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REVIEW

Targeting NF-κB and HIF-1 Pathways for the Treatment of Cancer: Part I

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Abstract The process of chronic inflammation is a common link which connects different kinds of environmental pollutants and infections with tumorigenesis. Transcription factor NF-κB is a common final target for many inflammatory and cell proliferation pathways, independent of the source of stimuli (e.g., cytokines, growth factors, environmental carcinogens, radiation, hypoxia, bacteria, and viruses). Overactivation of NF-κB has been confirmed in many tumors, resulting in worse prognosis for patient survival. Therefore, inhibition of cellular pathways for NF-κB activation is nowadays considered as a promising anti-cancer therapy and is extensively studied in clinical trials, or even has been adopted as an approved therapy in some kinds of cancer.

Keywords NF-κB inhibitors · Cancer · Treatment

Abbreviations

Akt	Serine/threonine protein kinase
cIAP2	Inhibitor of apoptosis protein 2
COX-2	Cyclooxygenase-2
CTR1	Copper transporter-1
CXCL	CXC motif chemokine ligand
HIF	Hypoxia-inducible factor
HSF1	Heat shock factor-1
HSR	Heat shock response
ICAM-1	Intercellular adheson molecule-1
IKK	IκB kinase
IκB	Inhibitor of NF-κB
MALT1	Mucosa-associated lymphoid tissue lymphoma translocation protein 1
MMP	Matrix metalloproteinase
NEMO	NF-κB essential modulator
NF-κB	Nuclear factor κB
NIK	NF-κB-inducing kinase
NSAIDs	Non-steroid anti-inflammatory drugs
PGE_2	Prostaglandin E_2
PI3K	Phosphatidylinositol 3-kinase
STAT-3	Signal transducer and activator of transcription 3
TAK1	Transforming growth factor-β-activated kinase-1
TNF	Tumor necrosis factor
TRAF	TNF receptor-associated factor
TRAIL	TNF-related apoptosis-inducing ligand
VEGF	Vascular-endothelial growth factor

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Introduction

Epidemiological analyses indicate that only one from every ten cancers originates as a consequence of either inherited or acquired mutations, while the rest of tumors are caused mostly by environmental and infectious factors (Aggarwal

et al. 2009). The process of chronic inflammation is a common link which connects different kinds of environmental pollutants and infections with tumorigenesis, and one of the most interesting and important aspects of this mechanism is intracellular inflammatory pathways based on the function of transcription factor NF-κB. Many pro-inflammatory and proliferation stimulants (e.g., cytokines, growth factors, chemical carcinogens, radiation) or bacterial and viral agents (e.g., hepatitis B/C, human papilloma, Epstein-Barr virus or *Helicobacter pylori*) are capable to activate NF-κB-dependent pathways. Similarly, various gene products engaged in tumor survival, proliferation, metastasis potential, and angiogenesis are regulated by NF-κB (Aggarwal et al. 2009; Beg and Baltimore 1996). NF-κB promotes expression of a wide range of proteins that suppress both the intrinsic and extrinsic pathways of apoptosis, including IAP1/2, XIAP, tumor necrosis factor (TNF) receptor-associated factor (TRAF)1, cFLIP, Bcl-2, Bcl-X_L, Bfl-1, and survivin (Fan et al. 2008; Luo et al. 2005). Therefore, upregulated NF-κB very efficiently protects cancer cells from apoptosis. Constitutive activation of NF-κB was shown in both laboratory tumor cell lines and solid as well as hematological cancers (Sethi et al. 2008b). Moreover, aberrant function of NF-κB could be provoked by chemotherapeutic agents (e.g., paclitaxel, doxorubicin, vinblastine, cisplatin) or radiation, which are commonly used for cancer treatment (Aggarwal et al. 2009; Aggarwal 2004). Thus, activation of NF-κB results in chemo- and radioresistance observed unfortunately in many patients (Ahn et al. 2007). Therefore, NF-κB is nowadays considered one of the most promising targets for anti-cancer therapy (Aggarwal et al. 2009; Sethi et al. 2008b). Even if the majority of evidence indicates pro-oncogenic activity of upregulated NF-κB, it should be mentioned, however, that under certain conditions, NF-κB can function as a tumor suppressor (Perkins 2004; Shishodia and Aggarwal 2004).

NF-κB Activation and NF-κB-Dependent Pathways

The NF-κB pathway is involved in many physiological processes such as immune responses, cell proliferation, cell death, and inflammation, but it is also thought to be a critical link between inflammation and cancer (Karin 2008). More than 200 different stimuli can activate NF-κB-dependent pathways (Pahl 1999). NF-κB transcription factors form a group of homo- or heterodimers composed of five NF-κB/Rel proteins. A dimer of p50 and p65 (RelA) subunits, which is the most common variant in cells, acts as a transcriptional activator. There are two signaling pathways activating NF-κB, the canonical and the alternative one. These pathways are activated by different stimuli and induce distinct NF-κB dimers (Ghosh and Hayden 2008; Scheidereit 2006; Shen and Hahn 2011). The p50/p65 dimer is stimulated along the canonical signaling pathway. In the inactive stage, the dimer is bound by inhibitory IκB proteins. Degradation of IκB is a prerequisite for NF-κB activation. It occurs in the proteasome after phosphorylation of specific serine residues of the IκB protein by IκB kinase (IKK) complexes and ubiquitination. The released NF-κB dimer is covalently modified, mainly by kinases, and transported to the nucleus. Shuttling of NF-κB between the cytoplasm and the nucleus is an important mechanism of transcriptional control by NF-κB (Tergaonkar et al. 2005). In the nucleus, NF-κB protein recruits chromatin remodeling proteins to the NF-κB target promoters. At this point, both interplay with chromatin regulators and with alternative binding sites are crucial for the control of specific responses. The pattern of gene expression also depends on changes in NF-κB activity due to cycles of degradation and re-synthesis of IκB. In this way, hundreds of genes involved in many physiological processes can be expressed in a tightly controlled fashion as the consequence of NF-κB activation (Ghosh and Karin 2002).

Several mutations are responsible for hyper-activation of the NF-κB pathway. NF-κB can be activated by oncogenic H-Ras expression, transforming proteins such as Vav, Pim-2 and B-Raf, and fusion proteins Bcr-Abl or MALT1/cIAP2 (Bassères and Baldwin 2006). NF-κB can be activated by different oncogenic signaling pathways, for example PI3 K/Akt, growth factors and growth factor receptors such as epidermal growth factor, platelet-derived growth factor and c-Kit receptor, and other activated transcription factors, for example STAT-3 or hypoxia-inducible factor (HIF)-1 (Bassères and Baldwin 2006; Scortegagna et al. 2008). NF-κB proteins when constitutively active lead to the development of inflammatory diseases, metabolic disorders, and many cancers (Baud and Karin 2009; Pikarsky et al. 2004). A number of genes involved in proliferation and cell invasion, as well as anti-apoptotic genes are upregulated by hyperactive NF-κB transcription factors to promote the oncogenic phenotype. NF-κB-dependent genes include those encoding cyclin D1, chemokines, cytokines matrix metalloproteinases (MMPs), and antiapoptotic proteins. In this way, disturbances in the NF-κB pathway can affect all cancer-associated mechanisms including self-sufficiency in growth, suppression of apoptosis, enhanced angiogenic properties, and ability to metastasize to distant sites. It is also well accepted that activation of NF-κB can contribute to resistance to chemo- and radiotherapy, due to prevention of tumor cells from apoptosis, enhancement of metastatic potential (through up-regulation of genes for MMPs and vascular cell adhesion molecule 1), and angiogenesis (through up-regulation

of NF-κB-dependent pro-inflammatory cytokines TNF-α, interleukin (IL)-1 and IL-6) (Naugler and Karin 2008).

Inhibitors of NF-κB Activation and NF-κB-Dependent Pathways

More than 785 inhibitors of the NF-κB pathway have been identified so far (Gilmore and Herscovitch 2006). Various steps along the NF-κB pathway are targeted by those drugs as shown in Fig. 1. The major pharmacological approaches to inhibit NF-κB include (1) repression of IKK activity, or (2) blocking the degradation of IκB by proteasome inhibitors.

Non-Steroid Anti-Inflammatory Drugs

There is growing evidence that non-steroid anti-inflammatory drugs (NSAIDs) could protect against colorectal cancer for which chronic inflammation is a considerable risk factor. Meta-analysis of population case–control studies indicated that NSAIDs users showed a 45% reduction in the risk of colorectal cancer (Din et al. 2004).

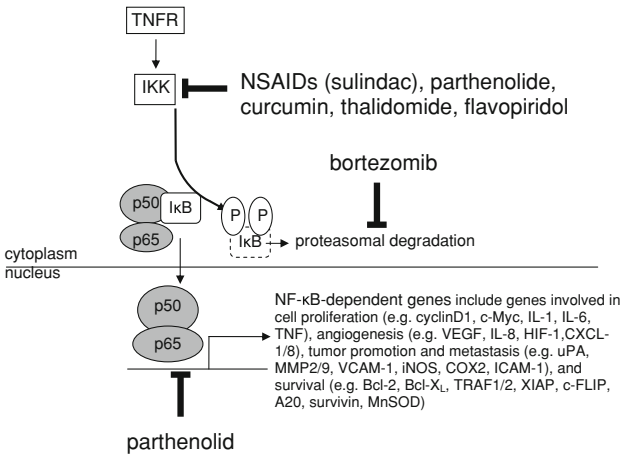

Fig. 1 Targeting the NF-κB pathway. In the canonical NF-κB pathway, dimers such as p50/65 are maintained in the cytoplasm by interaction with inhibitor IκB molecules, mainly IκBα. Binding of a ligand to a cell surface receptor, e.g., TNF receptor (TNFR), recruits adaptors to cytoplasmic domain of the receptor, which in turn attracts an IKK complex. Activated IKK phosphorylates IκB at two serine residues, which leads to its ubiquitination and degradation by the proteasome. Released NF-κB is further covalently modified, enters the nucleus where it binds to DNA and recruits chromatin remodeling enzymes to turn on target genes. Some of those genes involved in cancer development and progression are listed. The alternative NF-κB pathway is not shown. Several hundred inhibitors were demonstrated to target NF-κB pathway. Some of them are in various stages of clinical trails. Multiple steps along the NF-κB pathway were considered, although the major pharmacological approaches to inhibit NF-κB include (i) repression of IKK activity and (ii) blocking the degradation of IκB by proteasome inhibitors. Representative inhibitors of each category studied as potential anticancer drugs are shown

These results encouraged the study of NSAIDs' efficiency in protection against other cancer types, however, clinical trials showed disappointing results (Khuder and Mutgi 2001). Many popular NSAIDs including aspirin, ibuprofen, indomethacin, sulindac, and COXIBs are used to treat other diseases than cancer. Initially, their anti-cancer function was attributed exclusively to inhibition of cyclooxygenase (COX)-2 enzyme. Cyclooxygenase-2 is up-regulated by pro-inflammatory cytokines, HIF-1, and tumor promoters. A product of its enzymatic activity, prostaglandin E_2 (PGE_2), enhances NF-κB activity and inhibits tumor cell apoptosis. COX-2-derived PGE_2 is highly expressed in colorectal, gastric, and breast cancers (Wang and Dubois 2006). However, recent studies have shown that the protective effect of aspirin observed especially in colorectal cancer depends on deactivation of NF-κB signaling, by suppressing IKK activation. This contributes to blocking nuclear translocation of NF-κB and induction of apoptosis in cancer cells (Takada et al. 2004). The pro-apoptotic effects of aspirin were observed irrespective of COX-2 expression or aberrant activity of mutated β-catenin, p53, and DNA mismatch repair genes in colorectal cancer cells (Din et al. 2004; Din et al. 2005). Thus, it seems that the beneficial effects of aspirin are tissue-specific, independent on COX-2 inhibition, and restricted to colorectal tumors. Some other NSAIDs have also shown anti-NF-κB activity (Lee et al. 2007). Sulindac by inhibiting IKK activity induced regression of adenomas in patients who suffered from adenomatous polyposis (Takada et al. 2004), while celecoxib (the member of COXIBs drug family) supressed NF-κB factor via an IKK/Akt-dependent mechanism (Shishodia et al. 2004). Treatment of colon cancer cells with celecoxib, however, not only affected the NF-κB pathway but also increased the nuclear localization of active p53 (Swamy et al. 2003), and targeted the activity of pyruvate dehydrogenase kinase isozyme 1 and sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATP-ase (Schönthal 2007). Sulfasalazine, an anti-inflammatory NSAID used for treatment of chronic colon inflammatory diseases has recently been adopted for management of glioblastoma, due to its anti-IKK inhibitory potential (Robe et al. 2004).

Proteasome Inhibitors

The proteasome is an intracellular enzyme complex designed for degradation of proteins which have been marked by polyubiquitination. It plays a key role in the deactivation of cell signaling molecules, and dysregulation of its function usually results in apoptosis. IκB, the inhibitor of transcription factor NF-κB is one of the targets for the proteasome complex. Proteasome inhibitors are a novel class of drugs which have shown anti-cancer activity in both hematological and solid malignancies, and now

some of them have been adopted for clinical treatment. The best known agent from this group is bortezomib (Velcade®, PS-341) a dipeptidyl boronic acid capable of deactivating 26S proteasome by binding to its chymotrypsin-like active site (Dy et al. 2005). Bortezomib inhibits proteasomal degradation of IκB proteins leading to their accumulation inside cytoplasm and by this mechanism prevents NF-κB nuclear translocation. Both, increased cell apoptosis and decreased tumor chemoresistance result from bortezomib action. Moreover, it has also NF-κB-independent activity, mainly by stabilization of p53 and c-*myc*, or activation of c-Jun- and Fas-dependent pathways of apoptosis (Mitsiades et al. 2006). However, recent "in vitro" studies have put some doubt about the precise mechanism of bortezomib function, as bortezomib-dependent NF-κB inhibition could not be demonstrated in multiple myeloma cell lines. Instead, bortezomib was found to trigger paradoxical canonical activation of NF-κB (Hideshima et al. 2009). Possible mechanism of this phenomenon could be based on bortezomib-dependent activation of IKKβ, subsequent phosphorylation and degradation of IκBα, and translocation of p50/p65 into the nucleus. IKKβ inhibitors could stop this pathway; therefore, they are now considered as attractive enhancers of bortezomib cytotoxicity (Hideshima et al. 2009).

Nevertheless, on multiple myeloma cell-line cultures and bone marrow samples, bortezomib showed synergistic effects with chemotherapeutic agents, even in chemoresistant cases (Hideshima et al. 2001). Animal studies performed on a murine xenograft model of multiple myeloma showed that bortezomib provoked inhibition of tumor growth accompanied by increased tumor apoptosis and diminished vascular supply. This treatment significantly prolonged survival of experimental animals (LeBlanc et al. 2002). Based on the encouraging results of preclinical studies, the feasibility of bortezomib was checked in clinical trials performed initially on patients with refractory multiple myeloma, and further as a front-line management of this malignancy (Ludwig et al. 2005). The efficacy of the treatment was determined according to European Group for Blood and Marrow Transplantation criteria, and estimated regimens of bortezomib monotherapy (Richardson et al. 2004) or combined therapy using bortezomib with dexamethasone (Jagannath et al. 2005) or melphalan (Berenson et al. 2004), pegylated liposomal doxorubicin (Orlowski et al. 2005), and thalidomide (Zangari et al. 2004). Tested doses of bortezomib varied from 0.7–1.9 mg/m^2 and were characterized with acceptable and manageable toxicity including thrombocytopenia, peripheral neuropathy, fatigue, rash, nausea, and electrolytic disturbances concurrent with increase of the dose (Dy et al. 2005; Ludwig et al. 2005). Successful treatment was reported especially in first-line therapy in patient groups where bortezomib was combined with other drugs. The special role which bortezomib could play in therapy of multiple myeloma is based on the evidence of two types of mutations in genes encoding regulators of NF-κB signaling pathway. The first type of mutations leads to augmentation of function of positive regulators of that pathway, including NF-κB-inducing kinase (NIK), NF-κB1, NF-κB2, and receptors of the TNF receptor superfamily. The second type of mutations results in loss of proper function of negative regulators of the NF-κB signaling pathway, like TRAF and inhibitor of apoptosis proteins (Annunziata et al. 2007). Altogether, these mutations activate NF-κB signaling and promote growth of myeloma. Gene expression profiling revealed that some multiple myeloma cells are more sensitive to bortezomib than others, which could be correlated with outcome of clinical trials (Mulligan et al. 2007). Therefore, a subset of myeloma patients in which components of NF-κB signaling pathway are mutated seem to be the perfect target for anti-NF-κB therapy, while non-mutated patients will benefit less from this type of treatment. At present, two second-generation proteasome inhibitors: carfilzomib (PR-171) and salinosporamide (NPI-0052) are being tested. Compared with bortezomib they are irreversible inhibitors of the proteasome and possess oral bioavailability, lower toxicity, and demonstrate activity in part of patients refractory to bortezomib therapy (reviewed in Mitsiades et al. 2009).

The efficacy of bortezomib treatment was also investigated in other hematological malignancies, including patients with leukemia expressing constitutively Bcr/Abl tyrosine kinase, particularly in imatinib-resistant cases (Gatto et al. 2003). Bortezomib monotherapy indicated also complete and partial response in 20 and 100% patients with recurrent Hodgkin and B-cell lymphomas or mantle-cell and marginal-zone lymphomas, respectively (O'Connor et al. 2005).

Simultaneously with hematological cancer, bortezomib was tested in solid tumors. First preclinical studies showed its efficacy in cell lines of many different human cancers, including lung, prostate, ovarian, breast, colorectal, pancreatic, hepatocellular, and head/neck carcinoma (Denlinger et al. 2004; Frankel et al. 2000; Höpfner et al. 2008; Kondagunta et al. 2004). In all reported studies, bortezomib was found to arrest the cell cycle, to reduce the Bcl-2 and Bcl-X_L expression, to stabilize p53, p21 and p27, as well as to enhance chemotherapy-induced apoptosis (Ludwig et al. 2005). Inhibition of HIF-1 transcriptional activity and vascular-endothelial growth factor (VEGF) production under hypoxic conditions were additional benefits brought by the use of bortezomib (Birle and Hedley 2007). Similar results with improved survival and reduction of tumor size were obtained on murine tumor xenograft models (Williams et al. 2003). During preclinical studies bortezomib also

demonstrated its efficacy in combination with chemotherapeutics for the treatment of tumors refractory to standard cytotoxic drugs. In chemotherapy-resistant melanoma tumors studied in vitro and in xenografted mice, satisfactory induction of apoptosis was obtained by a combination of synthetic retinoid fenretinide and bortezomib (Hill et al. 2009). Commonly known, part of ovarian tumors resistance to cisplatin originates from the fact that cisplatin induces the degradation of copper transporter-1 (CTR1), which is a major influx transporter of platinum drugs to the cell. An in vitro study on ovarian cancer indicated that bortezomib is able to increase cisplatin concentration inside tumor cells and thus augment its cytotoxicity through blocking of cisplatin-induced CTR1 degradation (Jandial et al. 2009). Phase I and II clinical trials performed in advanced or refractory solid tumors showed only moderate anti-tumor efficacy independently of bortezomib monotherapy or combination therapies with different chemotherapeutics. No complete response was reported and partial response rates or stabilization of the disease were hardly moderate (Davis et al. 2004). A phase I trial on the combined use of bortezomib with temozolomide and concurrent radiotherapy in patients with recurrent and newly diagnosed high-grade gliomas proved safety of the used protocol. However, despite promising results in the group of patients receiving the highest doses of bortezomib, a phase II trial to characterize efficacy of such therapy is awaited (Kubicek et al. 2009). Another phase I study to evaluate the toxicity of bortezomib, etoposide, and carboplatin in different advanced solid tumors did not show any complete remission, but transient stabilization was obtained in 37.5% of patients (Lieu et al. 2009). A phase II study in patients with advanced and/or metastatic breast cancer treated with a combination of docetaxel with bortezomib showed a response rate of 38% in the group of patients treated with the maximal tolerated doses of both drugs, with an average progression free time of 5.4 months (Awada et al. 2008). Another phase II study of bortezomib in combination with gemcitabine and carboplatin as a first-line treatment of advanced non-small cell lung carcinoma (NSCLC) showed, that the median overall survival of patients was 11 months, however, only 19% of them survived 2 years while progression free survival was 5 months (Davies et al. 2009). A randomized phase II study comparing docetaxel/cetuximab and docetaxel/bortezomib in patients suffering from NSCLC revealed that neither combination gave satisfactory results (Lilenbaum et al. 2009). Even more disappointing conclusions were drawn from a study of bortezomib in combination with 5-fluorouracyl and radiotherapy for the treatment of locally advanced or metastatic rectal cancer. The authors concluded that the clinical applicability of the protocol is limited and that samples of the tumors did not show any evidence of NF-κB gene suppression (O'Neil et al. 2010). In conclusion, despite the fact that bortezomib was approved for treatment of multiple myeloma and mantle-cell lymphoma, its common use for therapy of solid tumors is still under extensive clinical investigation.

IκB Kinase-Dependent Pathway Inhibitors

Curcumin (chemically diferuloylmethane) is a polyphenolic antioxidant isolated from the rhizomes of turmeric plant (*Curcuma longa*) (Aggarwal et al. 2006; Bachmeier et al. 2008; Shankar et al. 2008). It is a component of Asiatic spices and known anti-inflammatory agent used in traditional medicine. Its anti-inflammatory action is multidirectional, and similarly its anti-cancer activity combines suppression of proliferation, angiogenesis, metastasis, and invasiveness. The mechanism of curcumin's anti-cancer activity was found to be based first on inactivation of TNF-induced NF-κB-dependent gene expression through inhibition of IKK complex (canonical pathway of NF-κB activation depending of IKKβ and NF-κB essential modulator NEMO), and second on inhibition of Akt activity (Aggarwal et al. 2006). However, not every study confirmed the inhibitory activity of curcumin on the Akt-pathway (Wang et al. 2008), and it seems that this phenomenon may depend on the histologic type of tumor. Curcumin suppressed also TNF-induced NF-κB-dependent gene expression induced by NIK, what suggests inhibition of noncanonical, IKKα-dependent NF-κB activation (Aggarwal et al. 2006; Israël 2010). There are plenty of NF-κB-dependent gene products which have been found to be inactivated simultaneously by curcumin (reviewed in Ravindran et al. 2009). This group includes factors engaged in tumor proliferation (e.g., COX-2, cyclin D), angiogenesis (VEGF), metastasis (MMP-2 and MMP-9, adhesion molecule ICAM-1), and defense against apoptosis (inhibitors of apoptosis IAPs, Bcl-2, Bcl-X_L) (Aggarwal et al. 2006). It was also found that curcumin abrogates the potential of breast cancer cells to metastasize to the lungs through inhibition of CXC motif chemokine ligands (CXCL)-1 and CXCL-2 (Bachmeier et al. 2008). Additionally, the inhibitory effect of curcumin on IKK resulted in the inhibition of IL-6 and IL-8 RNA synthesis (Cohen et al. 2009). Attempts to sensitize tumor cells to TNF-related apoptosis-inducing ligand (TRAIL)-dependent death, have led to the use of curcumin as pro-apoptotic modulator. Mice xenografted with TRAIL-resistant prostate cancer LNCaP tumors showed a decrease of tumor growth, metastases, and angiogenesis due to curcumin induced up-regulation of TRAIL-R1 and -R2 receptors, pro-apoptotic proteins Bax and Bak, and cell-cycle inhibitors p21 and p27 (Shankar et al. 2008). Curcumin proved also its efficacy in animals xenografted with head and neck squamous cancer without demonstrable toxicity (Wang et al. 2008), and potentiated

therapeutic effects in nude mice treated with thalidomide and bortezomib for chemoresistant multiple myeloma (Sung et al. 2009). Observations concerning the initial efficacy and safety of curcumin in prevention and treatment of cancer should be confirmed in clinical trials using curcumin or its standardized drug BCM-95®CG (Biocurcumax™) (Antony et al. 2008). Recently, in a phase II clinical trial, curcumin was found to be beneficial for patient with advanced pancreatic cancer (Dhillon et al. 2008).

Besides curcumin, also other IKK inhibitors have been tested in anti-cancer treatment. One of them is pinitol (3-*O*-methyl-chiroinositol), an active component of the Ayurvedic medicament talisapatra (Sethi et al. 2008a). Pinitol acts both through inhibition of IκBα phosphorylation/degradation and suppression of TNF-induced IKK activation. Inhibition of IKK function is probably mediated through modulation of upstream transforming growth factor-β-activated kinase-1 (TAK1); therefore, pinitol acts as inhibitor of canonical NF-κB activation pathway. Pinitol also inhibits nuclear translocation of p65. Pinitol enhanced TNF-induced apoptosis and augmented cell death in response to chemotherapeutic drugs (Sethi et al. 2008a). A similar mechanism of action was observed for another plant-derived compound, fisetin. Chemically, fisetin is a flavonol (3,7,3′,4′-tetrahydroxyflavone) found in the smoke tree (*Cotinus coggygria*) and some fruits and vegetables (Sung et al. 2007). It was recently demonstrated that fisetin increased the expression of IκBα in cytoplasm which was accompanied by inhibition of NF-κB level and activity in the nuclei (Li et al. 2011). Both agents, pinitol and fisetin, were shown to down-regulate proliferation, invasion and angiogenesis, as well as to up-regulate apoptosis of cancer cells in vitro (Sethi et al. 2008a; Sung et al. 2007), including prostate, colon, and liver cancer cells (Chen et al. 2002; Haddad et al. 2006; Lu et al. 2005). The next member of plant-derived IKK inhibitors is coronarin D, diterpene (E-labda-8(17),12-diene-15-ol) isolated from *Hedychium coronarium*, a plant used in traditional Indian medicine as anti-inflammatory drug. The exact mechanism of IKK suppression by coronarin D is unclear and could depend both on upstream kinase inactivation (suppression of the canonical pathway) and direct inhibition (probably suppression of the noncanonical pathway). Coronarin D inhibited pathways of NF-κB activation induced by IL-1, lipopolysaccharides, prooxidants and carcinogens, and was shown to potentiate the cytotoxic effects of chemotherapeutics against different cancer cell lines in vitro (Kunnumakkara et al. 2008). Substantial evidence was collected for the anticancer potential of other natural products, sesquiterpene lactones, derived from *Tanacetum parthenium.* One of them, parthenolide and its orally bioavailable dimethylamino derivative, were found to inhibit proliferation of various cancer cells by inducing apoptosis and necrosis in vitro mainly but not exclusively via inhibiting NF-κB pathway (Anderson and Bejcek 2008; Czyz et al. 2010; Duechler et al. 2008; Wen et al. 2002). Parthenolide is an especially promising anticancer drug candidate since it exerted potential to target either cancer stem cells or progenitor cells of cancer (Guzman et al. 2005; Zhou et al. 2008). Parthenolide inhibits NF-κB activity via targeting the IKK complex as first observed in HeLa cells (Bork et al. 1997) and suppresses NF-κB DNA-binding via the direct modification of the p65 subunit (García-Piñeres et al. 2001). Stimulation of human bronchial epithelial cell lines from patients suffering from cystic fibrosis with TNF/IL-1β demonstrated that degradation of IκBα was prevented by parthenolide; however, neither TNF/IL-1β stimulation nor parthenolide treatment had any influence on IκBβ status. Therefore, it seems that parthenolide functions mainly as inhibitor of the noncanonical NF-κB activation pathway (Saadane et al. 2007). Targeting IKKs is also one of the major mechanisms of flavopiridol and R-roscovitine (CYC202, selicilib), two drugs classified as cyclin-dependent kinase inhibitors, which demonstrated potential as anti-inflammatory and anti-cancer compounds (Dey et al. 2008; Takada and Aggarwal 2004). In a xenograft model, R-roscovitine has been combined with erlotinib and showed significantly greater activity than either agent alone (Fleming et al. 2008). Among the drugs initially studied as IKK inhibitor is evodiamine isolated from the fruit of *Evodia rutaecarpa* and traditionally used in Chinese medicine. Evodiamine was found to inhibit both constitutive and induced NF-κB activation through suppression of TNF-induced Akt activation and Akt-IKK association (Takada et al. 2005). It showed anti-proliferative activity against a variety of tumor cells, including prostate cancer, melanoma, and cervical cancer cells (Fei et al. 2003). Some other IKK inhibitors such as BAY 11-7082 and AS602868 have shown efficacy in leukemia models via their ability to induce apoptosis (Frelin et al. 2005; García et al. 2005).

The precise mechanisms of IKK inhibition are still under extensive investigation. A recent study on NF-κB activation upon hypoxic conditions showed that induction of IKK activity could be regulated by a calcium/calmodulin-dependent kinase-2 pathway, which is distinct from other ways of NF-κB activation. This process requires TAK1 kinase, but no TAK1-binding proteins. Ubiquitination of the IKKγ/NEMO complex as well as ubiquitin-conjugating complex containing Ubc13 are essential for stimulation of NF-κB through hypoxia (Culver et al. 2010). Therefore, some IKK-inhibitors may interfere also with this pathway.

Some comparative analysis of proteasome and IKK inhibitors was performed in prostate carcinoma cell line LNCaP (Gasparian et al. 2009). The efficacy of diverse proteasome inhibitors (MG132, lactacystin and epoxomicin)

to block NF-κB activity induced by TNF-α or 12-*O*-tetradecanoylphorbol-13-aceate (TPA) was compared with that of IKK inhibitors (BAY 11-7082 and PS1145). Proteasome inhibitors were more powerful in attenuating of NF-κB-regulated transcription, in blocking of TPA-induced formation of p50/p50 NF-κB complexes, and in enhancing TNF-α-induced apoptosis.

Targeting Nuclear-Cytoplasmic Shuttling

The p53 tumor suppressor function is constitutively diminished or switched off in many cancers, due to p53 mutations or pathological expression of inhibitors. Therefore, the use of therapeutic activators of the p53 response could improve the efficacy of cancer management protocols. A metabolite of *Streptomyces sp.*, leptomycin B (LMB) was found to induce activity of p53 by protection it from murine double minute-2 protein-dependent degradation, as well as to inhibit the export of proteins from the nucleus to the cytoplasm by impairment of the exportin-1 system (Menéndez et al. 2003). In the case of NF-κB, LMB inhibits its activity by blocking nuclear export of IκB (Rodriguez et al. 1999). Initially this drug proved its efficacy in preclinical studies performed on cervical cancer cell lines and in mouse xenograft models (Roberts et al. 1986). However, in a phase I clinical trial this drug administered intravenously showed high toxicity. Therefore, further studies are needed in order to develop a way of direct delivery of LMB to the tumor. Alternatively, chemical manipulation of LMB might generate synthetic LMB derivatives (called nuclear export inhibitors–NEIs), with high anti-cancer potential while being much less toxic (Mutka et al. 2009).

Proteotoxic stress, which usually results from oxydative stress, hypoxia or intoxication, is defined as accumulation of unfolded proteins, which are capable of decreasing proteasome and chaperone activities inside the cells. Cell defense mechanisms against proteotoxic stress are based on activation of signal transduction pathway called heat shock response (HSR), mediated by heat shock factor-1 (HSF1). Upon activation by proteotoxic stress, HSF1 translocates to the nucleus and stimulates transcription of inducible chaperones Hsp70 and Hsp27. Contrary to normal tissues, the HSR pathway and HSF1 function are constantly active in many cancer cells, being responsible for malignant transformation as well as for tumor defense against cytotoxic factors (Neznanov et al. 2009). 9-Aminoacridine (9AA) and its derivatives, e.g., the antimalarial drug quinacrine (QC), were shown to suppress Hsp70 expression and thus inhibit the HSR pathway in a concentration-dependent manner (Neznanov et al. 2009). Inhibition of HSF1 function by QC and 9AA affects this pathway at a point located downstream of HSF1 cytoplasmic activation, or nuclear translocation. QC exerts a similar action on NF-κB by keeping p65 complexes in the nucleus in their inactive state (Gurova et al. 2005; Neznanov et al. 2009). Combination of QC with bortezomib enhanced its toxicity and resulted in apoptosis of cancer cells in vitro. Reduction of tumor size was also observed in a syngeneic mouse tumor model of fibrosarcoma and melanoma (Neznanov et al. 2009). QC was also shown to suppress NF-κB and to stimulate p53 in human renal cell carcinoma, thus directing tumor cells to programmed death (Gurova et al. 2005). Recent studies indicate that QC could have an even broader spectrum of activity against other stress-inducible factors like interferon-inducible factors, HIF-1 or glucocorticoid receptor. The drug is relatively safe; however, yellow discoloration of the skin and psychosis may accompany treatment with QC higher doses (the usefulness of quinacrine as anti-cancer agent is extensively reviewed in Gurova 2009).

Immunomodulatory Drugs: Thalidomide and its Second-Generation Derivatives

Due to the main mode of their activity, thalidomide and its second-generation derivatives, that do not inhibit phosphodiesterase type 4, are called immunomodulatory drugs (IMiDs) (Aragon-Ching et al. 2007). One of the most important and well-known actions of thalidomide is its anti-angiogenic activity, which has been recognized as a reason for its teratogenic effects observed in the past. The mechanism for this activity depends on inhibition of VEGF and IL-6, and was successfully used for treatment of multiple myeloma (Gupta et al. 2001). Additionally, thalidomide was shown to inhibit the expression of COX-2 and the production of PGE_2 (Fujita et al. 2001). Other effects are based on the ability of thalidomide to stimulate lymphocyte proliferation and interferon γ, as well as IL-2 secretion (Kotla et al. 2009). The major concern during therapy with thalidomide is the high frequency of side effects (particularly neuropathy and thromboembolism) occurring with increasing doses, especially in elderly patients, and when thalidomide is combined with other chemotherapeutics (Dimopoulos and Eleutherakis-Papaiakovou 2004). A higher immuno-potentiating activity is shown by thalidomide's second generation derivative, lenalidomide (Revlimid®). Compared with thalidomide, lenalidomide is safer for the patients, as the incidence of somnolence, constipation, and neuropathy is less frequent, while teratogenic effects are completely absent (at least in animal models) (Kotla et al. 2009). Lenalidomide acts through the CD28-B7 co-stimulatory pathway, thus leading to increased Th1 pro-inflammatory activity, clonal T proliferation, and raised natural killer cell activity (Dredge et al. 2002). Both thalidomide and lenalidomide exert

direct anti-cancer activity in the absence of immunocompetent cells, inducing apoptosis in malignant cells probably by suppressing IκB kinase (Keifer et al. 2001)), and increasing p21 expression (Mitsiades et al. 2002). In vitro assays have demonstrated anti-angiogenic properties of IMiDs; they were able to stop the secretion of VEGF and fibroblast growth factor by tumor cells (D'Amato et al. 1994). Since TNF-α induces NF-κB expression in multiple myeloma cells inside the bone marrow, the use of IMiDs has been pathologically justifiable (Mitsiades et al. 2006). In the treatment of multiple myeloma, lenalidomide has successfully replaced thalidomide (which showed higher toxicity), especially when combined with dexamethasone (Richardson et al. 2006). Patients with relapsed or refractory multiple myeloma showed improved survival with complete or partial response in 25% of cases and prolonged progression-free period during monotherapy with lenalidomide or combined treatment with dexamethasone (Richardson et al. 2006). This was confirmed in phase I/II and III randomized double-blind controlled studies (comment in Richardson et al. 2006). It seems that lenalidomide could be also helpful for the management of chronic lymphocytic leukemia (Ramsay and Gribben 2009). In addition to lenalidomide, some other IMiDs were recently tested in clinical phase I studies in patients with refractory multiple myeloma. One of them, CC-4047, was shown to stimulate more efficiently than thalidomide a long-lasting anti-tumor Th1-cytokine-dependent reactions, while another one, ENMD-0995 demonstrated better anti-angiogenic activity than its parent drug (Aragon-Ching et al. 2007).

The anti-cancer activity of thalidomide was tested also in solid tumors, including metastatic renal cell carcinoma (Kraemer et al. 2009), glioma (Puduvalli et al. 2008), metastatic melanoma, pancreatic cancer, and prostate cancer (Lee et al. 2007). The results of a placebo-controlled randomized trial on patients with advanced pancreatic cancer indicated the efficacy of thalidomide in diminishing the extent of cachexia (Gordon et al. 2005). The use of low-dose thalidomide either as a monotherapy, or as a supplement for docetaxel treatment of prostate cancer patients, has shown efficacy in reducing the prostate-specific antigen levels (Figg et al. 2001). In higher doses, thalidomide has shown positive effects for stabilization of advanced leiomyosarcoma when combined with the alkylating agent temozolomide (Boyar et al. 2008). However, the benefit from using thalidomide in patients with endometrial cancer, either recurrent or refractory to routine chemotherapeutic regimens, was only very limited (McMeekin et al. 2007). The toxicity of lenalidomide used in the treatment of patients with metastatic solid tumors was acceptable, even at doses higher than those previously used in hematologic malignancies (Dahut et al. 2009).

Conclusion

Anti-cancer treatment using inhibitors of transcription factor NF-κB appeared so far to be a valuable way of management in hematological malignancies, especially multiple myeloma and some types of leukemia and lymphoma. Their general use in solid tumors is still questionable; however, they could be a part of polypharmacological approaches to overcome pathologic growth capabilities created by hypoxic and inflammatory conditions inside solid tumors. Inhibitors of NF-κB could effectively supplement both traditional anti-cancer treatment and different types of immunotherapy (Wilczynski and Duechler 2010). The only poorly solved problem, similarly met when other types of anti-cancer therapy are considered, is how to deliver NF-κB inhibitors exclusively to the tumor, in order to avoid general side effects. This problem should be the matter of the greatest concern in the near future.

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