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NF-κB inhibitors in treatment and prevention of lung cancer

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ABSTRACT

Intracellular signalling pathways have provided excellent resource for drug development particularly in the development of cancer therapeutics. A wide variety of malignancies common in human exhibit aberrant NF-κB constitutive expression which results in tumorigenic processes and cancer survival in a variety of solid tumour, including pancreatic cancer, lung, cervical, prostate, breast and gastric carcinoma. Numerous evidences indicate that NF-κB signalling mechanism is mainly involved in the progression of several cancers which may intensify an enhanced knowledge on its role in disease particularly lung tumorigenesis. This has led to tremendous research in designing a variety of NF-κB antagonists with enhanced clinical applications through different approaches the most common being suppression of IκB kinase (IKK) beta activity. Many NF-κB inhibitors for lung cancer are now under clinical trials. Preliminary results of clinical trials for several of these agents include small-molecule inhibitors and monoclonal antibodies. A few combinatorial treatment therapies are currently under investigation in the clinics and have shown promise, particularly NF-κB inhibition associated with lung cancer.

1. Introduction

Lung cancer comprises several types like bronchogenic carcinomas which is a lung malignant neoplasm arising from the bronchus/bronchiole and lung carcinoid tumour which is a neuroendocrine tumour and are the common cause of cancer deaths globally. Histologically lung cancers could be classified into small cell lung cancer (SCLC), squamous cell carcinoma (SCC) and adenocarcinoma (ADC) each of which derive from different compartments in the lung. Non-small cell lung cancer (NSCLC) include adenocarcinoma (and its relatively rare bronchioalveolar carcinoma [BAC]), squamous cell carcinoma and large cell carcinoma (undifferentiated NSCLC) are the major cancer affecting globally in both genders, which accounts for 80 % of lung cancers and more than 1.2 million deaths every year [1,2]. The predominant reason for the lung cancer includes smoking however other environmental factors like food and lifestyle may be involved [3].

Among lung cancers observed in different populations, ~85 % are caused by use of tobacco smoke, which leads to genetic and epigenetic abnormalities and further leading to invasive lesion and metastatic process. Conversely, another class of lung cancer, which accounts for ~20 % of ADCs, occurs in non-smoking patients and uses various signalling pathways for the development of tumors. Current existing therapies cure the disease to some possible extent and the overall 5-year survival rate was found to be ~15 % because NSCLC often affects the entire body (systemic) at the time of presentation. Advancement in the diagnostics have led to the development of Spiral CT (Spiral computed tomography) which gives some hope for early intervention at least for peripheral lung cancer [4,5]. Platinum-based chemotherapy regimens (cisplatin or carboplatin plus other cytotoxic agents) are the standard treatment for patients with NSCLC, however such regimens are limited by severe toxicities associated with gastrointestinal dysfunctions and efficacy of the treatment is limited due to multi-drug resistance of NSCLC cells [6].

Currently extensive molecular genetic studies are in progress for lung cancer targeting at particular genes and signalling cascade [6] which have shown that clinically overt lung cancers have numerous epigenetic alterations facilitating their oncogenic growth [7]. Targeted therapy is at present mainly based on several pathways in lung cancer with altered major components and functions [8]. The genetic abnormalities which is linked to increased risk of lung cancer development employs numerous pathways which are redundant for survival and therefore therapy should be considered from the context of signalling cascade which have their main functions modified, rather than focusing on individual factors/features [3].

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2. Background of NF-κB signalling cascade

The transcription factor nuclear factor-κB (NF-κB) was first identified in the year 1986 which was a nuclear factor that binds to the regulatory region of the gene encoded by the immunoglobulin kappa light-chain of activated B cells (hence the term, NF-κB) [9]. NF-κB is a Rel family transcription factor comprising of five members namely Rel-A (p65), Rel-B, Rel (c-Rel), NF-κB1 (p50/p105), and NF-κB2 (p52/p100) in mammals [10]. The canonical pathway of NF-κB is a prerequisite for the mechanism of inflammation and a crucial factor in modulating innate immunity, while the non-canonical pathway of NF-κB is required for lymphoid organ development as well as adaptive immunity [11]. In addition to the canonical and non-canonical pathway additional cascade of NF-κB activation exists, sometimes referred to as atypical activation pathways. The NF-kB upstream and downstream signaling agents are discussed in detail below.

2.1. NF-κB upstream signalling agents

In the canonical activation pathway signal can be transmitted by ligands which include tumor necrosis factor receptor (TNF-R), toll-like receptors (TLRs), interleukin-1 receptor (IL-1R) and so on as depicted in Fig. 1 [12]. An alternative pathway or non-canonical pathway for NF-κB stimulation, include different classes of receptors including CD40, receptor activator for nuclear factor kappa B (RANK), B-cell activation factor (BAF), lymphotoxin β-receptor (LTßR) [13,14], chemical stresses, oxidative stress, environmental hazards and a number of chemotherapeutic cytotoxic agents as well as metals [15].

2.2. NF-κB downstream signalling

In the canonical pathway, activation of the IκB kinase (IKK) complex leads to phosphorylation of IκBα which is primarily regulated by IKK2. The activated β-subunit of IKK (IKKβ) phosphorylates inhibitor of kappa B-a (IκBa) protein (i.e. the negative regulator of NF-κB) and further leads to the ubiquitination process and proteasome-mediated degradation of IκBa. This in turn releases p65/p50 heterodimer which then allows the translocation of the NF-κB complex into the nucleus for binding to enhancer κB sites elements on the promoter of the target genes [16]. Further depending on the availability of the genome mediated by means of epigenetic modifications and the type of cell, manifold rate of the target gene transcription take place. In alternative pathway, stimulation through these receptors leads to NF-κB inducing kinase (NIK) activation and in turn activates IKK1α homodimer which turns on p100/RelB by process of ubiquitination and proteasomal degradation thereby generating p52 subunit [17,18]. This complex (p52/RelB heterodimer) further translocate to nucleus bind to the κB sites on the promoter of the target genes and allow the process of transcription as represented in Fig. 2. In the atypical activation pathways activation of the IKK complex is mediated after genotoxic stress via the ataxia telangiectasia mutated (ATM) checkpoint kinase leading to ubiquitination of NF-κB Essential Modulator (NEMO or IKKγ) (pathway not shown) [19]. Others signalling cascade which are mainly associated with the activation of NF-κB include tyrosine kinases and Epidermal growth factor receptor (EGFR). Growth factor receptors like Epidermal Growth factor receptor can mediate atypical NF-kB activation. Epidermal growth factor (EGF) induces IKK independent NF-κB activation through phosphorylation at the tyrosine residue at the position 42 in IκBa in non-small cell lung adenocarcinoma cells [20–23].

3. Aberrations in NF-κB signalling in lung tumorigenesis

The pleiotropic transcription factor (NF-κB) influence the process of oncogenesis by upregulating the genes involved in cell proliferation, metastasis, angiogenesis and suppression of the apoptosis [24]. In normal cells, NF-κB proteins are sequestered in the cytoplasm (in inactive state) in complex with inhibitor-κB (I-κB). Degradation of I-κB by IKK mediated process releases the NF-κB to translocate in to the nucleus to allow transcription of target genes and further mediating its biological action [25,26]. Activation of NF-κB in a constitutive manner is proved to be an imperative mechanism contributing to tumorigenic processes in many variety of solid tumour, including pancreatic cancer, lung, breast, cervical, gastric and prostate cancer [27–32]. Although lung tumours among different patients display histological heterogeneity, the samples collected from the patients have shown increased level of NF-κB in both SCLC as well as in NSCLC conditions [33]. Molecular studies of IKK/NF-κB signalling pathways helps in early intervention of poorer disease-specific survival associated with disease advancement and poor prognosis in lung cancer patients [34]. Therefore, any molecular markers mediated with signalling cascade of NF-κB may be useful in assessment of clinical pathological features [35]. In lung cancer, the NF-κB signaling pathway is linked with the inflammatory signalling, oxidative stress intermediates, gluconeogenesis and glycolysis pathways as proven by proteomic studies [36]. Bromodomain-containing protein 4 (Brd4) helps in maintaining the constitutively active NF-κB in lung cancer cells by combining with acetylated Rel-A [37]. Studies have shown that SOD2 (Superoxide Dismutase 2) induces NF-κB action and increases IKKβ transcription in lung tumorigenesis. This event favours cancer progression and confers poor prognosis in patients [38]. TRAF6 (Tumor necrosis factor receptor (TNFR)-associated factor 6) is one of the amplified candidate oncogenes which contributes to the pathogenesis of human lung carcinoma. Therapeutic agent targeting TRAF6 may reduce NF-κB constitutive activation and suppress the lung tumorigenesis.

3.1. NF-κB aberrant activation and their role in lung cancer development

Chemotherapy drugs act by promoting the proliferating cells to

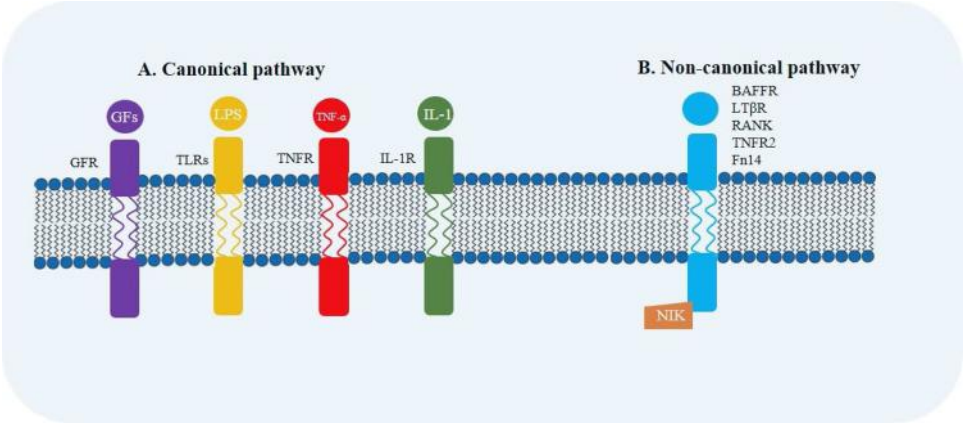

Fig. 1. Upstream signaling **of NF-κB.** Canonical and non-canonical pathway leading to the activation of NF-κB. The canonical pathway is induced by proinflammatory cytokines, tumor necrosis factor (TNF)-a, and interleukin-1β (IL-1β), growth factors or lipopolysaccharide (LPS) with its corresponding receptors such as Toll-like receptors (TLRs), tumor necrosis factor receptor (TNFR), Interleukin-1 receptor (IL-1R), growth factor receptor. Non-canonical pathway of NF-κB activation include different classes of receptors including B-cell activation factor (BAFFR), lymphotoxin β-receptor (LTßR), CD40, receptor activator for nuclear factor kappa B (RANK), TNFR2 and Fn14.

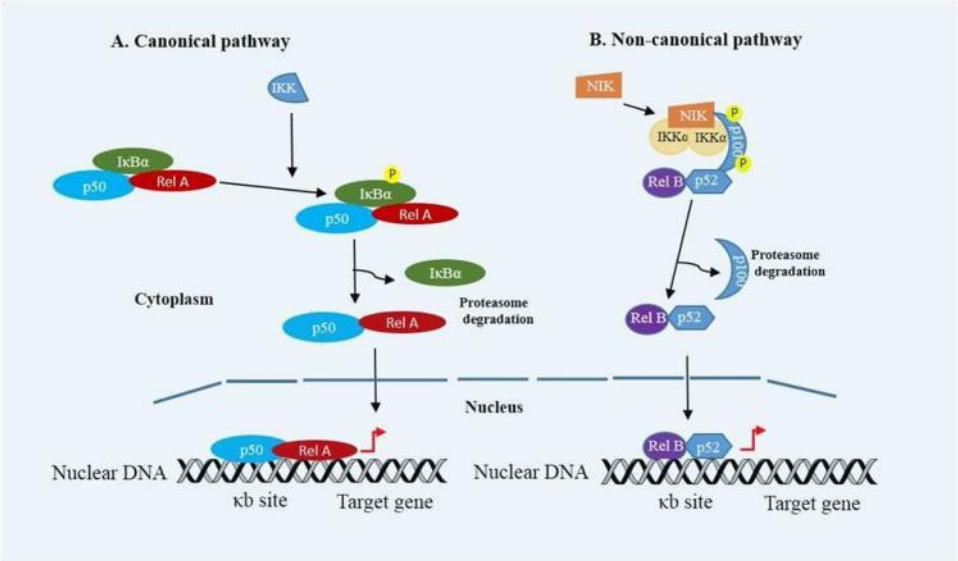

Fig. 2. Downstream signaling **of NF-κB. In canonical pathway the activation of** NF-κB results in the phosphorylation of IκBα by the IKK complex, leading to its ubiquitylation (Ub) and subsequent degradation by the 26S proteasome. The RelA/p50 complex then translocate to the nucleus to activate the transcription of target genes. The non-canonical pathway results in the activation of IKKα homodimer by the NIK. The formation of the complex NIK-IKKα-p100 leads to the phosphorylation of the p100 subunit. This results in 26S proteasome dependent processing of p100 to p52, which can lead to the activation of p52-RelB that target distinct κB element and induce the transcription of target genes.

undergo apoptosis process, for e.g. by interfering with the mechanism of DNA synthesis. Since NF-κB is constitutively activated in various types of cancers, they promotes drug resistance by providing an alternative survival mechanism which is by upregulating anti-apoptotic proteins and genes [39,40]. In certain cases both chemo- and radiation therapy induce activation of NF-κB, which result in developing resistance to the treatment options [41]. For e.g., commonly used chemo drugs like paclitaxel, gemcitabline, adriamycin and vinblastine can activate the NF-κB cascade [42]. Therefore, blocking of NF-κB will definitely increase the efficacy of anticancer therapeutics. Further, inhibition of NF-κB signaling with different approaches has been shown to enhance the efficacy of chemotherapeutics and radiotherapy for killing the malignant cells both in vitro and in vivo [43,44]. Highly carcinogenic tobacco smoke along with highly prone genetic susceptibility combine to promote the lung carcinogenesis. The gas phase of tobacco smoke releases free radicals which can activate the NF-κB cascade. A common carcinogen found in tobacco smoke, benzopyrene also has been shown to activate NF-κB possibly by damaging the DNA and inhibiting the apoptosis which results in epigenetic changes that can lead to lung tumorigenesis [45]. The occurrence of lung cancer is positively correlated with chronic obstructive pulmonary disease (COPD), an inflammatory lung disease which is mainly caused by tobacco smoke and this provides an environment for epithelial-mesenchymal transition (EMT) which leads to lung cancer progression. Research have shown that several inflammatory mediators which are present in the COPD lung can be triggered via the activation of the transcription factor NF-κB along with its upstream signalling kinase, IKK-2 thereby highlighting that NF-κB/IKK-2 signalling pathway may represent a therapeutic target to counteract the inflammation associated with COPD [46–48].

4. Mechanism of oncogene mediated NF-κB aberrant activation

Aberrant activation of NF-κB binds to a specific DNA sequences present in the target genes (collectively called κB sites) and regulates the transcription of different genes involved in cancer cell proliferation, survival, angiogenesis, metastasis as well as therapeutic resistance [49]. NF-κB activation is associated with production of a main inflammatory mediator known as Cyclooxygenase-2 (COX-2), as evidenced by the observations of impaired COX-2 expression after specific inhibition of NF-κB. Cyclooxygenase-2 catalyses the production of prostanoids, family of arachidonic acid metabolites which comprises prostacyclin's, prostaglandins (PGs) and thromboxanes [50]. Deregulated arachidonic acid metabolism is involved in chronic inflammation as well as carcinogenesis, which ultimately results in promoting tumor progression activities of the metabolic products which include PGs and leukotrienes [51]. Studies have demonstrated that in vitro and in vivo expressions of chemokine's, IL-8/CXC ligand CXCL8 and CXCL5 are regulated by COX-2 in NSCLC [52]. Another study has shown that COX-2 upregulates the expression of these chemokine's which leads to enhanced NSCLC cell growth and angiogenesis in vivo by means of activation and NF-κB nuclear translocation [53,54].

NF-κB signaling cascade promotes the proliferation of cells through activation of cyclin D1 gene by binding with cyclin D1 promoter [55,56]. It is well known that, Cyclin-dependent kinases (cdks) plays a vital role in cell cycle regulation which are modulated by binding with cyclins proteins [57]. Cyclin D binding, encoded by the CCNDl gene to cdk6 and cdk4 leads to the phosphorylation of the retinoblastoma (Rb) proteins. This Rb phosphorylation prevent it from supressing E2F family transcription factors which therefore leads to transcription of numerous genes which is prerequisite for the cell cycle event G1-to-S phase transition, thereby promoting cellular proliferation [58–60]. Therefore, the inhibition of NF-κB has been suggested to reduce the action of cyclin D1, which is also associated with delayed retinoblastoma (Rb) protein phosphorylation, which in turn results in deregulated cell-cycle progression that can be rescued by ectopic expression of cyclin D1 [55,56]. The Bcl-2 proteins (family of proto-oncogenes) is a negative regulator of apoptosis process and is often said to be impaired in various type of cancers. The promoter of human Bcl-2 [61–63] and inhibitors of apoptosis (IAPs) [64,65] has been identified to exert an NF-κB binding site which confer resistance to apoptosis process which was induced by the TNFα. Therefore, NF-κB activation in cancer cells during the chemotherapy or radiation therapy is predominantly linked with resistance to apoptosis which is considered as major preventive factor for effective cancer treatment [64–66].

In cancer cells, NF-κB signalling cascade also contribute to formation of blood vessels process (i.e., angiogenesis) through modulation of main pro-angiogenic factor known as vascular endothelial growth factor (VEGF) and one of pro-inflammatory cytokine IL-8 [67,68]. Studies shown blocking NF-κB by administration of antisense oligonucleotide inhibited the TNF-α-induced IL-8 and production of VEGF, along with tubular morphogenesis inhibition in vascular endothelial cells and thereby decreased in tumorigenicity [69–71]. Promotion of metastasis is an important phenomenon of cancer cells [72]. NF-κB induced production of VEGF is capable of provoking the vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1

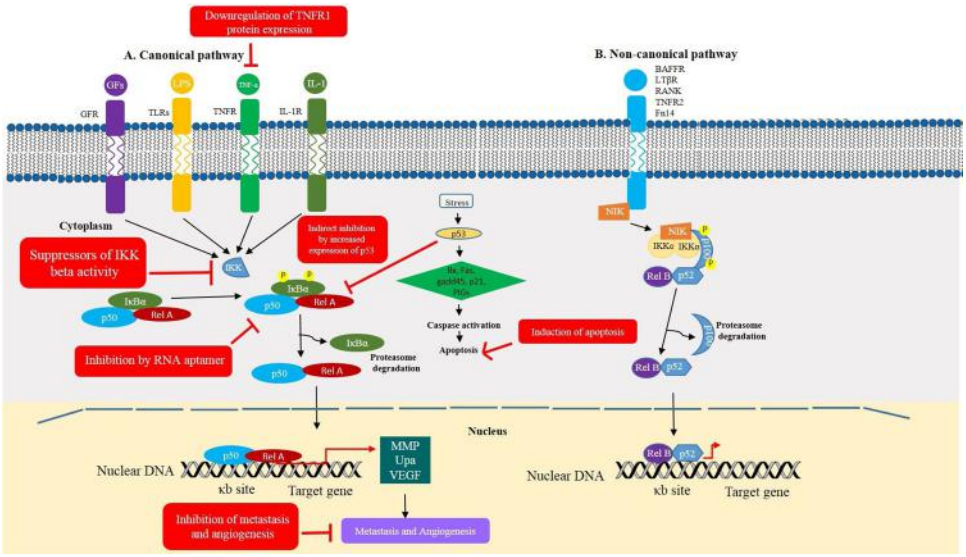

Fig. 3. Inhibition of NF-κB signalling pathway mediated either directly or indirectly by several therapeutic targets and their mechanism of action. Blocking, a key molecular target involved in the regulation of NF-κB transcription mainly by proteasome inhibiton and covalent modification of the enzymes has been reported. TNF-induced NF-kappaB inhibition acts by downregulation of TNFR1 protein expression. RNA oligonucleotides that bind to p50 with high affinity has shown to inhibit NF-κB pathway. Indirect inhibition by increased expression of tumor suppressor p53 thereby promoting apoptosis is specific to certain therapeutic agents. MMP, Upa and VEGF protein which lead to metastasis and angiogenesis are transcribed by NF-κB pathway. Inhibition of NF-κB results in downregulation of the genes thereby inhibiting the metastatic and angiogenesis property of cancer cells. Blocking NF-κB signaling pathway may also help sensitize cancer cells to TNF-related apoptosis- inducing ligand and block XIAP thereby promoting apoptosis in cancer cells.

(ICAM-1) and E-selectin expression [69] which in combination with other regulators such as proteolytic enzymes include MMPs (specifically MMP-9 & MMP-2) cooperate in the epithelial-mesenchymal transition (EMT) process for the progression of tumor metastasis [73–75]. Therefore, suppressing NF-κB activation will help to reduce tumor metastasis.

5. Cancer therapeutic agents targeting NF-κB in lung cancer

Since NF-κB has a convinced role in the initiation and progression of cancer, use of NF-κB inhibitors in the therapeutics of various cancer has been well documented by several researchers globally. Inhibition of NF-κB signalling by diverse methods has been shown to support or enhance the effectiveness of chemotherapeutic agents as depicted in Fig. 3.

5.1. Suppressors of IKK beta activity

IκBα is a significant molecular target involved in NF-κB transcription factors regulation during the inflammatory responses. Upon stimulation of IκBα, it is phosphorylated rapidly by the IKK, leads to ubiquitination and as well as subsequent degradation of IκBα followed by NF-κB nuclear translocation process. Once NF-κB is translocated in to the nucleus, it can positively regulate the expression of various genes which is mainly involved in the immune system function as well as inflammatory response, including IL-8, *IL-12* andTNFα. Several researchers have shown that NF-κB-DNA binding is inhibited by numerous therapeutic targets mediated by an effective mechanism that involves the downregulation of IKK expression. Proteosome inhibitors like bortezomib, carfilzomib, proteosome inhibitor 1 (PS1) and MG132 modulate NF-κB pathway [76–79]. Bortezomib is one of the first ever proteosome inhibitor approved by Food and Drug Administration (FDA) for treatment of cancer. Randomized clinical phase I and II trials have shown that Bortezomib exerts minimal activity in treatment of lung cancer in advanced clinical cases of NSCLC patients. However, bortezomib when combined with the additional cytotoxic agents like erlotinib, showed modest/insufficient activity [80,81]. Another class of proteosome inhibitor, carfilzomib (epoxyketone-based proteasome inhibitor) act specifically through targeting chymotrypsin-like (CT-L) activities of the constitutive immunoproteasome by a mechanism which is different from that of bortezomib. Carfilzomib unlike bortezomib has marginal off-target effects on non-proteasome and serine proteases which therefore may provide potent antitumor response. Studies have shown that the drug possess anti-proliferative action against lung cancer cell lines and also showed considerable survival advantage in SHP77 xenografts in vivo [82]. Another combination study of bortezomib along with gemcitabine hydrochloride resulted in enhanced expression of p21 and p53, further mediated by inducing S-phase & G2/M cell-cycle event arrests, respectively [83]. Combination studies of carfilzomib along with irinotecan has shown enhanced antitumor efficacy which regulates through enhanced apoptosis process and non-cross reactive mechanisms and also interference with degradation of topoisomerase-I (topo-I) in lung carcinoma [84]. Some of the drugs approved by FDA and those that are undergoing clinical trials are depicted in the Table 1 and their corresponding structure is shown in Fig. 4.

Clinical trials have reported that a combination of bortezomib and pemetrexed is tolerable at recommendation of the clinicians which is generally administered as single-agent doses for patients with advanced solid tumors like NSCLC [85]. Combination of bortezomib and chemotherapy drug, topotecan has shown to kill tumour cells. Topotecan has been shown to be involved in down regulation of the target enzyme, topoisomerase thereby stabilizing the action of bortezomib [86].

Aspirin, sodium salicylate and sulindac, classical example of non-steroidal anti-inflammatory drugs (NSAIDs) act through regulation of the mediators of inflammation namely COX-1 and COX-2. These targets also act by blocking the NF-κB pathway via inhibition of proteosomal degradation of IκB [87] thereby enhancing TNF-mediated apoptosis in lung cancer cells by inhibiting nuclear translocation of NF-κB and also interfere with DNA binding proteins [88,89]. Some of the compounds like doxorubicin, vinblastine and vincristine has been shown to be involved in phosphorylation and degradation of IκB by elevated level of protein kinase C in A549 human lung adenocarcinoma cell lines [90]. Sulfasalazine is also proven to inhibit TNF-α or 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced activation of NF-κB and enhance doxorubicin-induced cytotoxicity in a panel of human lung cancer cell lines [91,92]. Thalidomide mediates suppression of TNF-α-mediated phosphorylation of IKK as well as p65 and its nuclear translocation, and further binding with ICAM-1 promoter results in down-regulation of expression of ICAM-1, and inhibition of tumor cell invasiveness and metastasis [93]. However, studies of Phase II & III clinical trials failed to show significant survival advantage using this thalidomide in treatment of stage III/IV lung carcinoma [94]. Another NSAID, Nifedipine which is known as calcium channel blocker, is also shown to inhibit activation of NF-κB in lung cancer cells and macrophages stimulated through IL-1beta, TNF-α and TPA by suppressing IκBα

Table 1
Some of the NF-κB inhibitors of lung cancer in clinical trials/approved [142].

Compound name	Type	Institute / Company / Brand name	Target(s)	FDA approved / phase of development
Bevacizumab [118]	Recombinant humanized monoclonal antibody	Avastin	VEGF via NF-κB	FDA approved
Bortezomib [77,80,81]	Proteosome inhibitor	Velcade	NF-κB	FDA approved
Doxorubicin Hydrochloride [90]	Antineoplastic agents	Adriablastin	NF-κB	FDA approved
Carfilzomib [82]	Proteosome inhibitor	Kyprolis	NF-κB	Phase I/II trial
Erlotinib Hydrochloride and Quinacrine Dihydrochloride [117]	Tarceva - 9-aminoacridines (SN-390)	Seidman Cancer Center	NF-κB	Phase I
Bortezomib and Pemetrexed Disodium [85]	Proteosome inhibitor - multi-targeted antifolate	University of California	NF-κB	Phase I/II trial
Bortezomib and Topotecan [86]	Proteosome inhibitor – Topoisomerase inhibitor	National Cancer Institute	NF-κB and Topoisomerase	Phase I
Bortezomib and Gemcitabine [83]	Proteosome inhibitor – Antineoplastic agents	Masonic Cancer Center	NF-κB	Phase I
Carfilzomib and Irinotecan [143]	Proteosome inhibitor – Topoisomerase inhibitor	Cancer Research and Biostatistics Clinical Trials Consortium	NF-κB and Topoisomerase	Phase I/II trial

*Inhibitor clinical development information current as of Feb 2020 from the United States National Institutes of Health registry clinical trials and National Institute of health [Available from: http:// www.clinicaltrials.gov and https://www.cancer.gov/about-cancer/treatment/clinical-trials].

degradation mediated through IKK and subsequently suppressing the expression of MMP-9 and its activity [95–97].

Researchers have shown that a lipid peroxidation byproduct, 4-hydroxy-2- nonenal inhibits the activity of IKK and subsequently mediates suppression of phosphorylation and degradation of IκBα in H1299 lung carcinoma cell line [98]. Aurora-A kinase belonging to the class of serine/threonine kinases that function in mitosis has shown to be overexpressed in several types of cancer. Inhibition of Aurora-A suppressed NF-κB activity in A549 lung cancer cells has been reported after administration of the following compounds such as cisplatin, epotoside and adriamycin [99]. In normal conditions, molecular chaperones like Heat shock protein 90 (Hsp90), is found to stabilizes a wide variety of proteins include IκB. Pre-treatment of lung cancer cells with 17-allylamino-17-demethoxygeldanamycin (17-AAG), a Hsp90 inhibitor targeted IκB protein for degradation and consequently suppression of TNFα-mediated NF-κB activation [100]. Researchers have shown that epidermal growth factor (EGF) receptor can activate NF-κB as well as NF-κB regulated various gene expression through a different pathway unlike mediated by TNFα. This study demonstrates that, treatment with EGFR inhibitors may suppress the proliferation of NSCLC cells with mutations activated by EGFR mediated through the suppression of ligand-independent activation of NF-κB [101].

Studies have shown that by silencing Sphingosine kinase-1 (SPHK1) expression or by inhibiting the effect of SPHK1 with its inhibitor namely SK1-I, induced apoptosis in NSCLC cells both in vitro and in vivo possibly by attenuation of PI3K/Akt/NF-κB pathway. The results highlighted that activation by phosphorylation of IκBa and IKK predominantly increased in NSCLC cells with SPHK1 overexpression and diminished in SPHK1-knockdown cells as well as in SK1-I–treated cells [102]. Another inhibitor of NF-κB activator, BAY-11-7085 along with suberoylanilide hydroxamic acid (SAHA) which is a histone deacetylase inhibitor resulted in increase in apoptosis and cell death in tumorigenic NSCLC cell lines such as H358, H460, A549, H1299 and H157 [103].

A specific IKKβ inhibitor BMS-345541 or shRNA enriched erlotinib-induced apoptosis in erlotinib-sensitive as well as erlotinib-resistant EGFR-mutant lung cancer models mediated through inhibiting RELA phosphorylation in H1650 cells. IKKβ knockdown resulted in decreased NF-κB phosphorylation mediated by increased levels of Ikβ proteins [104].

5.2. Downregulation of TNFR1 protein expression

TNF is a pleiotropic pro-inflammatory cytokine which is mediated by TNF receptors (TNFRs) [TNFR1 (p60), and TNFR2 (p80)], which plays a vital role in induction of other cytokines and cell proliferation [105,106]. Both TNFR1 & TNFR2 involved in activation of NF-κB is linked with cellular activation, differentiation, cell survival and as well as cytokine production [105–107]. N-(4-Hydroxyphenyl) retinamide (a synthetic retinoid) has been potent to suppress TNF-induced NF-κB activation in H1299 cells [108]. Another compound suberorylanilide hydroxamic acid (SAHA, histone deacetylase inhibitor) was found to inhibit NF-κB activation in NSCLC cells, and also to inhibit growth of A549 tumor xenografts mediated via down regulation of TNFR1 protein expression in athymic nude mice [109].

5.3. Inhibition by RNA aptamer

RNA aptamers are short, single stranded RNA oligonucleotides that bind to a specific target with structural recognition i.e., high affinity and specificity, comparable to how an antibody binds to an antigen [110]. RNA aptamer that specifically target NF-κB (p50) was designed using adevnovirus delivery system and this aptamer was revealed to inhibit NF-κB activation in A549 cell line and as well as in A549-derived xenografted tumor growth both in vitro and in vivo condition respectively [111].

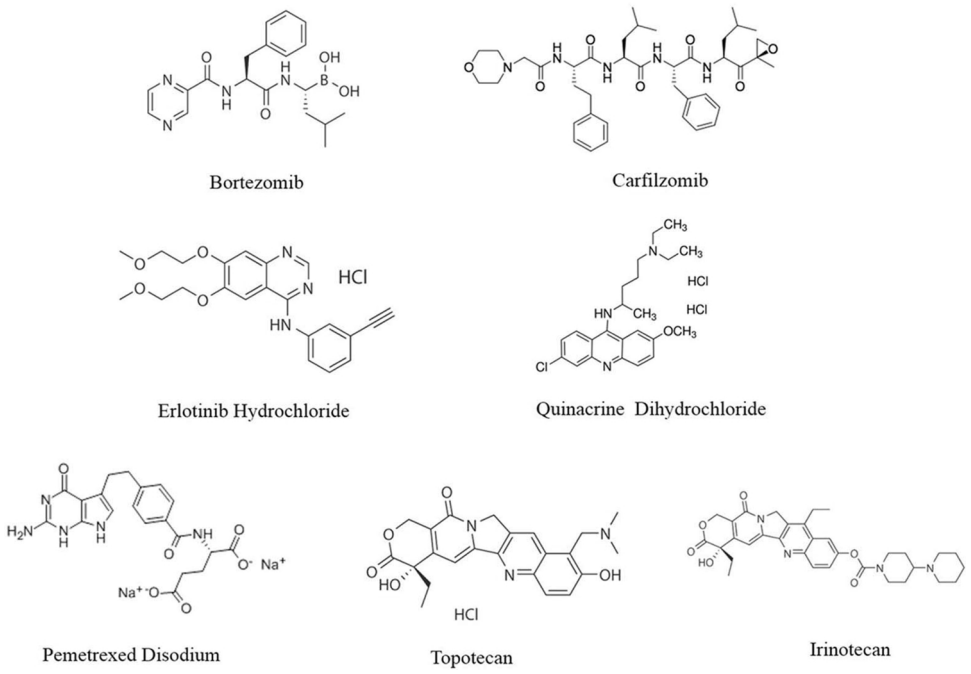

Fig. 4. Structures of some representative small molecule NF-κB inhibitors used in lung cancer therapy.

5.4. Indirect inhibition by increased expression of p53

Tumor suppressor p53, (encoded by the p53 gene, chromosome location: 17q13.1) is associated with the induction of apoptosis mechanism as well as cell cycle arrest [112,113]. Conversely, activation of NF-κB is commonly linked with the development of resistance to apoptosis process [114]. Therefore, it is well known that the tumor suppressor p53 and NF-κB have reciprocal inhibitory action. Antagonizing p53 mediated function by NF-κB has been well documented in chemoresistance of malignant cells [115]. Research has shown that in A549 human lung cancer cell line, nutlin-3 simultaneously increased the expression of p53 and repressed the expression of TNF induced NF-κB target genes MCP-1 and ICAM-1 [116]. Quinacrine belonging to the class of 9-aminoacridines are potent activators of p53 and inhibitors of NF-κB. Studies have demonstrated that inhibition of NF-κB by quinacrine sensitizes the NSCLC cells to erlotinib-induced cell death. Combination of erlotinib along with quinacrine was also shown to inhibit the FACT (facilitates chromatin transcription), the complex which is required for NF-κB transcriptional activity and cell-cycle progression in advanced NSCLC [117].

5.5. Inhibition of metastasis and angiogenesis

Bevacizumab (also known as Avastin), a humanized monoclonal antibody raised against VEGF was combined with standard first-line chemotherapeutics for treatment of stage IIIb and IV NSCLC [118]. Studies have demonstrated that plumbagin (5-hydroxy-2-methyl-14 naphthoquinone) inhibited TPA induced adhesion, invasion and migration in A549 cells. The compound also supressed the activation of the protein extracellular signal regulated kinase 1 and 2 (ERK 1/2) which is associated with downregulation of MMP-2 and urokinase-type plasminogen activator (u-PA) along with suppression of degradation of IκBα and NF-κB [119,120]. in vivo studies indicate that administration of rutin significantly decreased the tumour directed capillaries induced by B16F10 melanoma cells in C57BL/6 mice [84]. The compound α-Tomatine (steroidal glycoalkaloid) from *Lycopersicon esculentum* (tomato) suppressed invasion and migration of NCI-H460, human non-small cell lung cancer cells which is mediated by inhibition of degradation by dephosphorylation of the inhibitor of kappaBα (IκBα) and nuclear translocation of NF-κB [121]. Research in bioactive compounds such as β-carotene treatment in vivo has been shown to significantly reduce the number of tumor-directed capillaries. in vitro studies carried out in B16F-10 melanoma cells has shown that the main mechanism of action of β-Carotene treatment is mainly mediated by downregulation of the expression of matrix metalloproteinase (MMP-2 & MMP-9), prolyl hydroxylase and lysyl oxidase gene expression and upregulation of the expression of metalloproteinase (TIMP-1 and TIMP-2) [122]. Studies carried out in an active phenolic component amentoflavone derived from *Biophytum sensitivum* and Selaginella species has been shown that in A549 cells amentoflavone inhibited the degradation of inhibitory α subunit of NF-αB and further inhibited NF-κB translocation into the nucleus. Amentoflavone also down-regulated cyclooxygenase (COX)-2 and up-regulated the metalloprotease-1 and metalloprotease-2 expression thereby showing potent antimetastatic property [123,124].

5.6. Induction of apoptosis

Blocking NF-κB signalling cascade may also be responsible for cancer cells sensitizing to TNF-related apoptosis-inducing ligand (TRAIL or Apo2L). Researchers have shown that by complementary gene therapy modality (i.e.) combined treatment with Ad5hTRAIL and AdIKKβKA mediated promising apoptotic action of TRAIL-resistant A549 human lung cancer cell line, suggesting that combined dual gene therapy which involve exogenous TRAIL gene expression along with IKK inhibition may be an effective therapeutic modality for treatment of lung cancer [125]. X-linked inhibitor of apoptosis *(XIAP)* is one of the most effective member from IAP gene family to inhibit caspases and suppress the process of apoptosis. Studies have shown that antisense oligonucleotides (G4 AS ODNs) target the XIAP gene product and thus improving the efficacy of a cytotoxic agent VNB (a Vinca alkaloid) in NSCLC xenograft model. The probable mechanism of apoptosis induction is mediated by degradation of procaspase-3 and poly(ADP-ribose) polymerase proteins along with nuclear DNA condensation as well as fragmentation. Consecutive Cisplatin and Gambogic acid (CDDP-GA) treatment yielded in a robust synergistic action in following lung cancer cell lines NCI-H460, A549 and NCI-H1299. The mechanism of CDDP-GA is regulated by activation of caspase-3, -8 and 9, via increasing the expression of Fas and Bax which lead to decrease in the expression of

Bcl-2 (anti-apoptotic protein), XIAP and survivin in A549 & NCI-H460 lung cancer cell lines [126]. Certain compounds simultaneously act on other pathways along with inhibition of NF-κB to exert its action. For example, LGH00168 treatment increased the DR5 expression and decreased the expression of Bcl-2 and thereby inhibited the NF-κB pathway in A549 cells [127].

5.7. Natural compounds and their diverse mechanism

Several studies have shown that dietary components such as polyphenols, terpene, alkaloids and phenolic from different fruits and vegetables have shown anti-proliferation, pro-apoptotic, anti-angiogenic as well as anti-metastatic action. NF-κB is most recurrent targets of these above mentioned phototherapeutics [128]. Some of the dietary compounds were also reported to possess NF-κB suppression activity in lung cancer cells which include curcumin and its derivatives, resveratrol and its derivatives, epigallocatechin, genistein, flavopiridol, deguelin, gallic acid, luteolin, silibinin, parthenolide, anthocyanin, dehydroxymethylepoxy quinomicin and quinoclamine [129–131]. Several studies on crude extracts derived from strawberry, *Punica granatum*, deer berry and potato sprouts have found to possess NF-κB suppression action [132,133]. Among several natural products/medicinal plants, suppression of NF-κB activation in lung cancer cells were exposed in Triptolide derived from *Tripterygium wilfordii* (Chinese herb) [134], Zyflamend derived through a polyherbal preparation [135], herbal mixture PS-SPES [136], ursolic acid from cranberries and apples [137], embelia derived from *Embelia ribes* [138], Coix seed extract [139], methysticin from Kava [140] and phenanthrene-based tylophorine derivatives from Tylophora genus [141].

6. Challenges in translating NF-κB targeted therapies

One of the major challenges faced during administration of NF-κB inhibitors for lung cancer therapeutics is general safety as well as efficacy. Blocking or deregulation of NF-κB signalling may compromise immunity. Apart from cancer development numerous other factors such as eventual infection by microbes or physical and chemical damages may cause damage to the body [144]. As a consequence systemic administration of NF-κB inhibitors may deteriorate the immune function or response. Another crucial factor for consideration is the careful optimisation of doses and schedule of drugs [145–147].

Studies have reported about another pivotal role of NF-κB cascade (i.e) it may exert tumor suppressor function in other organs. This contradictory effect can occur at various stages of cancer which are probably linked with different chemical carcinogens and altered genetic makeup of the individuals. The consequence of NF-κB activation is dependent up on the different cell types, the type of stimulus it receives and also the mode of activation [148–150]. This dual action of NF-κB is a delineating factor in the systemic administration of broad spectrum inhibitors of NF-κB for the cancer therapeutics and researchers suggests to design improved therapeutics which can specifically activate the pro-apoptotic effect of NF-κB [151,152]. Another crucial aspect of consideration for using NF-κB inhibitors is a thorough understanding of the cancer stage or the treatment phase. At present, NF-κB inhibitors such as bortezomib and carfilzomib are some of the potent therapeutically useful drugs in the market [153]. Another important limitation is the latent off-target effect of the inhibitors of NF-κB. For example, bortezomib (proteosome inhibitor) activity does not limit to NF-κB action alone, rather it causes building-up of other proteins which are degraded by the proteasome machinery [154].

7. Conclusion and perspectives

Recent research progress in understanding many facets of NF-κB signalling cascade, have demonstrated a strong support for the possible interactions of NF-κB signaling in lung tumorigenesis. This review helps us to increase our understanding about the linkage of the transcription factor NF-κB associated with lung tumorigenesis, multiple mechanisms of aberrant activation or dysregulation of NF-kB signalling and details pertaining to several therapeutic agents targeting NF-κB signaling in lung tumorigenesis. Highly selective monoclonal antibodies have also shown potent action through inhibition of NF-κB signalling in lung cancer alone or in combination with other anti-proliferative agents. However, it is clear that, more detailed understanding about the mode of action of promising inhibitors/agents that are target specific needs to be further addressed in upcoming studies in order to decipher new insights and understanding into the specific design or development of drugs that effectively inhibit the NF-κB activity in lung cancer. Ultimately, this information provides novel therapeutic strategies for the treatment and management of this devastating lung cancer disease.

Declaration of Competing Interest

No conflict of interest.

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