ANTIOXIDANTS & REDOX SIGNALING
Volume 8, Numbers 3 & 4, 2006

Forum Review

NF-κB: A Stress-Regulated Switch for Cell Survival

ROBERTO PIVA,[1] GIUSEPPE BELARDO,[2] and M. GABRIELLA SANTORO[2]

ABSTRACT

Nuclear factor-κB (NF-κB), a stress-regulated transcription factor belonging to the Rel family, has a pivotal role in the control of the inflammatory and the innate immune responses. Its activation rapidly induces the transcription of a variety of genes encoding cell adhesion molecules, inflammatory and chemotactic cytokines, cytokine receptors, and enzymes that produce inflammatory mediators. More recently, NF-κB activation has been connected with multiple aspects of oncogenesis, including the control of cell proliferation, migration, cell cycle progression, and apoptosis. Interestingly, NF-κB is constitutively activated in several types of cancer cells, including hematological and epithelial malignancies. In addition, activation of NF-κB in cancer cells by chemotherapy or radiation therapy has been associated with the acquisition of resistance to apoptosis, which has emerged as a significant impediment to effective cancer treatment. Selective cyclopentenone inhibitors of the IκB kinase, the key enzyme controlling NF-κB activation, were recently shown to be potent inducers of apoptosis in chemoresistant lymphoid malignancies. Increasing evidence, summarized in this review, indicates that the development of selective NF-κB inhibitors may represent a promising therapeutic tool to sensitize tumor cells to apoptosis and increase the efficacy of conventional anticancer drugs in a wide spectrum of malignancies. *Antioxid. Redox Signal.* 8, 478–486.

INTRODUCTION

Nuclear factor-κB (NF-κB) was first described in 1986 as a nuclear factor controlling the transcription of the immunoglobulin κ light-chain gene in B cells (71). NF-κB is a term that refers to a family of heterodimeric transcription factors critical for the regulation of cell proliferation and survival during immune, inflammatory, and stress responses (32, 38). Mammalian cells express five NF-κB proteins sharing a highly conserved N-terminal domain called the Rel (for reticuloendotheliosis) homology domain (RHD), which is responsible for dimerization, interaction with inhibitory proteins, and DNA binding (18). Rel proteins are divided in two classes: members of one class include RelA (p65), RelB and c-Rel, which are synthesized as mature products, and share a transactivation domain (TAD) at their C-terminus required to promote transcription. The second group consists of the NF-κB1 (p105/p50) and NF-κB2 (p100/p52) proteins. They are synthesized as p105 and p100 precursors, which contain a series of C-terminal ankyrin repeat domains that mask the nuclear localization signal (NLS) within the Rel homology domain. p105 and p100 require ubiquitin-dependent proteolytic processing at the C-terminus to generate the active p50 and p52, respectively. The mature DNA-binding proteins of this class contain the RHD but lack transcription-modulating activity.

In resting cells, NF-κB exists as an inactive cytoplasmic complex, whose predominant form is a heterodimer composed of p50 and RelA subunits, bound to inhibitory proteins of the IκB family, including IκBα, IκBβ, and IκBγ (18). IκB proteins consist of an N-terminal regulatory domain followed by a series of ankyrin repeats essential for the binding to the NF-κB heterodimer. The interaction with IκB masks the nuclear localization sequence in the NF-κB complex, sequestering the factor in the cytoplasmic compartment (Fig. 1).

[1]Department of Pathology and Center for Experimental Research and Medical Studies (CERMS), University of Turin, Turin, Italy.
[2]Department of Biology, University of Rome Tor Vergata, Rome, Italy.

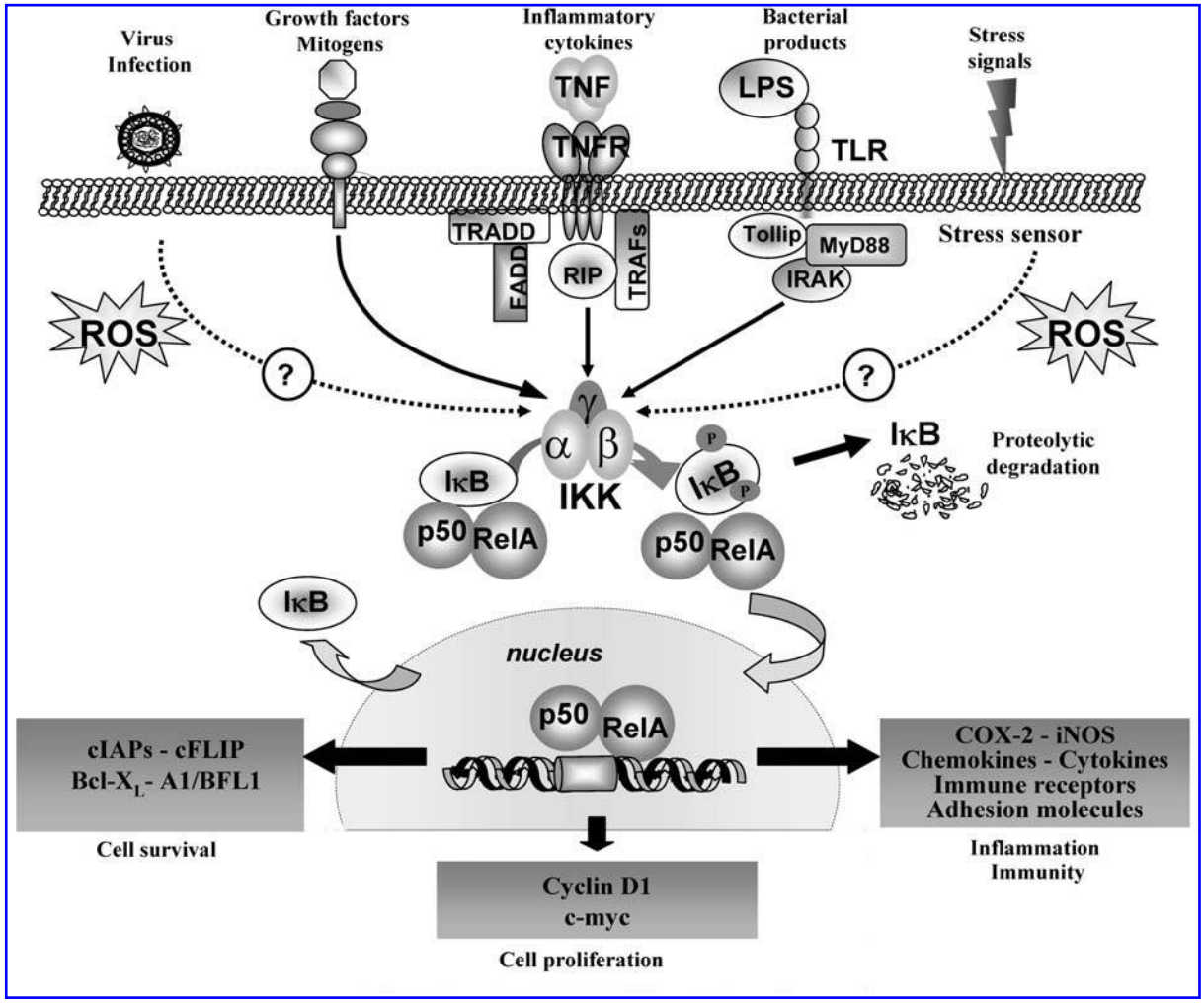

FIG. 1. The NF-κB pathway. NF-κB heterodimers (p50/RelA) are sequestered in the cytoplasm by IκB inhibitory proteins (IκB). Stimulation by stress-inducing agents, exposure to inflammatory cytokines, mitogens, or to a diverse array of bacterial and viral pathogens leads to the activation of signaling cascades converging on the IKK complex. Phosphorylation of IκB by activated IKK is a signal for its ubiquitylation and proteasome-dependent degradation. Freed NF-κB dimers translocate to the nucleus where they bind to κB elements and activate the transcription of a variety of genes involved in the control of cell proliferation and survival, in the inflammatory and immune response, as well as autoregulatory genes, including IκB itself. FADD, Fas-associated death domain; IRAK, interleukin (IL)-1-receptor-associated kinase; LPS, lipopolysaccharide; MyD88, myeloid differentiation primary response gene 88; RIP, receptor-interacting protein; ROS, reactive oxygen species; TLR, Toll-like receptor; Tollip, Toll-interacting protein; TNFα, tumor necrosis factor; TNFR, TNFα receptor; TRADD, TNFR-associated death domain; TRAFs, TNFR-associated factors.

THE NF-κB PATHWAY

The NF-κB complex is activated in response to a variety of stimuli, including viral and bacterial infection, exposure to proinflammatory cytokines, mitogens and growth factors, and stress-inducing agents including reactive oxygen species (ROS) (30) (Fig. 1). NF-κB signaling is regulated by two main pathways. The classical pathway applies to dimers that are composed of RelA, c-Rel and p50, and is normally triggered in response to microbial and viral infections and by proinflammatory cytokines which activate the β subunit of the IκB kinase (IKK) signalosome (28). IKK is a multisubunit complex that contains two catalytic subunits (IKK-α and IKK-β), which are able to form homo- or heterodimers, and the IKK-γ or NEMO regulatory subunit, which acts as a docking protein for IKK kinases or other signaling proteins (28, 61). Following different types of stimulation, the NF-κB/IκB complex is activated via the phosphorylation of the inhibitory proteins on two N-terminal serine residues (30). Phosphorylation targets IκBs for ubiquitylation by the β-TrCP-SCF ubiquitin ligase complex, which leads to its proteasome-mediated degradation, allowing the consequent release of NF-κB (Fig. 1).

In the alternative pathway, IKK-α is activated and it phosphorylates NF-κB2/p100 associated with RelB. This phosphorylation induces the ubiquitin-mediated processing of NF-κB2/p100 C-terminal ankyrin repeats to release RelB-p52 heterodimers (72). Following the degradation of the in-

hibitory proteins, freed NF-κB dimers translocate to the nucleus, where they bind to specific sequences (κB elements) in the promoter or enhancer region of target genes. In the nucleus, a second level of transcriptional activity control has been described that involves NF-κB phosphorylation and acetylation. Phosphorylation of RelA by protein kinase A (PKA), IKK and glycogen synthase kinase-3β (GSK-3β) on distinct sites has been described to facilitate NF-κB DNA binding and association with the transcriptional coactivator CBP/p300 (27, 62, 80), potently enhancing gene transactivation. Finally, direct and reversible acetylation of NF-κB was described as an additional regulatory mechanism for NF-κB transcriptional activity (13).

The multiple levels of control of NF-κB activity are not surprising considering the number of genes whose expression is regulated by this factor. NF-κB-binding sites have been identified in the promoter region of >150 cellular genes (50), including the NF-κB-inhibitory proteins A20 and IκBα, which provide a negative feedback mechanism to limit NF-κB activity (32, 66) (Fig. 1).

IMMUNE RESPONSE, INFLAMMATION, AND VIRAL INFECTION

Several proteins encoded by NF-κB target genes participate in the activation of the host immune and inflammatory responses. These include a plethora of cytokines and chemokines, receptors required for neutrophil adhesion and transmigration across blood vessel walls, receptors involved in immune recognition such as members of the major histocompatibility complex (MHC), as well as proteins involved in antigen presentation (50). For this reason, NF-κB was first identified as a central regulator of innate and adaptive immune responses.

This view was further supported by the finding that NF-κB is activated during infection with many viruses, including influenza virus, rotavirus, and herpesvirus (2, 3, 8, 66). NF-κB activation during viral infection was first interpreted as a protective response of the host to the viral pathogen. However, the identification of functionally important NF-κB-binding sites in the genome of several viruses, including the human immunodeficiency virus type 1 (HIV-1) (45), SV40 (67), and different members of the herpesvirus family (14, 57), led to the finding that NF-κB induction results in the transactivation of κB-containing viral promoters and in enhanced viral transcription (2, 3, 66).

Beyond the control on the immune response and viral infection, NF-κB also stimulates the expression of enzymes whose products contribute to the pathogenesis of the inflammatory process, including the inducible form of nitric oxide synthase (iNOS), cyclooxygenase 2 (COX-2), and a variety of pro-inflammatory cytokines (50). Interestingly, cytokines that are stimulated by NF-κB, such as TNF-α and IL-1β, are also potent NF-κB inducers, thus establishing a positive autoregulatory loop that can amplify the inflammatory response and lead to chronic inflammation (75). Consistent with its essential role in inflammation, NF-κB is also known to be the target of anti-inflammatory compounds, including non-steroidal anti-inflammatory drugs (79).

CELL STRESS

A variety of extracellular stresses, such as exposure to UV light, H_2O_2, and cigarette smoke, as well as intracellular stress, including endoplasmic reticulum protein overload, have been shown to activate NF-κB (11). One of the first models proposed to find a common mechanism converging on NF-κB was based on the possibility that all these conditions would cause oxidative stress, by increasing the intracellular concentration of reactive oxygen species, including H_2O_2, superoxides (O_2^-), or hydroxyl ($^{\bullet}OH$) radicals, which would function as specific signals to activate definite pathways (11, 69, 70). This hypothesis was based on several lines of evidence. First, it was shown that direct addition of H_2O_2 to culture medium activated NF-κB in human cells (40, 70). Second, antioxidant such as *N*-acetylcysteine (NAC) or pyrrolidine dithiocarbamate (PDTC) were found to inhibit NF-κB activation in a redox-dependent manner (69). Furthermore, ROS were found to be increased in some cell types in response to NF-κB inducers, and overexpression or inhibition of enzymes that affect intracellular ROS levels were shown to modulate NF-κB activation (11).

However, subsequent studies provided evidence against a model proposing ROS as second messengers for NF-κB activation. First, several cell lines were found to be insensitive to H_2O_2-induced NF-κB stimulation (44, 68). Furthermore, the increased understanding of the molecular mechanisms that trigger NF-κB activation evidenced that many pathways to NF-κB do not involve a ROS-producing step (reviewed in Ref. 11). Hayakawa *et al.* (22) have in fact recently shown that the NF-κB inhibitory activities of antioxidant molecules, such as NAC and PDTC, are independent of their antioxidant properties. In addition, strong phenolic radical scavengers such as EGCG (epigallocatechin-gallate) and the water-soluble vitamin E analog Trolox, are unable to inhibit NF-κB activation (22). In the case of UV radiation, NF-κB activation was found to depend on phosphorylation of IκBα at a cluster of C-terminal sites that are recognized by casein kinase 2 (CK2), determining its consequent degradation in a non-canonical manner (34). CK2 activity toward IκB is UV-inducible via activation of p38 MAP kinase, identifying the p38-CK2-NF-κB axis as an important component of the mammalian UV response (34). Finally, NF-κB activation in response to low-dose ionizing radiation has been instead attributed to the production of ROS, and is inhibited by antioxidants such as NAC (12, 43).

NF-κB, CELL SURVIVAL AND CANCER

A recent body of evidence has emphasized a central role for NF-κB in the control of cell proliferation and survival. In fact, NF-κB activates the expression of cyclin D1 and c-myc, which promotes directly the transition from the G1 into the S phase of the cell cycle, (20, 31, 37). Likewise, NF-κB con-

tributes to activate cell growth indirectly through the induction of the target genes encoding for growth factors such as IL-2, IL-6, GM-CSF, and CD-40 ligand, which stimulate the proliferation of lymphoid and myeloid cells (31). In addition, NF-κB enhances cell survival by switching on genes that dampen pro-apoptotic signals (32). Starting from the first observation that RelA$^{-/-}$ mice died at embryonic day 15 as a result of extensive liver apoptosis (6), a large amount of literature has described the anti-apoptotic function of NF-κB. Collectively, these findings show that NF-κB induces the expression of a number of genes whose products can inhibit apoptosis, including cellular inhibitors of apoptosis cIAP-1, cIAP-2, and X chromosome-linked IAP (XIAP), the FLICE-inhibitory protein cFLIP, members of the Bcl-2 family (Bcl-X_L and A1/Bfl-1), as well as TNFR-associated factors 1 and 2 (TRAF1 and TRAF2). NF-κB can also attenuate the apoptotic response to anticancer drugs and ionizing radiation (46, 55). Although NF-κB is considered primarily an anti-apoptotic transcription factor, able to inhibit apoptosis induced by both death receptors and mitochondria-dependent pathways, it should be noted that in some instances activation of NF-κB has also been associated with induction of apoptosis (32).

Interestingly, tumor cells of almost every tissue type frequently acquire the ability to constitutively activate NF-κB, via a host of genetic alterations and viral proteins (39). Recent studies have also documented a link between induction of NF-κB during chronic inflammation and cancer. In a colitis-associated cancer mouse model in which IKK-β had been knocked out specifically in macrophages or in enterocytes, it was found that inactivation of IKK-β reduced the incidence and development of inflammatory-associated cancer by acting through a different mechanism in each cell type (19). Loss of NF-κB function in macrophages reduced tumor incidence and size as a consequence to the loss of growth factors produced by inflammatory cells. On the other hand, in mice with inactivation of IKK-β in intestinal epithelial cells, the strong decrease in tumor incidence was not to due to reduced intestinal inflammation, but mainly to the lack of apoptosis inhibition (19). Consistent with these findings, using a mouse model of inflammatory hepatitis that predisposes to liver cancers, Pikarsky *et al.* presented evidence that the survival of hepatocytes and their progression to malignancy are regulated by NF-κB (52).

Constitutive NF-κB activity has now been observed in a diverse array of hematological and epithelial malignancies, including colorectal, breast, lung, pancreas, and prostate cancers, glioblastomas, and melanomas (56). The fact that many tumors show constitutively activated NF-κB, has suggested that the anti-apoptotic function of this factor may represent a major obstacle to cancer therapy. Intriguingly, several anticancer agents stimulate NF-κB activation, which can potentially lead to chemoresistance. These agents include taxanes, *Vinca* alkaloids, topoisomerase inhibitors, and many other drugs that simultaneously activate several different pathways that regulate both positively and negatively the cell death process (46, 50). Numerous studies have demonstrated that inhibiting NF-κB results in the reversal of chemoresistance, indicating that it may be possible to improve the efficacy of current anticancer agents by shifting the death–survival balance towards apoptosis through NF-κB inhibition. Even radiotherapy, which is a valuable tool in the treatment of several cancers, has been found to activate NF-κB in tumor cells (54). In this case it has been shown that fibrosarcoma and glioblastoma cells expressing a dominant-negative form of IκBα (IκBα super repressor) are more susceptible to radiation-induced apoptosis (5, 77). The mechanism for NF-κB involvement in chemo- and radioresistance has been linked to its counteracting action on p53 function (76) and to the expression of genes encoding anti-apoptotic proteins acting either at mitochondrial level (such as Bcl-X_L and A1/Bfl-1) or blocking caspase activation (such as IAP-1, IAP-2, XIAP, and c-FLIP). In addition, NF-κB transactivates the expression of the multidrug resistance gene 1 (MDR1) which prevents the intracellular accumulation of toxic compounds such as those used in chemotherapy (7).

In this perspective, inhibition of NF-κB is expected to be therapeutic in those tumors where NF-κB appears to play a unique survival role such as Hodgkin's and non-Hodgkin's B-cell lymphomas (4, 51), diffuse large B-cell lymphomas (15), acute myeloid leukemia (21), multiple myeloma (47), and Burkitt's lymphoma (48). A variety of agents can target different steps in the signaling pathway responsible for NF-κB activity (reviewed in Ref. 46). NF-κB inhibition may be achieved by targeting at origin the receptor signaling proteins responsible for its activation, or by interfering with the NF-κB dimerization or binding to DNA. However, both strategies reveal some disadvantages. In spite of great specificity, targeting the apical signals of NF-κB activation may not be effective as tumors can acquire alternative means of activating NF-κB downstream of the chosen target. On the other hand, inhibiting NF-κB dimerization or DNA binding will require the use of large and polar decoy molecules with poor cellular uptake and bioavailability (33). A more attractive and promising strategy for therapeutic intervention is to interfere with the process of IKK activation, which occurs in response to diverse upstream signals. Several antiinflammatory and immunosuppressive agents that inhibit IKK have been shown to exert antitumor activity, including the classical nonsteroidal anti-inflammatory drugs such as aspirin (36) and sulindac (78), and the immunomodulatory drug thalidomide (35).

CYCLOPENTENONE PROSTAGLANDINS AS NF-κB INHIBITORS

Cyclopentenone prostaglandins (cyPG) are naturally occurring arachidonic acid metabolites with potent biological activity (73). CyPG of the A and J series originate from dehydration within the cyclopentane ring of prostaglandin E and prostaglandin D, respectively, which produces a cyclopentenone structure characterized by the presence of a reactive α,β-unsaturated carbonyl. Cyclopentenone prostaglandins possess antiviral activity (63) and are considered key regulators in the resolution of inflammation (64). In addition to these effects, cyPG induce cell growth arrest and apoptosis in a number of cancer cell types (64, 65, 73). In particular, the terminal derivative of prostaglandin J_2 (PGJ_2) metabolism,

15-deoxy-$\Delta^{12,14}$-PGJ_2 (15d-PGJ_2), is emerging as the most potent antineoplastic agent of this class of prostaglandins. Anticancer activity of 15d-PGJ_2 has been reported both *in vitro* and *in vivo* in a multiplicity of tissues including breast, prostate, colon, lung, and lymphoid (49, 73). In most types of cancer, 15d-PGJ_2 inhibits tumor cell proliferation and induces apoptosis; however, the molecular mechanisms responsible for these effects were unraveled only recently. The proapoptotic activity of cyPG was found to be linked to their ability to inhibit NF-κB activity. We have shown that cyPG block phorbol ester- and TNFα-induced NF-κB activation by inhibition and direct modification of the IKK complex, via binding to cysteine 179 in the activation loop of the IKK-β subunit (59, 60). Cysteine residues in the DNA-binding domain of p50 and p65 are also targets of cyPG (74).

We have recently investigated the effect of the cyclopentenone prostaglandin 15d-PGJ_2 on NF-κB activity in B-cell malignancies previously described to display constitutive NF-κB activation such as multiple myeloma (MM) and Burkitt's lymphoma (BL) (53). Multiple myeloma is a malignant tumor that affects terminally differentiated B-cells, presently incurable as a consequence of the frequent development of refractoriness to conventional and combination therapy (25). Burkitt's lymphoma is an aggressive B-cell tumor whose hallmark are reciprocal translocations leading to the NF-κB-induced activation of the *c-myc* oncogene (29). Two Burkitt's lymphoma (HS-Sultan and BL-41 cells) and two multiple myeloma (U266 and RPMI-8226) cell lines were selected for these studies. In agreement with previous reports (17, 29, 47), all four cell lines tested were found to express constitutively high levels of NF-κB DNA-binding activity (Fig. 2A). 15d-PGJ_2 was found to be an efficient and rapid suppressor of constitutive NF-κB activity in these malignancies. As shown in Fig. 2A, a 3 h treatment with 10 μ*M* 15d-PGJ_2 is sufficient to inhibit NF-κB binding to κB DNA consensus sequences. This effect is accompanied by decreased levels of phosphorylated IκBα (53). A few hours following NF-κB inhibition, 15d-PGJ_2 massively induces apoptosis in all four types of B cell malignancy (Fig. 2B). On the contrary, 15d-PGJ_2 at the same concentration does not induce apoptosis in acute leukemia K562 cells that present very low levels of NF-κB DNA-binding activity (Figs. 2A and 2B), and whose survival depends on the activation of the Bcr/Abl-Stat5-Bax pathway (16). Under the conditions utilized, 15d-PGJ_2 also does not induce cell death in peripheral blood mononucleated cells from normal donors (53).

In the BL HS-Sultan cell line, approximately 80% of cells undergo apoptosis after treatment with 10 μ*M* 15d-PGJ_2 (Fig. 2C). In these cells, inhibition of NF-κB activity is rapidly followed by downregulation of anti-apoptotic proteins c-IAP1, c-IAP2, c-FLIP, and XIAP (Fig. 3A). Treatment with the anticancer drug, dexamethasone, that does not inhibit NF-κB activity, has no effect (Fig. 3A). IAP proteins are known to inhibit caspase-3, caspase-8, and caspase-9 activity. We have shown that 15d-PGJ_2 induces caspase 8 and caspase 9 activity in HS-Sultan cells (53). In particular, the downregulation of cFLIP by 15d-PGJ_2 may contribute to the induction of caspase-8 activity, while the decreased levels of XIAP may unleash caspase-9 action (53). Numerous reports have evidenced that interfering with NF-κB activity via proteasome inhibitors, IKK inhibitors, peptides, or antibodies arrested proliferation and induced cell death of multiple myeloma cells (9, 23–26, 42, 47). A direct proof that NF-κB is required for BL cell survival has been now provided by the knockdown of the NF-κB RelA/p65-subunit via lentivirus-mediated RNA interference (53). We have shown that silencing of p65 expression is accompanied by XIAP inhibition and induction of apoptosis in HS-Sultan cells (Fig. 3C). Similar results were obtained with the MM cell lines RPMI 8226 and U266 (data not shown), while K562 cells were insensitive to p65 knockdown (53). These results altogether indicate that inhibition of NF-κB plays a major role in the pro-apoptotic activity of 15d-PGJ_2 in aggressive B-cell malignancies. In addition, we have demonstrated that the cyclopentenone ring structure is responsible for the biological activity of cyPG (58), and have recently identified new cyclopentenone derivatives as potent NF-κB inhibitors with pro-apoptotic activity in BL cells (10) and in other types of human aggressive cancers characterized by aberrant regulation of NF-κB (Ciucci *et al.*, unpublished observations).

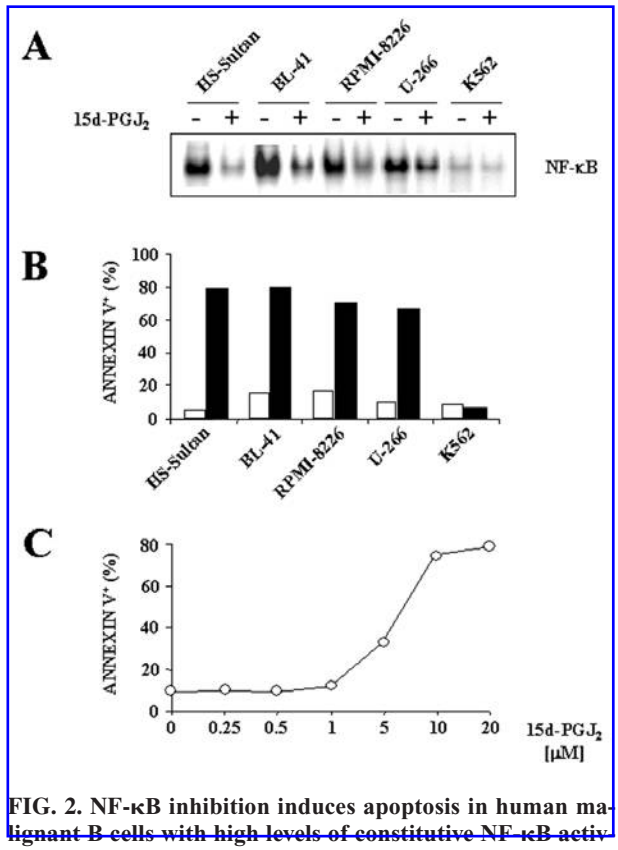

FIG. 2. NF-κB inhibition induces apoptosis in human malignant B cells with high levels of constitutive NF-κB activity. (**A**) Burkitt's lymphoma HS-Sultan and BL-41 cells, multiple myeloma U266 and RPMI-8226 cells, and acute leukemia K-562 cells were treated with 15d-PGJ_2 (10 μ*M*, +), or control diluent (−) for 3 h. NF-κB DNA-binding activity was analyzed by Electrophoretic Mobility Shift Assay, as described (53). (**B**) Apoptosis was evaluated by FACS analysis of Annexin V^+ cells in parallel samples 8 h after treatment (□, Control; ■, 15d-PGJ_2). (**C**) HS-Sultan cells were treated with 15d-PGJ_2 at the indicated concentrations for 24 h. Apoptosis was evaluated by FACS analysis of Annexin V^+ cells.

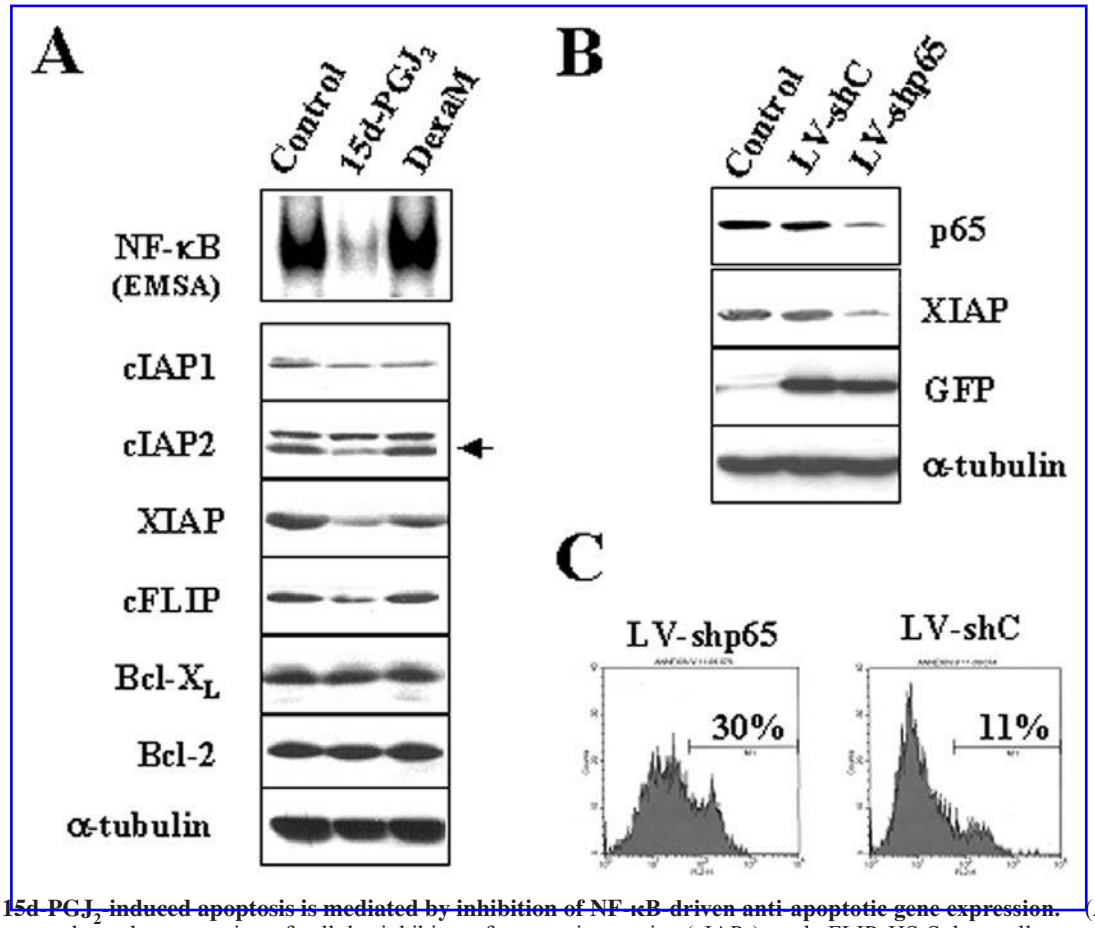

FIG. 3. 15d-PGJ$_2$ induced apoptosis is mediated by inhibition of NF-κB-driven anti-apoptotic gene expression. (**A**) 15d-PGJ$_2$ downregulates the expression of cellular inhibitor-of-apoptosis proteins (cIAPs), and cFLIP. HS-Sultan cells were treated with 15d-PGJ$_2$ (10 μ*M*), dexamethasone (10 μ*M*), or control diluent for 8 h. Whole cell extracts were analyzed for NF-κB DNA-binding activity by EMSA (*top panel*), or for the indicated anti-apoptotic proteins by Western blot (*lower panels*). α-Tubulin immunoblotting was used as a loading control. 15d-PGJ$_2$-induced NF-κB inhibition is associated with decreased expression of cIAP1, cIAP2 (*arrow*), XIAP, and cFLIP. Dexamethasone has no effect. (**B**) Knock down of p65-RelA by lentiviral-mediated RNA interference inhibits XIAP expression. HS-Sultan cells were mock-transduced (Control) or transduced with the lentiviral vector LV-shp65 (bearing the short hairpin RNA interference for the p65 gene and the gene reporter GFP) or the mutated control LV-shC (bearing random mutations in the hairpin sequence). Levels of p65, GFP, XIAP, and α-tubulin proteins were analyzed by Western blot 72 h after transduction. (**C**) Inhibition of p65 expression induces apoptosis in HS-Sultan cells. FACS analysis histograms of annexin V staining in HS-Sultan cells 5 days after infection with LV-shp65 or control LV-shC vectors, as described in **B**. The percent of apoptotic cells is indicated in the panels.

CONCLUSIONS AND PERSPECTIVES

Constitutive activation of cell survival signaling pathways is a general mechanism underlying tumor development and resistance to therapy, and constitutes a major clinical problem in cancer. Disruption of aberrantly regulated survival signaling mediated by the stress-regulated factor NF-κB has recently become an important task in the therapy of several chemoresistant and radioresistant cancers. Based on the demonstration that NF-κB plays an important role in cancer resistance to drug-induced apoptosis, the proteasome inhibitor PS-431 has been recently introduced in the therapy of MM and other chemoresistant malignancies (1, 24, 41). The initial results obtained with this novel approach to chemotherapy encourage the search for novel, more specific NF-κB inhibitors, especially targeted to the IκB kinase (33). The fact that cyclopentenone prostanoids with IKK inhibitory activity potently induce apoptosis in aggressive chemoresistant tumors stimulates the search for novel prostanoids or prostanoid-derived molecules for therapeutic intervention in the treatment of cancers characterized by aberrant regulation of NF-κB.

ACKNOWLEDGMENT

This study was supported by the Italian Ministry of University and Scientific Research (MIUR) and Italian Institute of Health (ISS).

ABBREVIATIONS

BL, Burkitt's lymphoma; cFLIP, FLICE-inhibitory protein; cIAP, cellular inhibitor of apoptosis protein; cyPG, cyclopentenone prostaglandins; 15d-PGJ_2, 15-deoxy-$\delta^{12,14}$-PGJ_2 ; IKK, IκB kinase; MM, multiple myeloma; NF-κB, nuclear factor-κB; ROS, reactive oxygen species; XIAP, X chromosome-linked IAP.

REFERENCES

1. Aghajanian C. Clinical update: novel targets in gynecologic malignancies. *Semin Oncol* 31: 22–26, 2004.
2. Amici C, Belardo G, Rossi A, and Santoro MG. Activation of IκB kinase by herpes simplex virus type 1. A novel target for anti-herpetic therapy. *J Biol Chem* 276: 28759–28766, 2001.
3. Amici C, Belardo G, Rozera C, Bernasconi D, and Santoro MG. Inhibition of herpesvirus-induced HIV-1 replication by cyclopentenone prostaglandins: role of IκB kinase (IKK). *AIDS* 18: 1271–1280, 2004.
4. Bargou RC, Emmerich F, Krappmann D, Bommert K, Mapara MY, Arnold W, Royer HD, Grinstein E, Greiner A, Scheidereit C, and Dorken B. Constitutive nuclear factor-κB-RelA activation is required for proliferation and survival of Hodgkin's disease tumor cells. *J Clin Invest* 100: 2961–2969, 1997.
5. Beg AA and Baltimore D. An essential role for NF-κB in preventing TNF-alpha-induced cell death. *Science* 274: 782–784, 1996.
6. Beg AA, Sha WC, Bronson RT, Ghosh S, and Baltimore D. Embryonic lethality and liver degeneration in mice lacking the RelA component of NF-κ B. *Nature* 376: 167–170, 1995.
7. Bentires-Alj M, Barbu V, Fillet M, Chariot A, Relic B, Jacobs N, Gielen J, Merville MP, and Bours V. NF-κB transcription factor induces drug resistance through MDR1 expression in cancer cells. *Oncogene* 22: 90–97, 2003.
8. Bernasconi D, Amici C, La Frazia S, Ianaro A, and Santoro MG. The Iκ B kinase is a key factor in triggering influenza A virus-induced inflammatory cytokines production in airway epithelial cells. *J Biol Chem* 280: 24127–24134, 2005.
9. Bharti AC, Donato N, Singh S, and Aggarwal BB. Curcumin (diferuloylmethane) down-regulates the constitutive activation of nuclear factor-κ B and IκBα kinase in human multiple myeloma cells, leading to suppression of proliferation and induction of apoptosis. *Blood* 101: 1053–1062, 2003.
10. Bickley JF, Ciucci A, Evans P, Roberts SM, Ross N, and Santoro MG. Reactions of some cyclopentenones with selected cysteine derivatives and biological activities of the product thioethers. *Bioorg Med Chem* 12: 3221–3227, 2004.
11. Bowie A and O'Neill LA. Oxidative stress and nuclear factor-κB activation: a reassessment of the evidence in the light of recent discoveries. *Biochem Pharmacol* 59: 13–23, 2000.
12. Brach MA, Hass R, Sherman ML, Gunji H, Weichselbaum R, and Kufe D. Ionizing radiation induces expression and binding activity of the nuclear factor κ B. *J Clin Invest* 88: 691–695, 1991.
13. Chen L, Fischle W, Verdin E, and Greene WC. Duration of nuclear NF-κB action regulated by reversible acetylation. *Science* 293: 1653–1657, 2001.
14. Cherrington JM and Mocarski ES. Human cytomegalovirus ie1 transactivates the alpha promoter-enhancer via an 18-base-pair repeat element. *J Virol* 63: 1435–1440, 1989.
15. Davis RE, Brown KD, Siebenlist U, and Staudt LM. Constitutive nuclear factor κB activity is required for survival of activated B cell-like diffuse large B cell lymphoma cells. *J Exp Med* 194: 1861–1874, 2001.
16. Donato NJ, Wu JY, Zhang L, Kantarjian H, and Talpaz M. Down-regulation of interleukin-3/granulocyte-macrophage colony-stimulating factor receptor beta-chain in BCR-ABL(+) human leukemic cells: association with loss of cytokine-mediated Stat-5 activation and protection from apoptosis after BCR-ABL inhibition. *Blood* 97: 2846–2853, 2001.
17. Feinman R, Koury J, Thames M, Barlogie B, Epstein J, and Siegel DS. Role of NF-κB in the rescue of multiple myeloma cells from glucocorticoid-induced apoptosis by bcl-2. *Blood* 93: 3044–3052, 1999.
18. Ghosh S, May MJ, and Kopp EB. NF-κB and Rel proteins: evolutionarily conserved mediators of immune responses. *Annu Rev Immunol* 16: 225–260, 1998.
19. Greten FR and Karin M. The IKK/NF-κB activation pathway-a target for prevention and treatment of cancer. *Cancer Lett* 206: 193–199, 2004.
20. Guttridge DC, Albanese C, Reuther JY, Pestell RG, and Baldwin AS, Jr. NF-κB controls cell growth and differentiation through transcriptional regulation of cyclin D1. *Mol Cell Biol* 19: 5785–5799, 1999.
21. Guzman ML, Neering SJ, Upchurch D, Grimes B, Howard DS, Rizzieri DA, Luger SM, and Jordan CT. Nuclear factor-κB is constitutively activated in primitive human acute myelogenous leukemia cells. *Blood* 98: 2301–2307, 2001.
22. Hayakawa M. Evidence that reactive oxygen species do not mediate NF-κB activation. *EMBO J* 22: 3356–3366, 2003.
23. Hideshima T, Chauhan D, Richardson P, Mitsiades C, Mitsiades N, Hayashi T, Munshi N, Dang L, Castro A, Palombella V, Adams J, and Anderson KC. NF-κB as a therapeutic target in multiple myeloma. *J Biol Chem* 277: 16639–16647, 2002.
24. Hideshima T, Mitsiades C, Akiyama M, Hayashi T, Chauhan D, Richardson P, Schlossman R, Podar K, Munshi NC, Mitsiades N, and Anderson KC. Molecular mechanisms mediating antimyeloma activity of proteasome inhibitor PS-341. *Blood* 101: 1530–1534, 2003.
25. Hideshima T, Richardson P, and Anderson KC. Novel therapeutic approaches for multiple myeloma. *Immunol Rev* 194: 164–176, 2003.
26. Hideshima T, Richardson P, Chauhan D, Palombella VJ, Elliott PJ, Adams J, and Anderson KC. The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. *Cancer Res* 61: 3071–3076, 2001.

27. Hoeflich KP, Luo J, Rubie EA, Tsao MS, Jin O, and Woodgett JR. Requirement for glycogen synthase kinase-3beta in cell survival and NF-κB activation. *Nature* 406: 86–90, 2000.
28. Israel A. The IKK complex: an integrator of all signals that activate NF-κB? *Trends Cell Biol* 10: 129–133, 2000.
29. Kanda K, Hu HM, Zhang L, Grandchamps J, and Boxer LM. NF-kappa B activity is required for the deregulation of c-myc expression by the immunoglobulin heavy chain enhancer. *J Biol Chem* 275: 32338–32346, 2000.
30. Karin M and Ben-Neriah Y. Phosphorylation meets ubiquitination: the control of NF-κB activity. *Annu Rev Immunol* 18: 621–663, 2000.
31. Karin M, Cao Y, Greten FR, and Li ZW. NF-κB in cancer: from innocent bystander to major culprit. *Nat Rev Cancer* 2: 301–310, 2002.
32. Karin M and Lin A. NF-κB at the crossroads of life and death. *Nat Immunol* 3: 221–227, 2002.
33. Karin M, Yamamoto Y, and Wang QM. The IKK NF-κB system: a treasure trove for drug development. *Nat Rev Drug Discov* 3: 17–26, 2004.
34. Kato T, Jr., Delhase M, Hoffmann A, and Karin M. CK2 is a C-terminal IκB kinase responsible for NF-κB activation during the UV response. *Mol Cell* 12: 829–839, 2003.
35. Keifer JA, Guttridge DC, Ashburner BP, and Baldwin AS Jr. Inhibition of NF-kappa B activity by thalidomide through suppression of IκB kinase activity. *J Biol Chem* 276: 22382–22387, 2001.
36. Kopp E and Ghosh S. Inhibition of NF-κ B by sodium salicylate and aspirin. *Science* 265: 956–959, 1994.
37. La Rosa FA, Pierce JW, and Sonenshein GE. Differential regulation of the c-*myc* oncogene promoter by the NF-κB rel family of transcription factors. *Mol Cell Biol* 14: 1039–1044, 1994.
38. Li Q and Verma IM. NF-κB regulation in the immune system. *Nat Rev Immunol* 2: 725–734, 2002.
39. Madrid LV and Baldwin AS Jr. Regulation of NF-κB by oncoproteins and tumor suppressor proteins. *Methods Mol Biol* 223: 523–532, 2003.
40. Meyer M, Schreck R, and Baeuerle PA. H2O2 and antioxidants have opposite effects on activation of NF-κB and AP-1 in intact cells: AP-1 as secondary antioxidant-responsive factor. *EMBO J* 12: 2005–2015, 1993.
41. Mitsiades N, Mitsiades CS, Poulaki V, Chauhan D, Fanourakis G, Gu X, Bailey C, Joseph M, Libermann TA, Treon SP, Munshi NC, Richardson PG, Hideshima T, and Anderson KC. Molecular sequelae of proteasome inhibition in human multiple myeloma cells. *Proc Natl Acad Sci USA* 99: 14374–14379, 2002.
42. Mitsiades N, Mitsiades CS, Poulaki V, Chauhan D, Richardson PG, Hideshima T, Munshi N, Treon SP, and Anderson KC. Biologic sequelae of nuclear factor-κB blockade in multiple myeloma: therapeutic applications. *Blood* 99: 4079–4086, 2002.
43. Mohan N and Meltz ML. Induction of nuclear factor κB after low-dose ionizing radiation involves a reactive oxygen intermediate signaling pathway. *Radiat Res* 140: 97–104, 1994.
44. Moynagh PN, Williams DC, and O'Neill LA. Activation of NF-κB and induction of vascular cell adhesion molecule-1 and intracellular adhesion molecule-1 expression in human glial cells by IL-1. Modulation by antioxidants. *J Immunol* 153: 2681–2690, 1994.
45. Nabel G and Baltimore D. An inducible transcription factor activates expression of human immunodeficiency virus in T cells. *Nature* 326: 711–713, 1987.
46. Nakanishi C and Toi M. Nuclear factor-κB inhibitors as sensitizers to anticancer drugs. *Nat Rev Cancer* 5: 297–309, 2005.
47. Ni H, Ergin M, Huang Q, Qin JZ, Amin HM, Martinez RL, Saeed S, Barton K, and Alkan S. Analysis of expression of nuclear factor κB (NF-κB) in multiple myeloma: downregulation of NF-κB induces apoptosis. *Br J Haematol* 115: 279–286, 2001.
48. Orlowski RZ, Eswara JR, Lafond-Walker A, Grever MR, Orlowski M, and Dang CV. Tumor growth inhibition induced in a murine model of human Burkitt's lymphoma by a proteasome inhibitor. *Cancer Res* 58: 4342–4348, 1998.
49. Padilla J, Leung E, and Phipps RP. Human B lymphocytes and B lymphomas express PPAR-gamma and are killed by PPAR-gamma agonists. *Clin Immunol* 103: 22–33, 2002.
50. Pahl HL. Activators and target genes of Rel/NF-κB transcription factors. *Oncogene* 18: 6853–6866, 1999.
51. Pham LV, Tamayo AT, Yoshimura LC, Lo P, Terry N, Reid PS, and Ford RJ. A CD40 signalosome anchored in lipid rafts leads to constitutive activation of NF-κB and autonomous cell growth in B cell lymphomas. *Immunity* 16: 37–50, 2002.
52. Pikarsky E, Porat RM, Stein I, Abramovitch R, Amit S, Kasem S, Gutkovich-Pyest E, Urieli-Shoval S, Galun E, and Ben-Neriah Y. NF-κB functions as a tumour promoter in inflammation-associated cancer. *Nature* 431: 461–466, 2004.
53. Piva R, Gianferretti P, Ciucci A, Taulli R, Belardo G, and Santoro MG. 15-Deoxy-delta 12,14-prostaglandin J2 induces apoptosis in human malignant B cells: an effect associated with inhibition of NF-κB activity and down-regulation of antiapoptotic proteins. *Blood* 105: 1750–1758, 2005.
54. Prasad AV, Mohan N, Chandrasekar B, and Meltz ML. Activation of nuclear factor κB in human lymphoblastoid cells by low-dose ionizing radiation. *Radiat Res* 138: 367–372, 1994.
55. Ravi R and Bedi A. NF-κB in cancer—a friend turned foe. *Drug Resist Updat* 7: 53–67, 2004.
56. Rayet B and Gelinas C. Aberrant rel/nfkb genes and activity in human cancer. *Oncogene* 18: 6938–6947, 1999.
57. Rong BL, Libermann TA, Kogawa K, Ghosh S, Cao LX, Pavan-Langston D, and Dunkel EC. HSV-1-inducible proteins bind to NF-κB-like sites in the HSV-1 genome. *Virology* 189: 750–756, 1992.
58. Rossi A, Elia G, and Santoro MG. 2-Cyclopenten-1-one, a new inducer of heat shock protein 70 with antiviral activity. *J Biol Chem* 271: 32192–32196, 1996.
59. Rossi A, Elia G, and Santoro MG. Inhibition of nuclear factor κB by prostaglandin A1: an effect associated with heat shock transcription factor activation. *Proc Natl Acad Sci USA* 94: 746–750, 1997.
60. Rossi A, Kapahi P, Natoli G, Takahashi T, Chen Y, Karin M, and Santoro MG. Anti-inflammatory cyclopentenone

prostaglandins are direct inhibitors of IκB kinase. *Nature* 403: 103–108, 2000.
61. Rothwarf DM, Zandi E, Natoli G, and Karin M. IKK-gamma is an essential regulatory subunit of the IκB kinase complex. *Nature* 395: 297–300, 1998.
62. Sakurai H, Suzuki S, Kawasaki N, Nakano H, Okazaki T, Chino A, Doi T, and Saiki I. Tumor necrosis factor-alpha-induced IKK phosphorylation of NF-κB p65 on serine 536 is mediated through the TRAF2, TRAF5, and TAK1 signaling pathway. *J Biol Chem* 278: 36916–36923, 2003.
63. Santoro MG. Antiviral activity of cyclopentenone prostanoids. *Trends Microbiol* 5: 276–281, 1997.
64. Santoro MG, Crisari A, Benedetto A, and Amici C. Modulation of the growth of a human erythroleukemic cell line (K562) by prostaglandins: antiproliferative action of prostaglandin A. *Cancer Res* 46: 6073–6077, 1986.
65. Santoro MG, Garaci E and Amici C. Prostaglandins with antiproliferative activity induce the synthesis of a heat shock protein in human cells. *Proc Natl Acad Sci USA* 86: 8407–8411, 1989.
66. Santoro MG, Rossi A, and Amici C. NF-κB and virus infection: who controls whom. *EMBO J* 22: 2552–2560, 2003.
67. Sassone-Corsi P, Wildeman A, and Chambon P. A *trans*-acting factor is responsible for the simian virus 40 enhancer activity in vitro. *Nature* 313: 458–463, 1985.
68. Schreck R and Baeuerle PA. Assessing oxygen radicals as mediators in activation of inducible eukaryotic transcription factor NF-κB. *Meth Enzymol* 234: 151–163, 1994.
69. Schreck R, Rieber P, and Baeuerle PA. Reactive oxygen intermediates as apparently widely used messengers in the activation of the NF-κB transcription factor and HIV-1. *EMBO J* 10: 2247–2258, 1991.
70. Schreck R, Meier B, Mannel DN, Droge W, and Baeuerle PA. Dithiocarbamates as potent inhibitors of nuclear factor κB activation in intact cells. *J Exp Med* 175: 1181–1194, 1992.
71. Sen R and Baltimore D. Multiple nuclear factors interact with the immunoglobulin enhancer sequences. *Cell* 46: 705–716, 1986.
72. Senftleben U, Cao Y, Xiao G, Greten FR, Krahn G, Bonizzi G, Chen Y, Hu Y, Fong A, Sun SC, and Karin M. Activation by IKKα of a second, evolutionary conserved, NF-κB signaling pathway. *Science* 293: 1495–1499, 2001.
73. Straus DS and Glass CK. Cyclopentenone prostaglandins: new insights on biological activities and cellular targets. *Med Res Rev* 21: 185–210, 2001.
74. Straus DS, Pascual G, Li M, Welch JS, Ricote M, Hsiang CH, Sengchanthalangsy LL, Ghosh G, and Glass CK. 15-deoxy-delta 12,14-prostaglandin J2 inhibits multiple steps in the NF- κB signaling pathway. *Proc Natl Acad Sci USA* 97: 4844–4849, 2000.
75. Tak PP and Firestein GS. NF-κB: a key role in inflammatory diseases. *J Clin Invest* 107: 7–11, 2001.
76. Tergaonkar V, Pando M, Vafa O, Wahl G, and Verma I. p53 stabilization is decreased upon NFkappaB activation: a role for NFκB in acquisition of resistance to chemotherapy. *Cancer Cell* 1: 493–503, 2002.
77. Yamagishi N, Miyakoshi J, and Takebe H. Enhanced radiosensitivity by inhibition of nuclear factor κB activation in human malignant glioma cells. *Int J Radiat Biol* 72: 157–162, 1997.
78. Yamamoto Y, Yin MJ, Lin KM, and Gaynor RB. Sulindac inhibits activation of the NF-κB pathway. *J Biol Chem* 274: 27307–27314, 1999.
79. Yin MJ, Yamamoto Y, and Gaynor RB. The anti-inflammatory agents aspirin and salicylate inhibit the activity of IκB kinase-beta. *Nature* 396: 77–80, 1998.
80. Zhong H, Voll RE, and Ghosh S. Phosphorylation of NF-κB p65 by PKA stimulates transcriptional activity by promoting a novel bivalent interaction with the coactivator CBP/p300. *Mol Cell* 1: 661–671, 1998.

Address reprint requests to:
M. Gabriella Santoro
Department of Biology
University of Rome Tor Vergata
Via della Ricerca Scientifica
00133 Rome, Italy

E-mail: santoro@bio.uniroma2.it

Received after final revision October 4, 2005; accepted October 8, 2005.

This article has been cited by:

1. Cristina Cruz-Teno, Pablo Pérez-Martínez, Javier Delgado-Lista, Elena M. Yubero-Serrano, Antonio García-Ríos, Carmen Marín, Purificación Gómez, Yolanda Jiménez-Gómez, Antonio Camargo, Fernando RodríguezCantalejo, Maria M. Malagón, Francisco Pérez-Jiménez, Helen M. Roche, José López-Miranda. 2012. Dietary fat modifies the postprandial inflammatory state in subjects with metabolic syndrome: the LIPGENE study. *Molecular Nutrition & Food Research* **56**:6, 854-865. [CrossRef]
2. Catherine A. Vaughan, Shilpa Singh, Brad Windle, Heidi M. Sankala, Paul R. Graves, W. Andrew Yeudall, Swati P. Deb, Sumitra Deb. 2011. p53 mutants induce transcription of NF-#B2 in H1299 cells through CBP and STAT binding on the NF-#B2 promoter and gain of function activity. *Archives of Biochemistry and Biophysics* . [CrossRef]
3. Sarah Frankland-Searby, Sukesh R. Bhaumik. 2011. The 26S proteasome complex: An attractive target for cancer therapy. *Biochimica et Biophysica Acta (BBA) - Reviews on Cancer* . [CrossRef]
4. Xiang Lu, Hui Zhang, Xi Li, Guo Chen, Qing-Shan Li, Yin Luo, Ban-Feng Ruan, Xian-Wei Chen, Hai-Liang Zhu. 2011. Design, synthesis and biological evaluation of pyridine acyl sulfonamide derivatives as novel COX-2 inhibitors. *Bioorganic & Medicinal Chemistry* . [CrossRef]
5. Richard C. Zangar, Nikki Bollinger, Thomas J. Weber, Ruimin M. Tan, L. Meng Markillie, Norman J. Karin. 2011. Reactive oxygen species alter autocrine and paracrine signaling. *Free Radical Biology and Medicine* . [CrossRef]
6. Huirong Jing, Gang Shen, Guangzhi Wang, Feng Zhang, Yubing Li, Fuwen Luo, Jihong Yao, Xiao-Feng Tian. 2011. MG132 Alleviates Liver Injury Induced by Intestinal Ischemia/Reperfusion in Rats: Involvement of the AhR and NF#B Pathways. *Journal of Surgical Research* . [CrossRef]
7. Jamunarani Veeraraghavan, Mohan Natarajan, Pallavi Lagisetty, Vibhudutta Awasthi, Terence S. Herman, Natarajan Aravindan. 2011. Impact of Curcumin, Raspberry Extract, and Neem Leaf Extract on Rel Protein-Regulated Cell Death/ Radiosensitization in Pancreatic Cancer Cells. *Pancreas* 1. [CrossRef]
8. Dong-Wook Han, Mi Hee Lee, Hak Hee Kim, Suong-Hyu Hyon, Jong-Chul Park. 2011. Epigallocatechin-3-gallate regulates cell growth, cell cycle and phosphorylated nuclear factor-#B in human dermal fibroblasts. *Acta Pharmacologica Sinica* **32**:5, 637-646. [CrossRef]
9. Wen Li, Shuji Kubo, Akico Okuda, Hideyuki Yamamoto, Haruyasu Ueda, Toshiyuki Tanaka, Hideji Nakamura, Hiromichi Yamanishi, Nobuyuki Terada, Haruki Okamura. 2010. Effect of IL-18 on Expansion of ## T Cells Stimulated by Zoledronate and IL-2. *Journal of Immunotherapy* **33**:3, 287-296. [CrossRef]
10. Rajan S. Giri, Hardik M. Thaker, Tony Giordano, Jill Williams, Donna Rogers, Kamala K. Vasu, Vasudevan Sudarsanam. 2010. Design, synthesis and evaluation of novel 2-thiophen-5-yl-3H-quinazolin-4-one analogues as inhibitors of transcription factors NF-#B and AP-1 mediated transcriptional activation: Their possible utilization as anti-inflammatory and anti-cancer agents. *Bioorganic & Medicinal Chemistry* **18**:7, 2796-2808. [CrossRef]
11. Rakhesh Madhusoodhanan, Mohan Natarajan, Jamunarani Veeraraghavan Nisha Singh, Ambarish Jamgade, Vibhudutta Awasthi, Shrikant Anant, Terence S. Herman, Natarajan Aravindan. 2009. Effect of Black Raspberry Extract in Inhibiting NF# B Dependent Radioprotection in Human Breast Cancer Cells. *Nutrition and Cancer* **62**:1, 93-104. [CrossRef]
12. J.C. Gallardo-PÃ©rez, M. Espinosa, G. Ceballos-Cancino, A. Daniel, S. RodrÃguez-EnrÃquez, A. Aviles, R. Moreno-SÃ¡nchez, J. Melendez-Zajgla, V. Maldonado. 2009. NF-kappa B is required for the development of tumor spheroids. *Journal of Cellular Biochemistry* **108**:1, 169-180. [CrossRef]
13. Ling Li, Anna Hsu, Philip K. Moore. 2009. Actions and interactions of nitric oxide, carbon monoxide and hydrogen sulphide in the cardiovascular system and in inflammation — a tale of three gases!. *Pharmacology & Therapeutics* **123**:3, 386-400. [CrossRef]
14. M. Redpath, C.M.G. Marques, C. Dibden, A. Waddon, R. Lalla, S. MacNeil. 2009. Ibuprofen and hydrogel-released ibuprofen in the reduction of inflammation-induced migration in melanoma cells. *British Journal of Dermatology* **161**:1, 25-33. [CrossRef]
15. Natarajan Aravindan, Sumathy Mohan, Terence S Herman, Mohan Natarajan. 2009. Nitric oxide-mediated inhibition of NF#B regulates hyperthermia-induced apoptosis. *Journal of Cellular Biochemistry* **106**:6, 999-1009. [CrossRef]
16. Daljinder K. Kahlon, Theresa A. Lansdell, Jason S. Fisk, Jetze J. Tepe. 2009. Structural–activity relationship study of highly-functionalized imidazolines as potent inhibitors of nuclear transcription factor-#B mediated IL-6 production. *Bioorganic & Medicinal Chemistry* **17**:8, 3093-3103. [CrossRef]

17. Rodrigo Franco, Roberto Sánchez-Olea, Elsa M. Reyes-Reyes, Mihalis I. Panayiotidis. 2009. Environmental toxicity, oxidative stress and apoptosis: Ménage à Trois. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis* **674**:1-2, 3-22. [CrossRef]
18. Philipp Baumann, Karin Müller, Sonja Mandl-Weber, Johann Leban, Robert Doblhofer, Astrid Ammendola, Roland Baumgartner, Fuat Oduncu, Ralf Schmidmaier. 2009. The peptide-semicarbazone S-2209, a representative of a new class of proteasome inhibitors, induces apoptosis and cell growth arrest in multiple myeloma cells. *British Journal of Haematology* **144**:6, 875-886. [CrossRef]
19. D.D. O'Rielly, C.W. Loomis. 2008. Spinal nerve ligation–induced activation of nuclear factor kappaB is facilitated by prostaglandins in the affected spinal cord and is a critical step in the development of mechanical allodynia. *Neuroscience* **155**:3, 902-913. [CrossRef]
20. Giuseppe M. Campo, Angela Avenoso, Salvatore Campo, Angela D'Ascola, Paola Traina, Dario Samà, Alberto Calatroni. 2008. NF-kB and caspases are involved in the hyaluronan and chondroitin-4-sulphate-exerted antioxidant effect in fibroblast cultures exposed to oxidative stress. *Journal of Applied Toxicology* **28**:4, 509-517. [CrossRef]
21. Junwu Su, Xuemei Li, Xizhong Cui, Yan Li, Yvonne Fitz, Lewis Hsu, Haresh Mani, Martha Quezado, Peter Q. Eichacker. 2008. Ethyl pyruvate decreased early nuclear factor-??B levels but worsened survival in lipopolysaccharide-challenged mice*. *Critical Care Medicine* **36**:4, 1059-1067. [CrossRef]
22. R. Piva, B. Ruggeri, M. Williams, G. Costa, I. Tamagno, D. Ferrero, V. Giai, M. Coscia, S. Peola, M. Massaia, G. Pezzoni, C. Allievi, N. Pescalli, M. Cassin, S. di Giovine, P. Nicoli, P. de Feudis, I. Strepponi, I. Roato, R. Ferracini, B. Bussolati, G. Camussi, S. Jones-Bolin, K. Hunter, H. Zhao, A. Neri, A. Palumbo, C. Berkers, H. Ovaa, A. Bernareggi, G. Inghirami. 2008. CEP-18770: A novel, orally active proteasome inhibitor with a tumor-selective pharmacologic profile competitive with bortezomib. *Blood* **111**:5, 2765-2775. [CrossRef]
23. Yin-Shan Yeung, Chi-Wai Yip, Chung-Chau Hon, Ken Y.C. Chow, Iris C.M. Ma, Fanya Zeng, Frederick C.C. Leung. 2008. Transcriptional profiling of Vero E6 cells over-expressing SARS-CoV S2 subunit: Insights on viral regulation of apoptosis and proliferation. *Virology* **371**:1, 32-43. [CrossRef]
24. Sataro Goto, Hisashi Naito, Takao Kaneko, Hae Young Chung, Zsolt Radák. 2007. Hormetic effects of regular exercise in aging: correlation with oxidative stress. *Applied Physiology, Nutrition, and Metabolism* **32**:5, 948-953. [CrossRef]
25. L R Saunders, E Verdin. 2007. Sirtuins: critical regulators at the crossroads between cancer and aging. *Oncogene* **26**:37, 5489-5504. [CrossRef]
26. Qing Lan, Tongzhang Zheng, Min Shen, Yawei Zhang, Sophia S. Wang, Shelia H. Zahm, Theodore R. Holford, Brian Leaderer, Peter Boyle, Stephen Chanock. 2007. Genetic polymorphisms in the oxidative stress pathway and susceptibility to non-Hodgkin lymphoma. *Human Genetics* **121**:2, 161-168. [CrossRef]
27. Vittorio Calabrese , Mahin D. Maines . 2006. Antiaging Medicine: Antioxidants and Aging. *Antioxidants & Redox Signaling* **8**:3-4, 362-364. [Citation] [Full Text PDF] [Full Text PDF with Links]