, activating NF-κB and the secretion of TNF-α via an NF-κB dependent pathway, and promote long-term positive input of NF-κB and TNF-α interaction [211]. Oct4 (POU-domain octamer binding transcription factor 4) is commonly expressed in malignant tumor cells like those of BC and breast CSC. In addition, Oct4 can promote chemoresistance by upregulating ABC proteins and radio-resistance is also associated with Oct4 expression. The overexpression of Oct4 suppressed IR-induced premature senescence subjected to ionizing radiation via IL-24 production activated by STAT3 and NF-κB that leads to resistance [212]. Furthermore, treatment with the selenium compound ebselen and γ-radiation significantly improved antitumor activity in MCF-7 tumor cell lines [89]. The selenium compounds force tumor cells against the redox threshold and eventually promote apoptosis and sensitize cells to radiation [213–215]. Thus, strategies that target these pathways might be helpful for novel therapeutic interventions that minimize tumor recurrence.

Table 1
Clinical Trials and study phases conducted on drugs and nanomedicines (Source: https://Clinicaltrials.gov).

Intervention/Drug/ Other Name	Title	Identifier	Purpose	Study/ Phase	Recruitment Status
Curcumin/ Meriva	Treatment with Meriva in induced inflammation and fatigue with BC women	NCT01740323	To find out if the curcumin reduces binding of NF-κB to DNA and eventually with its downstream IL-6 in patients after chemotherapy.	Phase II	Completed
Ritonavir	A Phase I/II trial of short course pre-operative Ritonavir to determine inhibition of Akt in BC.	NCT01009437	The phase I/II trial includes the best dose of ritonavir and its effects in women undergoing surgery for newly diagnosed BC	Phase I	Completed
Gemcitabine/ Dietary supplement: Genistein	Phase II trial of Gemcitabine and Genistein in metastatic BC patient.	NCT00244933	The phase II trial includes the working of gemcitabine hydrochloride with genistein in treating the women having stage IV BC	Phase II	Completed
Imx-110 (A nanoparticle encapsulated with STAT3/ NF-κB / poly-tyrosine kinase inhibitor and doxorubicin in lower dose)	A phase I/IIa open-label, Dose -Escalation safety, tolerability and pharmacokinetic with advanced stage	NCT03382340	To determine safety and pharmacokinetic in the patient with the advanced stage	Phase I Phase II	Recruiting

5.3. NF-κB inhibitors in BC therapy

Earlier, in vitro studies have provided proof-of-concept that the inhibition of NF-κB activation can reduce many pro-inflammatory effects. As a result of this, NF-κB is a compelling target for therapeutic intervention in BC. Although some medications are known to have some indirect NF-κB blocking properties, very few direct inhibitors of NF-κB are in use. These NF-κB inhibitors can reduce the activity of NF-κB and improves the BC treatment outcomes [216]. So far, Bortezomib, IKK inhibitors, thalidomide and its analogs, and PARP inhibitors are being investigated for BC therapy. Recently, Ji-Yeon et al. [217] found that Bortezomib inhibits Sp1 activity and interferes with the physical interaction of Sp1/p65, which results in downregulation of the NF-κB pathway. Although bortezomib showed anti-angiogenic properties in preclinical models of breast and other cancers, a phase I/II trial of bortezomib and capecitabine combination therapy in patients with metastatic BC revealed only moderate antitumor activity [218]. Besides, IKK related kinases are important NF-κB regulators and their inhibitor IKK16 was more effective than gefitinib (an EGFR inhibitor) in reducing the viability of TNBC cell lines. Therefore, the combination of IKK16 with gefitinib resulted in a synergistic antiproliferative effect [219]. In the mouse model, thalidomide is known to inhibit tumor growth by inhibiting angiogenesis and necrosis of BC tumour cells [220]. Furthermore, NF-κB inhibitors can be used alone or in combination with other breast cancer therapies such as chemotherapy and radiation therapy. Extensive animal and human studies are needed to fully understand the effectiveness and potential side effects of NF-κB inhibitors for breast cancer treatment.

6. Conclusions and future perspectives

BC is a potentially fatal malignancy that results from genetic mutations and an unhealthy lifestyle. Dysregulated tumor suppressor genes and oncogenes encode TFs that inhibit apoptosis, induce cell growth, cell cycle progression, and metastasis. NF-κB is a key regulator for various signalling pathways, including those responsible for resistance to chemotherapy and radiotherapies in various cancers, but especially in hormone-independent BC. Thus, targeting the aberrant molecular signaling pathways of NF-κB might be a potential strategy for BC therapy. Though conventional adjuvant therapies like chemo- and radiotherapies are advantageous, but they have serious adverse side effects, which include resistance to chemotherapy and disease recurrence due to the overactivation of NF-κB. Combination therapies aimed at inactivating NF-κB and sensitizing tumor cells have produced encouraging results, but these therapies should be locally and not systemically advantageous. Nanotechnology offers an attractive strategy for delivering drugs and conventional therapeutics to tumors and enhances drug pharmacokinetics, efficacies, and retentions. Hence, developments that target relevant molecular signaling pathways and TFs may result in effective inhibitors of NF-κB that improve BC therapy.

CRediT authorship contribution statement

All authors contributed to the conceptualization of this review, E. Pavitra, J. Kancharla, VK Gupta, and BLVKS wrote the original draft. K. Prasad, JG Kim, JY Sung, and M. B. Tej designed the figures and tables. R. Choi, J-H Lee, Y-K. Han, GSR Raju, LVKS Bhaskar, and YS Huh reviewed and edited the manuscript. All the authors have read and agreed for the submission of the final version of the manuscript for publication.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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