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Biochemical Pharmacology 64 (2002) 883–888

Biochemical Pharmacology

Nuclear factor-kappa B and cancer: its role in prevention and therapy

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Received 14 February 2002; accepted 12 April 2002

Abstract

Cancer is a hyperproliferative disorder in which invasion and angiogenesis lead to tumor metastasis. Several genes that mediate tumorigenesis and metastasis are regulated by a nuclear transcription factor, nuclear factor kappa B (NF-κB). A heterotrimeric complex consisting of p50, p65, and IκBα, NF-κB is present in its inactive state in the cytoplasm. When NF-κB is activated, IκBα is degraded and p50–p65 heterodimer is translocated to the nucleus, binds the DNA (at the promoter region), and activates gene. Research within the last few years has revealed that NF-κB is activated by carcinogens, tumor promoters, inflammatory cytokines, and by chemotherapeutic agents. The activation of NF-κB can suppress apoptosis, thus promoting chemoresistance and tumorigenesis. Interestingly, however, most chemopreventive agents appear to suppress the activation of the NF-κB through inhibition of NF-κB signaling pathway. These chemopreventive agents also sensitize the tumors to chemotherapeutic agents through abrogation of NF-κB activation. Overall, these observations suggest that NF-κB is an ideal target for chemoprevention and chemosensitization. This article reviews evidence supporting this hypothesis.

Keywords: Nuclear factor-κB; Chemoprevention; Chemosensitizaion

1. Introduction

From extensive research during last half of the century, the common saying that ''you are what you eat'' is becoming increasingly accepted. To prevent the onset of both cancer and cardiovascular diseases, the National Institute of Health in the United States has recommended a high-fiber, low-fat diet, consisting of more fruits and vegetables. The importance of the diet is further suggested by the epidemiological evidence that certain cancers (e.g. breast, prostate, colon, and lung) are more prevalent in the developed countries than in the developing countries, most likely because of differences in dietary constituents. The molecular mechanism by which diet mediates its preventive and therapeutic effects is an active area of current research. We propose that there are constituents of the every-day diet that regulate the activity of certain transcription factors such as NF-κB that play a critical role in carcinogenesis.

NF-κB is a transcription factor discovered by Sen and Baltimore in 1986, in the kappa light chain of immunoglobulins in B cells [1]. Research over the last few years has revealed that NF-κB is an inducible and ubiquitously expressed transcription factor for genes involved in cell survival, cell adhesion, inflammation, differentiation, and growth [2–5]. Active NF-κB complexes are dimers of various combinations of the Rel family of polypeptides consisting of p50 (NF-κB1), p52 (NF-κB2), c-Rel, v-rel, Rel A (p65), and Rel B (see [6,7]). These proteins share a conserved 300 amino acid region within their amino termini, termed RHD, that is responsible for DNA binding, dimerization, nuclear translocation, and interaction with heterologous transcription factors. Although all Rel family

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Abbreviations: NF-κB, nuclear factor kappa B; RHD, Rel homology domain; IκB, inhibitor of NF-κB; IKK, IκBα kinase; NEMO, NF-κB essential modifier; NNK, nicotine-derived 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; UV, ultra violet; cIAP, cellular inhibitor of apoptosis; TNF, tumor necrosis factor; TRAF, TNF receptor-associated factor; SOD, superoxide dismutase; CAM, cell adhesion molecules; COX, cyclooxygenase; iNOS, inducible nitric oxide synthase; uPA, urokinase-type plasminogen activator; MMP, matrix metalloproteinase; VEGF, vascular endothelial cell growth factor; IL, interleukin; EGFR, epidermal growth factor receptor; CAPE, caffeic acid phenethyl ester; PBIT; *S*,*S*′-1,4-phenylene-bis(1,2-ethanediyl)bis-isothiourea; PDTC, pyrrolidine dithocarbamate.

0006-2952/02/$ – see front matter
PII: S0006-2952(02)01154-1

members bind to DNA, only p65, c-Rel, and RelB contain a transactivation domain. In most resting cells, NF-κB is retained in the cytoplasm by binding to the inhibitory IκB proteins (IκBα, IκBβ, IκBε, p105, and p100), which blocks the nuclear localization sequences of NF-κB [8]. NF-κB is activated in response to a wide variety of stimuli that promote the dissociation of the IκBα through phosphorylation, ubiquitination, and degradation, thus unmasking of the nuclear localization sequence of NF-κB thereby allowing NF-κB to enter the nucleus and bind κB-regulatory elements [9]. The phosphorylation of IκBα is a critical step in the pathway leading to NF-κB activation, and this step is catalyzed by an IκBα kinase (IKK) complex (molecular mass of 700 kDa) consisting of IKK-α, IKK-β, IKK-γ (also called NEMO), and other proteins yet to be identified [10].

Because of the critical role of NF-κB in cell survival, cell adhesion, inflammation, differentiation, and cell growth, it has been implicated in carcinogenesis. Cancer is a hyperproliferative disorder that results from tumor initiation and tumor promotion, which ultimately produces tumor metastasis. Several genes that are involved in cellular transformation, proliferation, invasion, and angiogenesis are regulated by NF-κB [11,12]. The focus of this review is to present the evidence that NF-κB can lead to tumorigenesis and, therefore, establishes that agents that suppress NF-κB can abrogate carcinogenesis. We also present evidence that suppression of NF-κB can sensitize tumor cells to chemotherapeutic agents.

1.1. NF-κB is activated by carcinogens and tumor promoters

Several recent studies indicate that NF-κB is activated by various carcinogens and tumor promoters. These include benzo[a]pyrene, NNK, UV radiation, and phorbol esters [9,13–16]. For instance UV radiation has been shown to cause sunburn reactions (swelling, leukocyte infiltration, epidermal hyperplasia, and accumulation of proinflammatory cytokines) leading to skin cancer, and suppression of NF-κB blocks the sunburn-induced damage [17].

1.2. NF-κB is needed for cell survival and cell proliferation

In 1996, four independent reports showed that activation of NF-κB promotes cell survival and downregulation of NF-κB sensitizes the cells to apoptosis induced by cytokines and chemotherapeutic agents [18–21]. How NF-κB activation promotes cell survival is becoming increasingly clear. The expression of several genes including *bcl-2*, *bcl-x_L*, *cIAP*, *xIAP*, *TRAF1*, *TRAF2*, *SOD*, and *A20*, have been reported to be regulated by NF-κB and to mediate cell survival (Table 1). How these proteins enhance cell survival is not fully understood, but their role in blocking the apoptosis pathway has been demonstrated [3]. Studies from our laboratory and others have shown that expression of activated NF-κB promotes cell proliferation and suppression of NF-κB leads to abrogation of proliferation [22–24].

Table 1
Antiapoptotic genes products regulated by NF-κB[a]

Bcl-2
Bcl-x_L
TNF receptor-associated factor-1 (TRAF1)
TNF receptor-associated factor-2 (TRAF2)
Mn superoxide dismutase (MnSOD)
Survivin
Cyclin D1
γ-Glutamylcysteine synthetase (γ-GCS)
Cellular inhibitor of apoptosis (cIAP-1)
cIAP-2
xIAP
A20
Cyclooxygenase-2
c-Myc

[a] For references see [3].

1.3. NF-κB regulates the genes involved in tumor cell invasion and angiogenesis

Invasion and angiogenesis are critical events for tumor metastasis. Various genes that are involved in tumor cell invasion and angiogenesis have also been found to be regulated by NF-κB. These include the cell adhesion molecules (ICAM-1, VCAM-1, ELAM-1), COX2, iNOS, uPA, MMP-9, MMP-2, VEGF, chemokines, and inflammatory cytokines (Table 2). Thus, the suppression of NF-κB activation will likely abrogate the expression of these genes and, thus, prevent tumor metastasis.

1.4. NF-κB is constitutively expressed in tumor cells

While it is clear from these description that NF-κB is needed for tumor cell proliferation, invasion, and angio-

Table 2
NF-κB-regulated genes involved in carcinogenesis

Gene product	References
c-Myc	[34,35]
Epidermal growth factor receptor (EGFR)	[36]
Cell adhesion molecules	[37]
Inducible nitric oxide synthase (iNOS)	[38–40]
Vascular endothelial cell growth factor (VEGF)	[39,41]
Interleukin-6	[42]
Cyclin D1	[43,44]
Matrix metalloproteinase-9 (MMP-9)	[45]
Cyclooxygenase-2 (COX2)	[39,46,47]
Interleukin-8	[48]
Urokinase-type plasminogen activator (uPA)	[49]
Bcl-2	[50,51]
Bcl-x_L	[50,52]
Matrix metalloproteinase-2 (MMP-2)	[45]
Gro 1	[53]

genesis, tumor cells have been found to constitutively express the activated form of NF-κB. Several different tumor cell types, including leukemia, lymphoma, myeloma, melanoma, prostate, colon, breast, pancreas, and head and neck squamous cell carcinoma cell lines have been reported to express constitutively active NF-κB [23,25–27]. We and others have shown that samples obtained from cancer patients also exhibit constitutive NF-κB [24]. What causes the constitutive activation of NF-κB is not fully understood, but the roles of TNF, IL-1, pH, and hypoxia has been demonstrated. Our laboratory has shown that constitutive NF-κB in T cell cutaneous lymphoma [28] and in acute myelogenous leukemia [29] is due to constitutive expression of TNF and IL-1, respectively. Suppression of TNF and IL-1 production was found to downregulate the expression of active NF-κB, which correlated with inhibition of proliferation of these tumor cells.

1.5. NF-κB activation is suppressed by chemopreventive agent

How chemopreventive agents suppress tumorigenesis is not fully understood. Several assays have been developed to determine the chemopreventive ability of an agent [30]. We have noted that most agents that have chemopreventive effects suppress the activation of NF-κB. These include curcumin, resveratrol, emodin, green tea polyphenols, silymarin, β-lapachone, caffeic acid phenethyl ester, and sulindac (Table 3). Since NF-κB regulates the expression of numerous genes that are involved in carcingenesis (Table 2), the suppression of expression of these genes

Table 3
Chemopreventive agents that block NF-κB activation

Chemopreventive agent	Source	Chemical name	References
Curcumin	*Curcuma longa*	(*E*,*E*)-1,7-Bis(4-hydroxy-3-methoxy-phenyl)-1,6-heptadiene-3,5-dione; diferuloylmethane	[23,32,40,54]
Retinoids	Vitamin A	*N*-(4-Hydroxyphenyl) retinamide; all-*trans* retinoic acid	[55]
Capsaicin	*Capsicum* sp.	*N*-(4-Hydroxy-3-methoxybenzyl)-8-methylnon-*trans*-6-enamide	[54,56]
Vitamin E	Plants	α-Tocopherol; 5,7,8-trimethyltocol	[57]
Quercetin	*Rhododendron cinnabarinum*, widely distributed in plant kingdom in rinds and barks	3,3′,4′,5,7-Pentahydroxyflavone	[58]
Dihydroxy vitamin D3	Fish liver oils	1α,25-Dihydroxycholecalciferol	[57]
Resveratrol	Phytoalexin found in a variety of plants, abundant in *Polygonum cuspidatum* and grape fruits	*trans*-3,5,4′-Trihydroxystilbene	[33,59]
Silymarin	*Silybum marianum*	Silybin	[60]
Lapachone	Heartwood of bignoniaceous plants, e.g. Lapacha tree	β-Lapachone	[61]
Sulindac	Synthetic	(*Z*)-Fluoro-2-methyl-1-[[4-(methyl-sulfinyl)phenyl]methylene]-1H-indene-3-acetic acid	[62]
Celecoxib	Synthetic	1,2-Diarylpyrrole	[47]
Tea polyphenols	Green or black tea	(−)-Epigallocatechin-3-gallate; theaflavin	[63]
Sulforaphane	Cruciferous vegetables, e.g. Broccoli	1-Isothiocyanato-(4R)-(methylsulfinyl)butane	[46]
Aspirin	Synthetic	2-(Acetyloxy)benzoic acid	[64]
Caffeic acid phenethyl ester (CAPE)	Propolis from honeybee hives	3,4-Dihydroxycinnamic acid phenylethyl ester	[65]
S,*S*'-1,4-Phenylene-bis(1,2-ethanediyl)bis-isothiourea (PBIT)	Synthetic	*S*,*S*′-1,4-Phenylene-bis(1,2-ethanediyl)bis-isothiourea (PBIT)	[66]
Pyrrolidine dithocarbamate (PDTC)	Synthetic	Pyrrolidine dithocarbamate	[67]
Anethole	*Pimpinella anisum*, camphor, fennel	*p*-Propenylanisole	[68]
Oleandrin	*Nerium oleander*	(3β,5β,16β)-16-(Acetyloxy)-3-[(2,6-di-deoxy-3-*O*-methyl-α-arabino-hexopyranosyl)oxy]-14-hydroxycard-20(22)-enolide	[69]
Wortmannin	Antibiotic from *Penicillium wormanni*	[1*S*-(1α,6bα,9aβ,11α,11bβ)]-11-(Acetyloxy)-1,6b,7,8,9a,10,11,11b-octahydro-1-(methoxymethyl)-9a, 11b-dimethyl-3H-furo[4,3,2-de]indeno[4,5-h]-2-benzopyran-3,6,9-trione	[70]
Emodin	*Aloe barbandensis*, *Polygonum cuspidatum*	1,3,8-Trihydroxy-6-methyl-9,10-anthracenedione	[71]

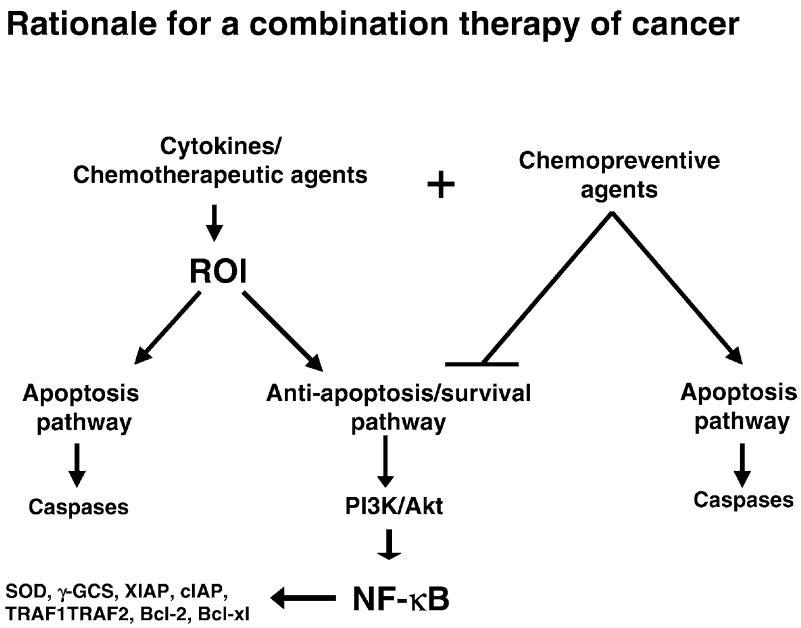

Fig. 1. Chemopreventive agents potentiate the effect of chemotherapeutic agents through downregulation of cell survival mechanisms. PI3K is phosphotidylinositol-3-kinase, SOD is superoxide dismutase, γ-GCS is gamma glutamylcysteine synthetase, and cIAP is cellular inhibitor of apoptosis.

through inhibition of NF-κB activation may be one of the mechanisms by which chemopreventive agents mediate their effects.

1.6. NF-κB is activated by chemotherapeutic agents leading to chemoresistance

It has been found that most chemotherapeutic agents activate NF-κB. These include taxol, doxorubicin, daunorubicin, etoposide, vincristin, vinblastin, ara-C, anthralin, AZT, ciprofirate, cisplatin, haloperidol, methamphetamine, phenobarbital, temoxifen, and camptothecin [9]. Even gamma irradiation, commonly used to treat cancer patients, has also been found to activate NF-κB [31]. The activation of NF-κB can lead to resistance to apoptosis ordinarily induced by chemotherapy or radiation therapy. Thus, while activating apoptosis, the same agent can also activate NF-κB, which can lead to antiapoptosis.

1.7. NF-κB suppression sensitizes the tumor cells to chemotherapeutic agents and to ionizing radiation

Most chemotherapeutic agents and ionizing radiation induce apoptosis through activation of various caspases. They also activate antiapoptosis through activation of NF-κB, which leads to eventual resistance of tumor cells to therapy. Since most chemotherapeutic agents are known to suppress the activation of NF-κB and NF-κB-regulated gene expression, we propose the use of chemotherapeutic agents or gamma radiation in combination with chemopreventive agents for the therapy of cancer (Fig. 1). Besides blocking NF-κB activation, chemopreventive agents such as curcumin and resveratrol are also known to induce apoptosis [23,32,33]. Thus, unlike chemotherapeutic agents, chemopreventive agents induce apoptosis without activating the antiapoptosis pathway. Because most chemopreventive agents are natural plant-derived products, there is minimum toxicity associated with them. This provides an additional rationale for combination therapy.

2. Conclusions

Evidence presented above suggests that activation of NF-κB can lead to tumor cell proliferation, invasion, angiogenesis, and metastasis. Thus, suppression of NF-κB in cancer cells may provide an additional target for prevention of cancer. NF-κB blockers can also be considered for the therapy of cancer, perhaps in combination with chemotherapeutic agents or gamma irradiation. Cancer is a multifactorial disease, and its treatment may also require multimodal therapy. In most instances when the diseases is diagnosed, numerous changes in the tumor have already taken place, thus creating a challenge for the physician to treat the patient. Most recent treatments for cancer have been a combination therapy consisting of chemotherapeutic agents, inhibitors of signal transduction and antibodies against various cell surface antigens. Therefore, it is reasonable to combine chemotherapeutic agents with chemopreventive agents for the treatment of cancer (Fig. 1).

Acknowledgments

This research was supported by grants from the Clayton Foundation, National Institute of Health (1P01 CA91844-1),

and by the Department of Defense (BC010610) to BBA. We will like to thank Walter Pagel for a careful review of the manuscript.

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