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Malignant function of nuclear factor-kappaB axis in prostate cancer: Molecular interactions and regulation by non-coding RNAs

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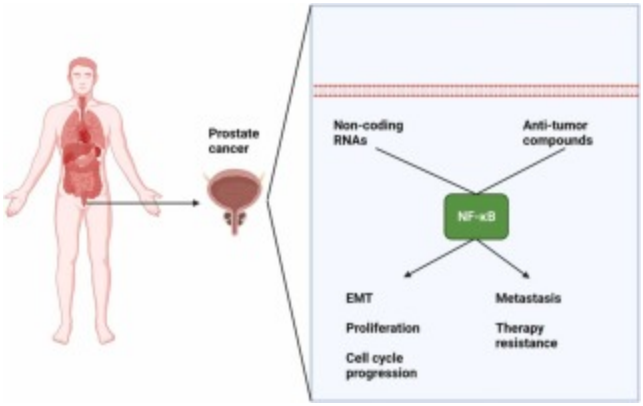
Abstract

Prostate carcinoma is a malignant situation that arises from genomic alterations in the prostate, leading to changes in tumorigenesis. The NF-κB pathway modulates various biological mechanisms, including inflammation and immune responses. Dysregulation of NF-κB promotes carcinogenesis, including increased proliferation, invasion, and therapy resistance. As an incurable disease globally, prostate cancer is a significant health concern, and research into genetic mutations and NF-κB function has the efficacy to facilitate the introduction of novel therapies. NF-κB upregulation is observed during prostate cancer progression, resulting in increased cell cycle progression and proliferation rates. Additionally, NF-κB endorses resistance to cell death and enhances the capacity for

metastasis, particularly bone metastasis. Overexpression of NF-κB triggers chemoresistance and radio-resistance, and inhibition of NF-κB by anti-tumor compounds can reduce cancer progression. Interestingly, non-coding RNA transcripts can regulate NF-κB level and its nuclear transfer, offering a potential avenue for modulating prostate cancer progression.

Graphical Abstract



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Keywords

NF-κB axis; Inflammation; Drug resistance; Prostate cancer; Urological cancers

1. Introduction

The life of men around the world, especially elderly individuals is threatened by prostate cancer (PCa) which accounts for the fifth reason of tumor-related death [1], [2]. 1.2 million new cases of PCa were detected in 2018 which led to 360,000 deaths [2]. The occurrence of PCa is various according to geographical locations with Western countries reporting higher occurance (6-fold higher) compared to non-Western countries [3]. One of factors contributing to the difference in incidence rate of PCa based on regions is racial changes. The highest incidence rate for PCa is observed in African Americans, followed by Caucasians, while the lowest incidence rate is observed in Asians. According to estimates, there is a threefold difference in incidence rate of PCa in Asians and African Americans [4] which can

emanate from alterations in genetic profile and polymorphisms. Notably, Japanese people that have emigrated to Western countries demonstrate higher rate of PCa compared to those in Japan [5], [6]. This shows that both genetic factors and environmental factors contribute to changes in incidence rate of PCa. In addition to rate, PCa development relies on other factors including age, family history, and genetic susceptibility [7]. The pathogenesis of PCa neoplasia is suggested to originate from a lesion known as HG-PIN that is premalignant with a number of aberrant features such as presence of epithelial cells in glands or ducts of prostate [8]. HG-PIN has a number of similar characteristics to PCa and is defined as a transitory stage between benign prostate epithelium and invasive cancer [8], [9]. The standard treatment strategy for men with PCa is ADT targeting androgen receptors (AR) [10], [11], [12]. The progression of PCa to CRPC results in resistance to ADT and its inefficacy in cancer treatment [13], [14], [15]. Localized PCa is suggested to be the early phase of this malignancy and is limited to prostate tissue. According to clinical and pathological tests including Gleason scoring and PSA levels, localized PCa can be indolent or aggressive. At this phase, several treatment strategies including surgery, radiation therapy and sometimes ADT are recommended. However, the most important issue in PCa treatment is recurrence in 35% of cases followed by metastasis of PCa. Metastasis elevates invasion of PCa cells to other tissues and organs such as bone, bladder, and lymph node [16], [17], [18].

Despite the challenges involved in diagnosing and treating PCa, the abnormal malignancy and metastasis of tumor cells should be considered. This progression is influenced by the interaction between transcriptional factors and downstream targets, aberrant level of oncogenic molecules, and changes in the TME (as shown in Fig. 1) [19], [20], [21], [22], [23]. TAMs are the main reasons for progression of PCa. Infiltration of TAMs to the tumor tissue is partly correlated with cancer cells secreting IL-1β to upregulate Marco expression on macrophages. Furthermore, CCL6 derived from lipid-loaded TAMs can promote the metastasis [24]. Besides, the release of cholesterol by macrophages in TME can develop therapy insensitivity in PCa [25]. The role of AR in PCa progression is inevitable. For instance, G3BP1 triggers AR via Cul3 down-regulation to elevate progression of PCa [26]. Cell cycle malignancy, proliferation and metastasis of PCa are amplified by LINC00852 overexpression [27]. Some of these genetic factors have advantageous features in the clinical course. Status of HNRNPC is enhanced in PCa tissues and is associated with T stage, N stage, Gleason score, PSA level, and overall survival of patients [28]. SEPT6 can reduce the level of UBC to disrupt progression of PCa [29]. Upon EMT induction, metastasis of PCa is accelerated followed by CKB suppression of Akt to inhibit EMT and progression of PCa [30]. After the development of CRPC, molecular interactions can increase tumorigenesis. Down-regulation of LOX in CRPC ensures progression via enhancing IGFBP3 expression (Fig. 1) [31].

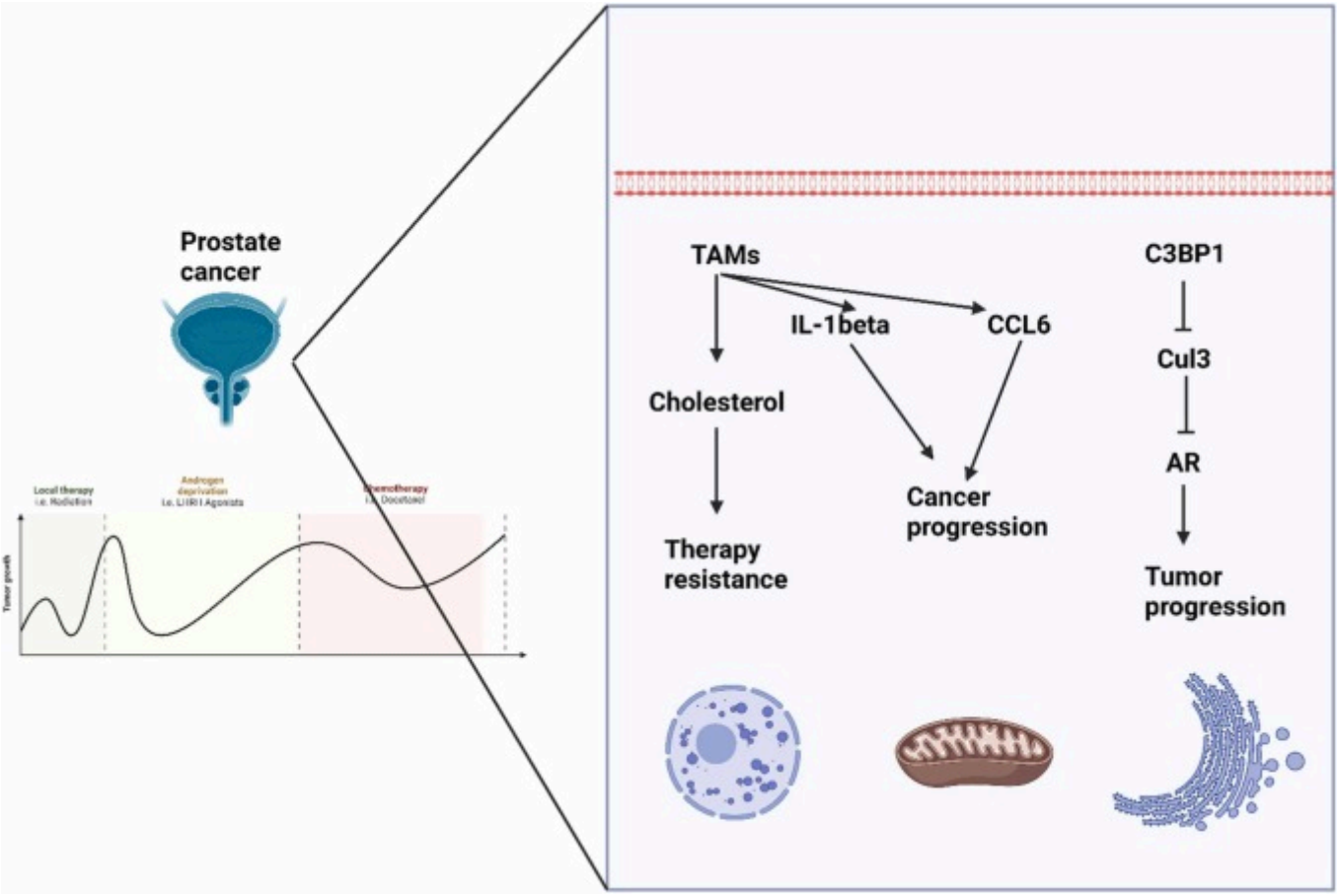

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Fig. 1. Molecular interactions in PCa. The progression of PCa is complicated, but it appears that changes in some of the molecular pathways and their interactions can affect carcinogenesis.

2. NF-κB and oncology

In 1986, NF-κB was recognized as a nuclear molecule that can bind to enhancer element of immunoglobulin kappa light-chain of activated B cells [32], [33]. It was then found that proteins with DNA binding activities are expressed in all cell types and control the expression of factors that impact biological mechanisms [34]. Since then, five members of NF-κB transcription factor have been recognized including p65 (RelA), RelB, c-Rel, NF-κB1 and NF-κB2. Among these members, NF-κB1 and NF-κB2 are synthesized as pro-forms known as p105 and p100, and are catalyzed by proteolytic enzymes to p50 and p52, respectively [35]. NF-κB1 and NF-κB2 are able to produce homo- or hetero-dimers and have similarities in their structures with Rel homology domain (RHD) which have pivotal function in dimerization and binding to DNA [36]. The interaction reactions are regulated by

NF-κB which is capable of impacting growth, apoptosis, migration, metastasis, and angiogenesis [37], [38]. The stresses, attacks and pathological invasions can stimulate NF-κB [38]. NF-κB exerts an important function during tumorigenesis [39]. Malignant tumor cells as well as the TME present with a hyperactivation of NF-κB [38]. The induction of NF-κB is dependent on the degradation of its inhibitors such as IκB proteins and a subsequent phosphorylation by IκB kinase (IKK) complex [38]. Based on the studies, the most important factors responsible for stimulation of NF-κB in solid tumors are IKK-activating cytokines including TNF and IL-1 [40], [41].

Cytokines are among the factors that can mediate NF-κB. As a pro-inflammatory cytokine, TNF-α recruits several adaptors such as TRADD, RIP, and TRAF2 to cytoplasmic membrane to induce a complex known as IKK [42], [43], [44]. The IKK complex is comprised of a scaffold protein called IKKγ, as well as IKKα and IKKβ kinases [45], [46]. IKK complex is responsible for phosphorylation of IκBα on Serine32 and Serine36 to mediate its degradation via proteasomal pathway. This is known as the canonical axis of NF-κB. There is an alternative axis independent of IKKγ and which includes a number of cytokines such as lymphotoxin B [47], BAFF [48], CD40 ligand [49] and viruses such as human T-cell leukemia virus [50] and Epstein-Barr virus [51]. The alternative pathway of NF-κB is based on TRAF protein recruitment to cell membrane and the NIK [52]. This results in stimulation of IKKα homodimer to mediate ubiquitination and cleavage of p100 to produce NF-κB protein p52 and moving it to the nucleus along with RelB. In both pathways, phosphorylation of factors that inhibit NF-κB are vital. This was confirmed by IκBα mutation in cells which showed a lack of phosphorylation and inactivation of NF-κB [44], [53]. Fig. 2 depicts an overview of NF-κB, a vital pathway for mediating tumorigenesis [54], [55]. *Fusobacterium nucleatum* triggers NF-κB and elevates expression level of downstream ICAM1 in colorectal carcinogenesis [56]. YAP is an upstream mediator and induces NF-κB to promote metastasis and stemness. YAP/NF-κB axis is induced by CARMA3 [57]. Natural products that suppress NF-κB exert pro-apoptotic function in pancreatic cancer [58]. In xenograft model of esophageal cancer, sufentanil inhibits NF-κB to decrease invasion of tumor cells [59]. In cervical cancer, upregulation of SMC4 provides unfavorable prognosis and it accelerates tumor progression via induction of NF-κB [60]. Onion peel extract down-regulates expression levels of NF-κB and L1CAM in inhibiting angiogenesis and proliferation [61]. OSMI-1 inhibits NF-κB to accelerate TRAIL-mediated apoptosis in colon cancer [62]. Moreover, suppression of NF-κB is effective for purpose of chemosensitivity in cancer [63]. Therefore NF-κB is a promising target in various human cancers (Table 1) [64], [65], [66], [67], [68], [69].

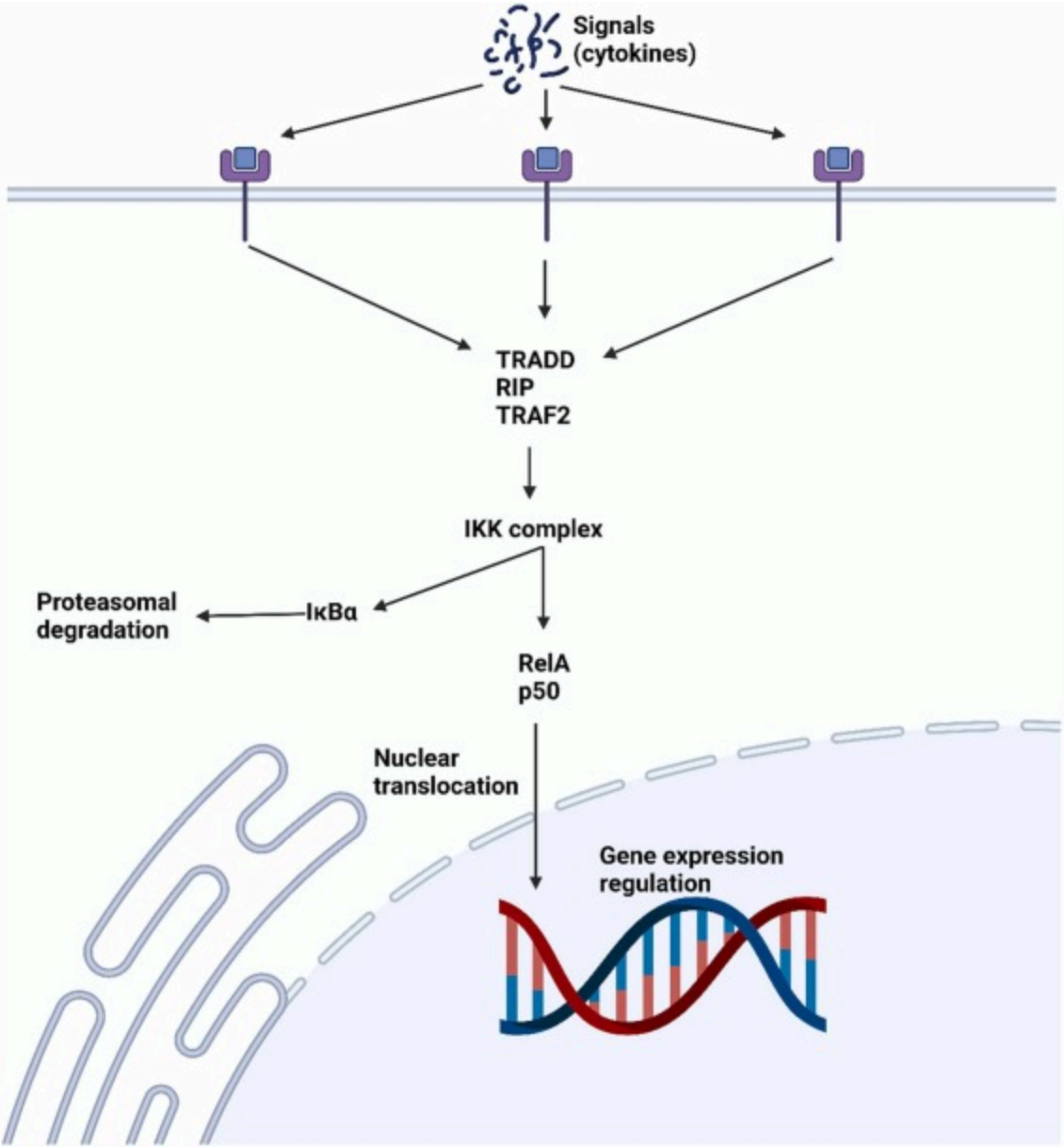

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Fig. 2. An overview of NF-κB. This is a simple description of NF-κB in which presence of signals such as cytokines can lead to recruitment of TRAD, RIP and TRAF that are essential for stimulation of IKK complex. Then, IKK complex mediates degradation of IκBα to induce nuclear transfer of RelA and p50.

Table 1. NF-κB in human tumors.

Cancer type	Molecular pathway	Remark	Ref
Breast cancer	Mammaglobin 1/NF-κB	Mammaglobin 1 increases NF-κB expression in promoting tumorigenesis	[70]
Lung cancer	NF-κB/STAT3	NF-κB and STAT3 down-regulation by magnolol stimulates apoptosis	[71]
Ovarian cancer	miR-200c/NF-κB	miR-200c and NF-κB loop determines response to cisplatin chemotherapy	[72]
Liver cancer	NF-κB	NF-κB upregulation prevents apoptosis and increases tumorigenesis	[73]
Breast cancer	ROS/Akt/NF-κB	ROS/Akt/NF-κB axis enhances EMT and invasion	[74]
Endometrial cancer	ERK/NF-κB/Akt	Modulation of growth and tumor formation	[75]
Pancreatic cancer	SIRT6/NF-κB	SIRT6 reduces NF-κB expression to stimulate ferroptosis and decrease glycolysis	[76]
Gastric cancer	USP4/NF-κB	USP4 enhances NF-κB expression in tumorigenesis	[77]
Colorectal cancer	ICAT/NF-κB	Increase in invasion through ICAT-mediated NF-κB upregulation	[78]
Colorectal cancer	NF-κB	NF-κB down-regulation by Ficus dubai extract stimulates apoptosis and cell cycle arrest	[79]
Prostate cancer	NF-κB	Lycorine reduces NF-κB expression	[80]
Gastric cancer	circPRRX1/miR-596/NF-κB	CircPRRX1 increases NF-κB expression through miR-596 sponging	[81]
Colon cancer	TRIM52/NF-κB	TRIM52 increases NF-κB expression to promote tumorigenesis	[82]
Bladder cancer	NF-κB	Epigallocatechin-3-gallate suppresses NF-κB expression	[83]
Endometrial cancer	miR-7–2–3p/NF-κB	miR-7–2–3p sponging by BMPR1B-AS in NF-κB induction	[84]

Cancer type	Molecular pathway	Remark	Ref
Colorectal cancer	GMEB2/NF-κB	GMEB2 increases NF-κB expression in enhancing carcinogenesis	[85]

3. NF-κB and prostate cancer proliferation

Based on the previous section, two facts are obvious, (i) PCa treatment is a challenge for physicians and (ii) NF-κB exerts oncogenic functions in various cancers. Therefore, any factor that induces NF-κB is of interest in enhancing PCa proliferation. Silencing HIST1H2BN reduces progression and growth of PCa, and low expression of HIST1H2BN decreases binding function of NF-κB p65 [86]. Mutations and variations in AR can lead to development of CRPC, an advanced form of PCa. NF-κB is a regulator of AR and can impact the progression and development of CRPC [87]. Activation of AR significantly increases the potential of PCa in proliferation. NF-κB elevates AR expression to potentiate PCa progression [88]. NF-κB increases CRPC progression by recruiting cytokines responsible for tumor progression. The hyperactivation of NF-κB in CRPC occurs by NSD2 and then, NF-κB promotes IL-6, IL-8 and TNF-α levels as cytokines to accelerate CRPC progression. The cytokines including IL-6, IL-8, and TNF-α induce NF-κB to promote CRPC malignancy [89]. Low expression levels of SIRP-α increases carcinogenesis. Enhancing level of SIRP-α impairs progression of PCa and induces apoptosis in tumor cells. SIRP-α reduces COX-2 level by inhibiting p38-MAPK/NF-κB axis to reduce growth of PCa cells and mediate apoptosis [90]. NF-κB can be induced by upstream mediators that increase the progression of PCa. Upregulation of HMGB1 increases the tumorigenesis through regulating NF-κB. HMGB1 upregulation increases PCa progression, and elevates TNFR1 expression to induce NF-κB leading to PCa malignancy [91].

The interaction of NF-κB with other pathways determines PCa progression. STAT3 is a regulator of NF-κB in PCa and increases its progression. For instance, STAT3 down-regulation impairs PCa metastasis to bone [92]. Methylation of STAT3 by EZH2 increases neuroendocrine differentiation [93]. IL-8 increases proliferation of PCa and suppresses apoptosis. The oncogenic activity of IL-8 emanates from upregulation of STAT3 to mediate Akt/NF-κB axis to elevate carcinogenesis [94]. Notably, the interaction of NF-κB and STAT3 is mutual. NF-κB can also regulate STAT3 in PCa tumorigenesis. Interestingly, consumption of broad-spectrum antibiotics leads to an increase in PCa growth in vivo. Therefore, disturbance in gut microbiota can evoke NF-κB to enhance IL-6 levels. Overexpressed IL-6 stimulates STAT3 and promotes PCa proliferation and progression via upregulating cyclin D1, c-Myc, Bcl-2, and survivin [95]. Notably, cytokines can also increase NF-κB expression in

PCa progression. MCOLN2 is upregulated in PCa which can increase tumorigenesis and trigger unfavorable prognosis. MCOLN2 increases IL-1β secretion which can induce NF-κB [96].

The expression of NF-κB has been investigated in clinical samples to shed light on the function of NF-κB in the tumorigenesis process. NF-κB and CK2α levels are enhanced in clinical PCa samples. Overexpression of NF-κB relies on CK2α to increase PCa progression [97]. Moreover, the NF-κB/SHh/GLI1 expression is increased in PCa and is accountable for PCa progression and poor prognosis [98]. The overexpression of NF-κB can render two important features in PCa cells including cell cycle acceleration and apoptosis inhibition. The level of CDCA3 increases in PCa which mediates an unfavorable prognosis. NF-κB increases cyclin D1 to increase PCa progression and accelerate cell cycle. CDCA3 stimulates NF-κB/cyclin D1 axis and reduces p21 expression level to inhibit apoptosis and accelerate cell cycle [99]. NF-κB induction by DDX20 is effective in elevating growth rate [100]. Down-regulation of NF-κB and its co-application with simvastatin can be advantageous in NF-κB suppression, LIN28 down-regulation, and subsequent overexpression of miRNA let-7 thereby minimizing tumorigenesis [101]. The function of NF-κB in regulating PCa proliferation is further confirmed by an experiment which suppresses the interaction between AR and NF-κB p52 and avoids the activity of NF-κB p52 and pARser81 in order to reduce the proliferation rate of PCa and reduces cyclin D1 level [102].

The proliferation rate of PCa cells can be accelerated via inducing Akt. Palmitic acid suppresses PI3K/Akt axis and prevents PCa progression [103]. Curcumol promotes miR-9 expression to suppress Akt thereby reducing Pca malignancy [104]. NF-κB stimulates Akt and elevates PCa progression. This is done in part by upregulation of SHARPIN which prevents apoptosis in PCa via Bcl-2 and survivin overexpression, and Bax and caspase-3 down-regulation. SHARPIN induces NF-κB/Akt to increase proliferation and inhibit apoptosis in PCa [105]. High levels of IL-6 increase tumorigenesis [106], [107]. PSCA is involved in increasing PCa progression and to this end, it evokes NF-κB to elevate IL-6 expression and promote proliferation [108]. Based on these discussions, the function of NF-κB in regulating PCa progression and proliferation is obvious and NF-κB or related molecular pathways can be targeted for cancer therapy (Fig. 3) [109], [110].

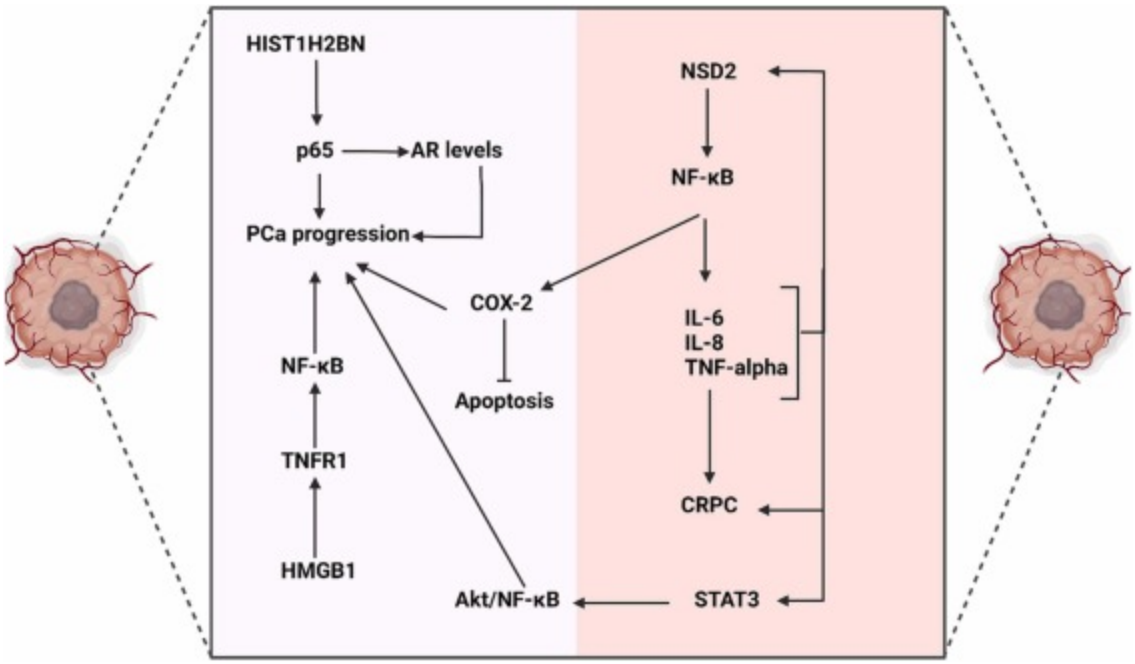

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Fig. 3. NF-κB and proliferation. P65 is responsible for increase in AR levels and notably, levels of p65 can be upregulated by HIST1H2BN to promote tumor progression. HMGB1 positively interacts with TNFR1 to increase NF-κB levels. Furthermore, NSD2 escalates NF-κB levels to intensify COX-2 in apoptosis hang-up and accelerating tumorigenesis. The important part is that IL-6, IL-8 and TNF-alpha levels can be escalated by NF-κB and these cytokines can induce STAT3 to promote NF-κB levels in promoting tumorigenesis.

4. NF-κB and prostate cancer invasion

Invasion in PCa is a serious challenge for treatment of cancer patients and is correlated with therapy resistance and aggressive behavior as well as a high burden of gene mutation. For instance, bone invasion can change patient prognosis. Modification of lncRNA PCAT6 promotes stability of IGF1R at mRNA level to increase bone metastasis in PCa [111]. CircLRP6 increases level of NRBP1 via miR-330–5p inhibition to escalate the invasion of PCa [112]. Wnt upregulation by PRKAR2B stimulates EMT mechanism in favor of PCa progression [113]. Suppressing Akt/Mcl-1 impairs invasion of PCa [114], while lncRNA PVT1 increases NOP2 expression thereby accelerating cancer invasion [115].

Exposure of PCa cells to lipopolysaccharide evokes NF-κB to escalate invasion and migration. The systematic administration of lipopolysaccharide evokes NF-κB in vivo. Notably, lipopolysaccharides increase PCa metastasis in vivo and do not exert any effects on the

proliferation rate of tumor cells. More importantly, once resistance develops, administration of dexamethasone not only does not suppress cancer invasion but promotes PCa metastasis [116]. In PCa cells, invasion decreases via the activity of CRMP4 which down-regulates VEGFC expression. However, the expression level of CRMP4 changes during PCa metastasis. For instance, calpain-2 is upregulated during PCa and can enhance carcinogenesis. Calpain-2 evokes NF-κB RelA/p65 to recruit DNMT1 and down-regulate CRMP4, leading to VEGFC overexpression and elevation in invasion of PCa cells [117]. Another interaction can be explored between Akt and NF-κB. Akt/NF-κB axis down-regulation by casticin is effective in suppressing invasion of prostate cancer cells as casticin can promote levels of E-cadherin after 48 h of treatment [118]. Changes in levels of E-cadherin can determine the invasion of PCa. E-cadherin is an epithelial marker with decreased levels during the malignant transformation. In the meantime, levels of N-cadherin and vimentin are enhanced to mediate EMT. The process of EMT and its regulation in cancer cells is complex because this molecular mechanism is responsible for increasing tumor metastasis and mediating therapy resistance [119], [120], [121]. The upregulation of NF-κB can mediate EMT to enhance the progression of PCa. miR-210–3p is associated with bone invasion in PCa. miR-210–3p diminishes the TNIP1 and SOCS1 levels to escalate NF-κB and mediate EMT which leads to progression and invasion of PCa [122]. Notch-4 is also an oncogenic factor that preserves mesenchymal-like breast tumor via upregulation of Slug and GAS1 [123], [124]. Overexpression of Notch4 in PCa can escalate the invasion through EMT stimulation. Knock-down of Notch4 impairs progression. The ability of Notch4 in increasing PCa metastasis and EMT induction is based on induction of NF-κB [125].

ITGBL1 is a driver of tumor progression and induces Akt thereby promoting tumorigenesis [126]. Upregulation of ITGBL1 is observed in various cancers with poor prognosis as it stimulates EMT and enhance cancer progression [127], [128], [129]. The upregulation of ITGBL1 in PCa can lead to EMT induction. ITGBL1 evokes EMT via NF-κB induction [130]. Since upregulation of NF-κB increases PCa metastasis, genetic tools including siRNA are utilized to target cancer suppression. For selective delivery of siRNA in PCa, siRNA delivery with cyclodextrin has shown effectiveness in suppressing NF-κB and SRF and reducing metastasis potential of tumor cells [131].

Hypoxia-mediated tumorigenesis occurs in PCa [132], [133]. Inhibiting hypoxia promotes infiltration of T cells in TME and prevents immune escape in PCa [134]. Besides, presence of hypoxia increases EMT [135], [136]. The expression level of NF-κB changes during hypoxia and is an essential molecule for exerting oncogenic function under hypoxia. Hypoxic microenvironments increase PCa progression via upregulation of CX3CR1. The ability of hypoxia in increasing CX3CR1 expression and promoting PCa progression is dependent on

induction of NF-κB and HIF-1 in PCa [137]. Therefore, NF-κB is one of the essential players in PCa progression during hypoxia [137]. Based on these studies, the function of NF-κB in increasing PCa malignancy is evident and its interaction with other networks escalate PCa metastasis. Notably, NF-κB is also a downstream target of other factors and induction of its nuclear transfer mediates upregulation of factors that are responsible for promoting carcinogenesis (Fig. 4) [138], [139], [140], [141], [142].

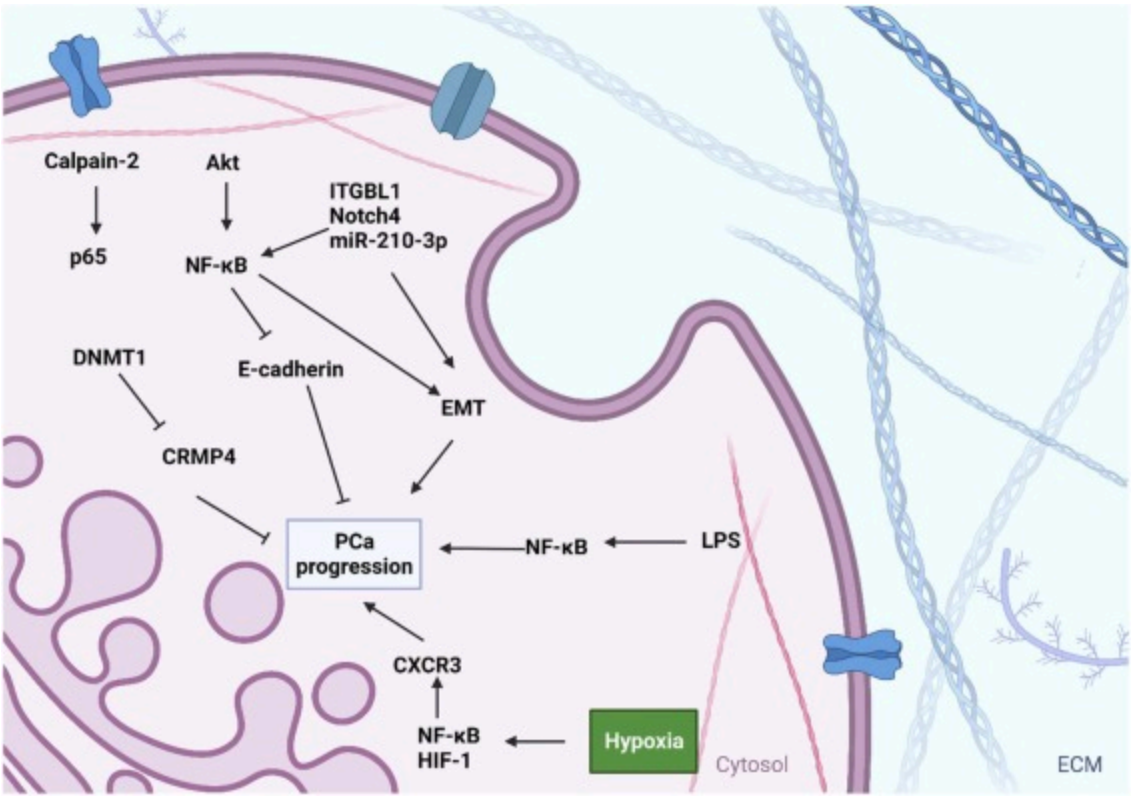

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Fig. 4. NF-κB axis and metastasis in PCa. NF-κB is a central and key player in increasing progression and escalates EMT through down-regulation of E-cadherin. Moreover, presence of hypoxia results in NF-κB and HIF-1 overexpression that increases CXCR3 levels in increasing tumorigenesis.

5. NF-κB and therapy resistance

An essential challenge in the treatment of PCa is drug resistance. The process of chemoresistance in PCa has been examined with significant attention directed towards the function of molecular networks in triggering resistance to chemotherapy. $NaAsO_2$ can stimulate drug resistance in PCa suggestingthat ROS-induced genotoxic stress is involved in

this process [143]. The low expression level of E-cadherin escalates drug resistance development in PCa due to induction of Notch [144]. LncRNA PCAT6 increases ZEB1 expression by miR-543 inhibition to confer chemoresistance in PCa [145]. Moreover, reducing expression level of P-glycoprotein can suppress chemoresistance in PCa [146]. Since NF-κB exerts oncogenic roles, it can confer resistance to chemotherapy in PCa. To investigate the function of NF-κB in drug resistance in PCa, its inhibition by adenovirus promoted apoptosis, enhanced paclitaxel sensitivity, and decreased expression level of P-gp [147]. The overexpression of NF-κB in PCa is mediated by TNF-α. Stimulation of NF-κB can inhibit apoptosis [148]. The oral administration of dimethylaminoparthenolide suppresses NF-κB and AR variants while increasing sensitivity of PCa cells to AR inhibition [149]. In Ki-Ras-transformed PCa cells, trichostatin A can induce apoptosis. Notably, the inhibition of NF-κB can exert synergistic impacts on increasing cell death in PCa cells exposed to trichostatin A via upregulation of caspase-8 and − 3 [150]. Although caspases are involved in the process of apoptosis, they have also function independently of apoptosis. The caspase-8 increases the levels of NF-κB to mediate IL-8 upregulation thereby increasing survival rate of PCa and triggering their insensitivity to enzalutamide chemotherapy [151].

The ability of NF-κB in increasing PCa viability and conferring resistance to chemotherapy emanates from upregulation of IL-8 and VEGFC. Notably, IGFBP-3 diminishes NF-κB expression to down-regulate IL-8 and VEGFC thereby preventing progression of PCa [152]. In previous sections, Akt induces NF-κB to increase PCa progression and drug resistance via Akt/NF-κB axis [153]. Hence, suppressing Akt/NF-κB axis may be considered as an effective strategy in promoting chemosensitivity. Astragaloside IV can increase sensitivity of PCa cells to carboplatin chemotherapy. This anti-cancer agent suppresses NF-κB via Akt down-regulation to prevent EMT thereby increasing carboplatin sensitivity in PCa [153]. Although previous studies remark the role of NF-κB as a downstream target in PCa, this pathway can affect other molecular pathways to trigger chemoresistance. Upregulation of SRD5A2 elevates growth of PCa and poor prognosis. Furthermore, NF-κB enhances the generation of androgens as well as all three isoforms of SRD5A. It has been reported that NF-κB and androgen receptor variant 7 increase SRD5A level to mediate resistance of PCa cells to 5α-reductase inhibitor chemotherapy [154].

Oxidative damage has been considered as a factor in development of age-related diseases. Interestingly, induction of oxidative stress can mediate apoptosis and reduce viability of cancer cells. Ttumor cells, especially PCa cells can develop resistance to oxidative stress-mediated damage. Doxosahexaenoic acid escalates sensitivity of PCa cells to oxidative damage via down-regulating nuclear transfer of NF-κB to increase DNA damage and reduce survival rate [155]. One of the chemotherapy compounds used in PCa is docetaxel which can

increase the stability of microtubules and prevent their depolymerization [156]. The insensitivity to docetaxel is correlated with FOXM1 and KIF20A among other molecular factors [157], [158]. Furthermore, inhibition of PI3K/Akt by quercetin can inhibit docetaxel insensitivity [159]. The induction of NF-κB stimulates docetaxel resistance in PCa. Nimbolide as an anti-cancer agent can suppress NF-κB and elevate the sensitivity to docetaxel chemotherapy [160]. Furthermore, induction of apoptosis via TRAIL pathway is used to reduce viability of PCa cells and inhibit NF-κB to partially escalate sensitivity to TRAIL-mediated apoptosis [161].

The radiotherapy response is also controlled by NF-κB. Overexpression of NF-κB by cancer-associated fibroblasts escalates survival rate of PCa and radio-resistance [162]. Suppressing NF-κB not only increases radio-sensitivity in PCa but is also effective in reducing lung toxicity [163]. AKR1B10 induces NF-κB via TLR4 overexpression to mediate radio-resistance [164]. Therefore, NF-κB can mediate radio-resistance in cancers. Activation of NF-κB reduces efficacy of X-rays in vitro and in vivo in PCa suppression. Notably, DMAPT suppresses NF-κB in escalating sensitivity of PCa cells to X-rays [165]. However, in PCa, only one experiment has investigated the function of NF-κB in radio-resistance and more research needs to be done on this topic (Fig. 5).

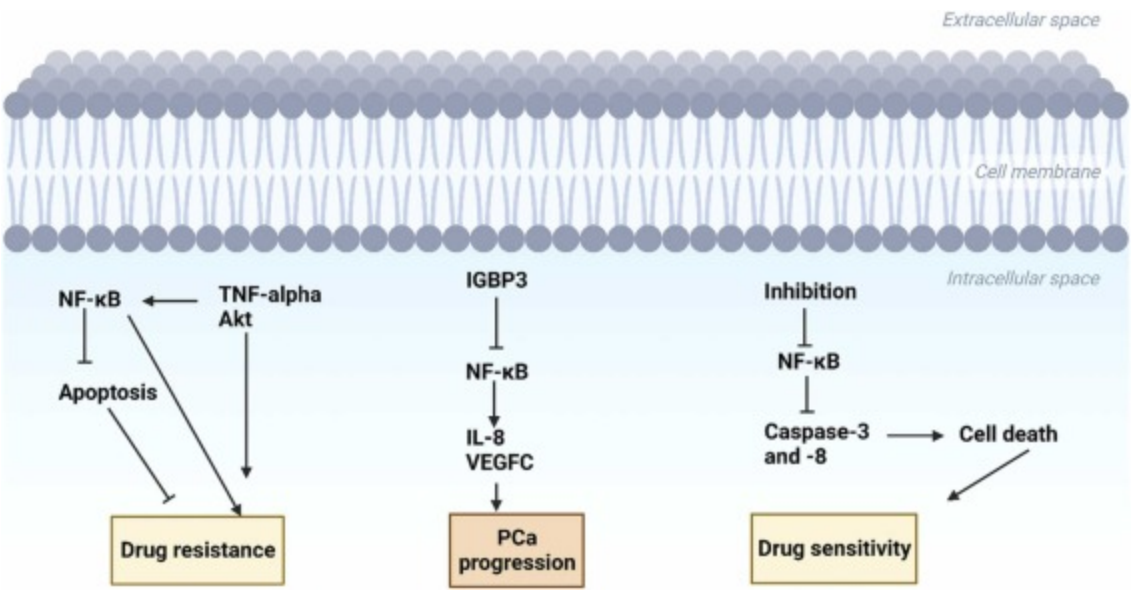

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Fig. 5. NF-κB and resistance. NF-κB overexpression prevents apoptosis to induce drug resistance and TNF-alpha and Akt can enhance NF-κB expression. NF-κB expression is suppressed by IGBP3 to reduce levels of IL-8 and VEGFC. NF-κB decreases caspase-3 and − 8

levels to suppress cell death and mediate drug resistance, while suppression of NF-κB enhances chemosensitivity.

6. Targeting NF-κB by anti-cancer compounds

Hyperactivation of NF-κB enhances growth and invasion of PCa cells. A recent experiment shows that the use of chelerythrine reduces the expression levels of NF-κB and AP-1 to decrease MMP-2, MMP-9, and uPA levels, and to increase TIMP-1 and TIMP-2 levels leading to PCa invasion suppression [166]. The invasion of PCa cells depends on two important factors including MMPs and EMT mechanism. Upregulation of MMP-2 and MMP-9 significantly enhances metastasis of PCa cells [167], [168]. Furthermore, EMT inhibition can reduce PCa metastasis [169], [170]. A recent experiment has revealed that use of eupatilin is related to PCa metastasis suppression due to a reduction in MMP-2, − 7, Twist and Slug levels. Eupatilin promotes PTEN expression and inhibits NF-κB thereby impairing PCa metastasis [171].

Thymoquinone is one of the promising agents in treatment of PCa. It inhibits TGF-β/Smad2/3 axis to inhibit EMT and decrease invasion of tumor cells [172]. A combination of thymoquinone and docetaxel stimulates apoptosis in PCa cells via suppressing PI3K/Akt [173]. IL-7 increases the progression of PCa and administration of thymoquinone results in suppression of Akt/NF-κB axis to prevent oncogenic function of IL-7 in PCa and reduce cancer metastasis via reducing MMP-3 and MMP-7 levels [174]. Based on the previous study, Akt induces NF-κB to enhance PCa progression [174]. Moreover, PI3K/Akt can mediate NF-κB expression to then increase PCa progression [175]. PI3K/Akt/NF-κB axis increases survival rate of cancer stem cells in PCa. As a flavonoid, apigenin suppresses PI3K/Akt/NF-κB axis to reduce MMP-2, MMP-9, Slug and Snail levels thereby impairing metastasis of cancer stem cells in PCa [175]. Another evidence for Akt's function as an upstream mediator of NF-κB is that imipramine suppresses Akt/NF-κB axis to impair PCa progression in a concentration-dependent manner [176]. Like previous anti-cancer agents, evodiamine can reduce NF-κB expression via inhibiting PI3K/Akt to reduce growth and metastasis of PCa cells [177]. Apigenin along with midkine silencing can exert synergistic impacts in suppressing PCa stem cells via down-regulating NF-κB [178]. The inhibition of NF-κB in PCa is via AR and ERβ. Bakuchiol reduces MMP-9 and PCNA levels to suppress metastasis of PCa, which is achieved via NF-κB inhibition. Silencing AR or ERβ by siRNAs abrogate the function of bakuchiol, showing that interaction of AR and ERβ is vital for suppressing NF-κB [179].

Multi-targeting is one of the features of anti-cancer agents and in PCa, they may interact with more than one network. Altholactone is a potent anti-cancer agent against PCa as it

prevents the overexpression of STAT3 and NF-κB by impacting IL-6 and p65, respectively. Additionally, TNF-α can accelerate apoptosis in tumor cells [180]. Hence, NF-κB facilitates an increase in growth and invasion of PCa cells as its inhibition by anti-tumor agents impairs tumorigenesis [181]. TME are enriched by immune cells known as macrophages [182], [183], [184], [185]. According to polarization theory, there are two kinds of macrophages including M1 and M2 macrophages. Tumor-associated macrophages (TAMs) generally have M2 polarization and secrete cytokines and chemokines that increase carcinogenesis [186], [187], [188], [189]. Somatostatin derivative (smsDX) has been used in PCa treatment because smsDX suppresses NF-κB to impair NF-κB-mediated invasion and malignant behavior of PCa cells [190]. Upregulation of NF-κB is positively associated with infiltration of macrophages in TME.

In fact, exposure of PCa cells to stress can lead to an increase in their progression. For instance, lipopolysaccharide insult can lead to increase in expression levels of NF-κB and p38 MAPK to potentiate PCa progression. Notably, sesamin administration leads to a decrease in expression levels of NF-κB and p38 MAPK to impair PCa malignancy via reducing MMP-9, VEGF, and ICAM-1 levels [191]. The important concept regarding NF-κB in PCa is that its inhibition by anti-cancer agents decreases tumor progression in vitro and in vivo [80]. Therefore, assessment of its applications in clinical trials are needed. Moreover, NF-κB is vital for PCa progression independent of androgen. For instance, celastrol suppresses NF-κB and increases the expression level of pro-apoptotic factors in interfering with PCa progression [192]. Another natural product popular in treatment of cancer is curcumin that is added as a spice to food and has been found to be an effective chemosensitizer [193], [194]. Curcumin application in PCa treatments has been increased in recent years as in addition to regulation of molecular pathways, curcumin impairs PCa progression [195], [196], [197]. Curcumin stimulates apoptosis and G2/M arrest in PCa cells via reducing NF-κB and AP-1 levels [198]. Therefore, it is highly suggested that future studies assess the complementation of therapies with natural anti-cancer agents for modulating NF-κB in PCa treatment (Table 2, Fig. 6).

Table 2. An overview of the role of NF-κB in PCa progression.

Molecular pathway	Remark	Ref
HMGB1/TNFR1/NF-κB	HMGB1 interacts with TNFR1 to induce nuclear translocation of NF-κB thereby increasing cancer progression	[91]
PSGR/NF-κB	PSGR induces NF-κB expression to increase tumor progression in xenograft model	[199]

Molecular pathway	Remark	Ref
NF-κB/inflammation	Brassica oleracea var suppresses NF-κB-mediated inflammation thereby reducing tumor progression	[200]
PSCA/PGRN-NF-κB-Integrin-α4	This axis increases adhesion to bone marrow epithelium and is involved in enhancing bone metastasis	[140]
TLR9/NF-κB/RELA	TLR9 stimulates NF-κB/RELA axis in enhancing tumor-propagating efficiency of cancer cells	[201]
ITGBL1/NF-κB/EMT	ITGBL1 increases NF-κB expression to stimulate EMT	[130]
IL-7/IL-7 receptor/AKT/NF-κB	IL-7/IL-7 receptor stimulates AKT/NF-κB axis to promote invasion of cancer cells	[202]
Lipopolysaccharide (LPS)/NF-κB	LPS stimulates NF-κB axis thereby enhancing cancer metastasis	[116]
RB/NF-κB	RB reduces NF-κB and PD-L1 levels in increasing tumor immunity	[203]
CDCA3/NF-κB/cyclinD1	Silencing CDCA3 suppresses NF-κB/cyclinD1 axis thereby decreasing tumor progression	[99]
SIRP-α/p38-MAPK/NF-κB/COX-2	SIRP-α suppresses p38-MAPK/NF-κB/COX-2 axis thereby reducing cancer progression	[90]
HIST1H2BN/NF-κB/EMT	HIST1H2BN stimulates EMT via activation of NF-κB	[86]
Notch-4/ NF-κB/EMT	Silencing Notch-4 suppresses NF-κB/EMT axis	[125]
FASN/NF-κB	Suppression of FASN/NF-κB increases sensitivity to radiotherapy	[204]
NF-κB/SHh/GLI1	Upregulation of NF-κB/SHh/GLI1 mediates poor prognosis	[98]

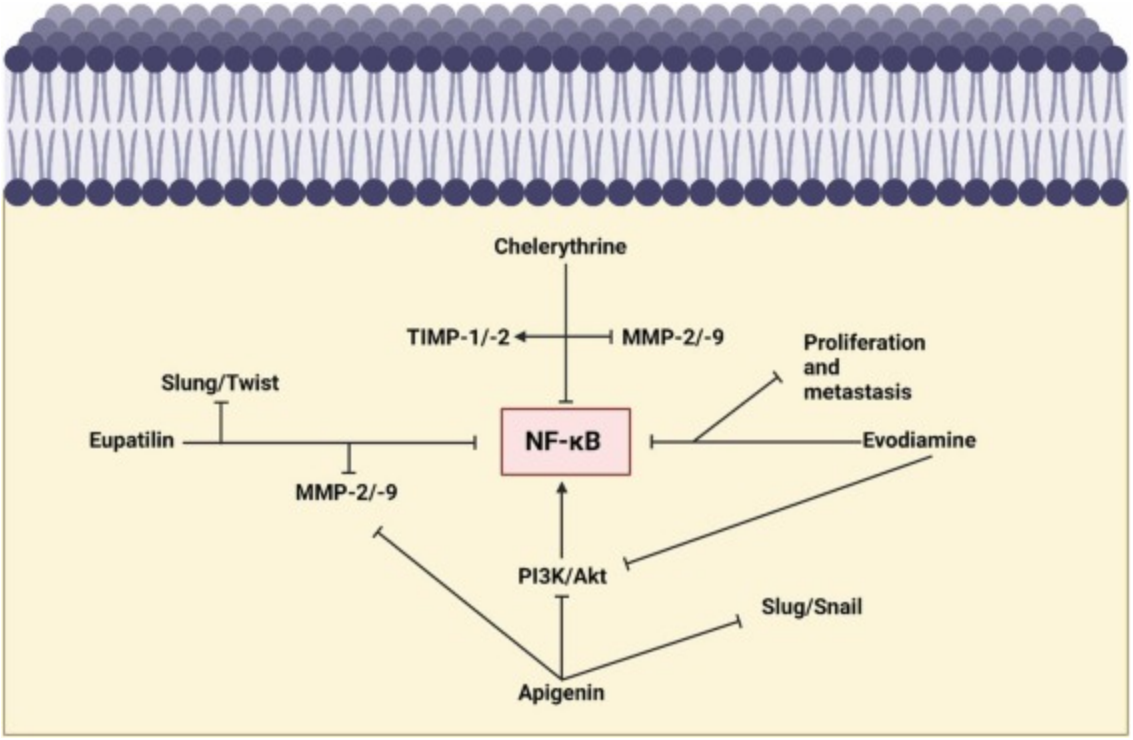

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Fig. 6. A number of anti-cancer drugs regulating NF-κB axis in PCa. The PI3K/Akt upregulation in PCa promotes NF-κB expression and evodiamine and apigenin suppresses PI3K/Akt axis to reduce NF-κB expression. Moreover, eupatilin and chelerythrine reduce NF-κB expression to impair metastasis via down-regulating MMP-2/− 9.

7. Regulation of NF-κB

7.1. microRNAs

microRNAs (miRNAs) are short oligonucleotides that exert regulatory functions via post-transcriptional modulation of genes [205]. The interest towards miRNAs is because of their function in regulating expression level of protein-coding genes. Moreover, miRNAs can affect more than one protein in cells. As well, a single gene can be controlled by more than one miRNA. miRNAs bind to 3′-UTR of mRNAs to prevent translation or induce degradation and thereby reduce gene expression. The aberrant expression of miRNAs can lead to the development of tumors making them promising targets in cancer therapy [206], [207]. Moreover, miRNAs regulate various networks in cancer such as NF-κB. A recent experiment has revealed that miR-302b is a suppressor of PCa progression and metastasis. In PCa, RELA stimulates NF-κB to increase metastasis of PCa cells. Notably, miR-302 is downregulated in

PCa and restoring its expression is of importance in impairing tumor progression in vitro and in vivo. miR-302b suppresses RELA NF-κB axis to inhibit EMT mechanism in PCa via increasing E-cadherin levels and reducing N-cadherin and vimentin levels [208]. On the other hand, there are miRNAs that increase the expression level of NF-κB thereby promoting PCa progression. NF-κB increases BMI1 levels to promote PCa progression and prevent apoptosis. Notably, miR-212 is down-regulation in PCa and correlates with low survival rate in patients. miR-212 induces cell cycle arrest and decreases growth rate of PCa cells via suppressing NF-κB to down-regulate BMI1 [209].

miR-532–3p is a new emerging target in cancer therapy with an onco-suppressor function. miR-532–3p reduces the expression levels of TROAP, β-catenin, and FOXP3 to suppress carcinogenesis [210], [211], [212]. High expression levels of miR-532–3p in PCa is vital for impairing progression of tumor cells. miR-532–3p down-regulates TRAF1, TRAF2 and TRAF3 to inhibit NF-κB and impair progression of PCa to reduce bone metastasis [213]. The expression level of onco-suppressor miRNAs decreases in PCa, miR-497 being one of them. miR-497 decreases the expression level of IKKβ to inhibit NF-κB thereby decreasing growth and invasion of PCa cells via down-regulating CDK8 and MMP-9 [214]. The NF-κB/EMT axis can be regulated by miRNAs in PCa. NDRG1 exerts an onco-suppressor function in PCa and can impair metastasis of PCa cells via EMT inhibition. miR-96–5p increases PCa metastasis and mediates EMT mechanism via NDRG1 down-regulation [215]. According to these studies, miRNAs are potent regulators of NF-κB in PCa and regulate various hallmarks of cancer cells [216], [217].

7.2. LncRNAs

Another membrane of non-coding RNA transcripts that possess linear structure, a length of more than 200 nts and pivotal function in tumorigenesis is lncRNAs [218], [219], [220]. The expression level of lncRNAs changes during cancer progression as they sponge (down-regulate) miRNAs during cancer progression. Furthermore, lncRNAs show interactions with other molecular pathways such as NF-κB pathway and are found in both nucleus and cytoplasm [221], [222], [223], [224]. The upregulation of lncRNA PCAT1 in PCa is in favor of increasing progression of tumor cells. LncRNA PCAT1 induces NF-κB and Akt molecular pathways leading to PCa progression. Notably, PCAT1 binds to PHLPP to displace it from FKBP51 thereby triggering Akt and NF-κB for PCa progression [225]. Polyphyllin-1 is effective in impairing the progression of PCa and for this purpose, it suppresses lncRNA HOTAIR and NF-κB/p65 to reduce MUC1 expression in cancer therapy [226]. More studies are required to delineate the true potential of lncRNA/NF-κB axis in PCa (Table 3, Fig. 7).

Table 3. The role of non-coding RNAs in regulating PCa progression via targeting NF-κB.

Non-coding RNA	Molecular pathway	Remark	Ref
miR-130b	MiR-130b/TNF-α/NF-κB/VEGFA	miR-130b suppresses TNF-α/NF-κB/VEGFA axis thereby decreasing angiogenesis	[217]
miR-543	MiR-543/Numb	Numb down-regulation by miR-543 thereby increasing NF-κB levels	[227]
miR-204–5p	NF-κB	miR-204–5p suppresses NF-κB axis thereby reducing bone invasion	[139]
miR-532–3p	NF-κB	miR-532–3p suppresses NF-κB axis in bone metastasis suppression	[213]
miR-141–3p	NF-κB	Poor expression of miR-141–3p leads to stimulation of NF-κB thereby increasing cancer invasion	[141]
LncRNA CHRF	miR-10b	CHRF increases miR-10b expression to induce NF-κB axis thereby increasing metastasis and EMT induction	[228]
LncRNA PCAT1	NF-κB	PCAT1 induces NF-κB and AKT pathways thereby increasing tumorigenesis	[225]
miR-210–3p	NF-κB	miR-210–3p induces EMT via NF-κB upregulation to increase invasion	[122]
LINC00624	LINC00624/TEX10/NF-κB	LINC00624 interacts with TEX10 to induce NF-κB axis	[229]
miR-96–5p	miR-96–5p/NDRG1/NF-κB	miR-96–5p reduces NDRG1 expression to induce NF-κB axis thereby increasing cancer invasion	[215]
miR-30e	NF-κB	miR-30e increases NF-κB expression to promote proliferation and invasion	[216]
CircNOLC1	NF-κB/CircNOLC1/miR-647/PAQR4	NF-κB promotes circNOLC1 expression to sponge miR-647 thereby increasing PAQR4 expression and mediating carcinogenesis	[230]

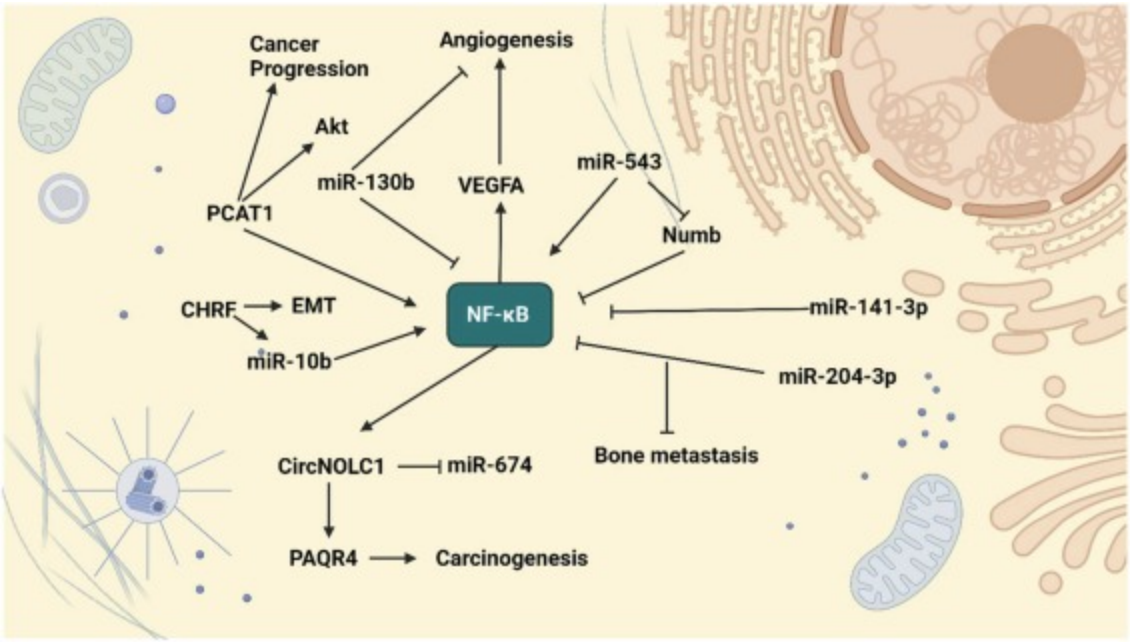

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Fig. 7. The schematic representation of NF-κB regulation by ncRNAs in PCa. According to this figure, NF-κB can stimulate angiogenesis through VEGFA expression, while miR-130b suppresses NF-κB. Moreover, NF-κB increases circNOLC1 expression to increase tumorigenesis through miR-647 down-regulation. CHRF and PCAT1 as lncRNAs are able to enhance tumorigenesis through NF-κB stimulation.

8. Conclusion and remarks

The progression of PCa cells is determined by various factors, including the availability of energy and oxygen for proliferation and migration, as well as genetic mutations. The presence of genetic abnormalities is crucial for the growth, migration, and resistance to therapy of PCa cells. NF-κB has been found to play a role in the progression of PCa cells, as evidenced by numerous pre-clinical and clinical studies. The expression levels of NF-κB are elevated in PCa cells, and it can be used as an indicator of PCa malignancy in pre-clinical studies and as a prognostic tool in clinical cases. The activation of NF-κB inhibits apoptosis in PCa cells, which is necessary for the survival of tumor cells. Moreover, NF-κB affects the expression levels of CDKs that regulate the cell cycle progression in PCa. The stimulation of NF-κB in PCa leads to the inhibition of apoptosis via the increase in Bcl-2 expression and activation of oncogenic pathways. Additionally, NF-κB is closely associated with the progression and metastasis of PCa cells, which leads to a reduced survival rate and prognosis for patients. The increased expression levels of NF-κB in PCa lead to the resistance

of tumor cells to chemotherapy and radiotherapy, making it challenging to treat patients. NF-κB also interacts with other molecular pathways such as PI3K/Akt and TLR4, and its regulation in PCa is largely influenced by non-coding RNAs such as miRNAs, lncRNAs, and circRNAs. Anti-cancer agents targeting NF-κB have been utilized in PCa therapy, but there are still some limitations in our knowledge, such as the role of NF-κB in radio-resistance in PCa and the use of nanoplatforms to deliver anti-cancer agents to suppress NF-κB in PCa treatment, both of which require further research.

There are several reasons of focusing on the NF-κB that first one is its versatile function in carcinogenesis that in addition of biological mechanisms, NF-κB can elevate tumorigenesis. Wealth evidence has confirmed NF-κB function in promoting PCa progression. Although various aspects of NF-κB, its modulation by molecular pathways and its targeting by anti-cancer compounds have been discussed in the current paper, there are still some limitations and gaps that should be considered in future studies. The anti-tumor compounds used in NF-κB targeting are phytochemicals and their therapeutic index is limited because of their short half-life, low blood circulation time and rapid metabolism. Therefore, future experiments should focus on the application of nanoparticles for delivery of such compounds in NF-κB regulation in PCa therapy. Increasing evidence has shown that nanostructures can regulate NF-κB in cancer therapy [231], [232], [233]; However, there is no experiment about nanoparticle-mediated NF-κB regulation in PCa that can be a good area for research in future. Moreover, pre-clinical evidence highlights the oncogenic role of NF-κB in PCa, its clinical application should be considered.

CRediT authorship contribution statement

All the authors participated in writing the draft, drawing figures, conceptualization, preparing figures, responding to reviewers and the final version was confirmed by all authors. Reyadh R Al-Rashidi, Sara Abdalrazzaq M. Noraldeen, Ali Kamil Kareem, Aisha Kamal Mahmoud, Wesam R. Kadhum, Andrés Alexis Ramírez-Coronel, Acim Heri Iswanto, Rasha Fadhel Obaid, Abduladheem Turki Jalil, Yasser Fakri Mustafa participated in writing first draft. Noushin Nabavi, Yuzhuo Wang and Lin Wang prepared figures, tables, and participated in conceptualization, collecting research papers. All the authors edited paper and finally approved it.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Data Availability

No data was used for the research described in the article.

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