The molecular mechanism of NF-κB dysregulation across different subtypes of renal cell carcinoma

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HIGHLIGHTS

- NF-κB is a cellular orchestrator that allow the shift of cellular response based on the environmental trigger.
- Dysregulated NF-κB genes have been implicated in different cancers, including RCC.
- Dysregulation of NF-κB would affect different layers of the pathway to sustain different cancer hallmarks.
- Understanding the lack of regulation of NF-κB in different RCC subtypes impedes disease progression and treatment resistance.

GRAPHICAL ABSTRACT
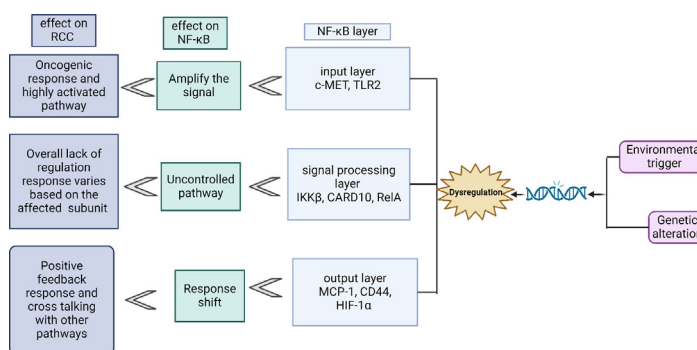
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ABSTRACT

Background: The nuclear factor kappa B (NF-κB) is a critical pathway that regulates various cellular functions, including immune response, proliferation, growth, and apoptosis. Furthermore, this pathway is tightly regulated to ensure stability in the presence of immunogenic triggers or genotoxic stimuli. The lack of control of the NF-κB pathway can lead to the initiation of different diseases, mainly autoimmune diseases and cancer, including Renal cell carcinoma (RCC). RCC is the most common type of kidney cancer and is characterized by complex genetic composition and elusive molecular mechanisms.
Aim of review: The current review summarizes the mechanism of NF-κB dysregulation in different subtypes of RCC and its impact on pathogenesis.
Key scientific concept of review: This review highlights the prominent role of NF-κB in RCC development and progression by driving the expression of multiple genes and interplaying with different pathways, including the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway. In silico analysis of RCC cohorts and molecular studies have revealed that multiple NF-κB members and target genes are dysregulated. The dysregulation includes receptors such as TLR2, signal-transmitting members including

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RelA, and target genes, for instance, HIF-1α. The lack of effective regulatory mechanisms results in a constitutively active NF-κB pathway, which promotes cancer growth, migration, and survival. In this review, we comprehensively summarize the role of dysregulated NF-κB-related genes in the most common subtypes of RCC, including clear cell RCC (ccRCC), chromophobe RCC (chRCC), and papillary RCC (PRCC).

Contents

Introduction

In terms of global incidence, kidney cancer is one of the ten most common cancers among men and the 14th most common cancer among women. The incidence of kidney cancer is increasing every year, with a 1 % annual increase rate recorded between 2010 and 2019 in the United States [1]. In 2020, more than 400,000 cases of kidney cancer were registered, and almost 180,000 deaths were reported [2]. The most common type of kidney cancer is renal cell carcinoma (RCC) (accounting for >90 % of the cases).

The interplay between inflammation and cancer has been investigated extensively in many cancer types since the first link was proposed in 1863 by Rudolf Virchow [3]. Inflammation represents an instant and unspecific innate response to the stimulus, including pathogens, physical injury, or dust particles. In some cases, immune cells and pro-inflammatory mediators persist in the absence of external stimuli, leading to chronic inflammation. Besides, chronic inflammation has been stated as a major cancer risk factor [4]. The histological and molecular changes induced by chronic inflammation were demonstrated to enhance cell proliferation [5].

The nuclear factor kappa B (NF-κB) pathway is a key pathway that regulates inflammation along with other cellular functions such as growth, apoptosis, and immune response [6]. Dysregulation of the NF-κB pathway has been associated with multiple conditions, such as inflammatory and neurodegenerative diseases as well as cancer [7]. NF-κB pathway can be activated by different stimuli and various receptors, enabling it to switch between cellular functions. The innate immune response due to microbes or cell damage trigger instant and expeditious NF-κB activation, inducing immune cells recruitment and pro-inflammatory cytokines release. Conversely, during cell stress, NF-κB activation could enhance the expression of anti-apoptotic genes to promote cell survival [8].

NF-κB pathway: An overview and its dysregulation

The NF-κB signaling pathway is a crucial regulator of body responses discovered at the end of the 20th century. Initially,

NF-κB was identified as an immunoglobulin (Ig) binding protein [9]. Activation of NF-κB can be initiated by a range of receptors that transduce the cell signals to generate a range of cellular responses [10]. The first layer of NF-κB is the input layer, which is composed of the different receptors and ligands that provoke canonical and non-canonical NF-κB activation. Correspondingly, a signal is then transmitted to a signal processing layer that consists of various mediators and adaptors linked to different receptors [11].

The NF-κB pathway constitutes different transcription factors that can directly affect gene transcription by binding to the promoter. The family of NF-κB transcription factors encompasses five transcription factors, which are RelA (p65), RelB, cRel, NF-κB1 (p50), and NF-κB2 (p52). Transcription factors shuttle between the signal processing and execution layers to bind to the target gene promoter. The execution layer is the last layer of NF-κB that represents the genes under the control of NF-κB transcription factors [12].

In the absence of stimuli, NF-κB transcription factors' nuclear localization signals are sequestered in the cytoplasm by binding to the inhibitors: IκBα, IκBβ or IκBε. The IκB family is a group of NF-κB inhibitors composed of five different members that inhibit the NF-κB pathway: IκBα, IκBβ, IκBε, IκBζ, and BCL3. Upon activation of the NF-κB pathway, one of the NF-κB inducible genes IκBα will be expressed to form a negative feedback response and bind to NF-κB transcription factors to ensure that the NF-κB pathway will remain firmly regulated after producing the target response [13]. Moreover, upon stimulation of NF-κB, IκBε is expressed but in delayed onset in comparison to IκBα, forming a second negative feedback loop [14].

A better understanding of this mechanism may provide a deeper understanding of how the NF-κB pathway consistently produces the intended response and ensures that the activation will cease to maintain balance and homeostasis after achieving the required response.

BCL3 is another member of the NF-κB inhibitor protein family. Under basal conditions, BCL3 is not highly expressed, but upon activation of NF-κB, it binds to the *Bcl-3* gene and induces its expression
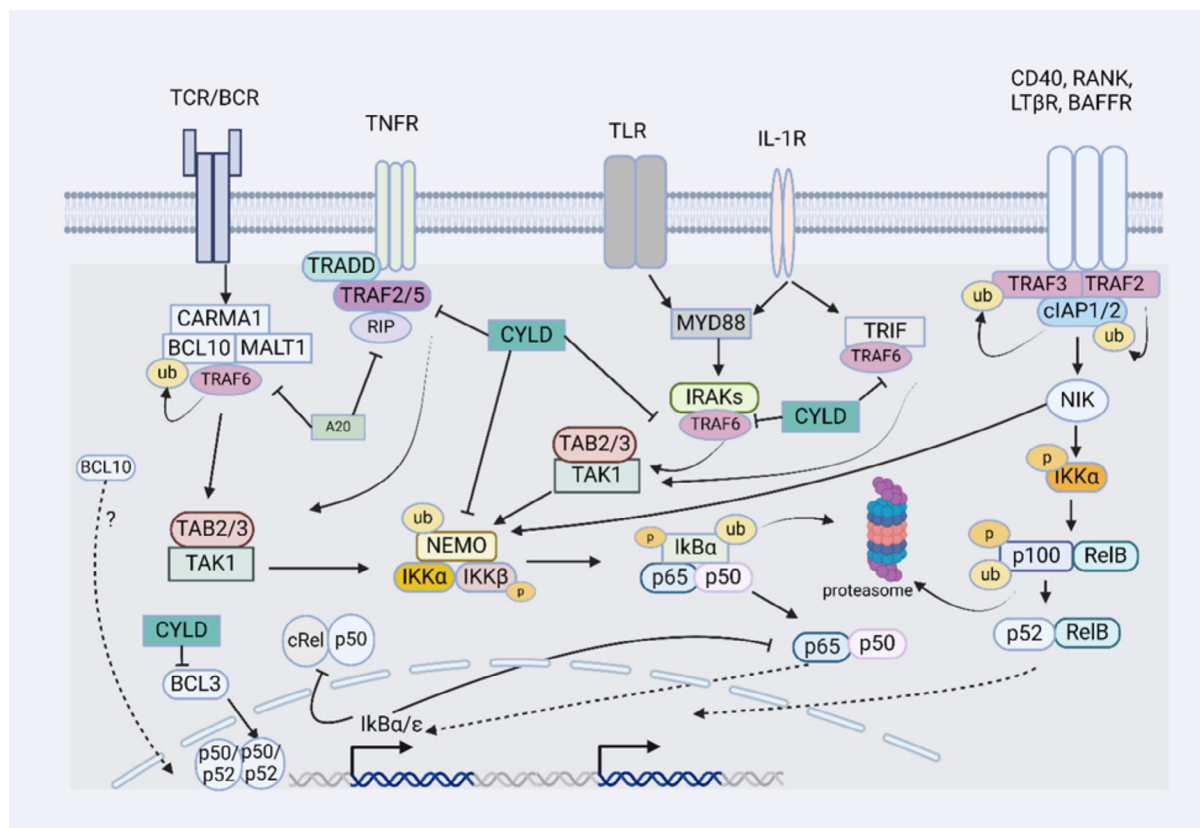
Fig. 1. Canonical and non-canonical NF-κB and the different mechanisms of regulations. The input layer of canonical NF-κB comprises different types of receptors, including BCR, TCR, TLR, IL-1R, and TNFR. These are activated in response to different triggers, resulting in canonical NF-κB pathway activation. Under basal conditions, IκBα masks the nuclear localization signal of p65 and p50, hence hindering NF-κB transcription factors from translocating to the nucleus. Stimulation of the receptors in the input layer transmits the signal to the processing layer through recruiting various adapters, resulting in β complex activation in the canonical NF-κB pathway. Subsequently, IKK phosphorylates IκBα to release p65-p50 and/or c-REL-p50 heterodimer that translocates to the nucleus and binds to the target gene promotor. Conversely, the non-canonical pathway is regulated by the TRAF-cIAP complex. Under basal conditions, NIK is instantly bound to TRAF3 and recruited to the E3 ubiquitin ligase complex consisting of TRAF2 and cIAP1/2. Thus, NIK will be ubiquitinated and degraded. Upon stimulation of the non-canonical NF-κB pathway by triggering lymphotoxin β, CD40, RANK, or BAFFR, NIK phosphorylates and activates IKKα that in turn phosphorylates p100, hence mediates its proteasomal processing. p52-RelB will translocate to the nucleus and stimulate gene transcription, producing the output response. NF-κB activity is regulated by several enzymes and proteins that keep NF-κB balanced. Mainly, IκBα/ε is induced in response to NF-κB activation to produce a negative feedback loop. In contrast, CYLD detaches the K63-ubiquitin chain and deactivates different subunits, including TRAF2, TRAF6, NEMO, and BCL3, therefore inactivating IKK kinase complex and inhibiting canonical NF-κB pathway activation. A20 regulates NF-κB through physically binding to TRAF2 to impede NF-κB activation, interfere with TRAF6 ubiquitination, and target RIP-1 for degradation. Also, A20 competes for the binding of ubiquitin chain on NEMO added by LUBAC, hence impeding IKKβ recognition by TAK-1 deubiquitinating TRAF6 and RIP1 as well as interfering with NEMO ubiquitination. Moreover, BCL3 regulates NF-κB and affects its transcriptional activity through binding to p50 and p52 homodimers. This figure was generated using Biorender. **BAFFR,** B-cell activating factor receptor; **BCR,** B-cell receptor; **cIAP1/2,** cellular inhibitor of apoptosis 1 and 2; **CYLD,** cylindromatosis; **IL-1R,** interleukin-1 receptor; **IKK,** inhibitor of nuclear factor-κB kinase; **IκB,** inhibitor of nuclear factor-κB; **LTβR,** lymphotoxin β receptor; **MyD88,** myeloid differentiation primary response gene 88; **NEMO,** NF-κB essential modulator; **TRIF,** TIR domain-containing adaptor inducing interferon-beta; **RIP1,** receptor-interacting protein 1; **NIK,** NF-κB-inducing kinase; **TAK1,** TGF-β-activated protein kinase 1; **TCR,** T-cell receptor; **TLR,** toll-like receptor; **TNFR,** Tumor necrosis factor-α receptor; **TRADD,** TNF-R-associated death domain; **TRAF2/5/6,** TNF-R-associated factor 2, 5 and 6.

[15]. Moreover, BCL3 can either suppress or promote NF-κB transcriptional activity based on the stimulus and cell type [16].

A major class of NF-κB are the regulators, which are the enzymes or protein subunits that modulate NF-κB pathway activity in response to various triggers. A20, encoded by tumor necrosis factor alpha induced protein 3 (TNFAIP3), is an NF-κB negative regulator. A20 could act as an oncoprotein or a tumor suppressor based on cancer type [17]. TNFAIP3 has a conserved site for RelB-p52, suggesting that it will be expressed after activation of the NF-κB pathway to form a negative feedback response [18]. Also, cylindromatosis (CYLD) is a deubiquitinase enzyme that regulates the canonical NF-κB pathway by different mechanisms [19] (Fig. 1).

This diversity in the NF-κB regulators explains that there is always a compensatory mechanism to keep NF-κB under control, so if any of the regulators got affected by genetic alterations or epigenetic modification, others will compensate [20]. This point has been confirmed in a knock-in mouse model where they replaced IκBα with the IκBβ gene. The mouse model exhibits no visible abnormalities in contrast to the IκBα-knockout model, which died very early due to multiple deficiencies [21]. Notably, Failure of regulatory mechanisms produces immense dysregulation of the NF-κB pathway, leading to autoimmune diseases or cancer [22].

Cells are subjected to environmental triggers at diverse intensities, which can lead to the constitutive activation of NF-κB. Some of these triggers such as smoking or ultraviolet light exposure could introduce DNA alterations and histone modification. But mostly these lesions or mutations could be repaired after removal of the trigger to restore balanced gene expression and keep critical pathways including NF-κB regulated [23–25].

NF-κB regulators can work in harmony to restrain the balance and impede the formation of uncontrollable responses by forming negative feedback responses [13]. For instance, IκBα can translocate to the nucleus by associating with proteins that possess nuclear localization signal (NLS) to enhance the dissociation of NF-κB from DNA. Still, these proteins are yet to be identified [26]. These findings suggest that not all the mechanisms of NF-κB regulation are still known.

One more level of regulation was observed in NF-κB, where some NF-κB subunits could play a dual role as pro- and anti-inflammatory, such as p50 and IKKβ [27]. Therefore, the same subunit known to activate NF-κB early during infection plays a regulatory role in the last phase of inflammation. As a result, mutations that affect these subunits could lead to aberrant NF-κB pathways. Based on these points, it can be hypothesized that the mutation frequency that may cause uncontrolled NF-κB pathway varies between individuals based on the exhibited level of NF-κB regulation.

Conversely, constant exposure to the trigger for a long time causes the accumulation of mutations that eventually lead to irreversible genetic mutations and irritable NF-κB response [28]. This dialogue occurs in cases where the repair and compensatory mechanisms are deficient, the damage will be major to cause dysregulated NF-κB pathway and producing autoimmune diseases or cancer. During cell transformation, aberrant NF-κB shifts the response from immunogenic to sustaining cancer hallmarks. This can explain why patients with very early cancer exhibit high levels of various inflammatory mediators, suggesting a high immunogenic response to cell dysplasia or necrosis. Despite this, most inflammatory mediators stabilize and return to normal levels after cancer progression [29].

Such response alteration occurs mainly because of two points. Notably, genetic alterations in NF-κB-target genes lead to constitutively active NF-κB pathway because of the positive feedback loop. Also, it is frequently accompanied by the activation of other oncogenic pathways such as MAPK or PI3K/Akt [30]. Several cancers have been linked to NF-κB dysregulation. However, the most prominent role has been reported in mucosa-associated lymphoid tissue (MALT) lymphoma. Gastric MALT lymphoma can be classified into two subtypes: translocation-positive and translocation-negative. Translocation-negative MALT lymphoma mainly activates immune response by upregulating co-stimulatory molecules. However, translocation of B-cell lymphoma/leukemia 10 (BCL10) to IgH locus is associated with upregulation and nuclear translocation of BCL10, inducing constant activation of the NF-κB pathway and sustaining different cancer hallmarks [30].

The dysregulation of NF-κB can happen at the three layers of the pathway. The input layer can be affected by upregulation or mutation of NF-κB activating receptor or ligand upregulation and, in some cases, both. The second type of dysregulation affects the signal processing layer; this layer represents the algorithmic and analytical part of this pathway. As a final layer, the execution layer is responsible for producing genes engaged in the NF-κB pathway and producing positive feedback loops, as well as activating other pathways [6,30]. The impact of dysregulated NF-κB genes in different health conditions is summarized in Table 1.

Various methods of inhibiting NF-κB are used to treat different cancers and immune diseases. For instance, corticosteroids alleviate the symptoms of almost all immune diseases by targeting the NF-κB pathway along with other immune-related pathways. Targeting NF-κB in immune diseases develops tolerance while blocking the immune triggers [29]. Besides, in cancer, NF-κB blockers inhibit the transcription of various oncogenes that will sustain cancer hallmarks. For this purpose, NF-κB inhibitors have been developed [50]. NF-κB inhibitors can be classified into different classes based on molecular target. BAY 11 is an irreversible selective NF-κB inhibitor that showed anti-cancer effect in several types of cancer. BAY 11 selectively interferes with TNF-α-induced NF-κB and stabilizes IκBα, hence BAY 11 suppresses proliferation and causes cell apoptosis [51]. In addition, multiple proteasome inhibitors are employed to target the NF-κB pathway including MG-115 and MG-132, however, proteasome inhibitors are non-specific to NF-κB [52]. Another class of NF-κB inhibitors is IKK complex inhibitors such as IKK-16 [53]. Each of these inhibitors targets a specific part of this pathway, however, the NF-κB pathway is composed of intricate layers and factors that would be very challenging to control and restore the balance. Each of the conditions caused by irritable NF-κB response could employ different mediators and factors. Thereby, identifying the molecular dynamic of NF-κB-linked diseases is a major milestone in controlling NF-κB and restoring a balanced pathway.

Role of NF-κB in different cancer hallmarks

Dysregulation of the NF-κB pathway may enhance cancer initiation, promotion, and spread [8]. NF-κB performs its tumorigenic role by sustaining different cancer hallmarks specifically, invasion and metastasis [54]. NF-κB induces the expression of SNAIL,

Table 1
Dysregulated genes related to different layers of NF-κB are implied in different disorders.

NF-κB layer	Dysregulated gene	Condition	The Effect of dysregulation	References
Input layer	c-MET	– Head and neck squamous cell carcinoma – Non-small cell lung cancer – Papillary renal cell carcinoma	Growth and invasion	[31–33]
	BAFF	– Rheumatoid arthritis – Systamic lupus erythematosus	B-lymphocyte proliferation and auto-antibodies formation	[34,35]
	TLR9	– Hepatocellular carcinoma	Proliferation	[36]
Processing layer	RELA	Psoriasis	Auto-immune reaction	[37]
	BCL10	– MALT lymphoma – pancreatic cancer – Extranodal NK-cell lymphoma		[30,38,39]
	IKKβ	Pneumonia	Defected immune response	[40]
	IKKβ	Sepsis	Enhanced pro-inflammatory cytokines	[41]
	IκBα	Multiple sclerosis	Defected negative feedback response and enhanced inflammation	[42]
	MyD88	colorectal cancer	Signal amplification and driving proliferation and metastasis	[43]
Execution layer	TNF-α	Rheumatoid arthritis	Produce immunogenic costimulatory signals in lymphocytes	[44]
	MCP-1	Renal cell carcinoma	Self-sufficiency growth signals	[45]
	BCL2	Gastric MALT lymphoma	Survival	[30]
	TLR2 and TLR4	Various cancer types and Tumor microenvironment	Anti-apoptotic signals, immune escape and chemotherapy resistance	[46–49]
	CCR2 and TLR6	Gastric MALT lymphoma	Positive feedback response, activate oncogenic pathway leading to survival and proliferation	

Table 2
NF-κB induces the expression of various genes that are implicated in cancer hallmarks including invasion, migration, and proliferation.

NF-κB subunit/s	NF-κB-responsive genes	Cancer hallmarks	References
p65	SNAIL	Migration and invasion	[66]
Canonical NF-κB pathway specifically IKKβ and p65	TWIST1	Invasion and migration	[67]
p65	MMP-9	Invasion and metastasis	[68]
Non-canonical NF-κB pathway subunits p52 and RELB	CXCL12	Migration and angiogenesis	[69]
P65, p50 and NF-κB2	VCAM-1	Migration and angiogenesis	[70]
All NF-κB subunits, especially p50	HIF-1α	Angiogenesis	[71]
c-REL and p65	GM-CSF	Growth and migration	[72]
Canonical NF-κB pathway subunits p65 and p50	VEGF	Angiogenesis, migration, and invasion	[73]
Canonical NF-κB pathway subunits p65 and p50	Indirect expression of ICAM1/2, E-selectin and VCAM1 through TNF-α and IL-1	Angiogenesis	[58]
p50	M-CSF	Immunosuppression	[74]
c-REL	IL-2	Immunosuppression	[6]
Canonical NF-κB pathway	Foxp3	Immunosuppression	[75]
p65 and -REL	ICAM-1	Proliferation and migration	[76]
p65 and p50	G-CSF	Proliferation	[77]
p65 and p50	Cyclin D	Proliferation	[61]
p65	Cyclin A	Proliferation	[61]
p65	MDM2	Anti-apoptotic	[78]
p65 and p50	BCL-2	Anti-apoptotic	[59]

TWIST1, SLUG, matrix metalloproteinase-9 (MMP-9), and C-X-C motif chemokine ligand 12 (CXCL12) which enhance cancer migration and result in epithelial-mesenchymal transition (EMT) [55]. Moreover, inhibiting NF-κB can effectively reverse EMT [56], confirming the critical role of NF-κB in metastasis.

Furthermore, stimulating angiogenesis is another hallmark of cancer. NF-κB as a part of an inflammation-induced pathway, could induce angiogenesis directly and indirectly. NF-κB directly induces the expression of hypoxia-inducible factor-1α (HIF-1α) and vascular endothelial growth factor (VEGF) during hypoxia. In response to platelet factor-4 (PF4) treatment, NF-κB binds to E-selectin to induce its expression. In contrast, the indirect effect is through NF-κB-activated macrophages and fibroblasts that in turn produce VEGF in the tumor microenvironment [57]. Besides, the indirect mechanism includes several pro-inflammatory cytokines such as IL-1 and TNF-α secreted in response to NF-κB activation which can trigger the expression of adhesion molecules such as intracellular adhesion molecule-1/2 (ICAM-1/2), E-selectin and VCAM-1 [58]. Besides, NF-κB has a critical role in evading apoptosis, where cancer cells tend to highly activate the NF-κB pathway, resulting in high expression of anti-apoptotic genes such as A1/Bfl-1 and BCL-xL and cIAP2 [59]. Furthermore, BCL-2 family members such as BCL-xL and A1/Bfl-1 inhibit apoptosis by suppressing mitochondrial depolarization and cytochrome *c* release. However, cIAP2 acts as an anti-apoptotic protein by mediating the ubiquitin degradation of receptor-interacting protein kinase 1 (RIPK1) involved in the TNFR signaling pathway and by directly binding to caspase 3, 7, and 9 and inhibits their activity [60]. NF-κB provides cancer cells with sustained proliferation ability. In detail, NF-κB regulates the collection of genes that control cell cycle and proliferation, such as cyclin D, and cyclin A. Numerous NF-κB members such as c-Rel, p65, and p50 interact with the cyclin E/cyclin-dependent kinase (CDK)2 and regulate the activity of this complex [61]. Moreover, NF-κB can positively regulate mouse double minute 2 (MDM2), thus inducing p53 instability and cell growth [62]. In addition, various pro-inflammatory cytokines induced by NF-κB such as IL-6, TNFα, and IL-1β, encourage cancer cell proliferation. Furthermore, constitutive activation of NF-κB maintains high levels of granulocyte colony-stimulating factor (G-CSF) which positively regulates growth and survival [6].

One of the crucial steps of cancer development is immune escape. Transformed cells can be detected by the immune system and eliminated. However, cancer cells develop various strategies to avoid immune response. The role of NF-κB in immune surveillance is major, thus multiple NF-κB transcription factors are included in immune cells regulation. Specifically, p65 maintains mature peripheral regulatory T cells (Tregs), whereas c-Rel contributes to the development of thymic Tregs. Hence, interference with c-Rel either by deletion or inhibition, diminishes Treg immunosuppressive effect and enhances the response to immune checkpoint blockade [63], hence the filtration of Tregs in the tumor site is linked to poor prognosis in many cancers such as kidney cancer [64]. Moreover, the p50 subunit of NF-κB contributes to shifting macrophage polarization toward M2 macrophage, thereby enhancing immunosuppression and tumor promotion [65]. Therefore, as a result, NF-κB could attribute to all stages of cancer by mediating cancer cells to proliferate and invade without getting stopped by the host immune system. In summary, several cancers have been linked to NF-κB dysregulation. However, the most prominent role has been reported in MALT lymphoma [30].

The role of NF-κB subunits in different cancer hallmarks is summarized in Table 2.

A highly activated NF-κB is implicated in renal inflammation in response to various triggers. NF-κB is initially activated to resolve the trigger and produce an immune response. However, the persistence of the cause or a failure in NF-kB regulatory mechanisms produces the activation of the immune system for a prolonged period, even after the resolution of the trigger, which leads to chronic inflammation. The constant activation of NF-κB incites a positive feedback response that will outweigh the inhibition regulatory mechanism imposed by the negative feedback loop. The resultant shift from chronic inflammation to renal cell carcinoma is usually sustained by the anti-apoptotic effect of the NF-κB pathway, which will be further amplified by cross-talking with other inflammatory pathways, including Janus kinase/signal transducer and activator of transcription (JAK/STAT), to enhance cell proliferation [79]. Exposure to inflammatory conditions for a long time usually triggers genetic alteration by different mechanisms, affecting the regulation of key pathways, mainly NF-kB, and shifting the response from immune to proliferation, survival, and metastasis [80].

Methodology

The current study employs data from different databases including COSMIC, TCGA, GEO, and GTex. The mutation frequency was obtained from the COSMIC database based on multiple projects like TCGA, Pan-Cancer Analysis of Whole Genomes project

(PCAWG), and AACR Project GENIE. The box plot figures were generated using Tumor, Normal, and Metastatic (TNM) plot tools that utilize data from different databases such as TARGET, GEO, and TCGA. The data of the TNM plot involves 277 Normal, 556 tumors, and 58 metastatic tissue samples obtained from the kidney.

NF-κB in kidney cancer

Kidney cancer is one of the least studied cancers due to the complexity of its genetic composition and the elusive molecular mechanisms. RCC, which is the major type of kidney cancer, can be subclassified into three major subtypes based on the kidney region where the cancer originates. The most common subtype of RCC is clear cell renal cell carcinoma (ccRCC), which accounts for more than 70 % of RCC. Therefore, it's the most studied subtype. Other subtypes represent a lower frequency of RCC, including papillary renal cell carcinoma (PRCC) and chromophobe renal cell carcinoma (chRCC) [81]. NF-κB role in RCC development and progression has been investigated in diverse studies [82–85].

When the cells are subjected to growth-stimulating triggers, guard mechanisms will be activated to induce cell cycle arrest or apoptosis to protect the cells from mutations and transformation. However, in RCC, multiple NF-κB-related genes are genetically altered; hence, the NF-κB-mediated survival mechanisms are utilized by cancer cells to promote tumor growth [85]. Based on data from TNM plot (tnmplot.com [86] cohort study that involved 277 Normal, 556 tumors, and 58 metastatic kidney cancer samples, RELA is highly expressed in tumor samples in contrast to healthy control and metastatic kidney cancer patients ($p = 1.05 \times 10^{-9}$) (Fig. 2A) [87]. No significant difference was detected in the expression of RELB and NF-κB2 between normal, tumor, and metastatic renal carcinoma, suggesting the substantial role of the canonical NF-κB pathway in driving tumor development in renal carcinoma. Moreover, the NFKBIA gene that encodes for IκBα was found to be highly expressed in tumor samples of kidney cancer compared with healthy control and metastatic kidney cancer with a p-value equal to 1.26×10^{-5} in TNM plot cohort [15] (Fig. 2B). The high expression of RELA in tumor samples, along with the elevated levels of IκBα as negative feedback, suggests the activation of the canonical NF-κB pathway upon exposure to harmful stimuli, which can progress to cancer with constant exposure to the stimuli and the lack of regulation possessed by the decreasing of NFKBIA seen in metastatic kidney cancer (Fig. 2B). This evidence proposes the prominent role of the canonical NF-κB in cancer initiation and the requirement of high levels of NF-κB-responsive genes in the initial stages of cancer. Importantly, the transformation is accompanied by other mutations that activate cancer-related pathways to shift the response from immune response to proliferation and survival [88]. A similar result was observed in the phosphorylated status of p65 and IκBα in RCC tissues obtained from fresh specimens. In detail,

specimens were obtained from three patients' tumor and normal corresponding tissues, and the expression of p-p65 and p-IκBα were assessed. Notably, the p-p65 and p-IκBα levels were significantly increased in RCC tissues compared with normal tissues, confirming the constant activation of NF-κB in RCC [89]. Accordingly, the dysregulation of NF-κB of RCC occurs at the transcriptional and post-translational levels. However, more studies must be done to detect the downstream target of NF-κB, which will provide insight into the molecular mechanism and dynamic NF-κB pathway in RCC. Additionally, A cohort study in the TNM plot database with 277 Normal, 556 tumors, and 58 metastatic kidney cancer participants found that TNFAIP3 was most highly expressed among metastatic renal cancer samples in comparison to tumor and control samples, with a $p = 1.43 \times 10^{-71}$, suggesting that high expression of A20 in correlated to metastasis in RCC (Fig. 3). Moreover, consistent with the previous study, the TNFAIP3 was found to be over-expressed in 3.93 % (21/534) in ccRCC based on a cohort study conducted by the COSMIC database, suggesting a tumor-promoting and anti-apoptotic role of A20 in kidney cancer [90]. However, the mechanism of the A20 tumor-promoting effect has not yet been studied in kidney cancer. Molecular analysis of A20 may reveal how the genetic and epigenetic alterations of TNFAIP3 promote kidney cancer progression.

In addition, caspase recruitment domain family member10 (CARD10)-mediated NF-κB activation in response to epidermal growth factor receptor (EGFR) has been implied in RCC. Activating CARD10 using EGF effectively activates NF-κB in renal tubular epithelial cells; hence, silencing CARD10 significantly reduces the migration and proliferation of RCC cell lines. This evidence confirms the role of the CARD10-mediated NF-κB pathway in enhancing the progression of RCC. Consistent with the previous study, CARD10 was found to be over-expressed in 7 % among 534 ccRCC patients based on a COSMIC cohort study, which confirms its role in augmenting NF-κB activity and providing a shift toward survival and cancer progression in response to growth factors such as EGF [91]. Moreover, HIF-1α, which is highly expressed in ccRCC, triggers various cells in the tumor microenvironment to release growth factors, including EGF, to promote intravasation and migration. Accordingly, CARD10-mediated NF-κB activation by EGF tends to be activated in the later stage of cancer in response to other oncogenic pathways [92].

Also, another NF-κB inducible gene that has a conserved site for p65. PPM1D encodes Wild-type P53-induced phosphatase 1 (Wip1), which acts as a serine/threonine phosphatase [93]. Many papers have demonstrated Wip1′s role as an oncoprotein. Wip1 was correlated to poor prognosis, higher TNM stage, and less differentiated tumor in kidney cancer. In a cohort study done in 277 Normal, 556 tumors, and 58 metastatic kidney cancer samples in the TNM plot database, tumor samples have the highest expression of PPM1D in comparison to healthy control and metastatic renal
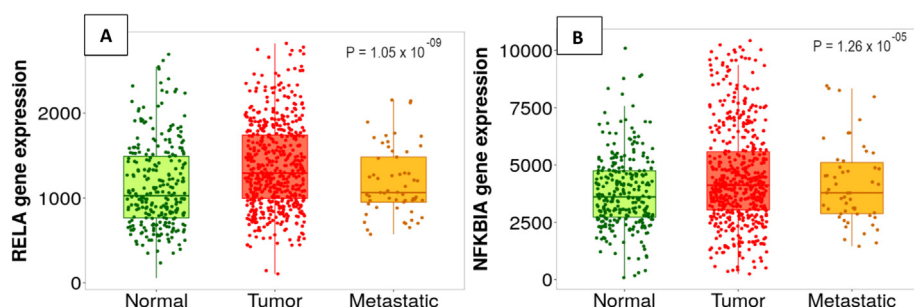

Fig. 2. Canonical NF-κB-related genes are elevated in kidney tumor tissues. **A** TNM box plot of RELA gene expression in kidney normal, tumor, and metastatic samples. **B** TNM box plot of NFKBIA gene expression in kidney 277 normal, 556 tumors, and 58 metastatic samples (N = 891).
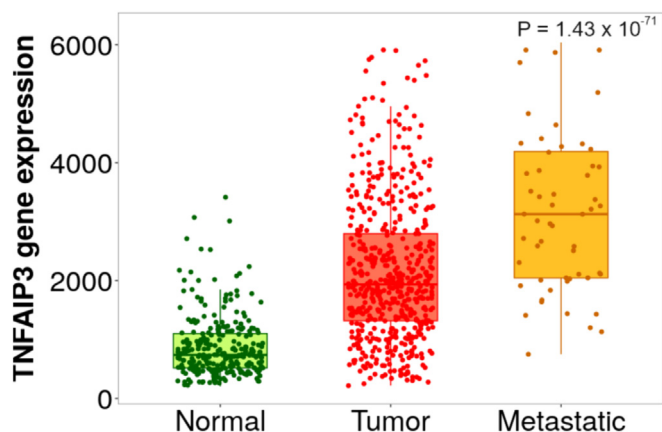
Fig. 3. TNFAIP3 expression is correlated positively with the tumor stage. TNM box plot of TNFIAP3 gene in kidney 277 normal, 556 tumors, and 58 metastatic samples (N = 891).
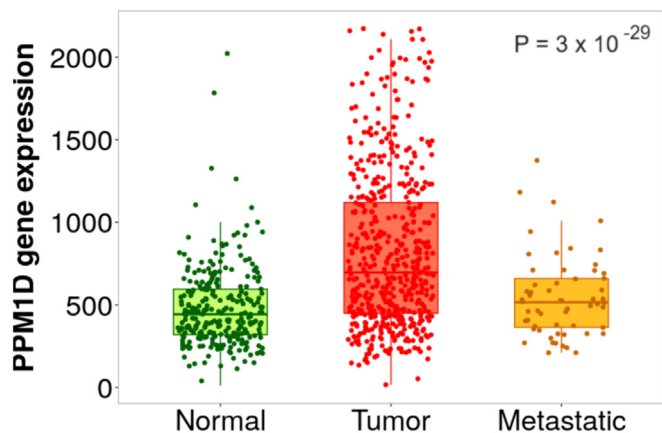

Fig. 4. PPM1D NF-κB-responsive gene is highly expressed in kidney tumor tissues. TNM box plot of PPM1D gene in 277 normal, 556 tumors, and 58 metastatic cancer kidney samples (N = 891).

cancer with p = 3×10^{-29}, supporting the evidence that PPM1D has a crucial role in cancer development rather than invasion and progression (Fig. 4). Also, referring to the COSMIC database, PPM1D is overexpressed in 2 % of 534 ccRCC samples [94]. Upregulation of PPM1D suggests the shift toward survival in response to triggers that can activate DNA damage response, such as radiation or chemotherapy instead of apoptosis or cell cycle arrest. Accordingly, this is consistent with the growing evidence that PPM1D plays a role in resistance to cancer treatments [95].

Cancer cells' genetic profiles vary; as a result, each of the subtypes exhibits a unique genetic mutation landscape. However, all RCC subtypes have a common gene mutation that drives carcinogenesis, mainly von Hippel-Lindau (VHL). VHL is a tumor suppressor gene that acts as an E3 ubiquitin ligase and induces HIF-1α degradation [96]. Moreover, different renal cancer subtypes exhibit different rates of VHL missense mutations that frequently lead to VHL inactivation; however, the highest rate of VHL mutations was found in ccRCC.

Role of NF-κB in ccRCC

The most frequently mutated gene in ccRCC, based on a cohort study done by the COSMIC database, is VHL. Notably, 52 % of the

VHL mutations were reported among 6232 ccRCC cases. Loss of the VHL gene in sporadic and familial ccRCC is correlated to the elevated NF-κB-signature genes, suggesting the inverse crosstalk between VHL and NF-κB in ccRCC. Moreover, VHL mutations or loss could drive NF-κB expression by accumulating HIF-α and transforming growth factor-alpha (TGF-α), resulting in PI3K/Akt/NF-κB pathway activation [97]. Referring to the COSMIC database, a cohort study that included 534 ccRCC patients found that 3.2 % (17/534) patients were overexpressing HIF1A, and 4.9 % (26/534) patients exhibited overexpression in the TGFA gene, suggesting the prominent role of this pathway in NF-κB activation in ccRCC. In addition, the increased expression of HIF1A allows the metabolic shift that occurs in ccRCC toward glycolysis and promotes angiogenesis and migration in hypoxic stressful conditions [92], whereas TGF-α overexpression sustains cell proliferation [98]. Similarly, immunofluorescence staining of ccRCC cells shows nuclear and cytoplasmic expression of HIF-1α, which is correlated to nuclear p50 expression. In contrast, restoring the ZIP1 tumor suppressor gene, significantly abrogated HIF-1α levels and p50 nuclear localization [99]. Thus, the pivotal role of NF-κB in regulating and interacting with a vast number of oncogenic pathways and proteins provides a continuous loop of sustaining RCC progression and migration.

Another previous study has reported that VHL presence does not affect the expression or the phosphorylation status of p65 and IκBα. Interestingly, tested VHL-wildtype or VHL-deficient ccRCC cell lines exhibited an activated NF-κB pathway, regardless of VHL status [89]. This evidence provides proof of concept that the NF-κB pathway is activated in RCC through interplaying with different pathways mainly, PI3K/Akt pathway. subsequently, not a single genetic alteration would drive NF-κB dysregulation.

ccRCC exhibits a total of 7 % mutation in TP53 in a total of 2316 samples, which will augment PI3K/NF-κB by the absence of one more tumor suppressor gene, allowing this pathway to be constitutively active. Moreover, this, in turn, will suppress the activity of p53 in ccRCC cells that harbor wild-type p53, rendering it inactive. As a result, the NF-κB pathway is not suppressed by the main regulators VHL and p53 (Fig. 5) [100]. Moreover, NF-κB activity has been assessed in a study that included 42 ccRCC and 3 PRCC samples. Two out of the three PRCC samples had activated the NF-κB pathway. Whereas, 5/7 (71 %) grade three ccRCC samples had activated NF-κB, which is the highest percentage compared to grades 1 and 2. Moreover, all three metastatic RCC cases exhibit highly activated NF-κB. 15/45 RCC samples (33 %) exhibit over 200 % increased NF-κB activity [82]. This evidence shows that despite the employing of different oncogenic pathways in the two different RCC subtypes, NF-κB is highly activated in both subtypes. NF-κB might be activated in different stages and by unique genetic alterations in each RCC subtype, however, its constant activation is a critical step in cancer development and progression.

The expression of p50 NF-κB subunit has been linked to different apoptosis and angiogenesis markers in ccRCC. In detail, 40 ccRCC samples were measured to express the p50 subunit of NF-κB, VEGF, EGFR, p53, and BCL-2. A significant correlation was detected between NF-κB level and EGFR (p = 0.004), VEGF (p = 0.001), BCL-2 (p = 0.01), and p53 (p-value = 0.p037) [83]. Consistent with this finding, 786–0 RCC cell lines with p50 knockout showed decreased expression of crucial angiogenic markers, primarily IL-6 [101]. Accordingly, p50 could act as a novel therapeutic target and prognostic marker in ccRCC. However, more research is needed to study the molecular complexes and mechanisms that employ the p50 subunit and its distinct role in ccRCC pathogenesis.

Y-box binding protein 1 (YBX1) is a transcription factor that exhibits oncogenic properties in several types of cancer. In ccRCC, YBX1 is associated with a higher stage and grade by activating the NF-κB pathway In detail, YBX1 interacts with RCC-related pro-
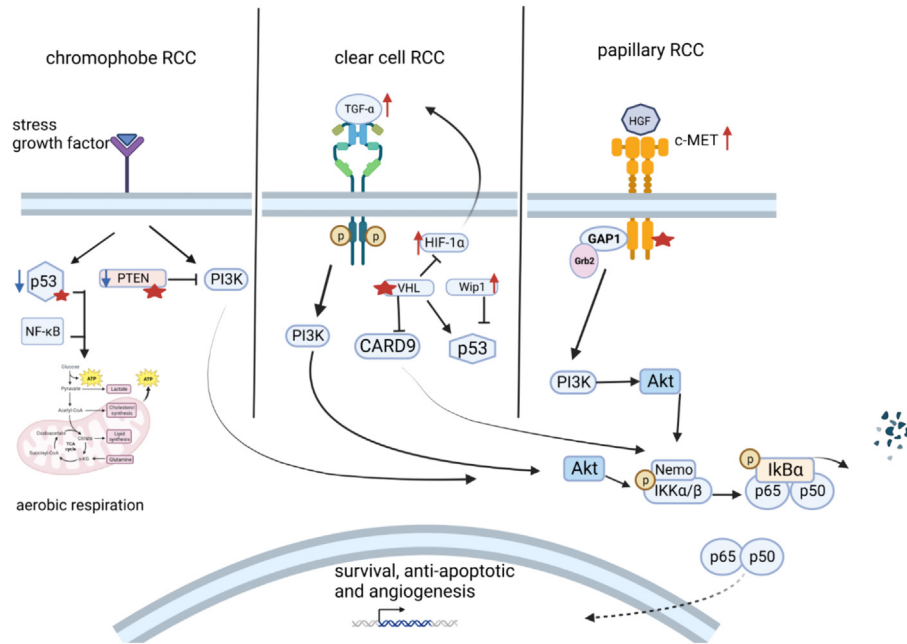
month from the exposure to FeNTA, IkBα levels increased, while EGFR and p65 expression remained elevated [102]. This study is consistent with the TNM plot data, which shows that IκBα is increased as negative feedback when patients are exposed to a trigger and an immune response is activated. Moreover, the persistence of the trigger shifts the response from immune to different cancer hallmarks based on the dysregulated gene. In this case, NF-κB activation induces the expression of proliferation-promoting genes such as cyclin D, shifting the response to cell growth and proliferation. Subsequently, the increased IκBα level because of the negative feedback loop can no longer counteract or suppress the consistently activated NF-κB pathway and restore the balance, especially since other oncogenic pathways will also be activated [103].

Cezanne (encoded by Otud7b) is another regulator of the canonical NF-κB pathway in the kidney, specifically in glomerular endothelial cells [104]. Notably, cezanne is under-expressed in 3 % of 534 cases of ccRCC [105], suggesting an uncontrolled constantly activated canonical NF-κB pathway in ccRCC and the shift toward cell growth.

Bcl-3 is a known proto-oncogene that enhances tumor progression [106]. In the context of ccRCC, Bcl-3 was found to be overexpressed by 3 % across 534 samples in a cohort study established by the COSMIC database [105]. In response to DNA damage, BCL3 was found to be upregulated, induce the expression of MDM2, and inhibit p53-mediated apoptosis; as a result, oncogenic pathways such as NF-κB will shift the cellular response toward survival, resulting in the propagation of cells with mutation and generation of transformed cells [107]. Another study revealed the presence of BCL3 in the nucleus of metastatic RCC. Particularly, co-immunoprecipitation demonstrated that nuclear extracts from metastatic lung tissues contain p50/BCL3 complexes. These studies provide insight into the role of NF-κB subunits in RCC by forming complexes and binding to the promoter of different genes to mediate cancer migration [108]. Conducting research on the molecular dynamic and relative expression of NF-κB members will enhance the understating of the specific mechanism employed.

Based on these findings we can suggest that the most dysregulated NF-κB-related factors and regulators in ccRCC are involved in the canonical NF-κB pathway. Altered genes were found at the regulatory, signal-transmitting, transcription factors, and inducible gene levels of the canonical pathway.

Role of NF-κB in chRCC

One of the most dysregulated genes in cancer is TP53. TP53 has a prominent role in RCC development, especially in chRCC. According to a cohort study done by the COSMIC database, chRCC has the highest rate of TP53 mutation RCC subtypes; notably, TP53 was found to be under-expressed in 34.4 % (28/66) chRCC patients, and it was mutated in 26 % out of 203 patients. p53 and NF-κB regulate each other negatively by different mechanisms. At the transcription level, NF-κB can bind to the promoter of MDM2 and indue its transcription, hence promoting p53 degradation. p53 and NF-κB compete for the limited pool of p300 and CREB-binding protein (p300/CBP), affecting the transcription of each other's genes [109]. In addition, p53 interferes with the non-canonical NF-κB pathway by decreasing NIK and inhibiting the NF-κB dependent gene transcription [110]. NF-κB was shown to interfere with p53 at the protein level through IKK-mediated p53 phosphorylation, which results in its ubiquitination and degradation [111]. Another mechanism where NF-κB can interfere with P53 is through some NF-κB-responsive genes, such as macrophage migration inhibitory factor (MIF) and IL-6, which can inhibit p53-mediated transcription. As a result, TP53-negative cancer cells are characterized by constant activation of the NF-κB pathway and enhanced tumor progression.

Also, it was demonstrated that even in p53-wild-type cancer cells that exhibit an over-activated NF-κB pathway, p53 will not be fully functional because NF-κB will shut the p53-mediated apoptotic role [112]. Based on COSMIC and TCGA databases, the second most frequent mutated gene in chRCC is Phosphatase and tensin homolog (PTEN). Specifically, PTEN was found to be mutated in 7 % in a study composed of 194 patients, and under expressed in 39.4 % of 66 patients [113]. PTEN loss or inactivating mutations allow Akt to be constitutively active so that it turns to phosphorylate MDM2 and stabilizes it, rendering p53 inactive. At the same time, the PI3K/Akt pathway activates NF-κB [114]. The formerly mentioned mechanism clarifies the role of Akt and NF-κB in inactivating p53; hence, in chRCC, this mechanism suppresses p53 even in patients expressing wild-type p53. In normal cases, p53 is activated in response to stress, inflammation, or DNA damage. However, deletion or suppression of p53 will shift the mechanism to favor the activation and upregulation of NF-κB, hence initiating the transformation process in chRCC. Moreover, by building a conclusion from these studies, we can say that Akt/NF-κB/p53 is the dominant pathway that induces cell transformation in chRCC (Fig. 5). Furthermore, 4.3 % (10/233) mutations were detected in the VHL gene among chRCC cases in a cohort study performed by the COSMIC database, suggesting the absence of another NF-κB regulator, switching NF-κB activity on.

CD44 is a gene regulated by the NF-κB pathway. CD44 acts as an adhesion receptor, and upon activation, it supports cancer migration and invasion in many cancers. Moreover, CD44 is activated and upregulated in response to T lymphocyte activation, whereby, after resolving the trigger, CD44 levels decrease. Notably, among a chRCC cohort study reported by the COSMIC database, 15.2 % (10/66) patients are overexpressing CD44 [114], indicating a highly active NF-κB, producing a positive feedback loop and shifting the response from immune activation to migration and invasion. This evidence provides insight into how NF-κB can be constantly active in chRCC, sustaining the release of factors needed for cancer development and progression.

Metabolic machinery in ccRCC versus chRCC

Cancer cells favor the shift to glycolysis even in the presence of oxygen because, along with ATP, glycolysis produces multiple metabolites that enter various biosynthetic pathways. For instance, glucose 6-phosphate produced by glycolysis enters the pentose phosphate pathway, generating nucleotides needed for DNA synthesis of highly replicating cancerous cells. p53-NF-κB crosstalk has a major impact on glucose metabolism in cancer cells. Consequently, different metabolic pathways are implicated in various renal carcinoma subtypes based on the TCGA database. In which mitochondrial genes in chRCC were found to be highly replicated, overexpressed, and mutated. Moreover, most Krebs cycle enzymes were upregulated, and at least one gene in each electron transport chain complex (ETC) was also upregulated [114]. Conversely, in ccRCC, genes for enzymes involved in the Krebs cycle were suppressed. However, enzymes that play a central role in glycolysis, the pentose phosphate pathway, and fatty acid synthesis were enriched [115,116]. Some studies demonstrated that NF-κB encourages aerobic respiration in cancer cells that harbor wild-type p53 by increasing the expression of some enzymes, such as the synthesis of cytochrome *c* oxidase 2 (SCO2). In contrast, in p53-deficient cells, NF-κB increases the tendency to glycolysis and the Warburg effect by enhancing the level of GLUT3 [117,118]. However, the dialogue in ccRCC and chRCC contradicts the previous study. Based on scientific findings, in some conditions, NF-κB exerts its pro-tumorigenic and metabolic functions through

mutated p53, which is the case in chRCC, where NF-κB can switch various mitochondrial respiration machinery even p53 is mutated. Whereas several studies have reported that while p53 is not mutated in high frequency in ccRCC, it's functionally inhibited by the upregulations of multiple p53 suppressors [118].

Role of NF-κB in PRCC

PRCC represents another rare subtype of RCC; hence, it is characterized by a distinct genetic background [116]. According to a cohort study done by the COSMIC database, the most mutated gene in PRCC is the MET gene, which was found to be mutated in 9 % across 709 patients, whereas 5 % of 286 patients exhibited an increase in gene copy number. Moreover, most cancers tend to mutate and/or upregulate MET, rendering it constitutively active to drive survival, angiogenesis, and migration through cross-talking with different signaling pathways, including NF-κB pathway [119]. Upon activation of c-MET receptor by HGF, one of the main downstream that is activated in response to c-MET is the PI3K/Akt pathway. Akt mediates NF-κB pathway activation through phosphorylation and activating the IKK complex, which subsequently activates the p65-p50 dimer through phosphorylating the inhibitory protein IκBα [120]. Even though MET is mutated in multiple cancers, the first mutations were detected in PRCC, indicating that this receptor plays a critical role in PRCC development and progression. Moreover, the missense mutations in MET frequently affect the tyrosine kinase domain, resulting in oncogenic signals. A constantly active c-MET receptor amplifies the input signal and activates NF-κB to drive cancer survival and proliferation and overcome the apoptotic signals.

TLR2 is one of the NF-κB-inducible genes that will further activate NF-κB upon expression. Hence, TLR2 was mutated in 0.6 %/338 patients in the COSMIC cohort among PRCC. This evidence provides a clue of how the mutations in any of the NF-κB layers could produce countless cycles of NF-κB that will sustain different cancer hallmarks (Fig. 5) [121].

Another gene related to NF-κB and PRCC is the I kappa B kinase interacting protein (IKIP). IKIP was shown to bind to IKKα/β and block its interaction with NEMO, hence negatively regulating the NF-κB pathway. While it acts as a pro-apoptotic molecule and is activated by p53, it was found that many cancers have an increased level of IKIP. According to TIMER and GEPIA databases, IKIP is highly expressed in PRCC, and its expression is negatively correlated to survival while positively linked to higher TNM stage. The reduced expression of IKIP indicates highly activated NF-κB in PRCC, which will induce the expression of oncogenes to sustain survival and migration [122].

Also, 2 % of 645 PRCC samples had VHL mutations in a COSMIC database-based cohort study, suggesting that VHL mutations have a weaker role in PRCC for switching the NF-κB activity. However, the upregulation of the c-MET receptor is the critical player in this cancer subtype to drive NF-κB constant activity [123].

Targeting NF-κB in RCC

The tumor-promoting role of NF-κB encourages scientists to use diverse methods to interfere with NF-κB in RCC. Notably, this includes pharmacological inhibitors as well as genetic interference. Knocking down the p50 subunit in RCC mouse model significantly decreases tumorigenicity. Besides, knocking down p50 in the RCC mouse cell line suppresses cell proliferation and causes late apoptosis [130]. This evidence supports the tumorigenic role of p50 observed in cohort studies done in RCC patients. Besides, Transfecting NOAT113026 long non-coding RNA in RCC cell lines suppresses cell invasion, colony formation, and proliferation by interplay with the p50 NF-κB subunit to interfere with its level [131].

A number of compounds isolated from natural herbs that exhibit anti-inflammatory and anti-cancer properties were found to inhibit NF-κB in RCC. Triptolidenol is a drug used in chronic nephritis, however, its role in ccRCC has been studied. In addition, Triptolidenol inhibited cell migration and induced cell cycle arrest and apoptosis in ccRCC cells by interfering with IKKβ kinase activity. Subsequently, suppressing the transactivation of NF-κB provides a mechanism to hinder RCC progression [132]. Physalin F is a plant extract with an anti-tumor effect. Physalin F showed an anti-cancer effect in RCC cell lines by targeting the NF-κB pathway. The cytotoxic role of Physalin F was mediated by decreased p65 and p50 nuclear translocation and gene transcription including Bcl-2 and Bcl-xL, hence inducing cell apoptosis [133]. Piperlongumine is a natural alkaloid that ablates c-Met expression at RCC cells' gene and protein levels. Furthermore, Piperlongumine was shown to suppress downstream signaling pathways including NF-κB pathway, hence it acts on metastatic RCC [134]. Liguistium wallichii is a natural herb used for medical purposes. The anti-cancer effect of Liguistium wallichii has been evaluated in experimental rat models of RCC. Liguistium wallichii showed a significant decrease in nuclear division and cancer RCC progression by targeting NF-κB activation and p65 nuclear localization. Thus, it is evident that NF-κB plays a major role in DNA replication and gene transcription, resulting in cancer development and progression [135].

These findings suggest that the anti-cancer effect exhibited by natural compounds is mostly through targeting NF-κB. In RCC, especially the ccRCC subtype, the immune mediators are elevated. subsequently, these compounds due to their anti-inflammatory effect were potent in mediating apoptosis by interfering with NF-κB-mediated gene transcription.

The expression of NF-κB has been linked to multiple drug resistance in ccRCC. Notably, the sensitivity of ccRCC to metformin, sorafenib, and gefitinib was better in the group with downregulated NF-κB than in the group with upregulated NF-κB [115]. Also, the NF-κB role has been implied in sunitinib resistance. One of the main tyrosine kinase inhibitors used in advanced ccRCC is sunitinib. However, over 20 % of ccRCC patients develop resistance, and even most patients who showed response in the initial period will develop resistance after months of treatment. Two pathways emanated by a stress response in the endoplasmic reticulum (ER) were shown to mediate sunitinib resistance in ccRCC. One of these two pathways is NF-κB, where sunitinib was shown to activate NF-κB by stabilizing inositol-requiring enzyme 1 (IRE1) in response to ER stress which further recruits and activates TRAF2 leading to canonical NF-κB pathway activation. Notably, targeting NF-κB effectively re-sensitizes RCC to sunitinib while blocking the other resistance mediating pathway, PERK, only suppress the release of pro-inflammatory mediators such as TNF-α and IL-6 [136]. This evidence suggests the main role of NF-κB pathway in mediating RCC resistance to tyrosine kinase inhibitors by promoting several cancer hallmarks.

In a study that used ccRCC cell lines and an RCC mouse model, the effect of BAY-11 was studied. BAY-11 NF-κB inhibitor effectively induced cell apoptosis in cultured cells in a concentration-dependent pattern. Importantly, this effect was accompanied by a decrease in p-p65, indicating that the anti-cancer effect observed was due to NF-κB inhibition. In addition, BAY 11 significantly reduced tumor growth in xenograft nude mice, while it had no effect on cell proliferation [89]. This study proves that NF-κB has a major role in mediating RCC survival and using a selective and irreversible NF-κB inhibitor which is BAY 11 deprives RCC cells of the genes that are needed to sustain survival they committed programmed death.

Most of the tested inhibitors except for BAY 11 are non-specific for the NF-κB pathway, hence the anti-cancer effect observed can't

be exploited to detect the molecular mechanism. Therefore, more studies involving RCC cell lines or mouse models are required to investigate the role of specific NF-κB inhibitors in RCC.

Conclusion and future perspectives

NF-κB pathway orchestrates cellular responses, including proliferation, apoptosis, and immune response. Extensive research has delved into the role of NF-κB in cancer, yet a major gap in the degree of NF-κB dysregulation that shifts the response remains to be discovered. An array of different inhibitors and subunits tightly controls the regulation of NF-κB. Major dysregulation in NF-κB can lead to chronic inflammation due to irritable NF-κB pathway that is unsusceptible to negative feedback response. Chronic inflammation is usually associated with extensive tissue damage, cell type changes, and genetic alterations. Genetic dysregulations of NF-κB multiple subunits could favor the shift of NF-κB from immune response to proliferation survival, and growth leading to a major imbalance in cellular guard mechanisms. In cancer, NF-κB tends to be constitutively active in an autonomous pattern, producing self-sufficient growth signals and promoting RCC cell survival.

Restoring NF-κB regulation could be a novel mechanism to control various auto-immune diseases as well as cancer. NF-κB inhibitors could have a limited role in restoring controlled NF-κB activity. Investigating new mechanisms to modulate the NF-κB pathway could provide a novel method to treat multiple types of cancer, especially RCC. Various molecular studies should be conducted to specify NF-κB subunits that are linked to RCC pathogenesis. Identifying the molecular dynamic of RCC subtypes is essential to overcome RCC's bad prognosis and current limited treatment options. Each subtype of RCC is characterized by some biomarkers or gene signature. Relative expression levels of different NF-κB subunits could have a major role in impacting its activity and shuttling to the nucleus, hence affecting NF-κB pathway activation and RCC progression. Therefore, NF-κB subunit involved in different RCC subtypes development could be used as a diagnostic and therapeutic biomarker.

Most pharmacological inhibitors of the NF-κB pathway target specific subunits of this pathway while this pathway is composed of tens of receptors, signal transduction complexes, and transcription factors. As a result, other subunits will compensate, and the overall activation will not be modulated. Accordingly, the detailed genetic composition of RCC is required to characterize the genetic landscape of each subtype and target it.

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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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