Gene Expression, Vol. 7, pp. 233–245, 1999
Printed in the USA.

1052-2166/99 $10.00 + .00

Regulation of NF-κB by the HTLV-1 Tax Protein

XIAO HUA LI AND RICHARD B. GAYNOR[1]

Division of Hematology-Oncology, Department of Medicine, Harold Simmons Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX 75235-8594

The Tax protein encoded by the human T-cell leukemia virus type 1 (HTLV-1) activates viral gene expression via the ATF/CREB pathway. Tax also induces a variety of cellular genes through activation of the transcription factor NF-κB. The ability of Tax to activate the NF-κB pathway plays an essential role in HTLV-1-induced cellular transformation. This review briefly summarizes the remarkable discoveries of the past several years that have greatly advanced our knowledge on signal-mediated activation of the NF-κB pathway. It highlights our current understanding of how viral agents like Tax modulate cellular signaling machinery to activate the NF-κB pathway.

HTLV-1 Tax protein NF-κB

HTLV-1 AND Tax

Human T-cell leukemia virus type 1 (HTLV-1) induces the proliferation of CD4-positive human T cells and is the etiological agent for the aggressive malignancy of activated CD4-positive T cells termed adult T-cell leukemia (35,85,102,120,121). Unlike most oncoviruses, HTLV-1 dose not contain a cellular oncogene but instead utilizes the virus-encoded transactivator, Tax, to transform human T cells [for a review see (88)]. Tax is able to transform cultured cells (86,95,100) and can also induce tumors in transgenic mice (47,81).

HTLV-1 gene expression is controlled by the viral long terminal repeat (LTR), which contains three 21-bp repeat regulatory elements that are crucial for Tax-mediated increases in gene expression (23,34). Though Tax itself does not specifically bind to DNA, it interacts with members of the ATF/CREB family of transcription factors and facilitates their increased binding affinity to the 21-bp repeats (9,14,19,84,109, 116,118,124). In addition, Tax is able to interact with the cellular coactivator CREB binding protein (CBP) on the HTLV-1 21-bp repeats (64). The Tax/CREB/CBP ternary complex may act as a scaffold to recruit additional regulatory components to the HTLV-1 LTR for viral gene expression (2,41).

The ability of Tax to activate diverse cellular genes may contribute directly to increases in T-cell proliferation early in the course of HTLV-1 infection that ultimately leads to lymphocyte transformation and to the development of adult T-cell leukemia. Cellular genes that are regulated by Tax include those involved in T-cell activation and growth such as the interleukin-2 (IL-2) gene and the gene encoding the alpha chain of IL-2 receptor (IL-2Rα) (29,54,71,94). Activation of cellular gene expression by Tax is thought to be manifested primarily through the NF-κB pathway. Both HTLV-1-infected and Tax-transfected T lymphocytes contain increased levels of NF-κB in the nucleus (65). In addition, Tax colocalizes with NF-κB in subnuclear regions that contain specific RNA transcripts from a promoter containing NF-κB binding sites (16,17,91). This suggests that Tax may function as a transcriptional cofactor acting cooperatively with NF-κB in the nucleus. However Tax-mediated NF-κB activation is thought to be primarily regulated at the level of NF-κB nuclear translocation (42,57,65,97,99). Induction of NF-κB nuclear migration by Tax occurs in the cytoplasm. For

[1]Address correspondence to Richard B. Gaynor, Division of Hematology-Oncology, Department of Medicine, U.T. Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75235-8594. Tel: (214) 648-7570; Fax: (214) 648-8862; E-mail: gaynor@utsw.swmed.edu

example, a Tax mutant defective in nuclear transport is still able to activate NF-κB-dependent transcription (82). The topic of Tax-mediated activation of NF-κB nuclear transport will be further discussed in later sections.

NF-κB REGULATION

NF-κB comprises a family of homo- and heterodimeric transcription factors. These proteins were first identified as transcriptional regulators that bind to the enhancer elements in the kappa light-chain gene in murine B lymphocytes (92). Subsequently, it was found that it is a ubiquitious transcription factor present in nearly all types of human cells. Homologous proteins have been also found in species like insects (33,55,96).

In mammalian cells, NF-κB comprises at least five members including NF-κB1 (p50 and p105), NF-κB2 (p52 and p100), RelA (p65), RelB, and c-Rel (6–8,10,40,93,108) (Fig. 1A). These proteins share a conserved amino-terminal Rel homology domain (RHD) of 300 amino acids that confers DNA binding, dimerization, and nuclear transport. RelA, RelB, and c-Rel contain divergent carboxy-terminal transactivation domains. The p50 and p52 proteins are the proteolytically processed forms of p105 and p100, respectively, and contain the amino-terminal RHD. The carboxy-terminus of the precusor proteins p105 and p100 contains ankyrin-like motifs and can act as inhibitors (see below) that interact with NF-κB and prevent its nuclear translocation. Active forms of NF-κB are commonly heterodimers that usually consist of p65 (RelA) and p50. Other subunits, such as RelB, c-Rel, and p52, may also be part of active NF-κB heterodimers. Different forms of NF-κB may activate different sets of target genes or be involved in tissue-specific activation.

NF-κB can function in conjunction with other transcription factors such as AP1 (activation protein 1) and NF-IL-6 (nuclear factor of interleukin-6) [(1) and references therein]. Cellular genes activated by NF-κB are involved in the regulation of the immune and inflammatory response [for recent reviews see (11,40)] in addition to other functions including the regulation of cell growth, apoptosis, and virus replication (46,104,110,111). These genes include those encoding proinflammatory cytokines such as TNF-α, IL-1, IL-6; chemotactic cytokines (chemokines) such as IL-8 that attract inflammatory cells to sites of inflammation; enzymes that generate mediators of inflammation; immune receptors such as the IL-2 receptor alpha chain (IL-2Rα); immunoregulatory molecules such as MHC class I and II, TCR-α and -β, IL-2, and β interferon (IFN-β); adhesion molecules that play a key part in the initial recruitment of leukocytes to sites of inflammation; acute phase response proteins; transcription factors such as c-myc, p53, the NF-κB subunits NF-κB1 and NF-κB2, and the NF-κB inhibitors IκBα and IκBε (11,40,83). Due to its ability to activate such diverse and important regulatory genes, NF-κB has become one of the most extensively studied transcription factors.

REGULATION OF NF-κB ACTIVATION

Products of a number of genes that are regulated by NF-κB can also stimulate its activation. For example, the proinflammatory cytokines IL-1 and TNF-α activate the NF-κB pathway and can also be activated by NF-κB (7,93). This positive feedback loop may amplify and perpetuate the inflammatory response in the absence of exogenous stimuli and thus contribute to the pathogenesis of chronic inflammatory disorders (11). In addition, genes encoding specific NF-κB inhibitory proteins like IκBα are also transactivated by NF-κB through κB recognition sequences in their promoter regions (22,98). Free IκB proteins can enter the nucleus, interact with NF-κB, and cause dissociation of preformed NF-κB–DNA complexes (122). These altogether provide a negative feedback loop that may contribute to specifically timed activation of NF-κB-responsive gene expression.

The most striking feature involved in activating NF-κB is a process that occurs in the cytoplasm and involves the degradation of a family of inhibitory proteins known as IκB (5,108). In most cells, NF-κB is sequestered by IκB proteins in the cytoplasm. IκB interaction with NF-κB masks the NF-κB nuclear localization signal and keeps NF-κB retained in the cytoplasm (12,38,45). Upon stimulation of cells by a variety of agents including TNF-α, IκBα is rapidly phosphorylated at residues Ser32 and Ser36 (Fig. 1B) or similar positioned amino-terminal serine phosphorylation sites in either IκBβ and IκBε (20,21,31, 101,112). The phosphorylated form of IκB is subject to polyubiqitination and 26S proteasome-mediated proteolytic degradation to result in NF-κB nuclear translocation and activation of gene expression (24,31). Numerous agents can trigger this process, including proinflammatory cytokines in addition to a variety of stimuli such as bacterial lipopolysaccharide (LPS), viral products like the Tax protein, mitogens like phorbol esters, UV light, and oxidants (6,63,93). Interestingly, phosphorylation of the IκB protein at these specific serine sites appears to be an important juncture at which all of these stimulatory pathways converge. Identification of the inducible kinases that

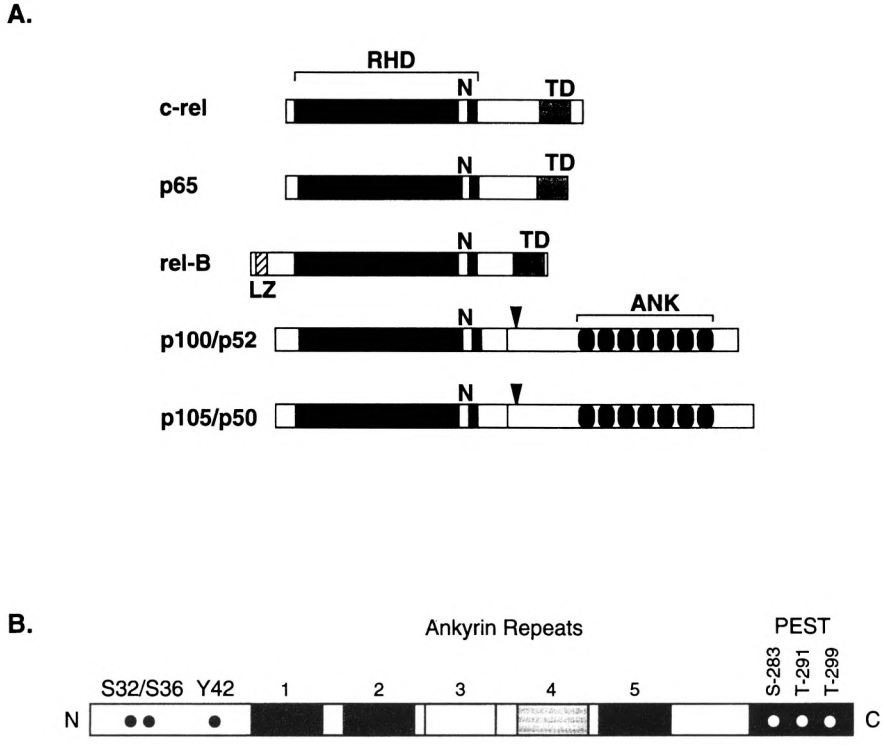

FIG. 1. Schematic of NF-κB and IκBα. (A) A schematic of the NF-κB family of proteins is shown with the Rel homology domain (RHD), the transactivation domain (TD), the nuclear localization signal (N), and the ankyrin repeats (ANK) indicated. (B) The IκBα protein is indicated with the position of serine residues 32 and 36, the five ankyrin repeats, and potential phosphorylation sites in the C-terminal PEST domain indicated.

result in amino-terminal phosphorylation of IκB and their regulation is a major issue in understanding NF-κB regulation.

IκB KINASES: IKKα AND IKKβ

The first reports about a putative IκB kinase described the partial purification and characterization of a high molecular weight (~700 kDa) kinase complex isolated from untreated HeLa cells. This kinase phosphorylated Ser32 and Ser36 of IκBα in an ubiquitination-dependent manner and could be activated by treatment of cells with the phosphatase inhibitor okadaic acid (24). The activity of a similar kinase complex was stimulated by treatment of cells with TNF-α or treatment of the purified kinase complex with the MAP3K family member MEKK1 (mitogen-activated protein kinase/extracellular signal-regulated kinase kinase 1) (66). MEKK1 activates the c-Jun N-terminal kinase/stress activated protein kinase (JNK/SAPK) pathway leading to activation of AP1 in response to TNF-α treatment of cells (30,90,115). The fact that MEKK1 increases NF-κB-mediated gene expression in transfected cells and stimulates phosphorylation of IκBα in vitro (49,66) has led to speculation that the signal transduction pathways leading to IκB phosphorylation might involve components of the MAP kinase pathway. This possibility is supported by an independent discovery that another MAP3K homolog protein, NIK (NF-κB inducing kinase), binds to both the TNF receptor-associated protein TRAF2 and the IL-1 receptor-associated protein TRAF6. Thus, NIK may be a common mediator of both TNF-α and IL-1 signal transduction pathways (70).

The first kinase that specifically phosphorylates IκBα was discovered using a yeast two-hybrid screen with NIK as the bait (87). The protein identified was a previously isolated kinase termed CHUK (later renamed as IKKα or IKK1) (28,75). Several observations suggest that this kinase is a NIK-activated IκB kinase that links TNF-α- and IL-1-induced signal transduction cascades to NF-κB activation (87). First, overexpression of CHUK activates an NF-κB-dependent reporter gene. Second, a catalytically inactive mutant of CHUK is a dominant-negative inhibitor of TNF-α-, IL-1-, TRAF-, and NIK-induced NF-κB activation. In addition, CHUK interacts with IκBα and specifically phosphorylates IκBα on both serine resi-

dues 32 and 36. Finally, the phosphorylation of IκBα by CHUK is greatly enhanced by NIK costimulation.

Shortly after the discovery of IKKα, a second IKK (IKKβ or IKK2) was identified by utilizing a cDNA database to search for genes having homology with CHUK or IKKα (113). Independent studies by several groups resulted in the biochemical characterization and molecular cloning of both IKKα and IKKβ from the 700–900-kDa IKK complex isolated from TNF-α-treated HeLa cells (32,74,123). These two kinases share 51% amino acid sequence homology and both contain a kinase domain, a leucine zipper domain necessary for dimerization, and a helix–loop–helix domain presumably involved in interactions with essential regulatory subunits (74,123). Though both proteins can undergo homotypic or heterotypic dimerization, the heterodimer form has been suggested to be the predominant state of this kinase (113).

Given that both immunoprecipitates containing IKK (32,74,123) and recombinant IKKα and IKKβ (67) can phosphorylate IκBα and/or IκBβ at specific serine residues, these proteins are likely to be bona fide IκB kinases. Furthermore, the activity of both kinases can be stimulated by NIK and either IL-1 or TNF-α treatment. Dominant-negative IKKs or NIK can also inhibit TNF-α- and IL-1-induced NF-κB activation. Although both proteins contribute to IκB kinase activity (113,123), IKKβ appears to be a more potent IκB kinase than IKKα (74,113). In addition, the substrate specificity of the two IKK subunits for IκBα and IκBβ appears to be slightly different (113).

The question of whether both NIK and MEKK1 are direct upstream kinases that regulate IKK activity is not clear at the present time. Evidence supporting a direct role for NIK in IKK activation is based on the fact that IKKα and IKKβ associate with NIK both in vivo and in vitro (27,87,113). NIK is also detected in the 700-kDa IKK complex (27). Transfection experiments demonstrate that NIK can activate IKKα and IKKβ activity (87,113). However, no evidence has been presented that demonstrates that IKK activation is directly mediated by NIK.

Data indicate that MEKK1 might be a direct activator of IKK kinase activity (67,117). In one study (67), MEKK1 was shown to induce the in vivo activation of both IKKα and IKKβ. In addition, MEEK1 is present in the inducible, high-molecular-weight IκB kinase complex (74). Treatment of the IKK complex with purified MEKK1 induces phosphorylation of IKKα in vitro (67). Conversely, it was shown that incubation of purified catalytic domain of MEKK1 with IKKs increases IKKα but not IKKβ phosphorylation of IκBα (117). Furthermore, recombinant MEKK1 is able to phosphorylate IKKβ in vitro (117). The discrepancy regarding whether MEKK1 only activates IKKβ or both IKKα and IKKβ may be due to differences in the experimental methods used in these different studies. Further studies are needed to determine whether NIK, MEKK1, or other kinases are all directly involved in the phosphorylation and activation of IKKs and whether NIK and MEKK1 have different substrate specificity.

CHARACTERIZATION OF COMPONENTS OF THE IKK COMPLEX

One interesting feature of the IKKα and IKKβ kinases is that they exist in a large complex with several other components including MEKK1, NIK, RelA, p50, and IκBα (27,74,89). The identification of several novel proteins that are not kinases yet are presented in the IKK complex (27,74,89,114) suggests that these proteins may have regulatory functions. A protein designated IKKγ was found in an IKK complex purified using a monoclonal antibody against IKKα (89). Molecular cloning and sequencing indicated that IKKγ was composed of several potential coiled-coil motifs and interacts preferentially with IKKβ to activate the IKK complex. An IKKγ carboxy-terminal truncation mutant that still binds to IKKβ blocks the activation of IKKβ in response to TNF-α but has only a small effect on basal kinase activity. Using genetic complementation experiments with cell lines that were unresponsive to stimuli that activate NF-κB (114), a protein designated NEMO (NF-κB Essential Modulator) was identified. NEMO is the mouse homologue of IKKγ. Thus, IKKγ/NEMO has been suggested to be a mediator that connects the IKK proteins with upstream activators.

A second regulatory component was recently identified in an IKK complex purified from IL-1-treated cells and was named IKAP (IKK-complex-associated protein) (27). IKAP interacts directly with NIK, IKKα, and IKKβ and potentially regulates the activity of these three kinases. It has been suggested that IKAP functions as a scaffold protein, which is involved in the formation of the IKK complex. Indeed, the highest level of IKK activity is achieved when NIK, IKKα, and IKKβ are coexpressed together with IKAP in transfected cells. The role of another protein that chromatographed with IKK was identified as MAP kinase phosphatase-1 (74). The function of this protein in regulating IKK activity remains to be elucidated.

It is plausible to speculate that the IKK complex may act as an intrinsic control system that involves both positive and negative regulatory mechanisms. IKKα and IKKβ receive signals transmitted by a va-

riety of pathways activated by different stimuli. At the same time, their activation leads to upregulation of diverse NF-κB-dependent genes involved in a variety of functions. Thus, it is expected that IKK complex must have a highly sophisticated regulatory machinery. This machinery must have the ability to intrinsically regulate itself in order to process as well as to transmit information to allow diverse biological events to occur. In this scenario, it may not be surprising that the catalytic subunits of IKKα and IKKβ are contained within a large protein complex together with several different regulatory components. As suggested in a recent review (4), a large protein complex may not be easily accessible to low-molecular-weight inhibitory molecules that can readily downregulate the IKK pathway.

ASPIRIN INHIBITS IKKβ KINASE ACTIVITY

Because NF-κB is one of the key factors that regulates the immune and inflammatory response, determining the specific pathways that modulate its activity is critical for better understanding the pathogenesis of immune and inflammatory disorders (Fig. 2). Potentially this will provide new insights for designing highly specific and potent drugs. We will use the following example to illustrate how recent advances in our knowledge in signal-mediated NF-κB activation has allowed us to better understand the effects of the widely used drug, aspirin.

Some nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin and other aspirin-like agents, block NF-κB activity (43,62) by preventing the degradation of IκB (62). This function of aspirin is independent of its effects on inhibiting cyclo-oxygenase activity and therefore prostaglandin synthesis (106,107). Because IKKα and IKKβ are key proteins in regulating IκBα protein levels in response to various stimuli, it was possible that these kinases are a direct target for aspirin-like agents. One recent study from our laboratory has clearly demonstrated such a link (119). Both aspirin and its derivative sodium salicylate, but not the cyclo-oxygenase inhibitor indomethacin, markedly reduce IKKβ kinase activity and NF-κB activation. The effect of these drugs is due to their direct binding to IKKβ but not IKKα, to inhibit ATP binding.

Tax-MEDIATED NUCLEAR TRANSPORT OF NF-κB

Studies have suggested that Tax-mediated activation of NF-κB is due to inducing a process in the cytoplasm of cells that triggers NF-κB nuclear localization. Two mechanisms have been proposed to be involved in this process. Tax has been reported to directly interact in the cytoplasm with the NF-κB precusors p100 and p105 (15,48,59,78). These proteins can function as cytoplasmic inhibitors of RelA nuclear localization through their ankyrin repeats. This interaction may overcome the cytoplasmic sequestration of p65 by p100 and p105, to permit the cyto-

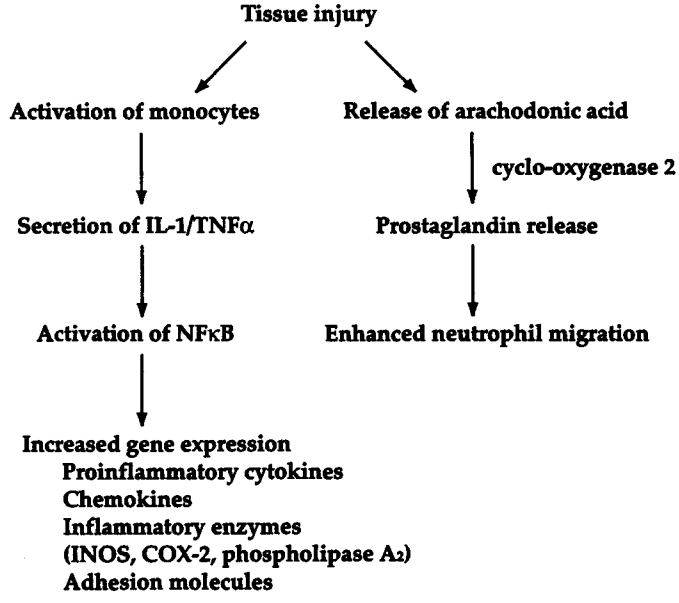

FIG. 2. Pathogenesis of the inflammatory response. Two major pathways that mediate the inflammatory response are indicated. One pathway leads to the generation of prostaglandins and is catalyzed by cyclo-oxygenase 2 whereas the other pathway is mediated by activation of NF-κB.

plasmic release and nuclear transport of p65 (15,59, 76,77).

Alternatively, Tax may activate a signal transduction pathway that leads to phosphorylation and degradation of IκB. The constitutive nuclear translocation of NF-κB, which is associated with increased phosphorylation and degradation of both IκBα and IκBβ, is found in both HTLV-1-infected and Tax-transfected cells. This suggests that Tax may induce the nuclear localization of NF-κB by acting prior to or at the level of IκB phosphorylation (20,42,58,65,73,97). Furthermore, IκB mutants lacking the two N-terminal serine sites phosphorylated by IKK are resistant to Tax-mediated degradation (20,58). This indicates that Tax is directly involved in induction of a specific kinase activity necessary for IκB phosphorylation/degradation.

Recent advances in the characterization of the IKK complex has made it possible to study mechanisms involved in Tax activation of IκB phosphorylation. This research has been focused mainly on addressing the following questions. Dose Tax regulate the same signal transduction pathways that are directed by cytokine? What is the molecular target for Tax in regulating IκB phosphorylation? What is the mechanism? Studies by our lab and several other groups have shown that IKK activity is stimulated in cells that either stably or transiently produce the Tax protein [(26,39,103,117); Li et al., unpublished results]. Kinase-defective mutants of IKKβ effectively block Tax-mediated increases in NF-κB-dependent gene transcription (39,103,117). This suggests that Tax plays a role in modulating IKK activity during NF-κB activation.

Stimulation of the IKK activity by Tax could be due to a direct effect on either IKK or their upstream activators. The possibility that the IKK molecules are a direct target for Tax in NF-κB activation arises from observations using immunoprecipitation studies of Tax from HTLV-1-infected cells. These studies indicate that Tax associates with specific kinase activity that phosphorylates IκBα on serine residues 32 and 36, suggesting that Tax can directly interact with the IKKs (26).

Several other observations have led to the conclusion that Tax acts at steps upstream of IKKs (39,103,117). Because we were unable to detect a direct interaction between Tax and IKK, we analyzed a number of regulatory proteins previously demonstrated to be involved in activation of the NF-κB pathway, including NIK, MEKK1, the TNF receptor associated protein TRAF2, and the small GTPases Rac2, CDC42, RhoA (117). Studies using dominant-negative mutants of these regulatory proteins show that only the kinase-defective MEKK1 mutant effectively blocks Tax activation of NF-κB-dependent gene expression. A dominant-negative NIK protein also results in a modest level of inhibition, whereas the other proteins did not have any effect. Conversely, the dominant-negative MEKK1 protein did not efficiently inhibit NF-κB-dependent gene expression induced by TNF-α, whereas a dominant-negative mutant of either NIK and TRAF2 strongly blocked TNF-α-mediated gene activation. This suggests that whereas only NIK is directly involved in TNF-α-induced IKK activation, MEKK1 and/or NIK may both be involved in Tax-mediated activation of the NF-κB pathway.

A direct and specific interaction between Tax and the amino-terminus of MEKK1 occurs both in vitro and in vivo (117). A Tax mutant defective in activation of gene expression via the NF-κB pathway is not capable of interacting with MEKK1. This suggests that MEKK1 is the direct target of Tax to result in activation of IKK kinase activity. Tax is able to stimulate MEKK1 kinase activity to phosphorylate downstream kinases as well as increase its autophosphorylation. Expression of both Tax and MEKK1 results in enhanced NF-κB activation, further suggesting that Tax activation of the NF-κB pathway might be mediated by direct effects on MEKK1.

It has been suggested that MEKK1 may act as an direct upstream effector of IKKs (67) and that IKKβ might be a preferential substrate involved in mediating the Tax-dependent activation (117). Overexpression of MEKK1 enhanced the kinase activity of both endogenous and coexpressed IKKβ but not IKKα (117). Given the fact that dominant-negative IKKβ, but not IKKα, mutants are able to interfere with activation of NF-κB-dependent gene expression in the presence of MEKK1 (117), MEKK1 was a likely target for Tax activation of IKK. MEKK1 can phosphorylate IKKβ and this may increase its ability to phosphorylate IκB (117). It is possible that Tax may induce a conformational change in MEKK1 that increases its enzymatic activity. Although NIK is exclusively an activator of the NF-κB pathway, MEKK1 acts at the convergence between the JNK and NF-κB pathways (60). It is tempting to think that Tax may be able to alter MEKK1 substrate specificity so that phosphorylation of IKKβ becomes its primary target (Fig. 3).

However, MEKK1 is obviously not the only target for Tax. NIK appears to be also involved in Tax-mediated NF-κB activation (39,103,117). It is possible that NIK and MEKK1 function coordinately in Tax-stimulated NF-κB activation. Whether or not NIK and MEKK1 act directly as upstream IKK kinases, and how Tax affects their enzymatic activities

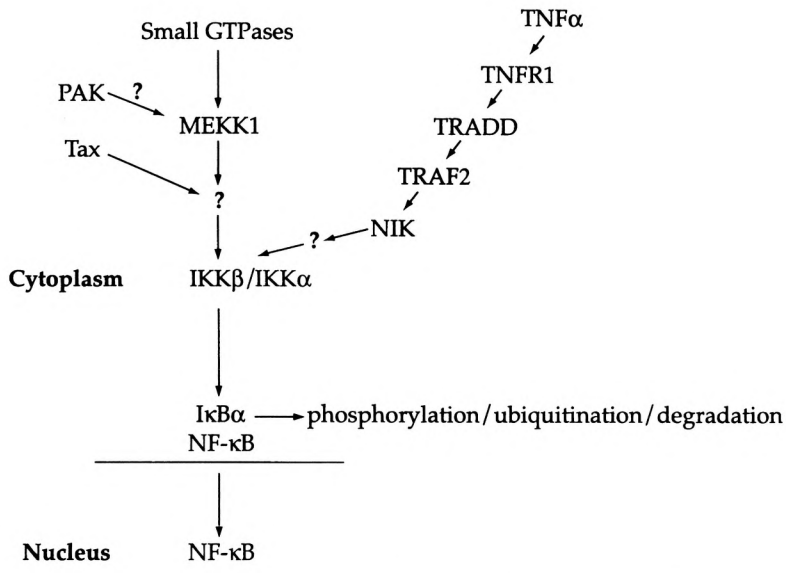

FIG. 3. Schematic of signal transduction pathways leading to NF-κB activation. The TNF-α pathway leading to activation of NF-κB is indicated as is a second pathway through MEKK1 that is the likely target for Tax activation.

and substrate specificity, will need further investigation.

What other mechanisms could Tax utilize to activate NF-κB? In an attempt to answer this question, we recently isolated an IKK complex from HTLV-1-infected cells. The activity of both IKKα and IKKβ in this complex is much higher than that in complexes isolated from uninfected cells. Surprisingly, both kinases are found in a much lower molecular weight complex in HTLV-1-infected cells compared to the high-molecule-weight IKK complex found in both unstimulated (24) and cytokine-induced cells (32,74) (Li et al., unpublished). Furthermore, the active IKK complex did not contain substantial quantities of MEKK1, NIK, and Tax. These findings suggest that IKKs are possibly removed from the large molecular weight complex during the process of Tax activation (Fig. 4).

Apparently Tax uses a distinct mechanism to initiate and maintain activation of IKKs. This likely involves modifying the composition of the IKK complex. The mechanism that Tax uses to modify the IKK remains to be determined. Once the IKK complex is induced, maintaining it in the constitutively active state would be the simplest way to maintain high levels of IKK activity. This model may explain the persistent NF-κB activation by Tax that results from constitutive IKK activation (26). Once the IKK complex is stimulated, maintaining this activity would be a way for HTLV-1 to establish a persistent infection in a continuously proliferating environment.

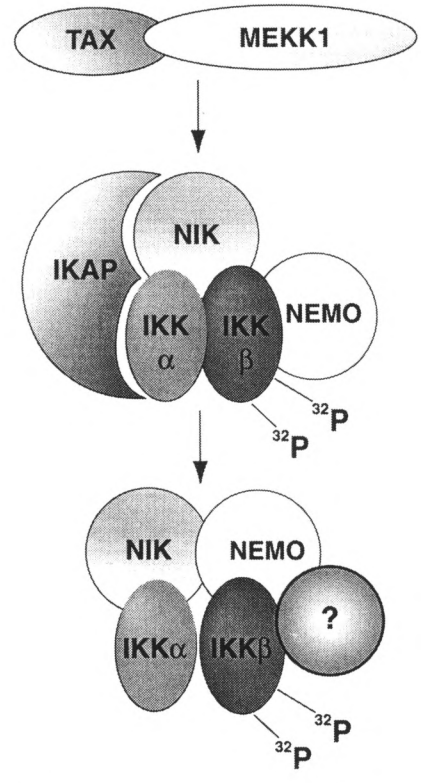

FIG. 4. Model for Tax modification of the NF-κB pathway. Tax interaction with MEKK1 leads to phosphorylation of IKKβ and the loss of potential inhibitory proteins in the IKK complex.

NF-κB AND APOPTOSIS

NF-κB is involved in protecting cells from programmed cell death. Cells responsive to TNF-α and IL-1, strong activators of the NF-κB pathway, become resistant to cell killing induced by these cytokines (104). This indicates that TNF-α and IL-1 can activate cell mechanisms that promote as well as antagonize cell death. Furthermore, certain stimuli leading to programmed cell death can also activate NF-κB (7,8,93,108). The direct role of NF-κB as an antiapoptotic factor was first proposed because disruption of the p65/RelA locus in mice results in embryonic death concomitant with massive apoptosis in liver (13). In addition, inhibition of NF-κB nuclear transport enhances cell killing (104) by a variety of different apoptotic stimuli (110). This implicates a feedback loop in which NF-κB activation suppresses signals needed to induce cell death.

Studies have now begun to address the mechanisms by which NF-κB antagonizes apoptosis. These studies involve molecular dissection of cell surface receptors containing death domains (e.g., TNFR1) (51–53,69) and determining the functional interaction between NF-κB and apoptotic factors (72,111). Through the TNF-α receptor, TNFR1, TNF-α elicits an unusually wide spectrum of cellular responses leading to inflammation, cellular proliferation, and apoptosis through activating different effectors. These effects are mediated by distinct pathways and are determined by factors recruited to the TNFR1 complex. Recruitment of FADD (Fas-associated death domain) (25,44,52) to the complex results in apoptosis as a consequence of activation of an apical apoptotic protease associated with TNFR1, namely caspase-8 (also called FLICE or MACH) (18,79). Interaction with the signal transducers RIP (receptor interacting protein) (51,80) and TRAF2 (52,69) leads to both JNK and NF-κB activation (61). However, activation of NF-κB, but not JNK, protects cells from TNF-α-mediated cell apoptosis (69,105). MEKK1 and NIK may be activated and/or recruited by RIP and TRF2 by yet unidentified mechanisms (60).

It has been suggested that the NF-κB protection of cells from apoptosis is, at least in part, mediated by suppression of caspase-8 activity (111). Caspase-8 functions at the apex of the apoptotic cascade and transmits death signals by activating downstream proteases (3,18,79). Using cell lines in which the nuclear transport of NF-κB was inhibited, it was demonstrated that the activity of caspase-8 was substantially induced by TNF-α (111) and that NF-κB activation suppresses the initiation of apoptosis (104,105,111). NF-κB induces the expression of genes encoding the TNFR1-associated proteins including TRAF1 and TRAF2, and the suppressors of caspase-1-induced apoptosis, c-IAP1 and c-IAP2 (111). These four proteins together provide maximum protection against TNF-α-induced apoptosis. Furthermore, activation of TRAF1, TRAF2, c-IAP1, and c-IAP2 expression is associated with inhibition of the caspase-8 activity (111). Therefore, NF-κB-mediated suppression of TNF-α-induced apoptosis is, at least in part, through activation of a group of genes whose products function cooperatively at the earliest checkpoint of apoptosis. This finding also provides a reason why the synthesis of new proteins is required for NF-κB-mediated prevention of apoptosis and is consistent with earlier findings that induced resistance to cell killing in response to TNF-α is enhanced in the presence of inhibitors of protein synthesis (50).

NF-κB is also able to interfere with the activity of oncogenic Ras to suppress p53-independent apoptosis (72). NF-κB is activated in response to oncogenic Ras (36) and this activation is largely due to stimulation of the transcription function of RelA/p65 subunits, but not through its induced nuclear transport (37). Regulation of NF-κB by oncogenic Ras may play an important role in the early stages of tumorigenesis as a large number of antiapoptotic proteins are expressed in tumor cells.

It is also important to note that specific proteins can be involved in both pro- and antiapoptotic responses. Involvement of NF-κB in proapoptotic pathways in certain cell types in response to particular stimuli has been reported (56,68).

CONCLUDING REMARKS

The past few years have been remarkable times for discoveries in NF-κB activation. The transmission of signals from the cell surface that lead to the activation of gene expression is much better understood than ever before. The link between NF-κB activation and the etiology of human cancers has just begun to be understood. The molecular cloning of the IκB kinases and characterization of the IKK complex have opened up new avenues of future research. Based on our knowledge of cytokine-stimulated IKK activation process, the responses to other stimuli including viral agents can now be studied in a much more direct manner. We are beginning to understand how oncoproteins such as the HTLV-1 Tax protein interact with cellular factors to activate cellular signal transduction pathways and modulate NF-κB activity. Further understanding of the IKK complex will likely demonstrate how this complex transmits information for specific cellular responses such as inflammation,

immune function, and cellular survival. Components in the IKK complex could be potential therapeutic targets to treat human disorders involving abnormalities in cellular proliferation. Finally, understanding the molecular targets for Tax in the IKK complex will be beneficial to better understand cellular regulation and to develop potential new treatments for human malignancy.

REFERENCES

1. Akira, S.; Kishimoto, T. NF-IL6 and NF-kappa B in cytokine gene regulation. Adv. Immunol. 65:1–46; 1997.
2. Armstrong, A. P.; Franklin, A. A.; Henbogaard, M. N.; Giebler, H. A.; Nyborg, J. K. Pleiotropic effect of the human T-cell leukemia virus Tax protein on the DNA binding activity of eukaryotic transcription factors. Proc. Natl. Acad. Sci. USA 90:7303–7307; 1993.
3. Ashkenazi, A.; Dixit, V. M. Death receptors: Signaling and modulation. Science 281:1305–1308; 1998.
4. Baeuerle, P. A. Pro-inflammatory signaling: Last pieces in the NF-kappaB puzzle? Curr. Biol. 8:R19–22; 1998.
5. Baeuerle, P. A.; Baltimore, D. IκB: A specific inhibitor of the NF-κB transcription factor. Science 242: 540–546; 1988.
6. Baeuerle, P. A.; Baltimore, D. NF-κB: Ten years after. Cell 87:13–20; 1996.
7. Baeuerle, P. A.; Henkel, T. Function and activation of NF-κB in the immune system. Annu. Rev. Immunol. 12:141–179; 1994.
8. Baldwin, A. S. The NF-κB and IκB proteins: New discoveries and insights. Annu. Rev. Immunol. 14: 649–681; 1996.
9. Baranger, A. M.; Palmer, C. R.; Hamm, M. K.; Glebler, H. A.; Brauweiler, A.; Nyborg, J. K.; Schepartz, A. Mechanism of DNA-binding enhancement by the human T-cell leukaemia virus transactivator Tax. Nature 376:606–608; 1995.
10. Barnes, P. J. Nuclear factor-kappa B. Int. J. Biochem. Cell. Biol. 29:867–870; 1997.
11. Barnes, P. J.; Karin, M. Nuclear Factor-κB-A pivotal transcription factor in chronic inflammatory diseases. N. Engl. J. Med. 336:1066–1071; 1997.
12. Beg, A. A.; Ruben, S. M.; Scheinman, R. I.; Haskill, S.; Rosen, C. A.; Baldwin, A. S., Jr. IκB interacts with the nuclear localization sequences of the subunits of NF-κB: A mechanism for cytoplasmic retention. Genes Dev. 6:1899–1913; 1992.
13. Beg, A. A.; Sha, W. C.; Bronson, R. T.; Ghosh, S.; Baltimore, D. Embryonic lethality and liver degeneration in mice lacking the RelA component of NF-κB. Nature 376:167–170; 1995.
14. Beimling, P.; Moelling, K. Direct interaction of CREB protein with 21bp Tax-response elements of HTLV-I LTR. Oncogene 7:257–262; 1992.
15. Beraud, C.; Sun, S.-C.; Ganchi, P.; Ballard, D. W.; Greene, W. C. Human T-cell leukemia virus type I Tax associates with and is negatively regulated by the NF-κB2 p100 gene product: Implication for viral latency. Mol. Cell. Biol. 14:1374–1382; 1994.
16. Bex, F.; McDowall, A.; Burny, A.; Gaynor, R. B. The HTLV-I transactivator protein Tax colocalizes with NF-κB proteins in unique nuclear bodies. J. Virol. 71: 3484–3497; 1997.
17. Bex, F.; Yin, M.-J.; Burny, A.; Gaynor, R. B. Differential transcriptional activation by HTLV-I Tax mutants is mediated by distinct interactions with CREB binding protein and p300. Mol. Cell. Biol. 18:2392–2405; 1998.
18. Boldin, M. P.; Goncharov, T. M.; Goltsev, Y. V.; Wallach, D. Involvement of MACH, a novel MORT1/FADD-interacting protease, in Fas/APO-1- and TNF receptor-induced cell death. Cell 85:803–815; 1996.
19. Brauweiler, A.; Garl, P.; Franklin, A. A.; Giebler, H. A.; Nyborg, J. K. A molecular mechanism for human T-cell leukemia virus latency and Tax transactivation. J. Biol. Chem. 270:12814–12822; 1995.
20. Brockman, J. A.; Scherer, D. C.; McKinsey, T. A.; Hall, S. M.; Qi, X.; Lee, W. Y.; Ballard, D. W. Coupling of a signal response domain in IκBα to multiple pathways for NF-κB activation. Mol. Cell. Biol. 15: 2809–2818; 1995.
21. Brown, K.; Gerstberger, S.; Carlson, L.; Fransozo, G.; Siebenlist, U. Control of IκBα proteolysis by site-specific, signal-induced phosphorylation. Science 267:1485–1488; 1995.
22. Brown, K.; Park, S.; Kanno, T.; Fransozo, G.; Siebenlist, U. Mutual regulation of the transcriptional activator NF-κB and its inhibitor, IκBα. Proc. Natl. Acad. Sci. USA 90:2532–2536; 1993.
23. Cann, A. J.; Rosenblatt, J. D.; Wachsman, W.; Shah, N. P.; Chen, I. S. Y. Identification of the gene responsible for human T-cell leukemia virus transcriptional regulation. Nature 318:571–574; 1985.
24. Chen, Z. J.; Parent, L.; Maniatis, T. Site-specific phosphorylation of IκBα by a novel ubiquitination-dependent protein kinase activity. Cell 84:853–862; 1996.
25. Chinnaiyan, A. M.; Tepper, C. G.; Seldin, M. F.; O'Rourke, K.; Kischkel, F. C.; Hellbardt, S.; Krammer, P. H.; Peter, M. E.; Dixit, V. M. FADD/MORT1 is a common mediator of CD95 (Fas/APO-1) and tumor necrosis factor receptor-induced apoptosis. J. Biol. Chem. 271:4961–4965; 1996.
26. Chu, Z.-L.; DiDonato, J. A.; Hawiger, J.; Ballard, D. W. The Tax oncoprotein of human T-cell leukemia virus type 1 associates with and persistently activates IκB kinases containing IKKα and IKKB. J.Biol. Chem. 273:15891–15894; 1998.

27. Cohen, L.; Henzel, W. J.; Baeuerle, P. A. IKAP is a scaffold protein of the IkappaB kinase complex. Nature 395:292–296; 1998.
28. Connelly, M. A.; Marcu, K. B. CHUK, a new member of the helix–loop–helix and leucine zipper families of interacting proteins, contains a serine-threonine kinase catalytic domain. Cell. Mol. Biol. Res. 41:537–549; 1995.
29. Cross, S. L.; Feinberg, M. B. Wolf, J. B.; Holbrook, N. J.; Wong-Staal, F.; Leonard, W. J. Regulation of the human interleukin-2 receptor alpha chain promoter: Activation of a nonfunctional promoter by the transactivator gene of HTLV-I. Cell 49:47–56; 1987.
30. Derijard, B.; Raingeaud, J.; Barraett, T.; Wu, I. H.; Han, J.; Ulevitch, R. J.; Davis, R. J. Independent human MAP kinase signal transduction pathways defined by MEK and MKK isoforms. Science 267:682–685; 1995.
31. Didonato, J.; Mercurio, R.; Rosette, C.; Wu-Li, J.; Suyang, H.; Ghosh, S.; Karin, M. Mapping of the inducible IkB phosphorylation sites that signal its ubiquitination and degradation. Mol. Cell. Biol. 16: 1295–1304; 1996.
32. Didonato, J. A.; Hayakawa, M.; Rothwarf, D. M.; Zandi, E.; Karin, M. A cytokine-responsive IκB kinase that activates the transcription factor NF-κB. Nature 388:548–554; 1997.
33. Dushay, M. S.; Asling, B.; Hultmark, D. Origins of immunity: Relish, a compound Rel-like gene in the antibacterial defense of Drosophila. Proc. Natl. Acad. Sci. USA 93:10343–10347; 1996.
34. Felber, B. K.; Paskalis, H.; Kleinman-Ewing, D.; Wong-Staal, F.; Pavlakis, G. N. The pX protein of HTLV-I is a transcriptional activator of its long terminal repeats. Science 229:675–679; 1985.
35. Feuer, G.; Chen, I. S. Mechanisms of human T-cell leukemia virus-induced leukemogenesis. Biochim. Biophys. Acta 1114:223–233; 1992.
36. Finco, T. S.; Baldwin, A. S., Jr. Kappa B site-dependent induction of gene expression by diverse inducers of nuclear factor kappa B requires Raf-1. J. Biol. Chem. 268:17676–17679; 1993.
37. Finco, T. S.; Westwick, J. K.; Norris, J. L.; Beg, A. A.; Der, C. J.; Baldwin, A. S., Jr. Oncogenic Ha-Ras-induced signaling activates NF-kappaB transcriptional activity, which is required for cellular transformation. J. Biol. Chem. 272:24113–24116; 1997.
38. Ganchi, P.; Sun, S.-C.; Greene, W. C.; Ballard, D. W. IκB/MAD-3 masks the nuclear localization signal of NF-κB p65 and requires the transactivation domain to inhibit NF-κB p65 DNA binding. Mol. Biol. Cell 3:1339–1352; 1992.
39. Geleziunas, R.; Ferrell, S.; Lin, X.; Mu, Y.; Cunningham, E. T., Jr.; Grant, M.; Connelly, M. A.; Hambor, J. E.; Marcu, K. B.; Greene, W. C. Human T-cell leukemia virus type 1 Tax induction of NF-kappaB involves activation of the IkappaB kinase alpha (IKKalpha) and IKKbeta cellular kinases. Mol. Cell. Biol. 18:5157–5165; 1998.
40. Ghosh, S.; May, M. J.; Kopp, E. B. NF-κB and Rel proteins: Evolutionarily conserved mediators of immune responses. Annu. Rev. Immunol. 16:225–260; 1998.
41. Giebler, H. A.; Loring, J. E.; van Orden, K.; Colgin, M. A.; Garrus, J. E.; Escudero, K. W.; Brauweiler, A.; Nyborg, J. K. Anchoring of CREB binding protein to the human T-cell leukemia virus type 1 promoter: A molecular mechanism of Tax transactivation. Mol. Cell. Biol. 17:5156–5164; 1997.
42. Good, L.; Sun, S. C. Persistent activation of NF-κB B/Rel by human T-cell leukemia virus type 1 Tax involves degradation of IκB. J. Virol. 70:2730–2735; 1996.
43. Grilli, M.; Pizzi, M.; Memo, M.; Spano, P. Neuroprotection by aspirin and sodium salicylate through blockade of NF-kappaB activation. Science 274: 1383–1385; 1996.
44. Grimm, S.; Stanger, B. Z.; Leder, P. RIP and FADD: Two "death domain"-containing proteins can induce apoptosis by convergent, but dissociable, pathways. Proc. Natl. Acad. Sci. USA 93:10923–10927; 1996.
45. Henkel, T.; Zabel, U.; van, Z. K.; Muller, J. M.; Fanning, E.; Baeuerle, P. A. Intramolecular masking of the nuclear location signal and dimerization domain in the precursor for the p50 NF-kappa B subunit. Cell 68:1121–1133; 1992.
46. Hennighausen, L.; Furth, P. A. NF-κB and HIV [letter; comment]. Nature 343:218–219; 1990.
47. Hinrichs, S. H.; Nerenberg, M.; Reynolds, R. K.; Khoury, G.; Jay, G. A transgenic mouse model for human neurofibromatosis. Science 237:1340–1343; 1987.
48. Hirai, H.; Fujisawa, J.; Suzuki, T.; Ueda, K.; Muramatsu, M.; Tsuboi, A.; Arai, N.; Yoshida, M. Transcriptional activator Tax of HTLV-1 binds to the NF-κB precursor p105. Oncogene 7:1737–1742; 1992.
49. Hirano, M.; Osada, S.; Aoki, T.; Hirai, H.; Hosaka, M.; Inoue, J.; Ohno, S. MEK kinase is involved in tumor necrosis factor α-induced NF-κB activation and degradation of IkBa. J. Biol. Chem. 271:13234–13238; 1996.
50. Holtmann, H.; Hahn, T.; Wallach, D. Interrelated effects of tumor necrosis factor and interleukin 1 on cell viability. Immunobiology 177:7–22; 1988.
51. Hsu, H.; Huang, J.; Shu, H. B.; Baichwal, V.; Goeddel, D. V. TNF-dependent recruitment of the protein kinase RIP to the TNF receptor-1 signaling complex. Immunity 4:387–396; 1996.
52. Hsu, H.; Shu, H. B.; Pan, M. G.; Goeddel, D. V. TRADD–TRAF2 and TRADD–FADD interactions define two distinct TNF receptor 1 signal transduction pathways. Cell 84:299–308; 1996.
53. Hsu, H.; Xiong, J.; Goeddel, D. V. The TNF receptor 1-associated protein TRADD signals cell death and NF-κB activation. Cell 81:495–504; 1995.
54. Inoue, J.; Seiki, M.;Taniguchi, T.; Tsuru, S.; Yoshida, M. Induction of interleukin 2 receptor gene expression by p40x encoded by human T-cell leukemia virus type 1. EMBO J. 5:2883–2888; 1986.
55. Ip, Y. T.; Reach, M.; Engstrom, Y.; Kadalayil, L.;

Cai, H.; Gonzalez-Crespo, S.; Tatei, K.; Levine, M. Dif, a dorsal-related gene that mediates an immune response in *Drosophila*. Cell 75:753–763; 1993.
56. Jung, M.; Zhang, Y.; Lee, S.; Dritschilo, A. Correction of radiation sensitivity in ataxia telangiectasia cells by a truncated I kappa B-alpha. Science 268: 1619–1621; 1995.
57. Kanno, T.; Brown, K.; Franzoso, G.; Siebenlist, U. Kinetic analysis of human T-cell leukemia virus type I tax-mediated activation of NF-κB. Mol. Cell. Biol. 14:6443–6451; 1994.
58. Kanno, T.; Brown, K.; Siebenlist, U. Evidence in support of a role for human T-cell leukemia virus type I Tax in activating NF-kappa B via stimulation of signaling pathways. J. Biol. Chem. 270:11745–11748; 1995.
59. Kanno, T.; Franzoso, G.; Siebenlist, U. Human T-cell leukemia virus type I Tax-protein-mediated activation of NF-κB from p100 (NF-κB2)-inhibited reservoirs. Proc. Natl. Acad. Sci. USA 91:12634–12638; 1994.
60. Karin, M.; Delhase, M. JNK or IKK, AP-1 or NF-kappaB, which are the targets for MEK kinase 1 action? Proc. Natl. Acad. Sci. USA 95:9067–9069; 1998.
61. Kelliher, M. A.; Grimm, S.; Ishida, Y.; Kuo, F.; Stanger, B. Z.; Leder, P. The death domain kinase RIP mediates the TNF-induced NF-kappaB signal. Immunity 8:297–303; 1998.
62. Kopp, E.; Ghosh, S. Inhibition of NF-κB by sodium salicylate and aspirin. Science 265:956–959; 1994.
63. Kopp, E. B.; Ghosh, S. NF-kappa B and rel proteins in innate immunity. Adv. Immunol. 58:1–27;.1995
64. Kwok, R. P. S.; Laurance, M. E.; Lundblad, J. R.; Goldman, P. S.; Shih, H.-M.; Connor, L. M.; Marriott, S. J.; Goodman, R. H. Control of cAMP-regulated enhancers by the viral transactivator Tax through CREB and the co-activator CBP. Nature 380:642–646; 1996.
65. Lacoste, J.; Petropoulos, L.; Pépin, N.; Hiscott, J. Constitutive phosphorylation and turnover of IκBα in human T-cell leukemia virus type I-infected and tax-expressing T cells. J. Virol. 69:564–569; 1995.
66. Lee, F. S.; Hagler, J.; Chen, Z. J.; Maniatis, T. Activation of the IκBα kinase complex by MEKK1, a kinase of the JNK pathway. Cell 88:213–222; 1997.
67. Lee, F. S.; Peters, R. T.; Dang, L. C.; Maniatis, T. MEKK1 activates both IkappaB kinase alpha and IkappaB kinase beta. Proc. Natl. Acad. Sci. USA 95: 9319–9324; 1998.
68. Lee, H.; Arsura, M.; Wu, M.; Duyao, M.; Bucker, A.; Sonenshein, G. Role of rel-related factors in control of c-myc gene transcription in receptor-mediated apoptosis of the murine B cell WEHI 231 line. J. Exp. Med. 181:1169–1177; 1995.
69. Liu, Z.-g.; Hsu, H.; Goeddel, D. V.; Karin, M. Dissection of TNF receptor 1 effector functions: JNK activation is not linked to apoptosis while NF-κB activtion prevents cell death. Cell 87:565–576; 1996.
70. Malinin, N. L.; Boldin, M. P.; Kovalenko, A. V.; Wallach, D. MAP3K-related kinase involved in NF-κB induction by TNF, CD95 and IL-1. Nature 385: 540–548; 1997.
71. Maruyama, M.; Shibuya, H.; Harada, H.; Hatakeyama, M.; Seiki, M.; Fujita, T.; Inoue, J.; Yoshida, M.; Taniguchi, T. Evidence for aberrant activation of the interleukin-2 autocrine loop by HTLV-1-encoded p40x and T3/Ti complex triggering. Cell 48:343–350; 1987.
72. Mayo, M. W.; Wang, C. Y.; Cogswell, P. C.; Rogers-Graham, K. S.; Lowe, S. W.; Der, C. J.; Baldwin, A. S., Jr. Requirement of NF-kappaB activation to suppress p53-independent apoptosis induced by oncogenic Ras. Science 278:1812–1815; 1997.
73. McKinsey, T. A.; Brockman, J. A.; Scherer, D. C.; Al-Murrani, S. W.; Green, P. L.; Ballard, D. W. Inactivation of IκBβ by the Tax protein of human T-cell leukemia virus type 1: A potential mechanism for constitutive induction of NF-κB. Mol. Cell. Biol. 16: 2083–2090; 1996.
74. Mercurio, F.; Zhu, H.; Murray, B. W.; Shevchenko, A.; Bennett, B. L.; Li, J.; Young, D. W.; Barbosa, M.; Mann, M. IKK-1 and IKK-2: Cytokine-activated IκB kinases essential for NF-κB activation. Science 278: 860–866; 1997.
75. Mock, B. A.; Connelly, M. A.; McBride, O. W.; Kozak, C. A.; Marcu, K. B. CHUK, a conserved helix–loop–helix ubiquitous kinase, maps to human chromosome 10 and mouse chromosome 19. Genomics 27:348–351; 1995.
76. Munoz, E.; Courtois, G.; Veschambre, P.; Jalinot, P.; Israel, A. Tax induces nuclear translocation of NF-κB through dissociation of cytoplasmic complexes containing p105 or p100 but does not induce degradation of Iκ-Bα/MAD3. J. Virol. 68:8035–8044; 1994.
77. Munoz, E.; Israel, A. Activation of NF-kappa B by the Tax protein of HTLV-1. Immunobiology 193: 128–136; 1995.
78. Murakami, T.; Hirai, H.; Suzuki, T.; Fujisawa, J.; Yoshida, M. HTLV-1 Tax enhances NF-kappa B2 expression and binds to the products p52 and p100, but does not suppress the inhibitory function of p100. Virology 206:1066–1074; 1995.
79. Muzio, M.; Chinnaiyan, A. M.; Kischkel, F. C.; O'Rourke, K.; Shevchenko, A.; Ni, J.; Scaffidi, C.; Bretz, J. D.; Zhang, M.; Gentz, R.; Mann, M.; Krammer, P. H.; Peter, M. E.; Dixit, V. M. FLICE, a novel FADD-homologous ICE/CED-3-like protease, is recruited to the CD95 (Fas/APO-1) death-inducing signaling complex. Cell 85:817–827; 1996.
80. Natoli, G.; Costanzo, A.; Guido, F.; Moretti, F.; Levrero, M. Apoptotic, non-apoptotic, and anti-apoptotic pathways of tumor necrosis factor signalling. Biochem. Pharmacol. 56:915–920; 1998.
81. Nerenberg, M.; Hinrichs, S. H.; Reynolds, R. K.; Khoury, G.; Jay, G. The tat gene of human T-lymphotropic virus type 1 induces mesenchymal tumors in transgenic mice. Science 237:1324–1329; 1987.
82. Nicot, C.; Tie, F.; Giam, C. A. Cytoplasmic forms of human T-cell leukemia virus type 1 Tax induce NF-kappaB activation. J. Virol. 72:6777–6784; 1998.

83. Peltz, G. Transcription factors in immune-mediated disease. Curr. Opin. Biotechnol. 8:467–473; 1997.
84. Perini, G.; Wagner, S.; Green, M. B. Recognition of bZIP proteins by the human T-cell leukemia virus transactivator Tax. Nature 376:602–605; 1995.
85. Poiesz, B. J.; Ruscetti, R. W.; Gazdar, A. F.; Bunn, P. A.; Minna, J. D.; Gallo, R. C. Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. Proc. Natl. Acad. Sci. USA 77:7415–7419; 1980.
86. Pozzatti, R.; Vogel, J.; Jay, G. The human T-lymphotropic virus type I tax gene can cooperate with the ras oncogene to induce neoplastic transformation of cells. Mol. Cell. Biol. 10:413–417; 1990.
87. Regnier, C. H.; Song, H. Y.; Gao, X.; Goeddel, D. V.; Cao, Z.; Rothe, M. Identification and characterization of an IκB kinase. Cell 90:373–383; 1997.
88. Ressler, S.; Connor, L. M.; Marriott, S. J. Cellular transformation by human T-cell leukemia virus type I. FEMS Microbiol. Lett. 140:99–109; 1996.
89. Rothwarf, D. M.; Zandi, E.; Natoli, G.; Karin, M. IKK-gamma is an essential regulatory subunit of the IkappaB kinase complex. Nature 395:297–300; 1998.
90. Sanchez, I.; Hughes, R. T.; Mayer, B. J.; Yee, K.; Woodgett, J. R.; Avruch, J.; Kyriakis, J. M.; Zon, L. I. Role of SAPK/ERK kinase-1 in the stress-activated pathway regulating transcription factor c-Jun. Nature 372:794–798; 1994.
91. Semmes, O. J.; Jeang, K.-T. Localization of human T-cell leukemia virus type 1 Tax to subnuclear compartments that overlap with interchromatin speckles. J. Virol. 70:6347–6357; 1996.
92. Sen, R.; Baltimore, D. Inducibility of kappa immunoglobulin enhancer-binding protein NF-kappa B by a posttranslational mechanism. Cell 47:921–928; 1996.
93. Siebenlist, U.; Franzoso, G.; Brown, K. Structure, regulation and function of NF-kappa B. Annu. Rev. Cell Biol. 10:405–55; 1994.
94. Siekevitz, M.; Feinberg, M. B.; Holbrook, N.; Wong-Staal, F.; Greene, W. C. Activation of interleukin 2 and interleukin 2 receptor (Tac) promoter expression by the transactivator (tat) gene product of human T-cell leukemia virus type 1. Proc. Natl. Acad. Sci. USA 84:5389–5393; 1987.
95. Smith, M. R.; Greene, W. C. Type I human T-cell leukemia tax protein transforms rat fibroblasts through the cyclic adenosine monophosphate response element binding protein/activating transcription factor pathway. J. Clin. Invest. 88:1038–1042; 1991.
96. Steward, R. Dorsal, an embryonic polarity gene in *Drosophila*, is homologous to the vertebrate proto-oncogene, c-rel. Science 238:692–694; 1987.
97. Sun, S.-C.; Elwood, J.; Béraud, C.; Greene, W. C. Human T-cell leukemia virus type I tax activation of NF-kB/Rel involves phosphorylation and degradation of IkBa and RelA (p65) mediated induction of the c-rel gene. Mol. Cell. Biol. 14:7377–7384; 1994.
98. Sun, S.-C.; Ganchi, P.; Ballard, D. W.; Greene, W. C. NF-κB controls expression of inhibitor IκBα: Evidence for an inducible autoregulatory pathway. Science 259:1912–1915; 1993.
99. Suzuki, T.; Hirai, H.; Murakami, T.; Yoshida, M. Tax protein of HTLV-1 destabilizes the complexes of NF-κB and IκB-α and induces nuclear translocation of NF-κB for transcriptional activation. Oncogene 10: 1199–1207; 1995.
100. Tanaka, A.; Takahashi, C.; Yamaoka, S.; Nosaka, T.; Maki, M.; Hatanaka, M. Oncogenic transformation by the tax gene of human T-cell leukemia virus type I *in vitro*. Proc. Natl. Acad. Sci. USA 87:1071–1075; 1990.
101. Traenckner, E. B. M.; Pahl, H. L.; Henkel, T.; Schmidt, K. N.; Wilk, S.; Baeuerle, P. A. Phosphorylation of human IκBα on serines 32 and 36 controls IκBα proteolysis and NF-κB activation in response to diverse stimuli. EMBO J. 14:2876–2883; 1995.
102. Uchiyama, T. Human T cell leukemia virus type I (HTLV-I) and human diseases. Annu. Rev. Immunol. 15:15–37; 1997.
103. Uhlik, M.; Good, L.; Xiao, G.; Harhaj, E. W.; Zandi, E.; Karin, M.; Sun, S. C. NF-kappaB-inducing kinase and IkappaB kinase participate in human T-cell leukemia virus I Tax-mediated NF-kappaB activation. J. Biol. Chem. 273:21132–21136; 1998.
104. Van Antwerp, D. J.; Martin, S. J.; Kafri, T.; Green, D. R.; Verma, I. M. Suppression of TNF-α-induced apoptosis by NF-κB. Science 274:787–789; 1996.
105. Van Antwerp, D. J.; Martin, S. J.; Verma, I. M.; Green, D. R. Inhibition of TNF-induced apoptosis by NF-κB. Trends Cell Biol. 8:107–111; 1998.
106. Vane, J. Towards a better aspirin [news; comment]. Nature 367:215–216; 1994.
107. Vane, J. R. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat. New Biol. 231:232–235; 1971.
108. Verma, I. M.; Stevenson, J. K.; Schwartz, E. M.; Van Antwerp, D.; Miyamoto, S. Rel/NF-kB/IkB family: Intimate tales of association and dissociation. Genes Dev. 9:2723–2735; 1995.
109. Wagner, S.; Green, M. R. HTLV-I Tax protein stimulation of DNA binding of bZIP proteins by enhancing dimerization. Science 262:395–399; 1993.
110. Wang, C. Y.; Mayo, M. W.; Baldwin, A. S. J. TNF- and cancer therapy-induced apoptosis: Potentiation by inhibition of NF-kB. Science 274:784–787; 1996.
111. Wang, C. Y.; Mayo, M. W.; Korneluk, R. G.; Goeddel, D. V.; Baldwin, A. S., Jr. NF-kappaB antiapoptosis: Induction of TRAF1 and TRAF2 and c-IAP1 and c-IAP2 to suppress caspase-8 activation. Science 281:1680–1683; 1998.
112. Whiteside, S. T.; Ernst, M. K.; LeBail, O.; Laurent-Winter, C.; Rice, N.; Israel, A. N- and C-terminal sequences control degradation of MAD3/IκBα in response to inducers of NF-κB activity. Mol. Cell. Biol. 15:5339–5345; 1995.
113. Woronicz, J. D.; Gao, X.; Cao, Z.; Rothe, M.; Goeddel, D. V. IκB kinase-β: NF-κB activation and com-

plex formation with IkB kinase-α and NIK. Science 278:866–869; 1997.
114. Yamaoka, S.; Courtois, G.; Bessia, C.; Whiteside, S. T.; Weil, R.; Agou, F.; Kirk, H. E.; Kay, R. J.; Israel, A. Complementation cloning of NEMO, a component of the IkappaB kinase complex essential for NF-kappaB activation. Cell 93:1231–1240; 1998.
115. Yan, M.; Dai, T.; Deak, J. C.; Kyriakis, J. M.; Zon, L. I.; Woodgett, J. R.; Templeton, D. J. Activation of stress-activated protein kinase by MEKK1 phosphorylation of its activator SEK1. Nature 372:798–800; 1994.
116. Yin, M.; Gaynor, R. B. Complex formation between CREB and Tax enhances the binding affinity of CREB to the HTLV-I 21bp repeats. Mol. Cell. Biol. 16:3156–3168; 1996.
117. Yin, M.-J.; Chrisdterson, L. B.; Yamamoto, Y.; Kwak, Y.-T.; Xu, S.; Mercurio, F.; Barbosa, M.; Cobb, M. H.; Gaynor, R. B. HTLV-I Tax protein binds to MEKK1 to stimulate IκB kinase activity and NF-κB activation. Cell 93:875–884; 1998.
118. Yin, M.-J.; Gaynor, R. B. HTLV-1 21 bp repeat sequences facilitate stable association between Tax and CREB to increase CREB binding affinity. J. Mol. Biol. 264:20–31; 1996.
119. Yin, M.-J.; Yamamoto, Y.; Gaynor, R. Specific inhibition of IκB kinase activity by the anti-inflammatory agents aspirin and salicylate. Nature 396:77–80; 1998.
120. Yodoi, J.; Uchiyama, T. Diseases associated with HTLV-I: Virus, IL-2 receptor dysregulation and redox regulation. Immunol. Today 13:405–411; 1992.
121. Yoshida, M.; Miyoshi, I.; Hinuma, Y. Isolation and characterization of retrovirus from cell lines of human adult T-cell leukemia and its implication in the disease. Proc. Natl. Acad. Sci. USA 79:2031–2035; 1982.
122. Zabel, U.; Henkel, T.; Silva, M. S.; Baeuerle, P. A. Nuclear uptake control of NF-kappa B by MAD-3, an I kappa B protein present in the nucleus. EMBO J. 12:201–211; 1993.
123. Zandi, E.; Rothwarf, D. M.; DelhaSe, M.; Hayakawa, M.; Karin, M. The IkB kinase complex (IKK) contains two kinase subunits, IKKα and IKKβ, necessary for IκB phosphorylation and NF-κB activation. Cell 91:243–252; 1997.
124. Zhao, L. J.; Giam, C. Z. Human T-cell lymphotropic virus type I (HTLV-I) transcriptional activator, Tax, enhances CREB binding to HTLV-I 21-base-pair repeats by protein–protein interaction. Proc. Natl. Acad. Sci. USA 89:7070–7074; 1992.