### **Transcription Factor NF-кВ**

### A Sensor for Smoke and Stress Signals

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ABSTRACT: Nuclear factor-kappa B (NF-KB) is a transcription factor that resides in the cytoplasm of every cell and translocates to the nucleus when activated. Its activation is induced by a wide variety of agents including stress, cigarette smoke, viruses, bacteria, inflammatory stimuli, cytokines, free radicals, carcinogens, tumor promoters, and endotoxins. On activation, NF-KB regulates the expression of almost 400 different genes, which include enzymes (e.g., COX-2, 5-LOX, and iNOS), cytokines (such as TNF, IL-1, IL-6, IL-8, and chemokines), adhesion molecules, cell cycle regulatory molecules, viral proteins, and angiogenic factors. The constitutive activation of NF-KB has been linked with a wide variety of human diseases, including asthma, atherosclerosis, AIDS, rheumatoid arthritis, diabetes, osteoporosis, Alzheimer's disease, and cancer. Several agents are known to suppress NF-KB activation, including Th2 cytokines (IL-4, IL-13, and IL-10), interferons, endocrine hormones (LH, HCG, MSH, and GH), phytochemicals, corticosteroids, and immunosuppressive agents. Because of the strong link of NF-kB with different stress signals, it has been called a "smoke-sensor" of the body.

KEYWORDS: NF-κB; stress; smoke; gene expression; cancer

### WHAT IS NF-ĸB?

Nuclear transcription factor  $\kappa B$  (NF- $\kappa B$ ) was identified by David Baltimore in 1986 as a factor in the nucleus that binds the promoter of the kappa chain of immunoglobulins in B cells.<sup>1</sup> NF- $\kappa B$  has since been shown to be present in the cytoplasm of every cell type in its inactive state and is conserved in animals all the way from Drosophila to man. Five different mammalian NF- $\kappa B$  family members have been identified and cloned: NF- $\kappa B1$  (p50/p105), NF- $\kappa B2$  (p52/p100), RelA(p65), RelB, and c-Rel. All family members share a highly conserved Rel homology domain (RHD; ~300 aa) responsible for DNA binding, a dimerization domain, and the ability to interact with I $\kappa Bs$ , the intracellular inhibitor for NF- $\kappa B$ . Two different NF- $\kappa B$  activation pathways have been identified, a canonical pathway initiated by NF- $\kappa B1$  (p50/p105) and a noncanonical pathway initiated by NF- $\kappa B2$ 

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(p52/p100). Before the NF- $\kappa$ B complex is translocated into the nucleus, NF- $\kappa$ B1 and NF- $\kappa$ B2 are cleaved to the active p50 and p52 subunits, respectively.

In resting cells, NF- $\kappa$ B, consisting of p50 and RelA, is sequestered in the cytoplasm in an inactive form through its association with one of several inhibitory molecules, including I $\kappa$ B- $\alpha$ , I $\kappa$ B- $\beta$ , I $\kappa$ B- $\gamma$ , p105, and p100, among which I $\kappa$ B- $\alpha$  is the most abundant. In response to environmental stimuli, including cytokine/chemokines, viral and bacterial pathogens, and stress-inducing agents, inactive NF- $\kappa$ B/I $\kappa$ B complex is activated by phosphorylation on two conserved serine (S) residues within their N-terminal domain of I $\kappa$ B proteins. Phosphorylation of these conserved S residues in response to stimulators leads to the immediate polyubiquitination of I $\kappa$ B proteins by the SCF- $\beta$ -TrCP complex (FIG. 1). This modification subsequently targets I $\kappa$ B proteins for rapid degradation by the 26S proteasome.

Activation of the NF- $\kappa$ B signaling cascade results in complete degradation of I $\kappa$ B, allowing the translocation of NF- $\kappa$ B to the nucleus, where it induces transcription. Activated NF- $\kappa$ B binds to specific DNA sequences in target genes, designated as  $\kappa$ B-elements, and regulates transcription of over 400 genes involved in immuno-regulation, growth regulation, inflammation, carcinogenesis, and apoptosis.

### WHAT ACTIVATES NF-ĸB?

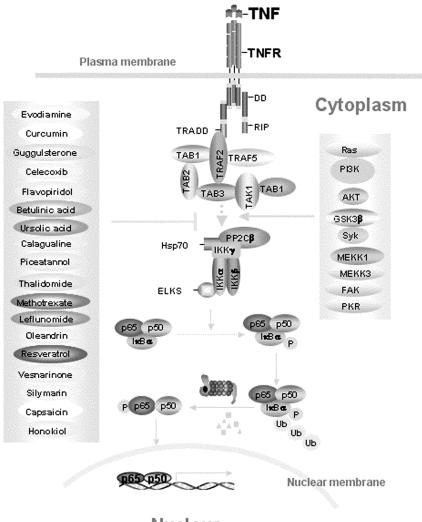
Extensive research in the last two decades has shown that a large number of stimuli can activate NF- $\kappa$ B (TABLE 1). These include bacteria and fungi, bacterial and fungal products, viruses and viral proteins, inflammatory cytokines, parasites, mitogens, physiological stress, physical stress, oxidative stress, environmental and occupational particles, heavy metals, intracellular stresses, viral or bacterial products, UV light, X-rays, gamma radiation, chemotherapeutic agents, carcinogens, cigarette smoke, hydrogen peroxide, colony-stimulating factors, mechanical stress, psychological fear, Th1 cytokines, hypoxia and hyperoxia, chemotherapeutic agents, endotoxins, and tumor promoters. The diversity of the stimuli that can stimulate NF- $\kappa$ B activation suggests that it can be used as a "smoke-detector" or "stress-sensor."

The mechanisms by which these diverse stimuli activate NF- $\kappa$ B are not identical. Perhaps the best understood of these pathways is the tumor necrosis factor (TNF)induced NF- $\kappa$ B activation pathway (FIG. 1). The sequential recruitment of TNFR, TRADD, TRAF2, RIP, and IKK leads to TNF-induced NF- $\kappa$ B activation.<sup>2</sup> Recent work from our laboratory has implicated ras,<sup>3</sup> syk,<sup>4</sup> and  $\beta$ -GSK<sup>5</sup> in TNF-induced NF- $\kappa$ B activation. Others have implicated AKT,<sup>6</sup> MEK3,<sup>7</sup> and FAK.<sup>8</sup> TNF-induced NF- $\kappa$ B activation is mediated through the production of reactive oxygen species as SOD<sup>9</sup> and  $\gamma$ -GCS<sup>10</sup> inhibited the activation. Numerous studies have indicated that NF- $\kappa$ B activated by several agents, however, differs from that of TNF.<sup>11,12</sup> For example, we have shown that NF- $\kappa$ B activated by pervanadate<sup>13,14</sup> and hydrogen peroxide<sup>12</sup> differs from that activated by TNF. Others have shown that activation of NF- $\kappa$ B by hypoxia,<sup>15</sup> UV,<sup>16</sup>  $\gamma$ -radiation,<sup>17</sup> X-rays,<sup>18</sup> ds RNA,<sup>19</sup> erythropoietin,<sup>20</sup> and hepatitis C virus<sup>21</sup> differs significantly from that activated by TNF. Although activation of NF- $\kappa$ B by UV, X-ray, hypoxia, pervanadate, erythropoietin, H<sub>2</sub>O<sub>2</sub>, and hepatitis C virus (NS5A) has been shown to be IKK-independent.

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H. Measles Virus         (mouse)         Lead         Beta-D-glucan ligand           Nolony Murine Leukemia         Croins's decase/ulcerative         Lad chromate         DD11bCD15L-ligand           Virus         maganese         Maganese         Complexent ligand           Nickel         Commed epidemic         Nickel         Complexent ligand           NRNA (in vitro         Corneal epidemic         Nickel         CD25-Ligand (B7-1)           Neveratel disease virus         Cornary styrey hypeas         Oily fly as in the complexent ligand virus           Nins         Hennorthage         Wood stroke         CD3-Ligand (Complement)           Virus         Hennorthage         Wood stroke         CD4-Ligand (Gomplement)           Sindibis Virus         Hypertohestrolemia         Zymasan (yeast cell wall         CD4-Ligand (G02a)           Sindibis Virus         Hypertohestrolemia         Zymasan (yeast cell wall         CD4-Ligand (G02a)           Sindibis Virus         Hypertohestrolemia         Zymasan (yeast cell wall         CD4-Ligand (G02a)           Virus         Hypertohestrolemia         Zymasan (yeast cell wall         CD4-Ligand (G02a)           Virus         Hypertohestrolemia         Zymasan (yeast cell wall         CD4-Ligand (G02a)           Virus         Hypertohestrolemia         Prode o	si i i i i i i i i i i i i i i i i i i	(mouse) Crohn's disease/ulcerative	Lead	BAFF (B cell-activating factor)		Cardiant Tottophotos
Molony Murine Leukemia         Crohn's disease/ulcerative         Lead chromate         CD11b/CD18-Ligand           Virus         oiltis         Marganese         (Complement)           mRNA (in vitro         Connel epidenci         Marganese         (Complement)           mrscribed         oiltis         Noise         CD2-Ligand (B7-1)           narscribed         Noise         CD2-Ligand (B7-1)           Newcastle disease virus         Coronary artery by-pass         Oily fly ash         CD3-Ligand (B7-1)           Newcastle disease virus         Coronary artery by-pass         Oily fly ash         CD3-Ligand (B7-1)           Newcastle disease virus         Coronary artery by-pass         Oily fly ash         CD3-Ligand (B7-1)           Newcastle disease virus         Coronary artery by-pass         Oily fly ash         CD3-Ligand (B7-1)           Newcastle disease virus         Popolarization         Sinda Particles         CD3-Ligand           Rinnovirus         Hypertholesterolernia         Zymosan (yeast cell wall         CD4-Ligand (gp120)           Rinnovirus         Hypertholesterolernia         Zymosan (yeast cell wall         CD4-Ligand (gp20)           Nins Atan         Hypertholesterolernia         Zymosan (yeast cell wall         CD4-Ligand (gp20)           Nins Atan         Virus Mara	-,	Crohn's disease/ulcerative		Beta-D-glucan ligand	Catalase	Calyculin A
Virus         colitis         Manganese         (Complement)           mRNA (in vitro         Corneal epidemic         Nickel         D23-Ligand (B7-1)           mRNA (in vitro         Corneal epidemic         Nickel         CD3-Ligand (B7-1)           newcasife diversae vitrus         Consol snucle         CD3-Ligand (B7-1)         CD4-Ligand (B7-1)           Nitras         Hyperchostentia         Silice Particles         CD3-Ligand (B7-1)         CD4-Ligand (B7-1)           Rinhovitus         Hyperchostentia         Zymosan (yeast cell wall         CD4-Ligand (B7-1)         CD4-Ligand (B7-1)           Sendai paramyxovitus         Hyperchostentia         Zymosan (yeast cell wall         CD4-Ligand (B7-10)         CD4-Ligand (B7-10)           Virus         Hyperchostentia         Zymosan (yeast cell wall         CD4-Ligand (B7-10)         CD4-Ligand (B7-20)           Virus Mara         Hyperchostentia         Zymosan (yeast cell wall         CD4-Ligand (B7-10)         CD4-Ligand (B7-10)           Virus Mara	~		Lead chromate	CD11b/CD18-Ligand	C2-Ceramide (N-acetyl-sphingosine)	Ceramide-beta-galactose
mRNA (in vitro         Corneal epidemic         Nickel         CD28-Ligand (87-1)           Neversate disease virus         Connary entry hys-pass         Nixel         CD24-Ligand (87-1)           Neversate disease virus         Connary entry hys-pass         Niy esit         CD3-Ligand (Complement)           Respiratory Syncytia         Depolarization         Nival         CD3-Ligand (Complement)           Respiratory Syncytia         Depolarization         Nood snoke         CD3-Ligand           Rinovins         Hypertholestrentemia         CD3-Ligand         CD3-Ligand           Sincla Paramycovins         Hypertholestrentemia         CD4-Ligand         CD4-Ligand           Vitra Nara         Hypertholestrentemia         CD4-Ligand         CD4-Ligand           Vitra Nara         Hypertonocysteinemia         Therapeuticlaly used drugs         M3 Cholinergic receptor           Vitra Nara         Hypertonocysteinemia         Therapeuticlaly used drugs         M3 Cholinergic receptor           Vitra Nara         Hypero		colitis	Manganese	(Complement)	Cerulein	2-chloroethyl ethyl sulfide (mustard
transcribed) keratoconjunctivitis Noise CD2-Ligand Nevcastle disease virus Coronary attery by-pats Oily fly sah CD3-Ligand (Complement) Respiratory Syncytial Henorhage Silica Particles CD3-Ligand (Complement) Nins Hinovirus Hypercholesterolernia Zymosan (yeast cell wall CD4-Ligand (gp120) Sindbis Virus Hypercholesterolernia Zymosan (yeast cell wall CD4-Ligand (gp120) Sindbis Virus Hyperchonecysteinenia Vaceina Virus Myperchonecysteinenia Vaceina Virus Hyperchonecysteinenia Vaceina Virus Hyperconic Shock Therapeutically used drugs M3 Cholnergie receptor Vest Nie Flaxavirus Hyperconationing 2-(1-adamantylamino)-G. FL-Ligand (gp20) Stehenia fransien, focal) 3-arebxamile) Fi-2-a.Receptor-Ligand (gG2a) Virus LPA Hurnan labor (childbirth) 1-D-Arabinofinamosyl- Fi-2-a.Receptor-Ligand (IgG2a) Adenovirus 5: ELA Liver Regeneration methylpyridine (AdAMP) Heat shock protein 60 (HSP60) Adenovirus 5: SI-10, virus) North Heat shock protein 60 (HSP60) Adenovirus 23/10K Hurnan labor (childbirth) 1-D-Arabinofinamosyl- Northen (in optosine (ar-C)) North Adenovirus 23/10K Hurnan labor (childbirth) Anthralino Adenovirus 23/10K Hurnan labor (childbirth) Adenovirus 23/10K Hurnan labor (childbirth) Adenovirus 23/10K Hurna labor (childbirth) Adenovirus 23/10K Hurna labor (childbirth) Adenovirus 24/10K Hurna labor (childbirth) Adenovirus 24/10K Hurna labor (childbirth) Adenovirus 23/10K Hu		Corneal epidemic	Nickel	CD28-Ligand (B7-1)	Chelidonium majus extract	analog)
Newcastle disease virus         Coronary artery by-pass         Oily fly ash         CD35-Ligand           Respiratory Syncytial         Depolarization         Silica Particles         CD31-Ligand           Respiratory Syncytial         Depolarization         Silica Particles         CD31-Ligand           Respiratory Syncytial         Hypercholesterolemia         Wood smoke         CD40-Ligand           Rinnovirus         Hypercholesterolemia         Zymsanl yeast cell wall         CD41-Ligand           Sendai praamyxovirus         Hypercholesterolemia         Zymsanl yeast cell wall         CD41-Ligand           Stendai praamyxovirus         Hyperchoncoysteinemia         Zymsanl yeast cell wall         CD41-Ligand           Vaccinia Virus         Hyperchoncoysteinemia         Zymsanl yeast cell wall         CD41-Ligand           Vaceinia Virus         Hyperchoncoysteinemia         Zymsanl yeast cell wall         CD41-Ligand           Virat products         Iterapeutically used drugs         M3 Cholinergic receptor           Vest Nile Flavavirus         Hypercoxia         J4-Ladamanylamino-6-         F1-Ligand           Vest Nile Flavavirus S E1A         Luver Regreation         2-Ladamanylamino-6-         F1-Ligand           Adenovirus E3/19K         Human labor (childbirth)         1-b-D-Arabinofiramosyl-         J6-Ligand <tr< td=""><td>~ -</td><td>keratoconjunctivitis</td><td>Noise</td><td>CD2-Ligand</td><td>Collagen lattice</td><td>Cobalt chloride</td></tr<>	~ -	keratoconjunctivitis	Noise	CD2-Ligand	Collagen lattice	Cobalt chloride
Respiratory Syncytial         Depolarization         Silica Particles         CD3-Ligand           Virus         Hemorhage         Wood smole         CD3-Ligand           Rinovirus         Hemorhage         Wood smole         CD40-Ligand           Rinovirus         Hypertobrenia         Yerestolisterolenia         CD4-Ligand           Sindbis Virus         Hypertobrenia         Zymsan (yeast cell wall         CD4-Ligand           Sindbis Virus         Hypertobrenia         product)         CD4-Ligand           Vact Nile         Virus         Therapeutically used drugs         M3 Cholineigand           Vact Nile         Hyperosmoit Shock         Therapeutically used drugs         M3 Cholineigand           Vact Nile         Havavirus         ARB-23757 (oxo-quinoline         M3 Cholineigand           Viral product         Ischemic preconditioning         2-tadamanylamino)-6-         F1-Ligand (gC2a)           Adenovirus 5. ELA         Liver Regretation         P4-Ligand (m2C3)         MACM           Adenovirus 5. ELA         Human labor (childbirth)         1-b-D-Arabinofuramosyl-         Ly6A/E-Ligand           Adenovirus 23/19K         Human labor (childbirth)         1-b-D-Arabinofuramosyl-         No-CAM           Adenovirus E3/19K         Human labor (childbirth)         1-b-D-Arabinofuramosyl	Respiratory Syncytial	Coronary artery by-pass	Oily fly ash	CD35-Ligand (Complement)	Collagen Type I	Con A
Virus         Hemorrhage         Wood smoke         CD40-Ligand           Rhinovirus         Hypercholesterolernia         Zymosan (yreat cell wall         CD43-Ligand           Sendai paramyxovirus         Hypercholesterolernia         Zymosan (yreat cell wall         CD44-Ligand (gp120)           Sindbis Virus         Hypercholesterolernia         Zymosan (yreat cell wall         CD44-Ligand (gp120)           Sindbis Virus Akara         Hyperosmotic Shock         Therapeutically used drugs         M3 Cholinergic receptor           Vest Nile Flavavirus         Hyperosmotic Shock         Therapeutically used drugs         M3 Cholinergic receptor           Vest Nile Flavavirus         Hyperosmotic Shock         Therapeutically used drugs         M3 Cholinergic receptor           Vest Nile Flavavirus         Elschemic preconditioning         2-1-adaramiyamino)-6-         Fi-1-Ligand (g2a)           Adenovirus E3/10K         Human labor (childhirth)         1-1-D-Arabinofiruanosy-1-         J/orb.Ligand           Adenovirus E3/10K         Human labor (childhirth)         1-D-D-Arabinofiruanosy-1-         J/orb.Ligand           Adenovirus E3/10K         Human labor (childhirth)         1-D-D-Arabinofiruanosy-1-         J/orb.Ligand           Adenovirus E3/10K         Human labor (childhirth)         1-D-D-Arabinofiruanosy-1-         J/orb.Ligand           Adenovirus E3		Depolarization	Silica Particles	CD3-Ligand	Cryptdins	Cycloheximide
Rhinovirus         Hypercholesterolernia         Zymosan (yeast cell wall         CD43-Ligand           Stadia paramysovirus         Hypertholesterolernia         Zymosan (yeast cell wall         CD43-Ligand           Sindbis Virus         Hyperboncysteinennia         Product)         CD4-Ligand (gp120)           Sindbis Virus         Hyperboncysteinennia         Product)         CD4-Ligand (gp120)           Vascrind Virus         Hyperboncysteinennia         Protuct)         CD4-Ligand (gp120)           Vascrind Virus         Hyperboncysteinennia         ABR-25757 (oxo-quinoline-         Biolinergic receptor           Viral products         Eschemic preconditioning         Prot-A-Ligand (lgG2a)         Protoxia         2-(1-damanuylamino).6.         Fi-L-Ligand           Adenovirus 5. E1A         Liver Regeneration         methylpyridine (AdAMP)         Heat shock protein 60 (HSP60)           Adenovirus 5.10K         Human labor (childbirth)         1-D-D-Arabinofiramosyl-         JoAch-Ligand           Adenovirus E3/10K         Human labor (childbirth)         1-D-D-Arabinofiramosyl-         JoAch-Ligand           Aritos Nine Fever         Mechanical Vertilation (in optosine (ar=C))         N-CAM         Arabinofiramosyl-           Aritos Virus IAP         Aritos Virus IAP         Arithaline (AZT)         Sphingosine 1-phosphate	Virus	Hemorrhage	Wood smoke	CD40-Ligand	Cysteinyl leukotrines	Cyclopiazonic Acid
Sendai paramyxovirus         Hyperglycemia         product)         CD4-Ligand (gp120)           Sendai paramyxovirus         Hyperhomcoysteinemia         CD4-Ligand (gp120)           Vascinia Virus         Hyperhomcoysteinemia         CD66-Ligand (gp120)           Vascinia Virus         Hyperhomcoysteinemia         CD66-Ligand (gp120)           Vest Nile Flavarius         Hyperoxia         ABR-25757 (xxx-quinoline- agonist           Vest Nile Flavarius         Ischemia (transient, focal)         S-embxamiclo           Viral products         Ischemia (transient, focal)         S-embxamiclo           Adenovirus 5: E1A         Liver Regretation         2-(1-adaramylamino)-6-           Adenovirus 5: VISK         Human labor (childbirth)         1-b-D-Arabinofuranosyl-           Adenovirus 5: VISK         Human labor (childbirth)         1-b-D-Arabinofuranosyl-           Virus IAP         Human labor (childbirth)         1-b-D-Arabinofuranosyl-         N-G-ME           Virus IAP         Human labor (childbirth)         1-b-D-Arabinofuranosyl-         N-G-M         Man           Virus IAP         Nitros Nitro         Nathralin         N-G-G         Man           Aritican Svine Fever         Mechanical Vertulation (in vytos)         N-G-G         Man           Arinbody to Dengue Virus         Muscle disuse	Rhinovirus	Hypercholesterolemia	Zymosan (yeast cell wall	CD43-Ligand	Deoxycholic acid (bile acid)	Diquat
Sindbis Virus         Hyperobonocysteinemia         CD66s-Ligand           Vaccina Virus Akara         Hyperosmotic Stock         Therapeutically used drugs         M3 Cholinergic receptor           Vaccina Virus Akara         Hyperosmotic Stock         Therapeutically used drugs         M3 Cholinergic receptor           West Nite Flavavius         Hyperosmotic Stock         Therapeutically used drugs         M3 Cholinergic receptor           Viral products         Ischemic fransient, focal)         3-carboxamide)         3-carboxamide)         Fil-1-Ligand (1gG2a)           Adenovirus 5: E1A         Liver Regreation         2-tadmanylymidine (AdAMP)         Han shock proti 60 (HSP60)           Adenovirus 5: E1A         Human labor (childbirth)         1-b-D-Arabinofuranosyl.         Ly6A/E-Ligand           Virus IAP         Human labor (childbirth)         1-b-D-Arabinofuranosyl.         Ly6A/E-Ligand           Virus IAP         Mathaline         Arabinofuranosyl.         Dy6-Ligand           Virus IAP         Nirus IAP         PGG-Ligand         Mathalin           Antibody to Dengue Virus         Muscle disuse         Azidothymidine (AZT)         Sphingosine 1-phosphate	Sendai paramyxovirus	Hyperglycemia	product)	CD4-Ligand (gp120)	Des-Arg10-kallidin (B1 receptor	2,4-dinitrofluorobenzene
Vaccinia Vins Akara         Hyperosmotic Shock         Therapeutically used drugs         M3 Cholinergic receptor           West Nile Flavavirus         Hyperosia         AR8.23757 (ox-quinoline- agorist         M3 Cholinergic receptor           Neat Nile Flavavirus         Hyperosia         AR8.23757 (ox-quinoline- agorist         M3 Cholinergic receptor           National Stema         Isterming preconditioning         2-atmateconditioning         Fe2-atmatecport-Ligand (1902a)           Adenovirus E3.19K         Human labor (childbirth)         2-th-admaniyamino)-6         Fe1-Ligand           Adenovirus E3.19K         Human labor (childbirth)         2-th-D-Arabinofuranosyl-         LyteArE-Ligand           Adenovirus E3.19K         Human labor (childbirth)         1-b-D-Arabinofuranosyl-         JybArE-Ligand           Adenovirus E3.19K         Human labor (childbirth)         1-b-D-Arabinofuranosyl-         JybArE-Ligand           Aritican Swine Fever         Mechanical Ventilation (in sytosine (ar-C))         N.CAM         N.CAM           Virus. IAP         Virus (Mased Gisuse         Arathaline (AZT)         Sphingosine 1-phosphate	Sindbis Virus	Hyperhomocysteinemia		CD66a-Ligand	agonist)	Ethanol
West Nite Flaxwirus         Hyperoxia         ABR.25757 (oxo-quinoline- ischeming remotin- scheming remotinioning         ABR.25757 (oxo-quinoline- scheming remotinioning         ABR.25757 (oxo-quinoline- Fi-La_Receptor-Ligand (lgG2a)           Adenovirus 5: E1A         Liver Regeneration         2-(1-adamaniylamino).6.         Fi-L-lagand           Adenovirus 5: E1A         Liver Regeneration         periodicioning         2-(1-adamaniylamino).6.         Fi-L-lagand           Adenovirus 5: E1A         Liver Regeneration         methylpyridine (AdAMP)         Heat shock protein 60 (HSP60)           Adenovirus 5: S19K         Human labor (childbirth)         1-D-D-Arabinofinamosyl-         LyoA/E-Ligand           Adenovirus 5: S10K         Human labor (childbirth)         1-D-D-Arabinofinamosyl-         LyoA/E-Ligand           Adenovirus 5: Virus 1AP         Nirus 1AP         Nirus 1AP         Nirus 1AP         Nirus 1AP           Antibuloty to Dengue Virus         Muscle disuse         Azidothynidine (AZT)         Sphingosine 1-phosphate	Vaccinia Virus Akara	Hyperosmotic Shock	Therapeutically used drugs	M3 Cholinergic receptor	1,25-dihydroxycholecalciferol	Ferrocene
Istochemia (transfert, focal)         Scarboxamide)         Fc-2a-Receptor-Ligand (1gC2a)           Viral products         Istochemic preconditioning         2-(1-admanylamino)-6-         Fit-1-Ligand (1gC2a)           Adenovirus 5. E1A         Liver Regretation         methylpyridine (AdAMP)         Heat shock protein 60 (HSP60)           Adenovirus 5. E1A         Human labor (childbirth)         1-b-D-Arabinofuranosyl-         Ly6A/E-Ligand           Adenovirus E3/19K         Human labor (childbirth)         1-b-D-Arabinofuranosyl-         Ly6A/E-Ligand           Ariton Swine Fever         Mechanical Ventilation (in vytosine (ara-C))         N-C-AM         PGG-Glucan (Betafetcin)           Ariton String Liver         Anthralin         PGG-Glucan (Betafetcin)         PGG-Glucan (Betafetcin)           Antibody to Dengue Virus         Muscle disuse         Azidothymidine (AZT)         Sphingosine 1-phosphate	West Nile Flavavirus	Hyperoxia	ABR-25757 (oxo-quinoline-	agonist	Double-stranded polynucleotides	Forskolin
Viral products         Ischemic preconditioning         2-(1-adamanylamino)-6-         FIL-1-Ligand           Adenovirus E319K         Liver Regeneration         methylpyridine (AdAMP)         Heat shock protein 60 (HSP60)           Adenovirus E319K         Human labor (childbirth)         1-b-Arabinofuranosyl-         Ly6AFE-Ligand           Aftican Swine Fever         Mechanical Ventilation (in sytosine (ara-C))         N-CAM         N-CAM           Aftican Swine Fever         Mechanical Ventilation (in sytosine (ara-C))         N-CAM         PGG-Glucan (Betafectin)           Antibody to Dengue Virus         Masc disuse         Aritothymidine (AZT)         Sphingosine 1-phosphate	m	Ischemia (transient, focal)	3-carboxamide)	Fc-2a-Receptor-Ligand (IgG2a)	f-Met-Leu-Phe	Gadolinium chloride
Adenovirus 5: E1A         Liver Regeneration         methylpyridine (AdAMP)         Heat shock protein 60 (HSP60)           Adenovirus E3/19K         Human labor (childbirth)         1-b-D-Arabinofuranosyl-         Lydx/E-Ligand           Afternovirus E3/19K         Human labor (childbirth)         Procentine         Procentine           Afternovirus Nucle         Arabinofu (no sytosine (ara-C))         N-CAM         Procentine           Arritody to Dengue Virus         Muscle disuse         Araidothynidine (AZT)         Sphingosine 1-phosphate	Viral products	Ischemic preconditioning	2-(1-adamantylamino)-6-	Flt-1-Ligand	Fibrinogen	Glass fibers
Adenovirus E3/19K         Human labor (childbirth)         1-b-D-Arabinofuranosyl-         Ly6A/E-Ligand           African Swire Fever         Mechanical Ventilation (in system (ara-C))         N-C-AM         N-C-AM           Virus LAP         Anthrahin         PGG-Glucan (Berafectin)         PGG-Glucan (Berafectin)           Antibody to Dengue Virus         Musc disuse         Azidothymidine (AZT)         Sphingosine 1-phosphate		Liver Regeneration	methylpyridine (AdAMP)	Heat shock protein 60 (HSP60)	Free fatty acids	HDAC inhibitors (sodium butyrate
African Swine Fever         Mechanical Ventilation (in cytosine (ara-C))         N-CAM           Virus: IAP         vitro)         Anthralin         PGG-Glucan (Betafectin)           Antibody to Dengue Virus         Muscle disuse         Azidothymidine (AZT)         Sphingosine I-phosphate	1	Human labor (childbirth)	1-b-D-Arabinofuranosyl-	Ly6A/E-Ligand	Heat shock protein 25 (Hspb1)	and trichostatin A)
Virus IAP vitro) Anthralin PGG-Glucan (Betafectin) Antibody to Dengue Virus Muscle disuse Azidothymidine (AZT) Sphingosine 1-phosphate		Mechanical Ventilation (in	cytosine (ara-C))	N-CAM	Heat shock protein 60 (HSP 60)	Linoleic acid
Antibody to Dengue Virus Muscle disuse Azidothymidine (AZT) Sphingosine 1-phosphate	Virus: IAP	vitro)	Anthralin	PGG-Glucan (Betafectin)	Hemoglobin	L-NMA
	Antibody to Dengue Virus	Muscle disuse	Azidothymidine (AZT)	Sphingosine 1-phosphate	Homocysteine	Lysophosphatidic acid
ular Dystrophy (type Baicalein Trail-receptor-1-Lignad (Trail) 1	-	Muscular Dystrophy (type	Baicalein	Trail-receptor-1-Lignad (Trail)	Hyaluronan	Malondialdehyde
Ureaplasma urealyticum CMV: iel 2A) Bleomycin Trail-receptor-2-Ligand (Trail) 12(R)-H	-	2A)	Bleomycin	Trail-receptor-2-Ligand (Trail)	12(R)-Hydroxyeicosatrienoic acid	MDMA ("Ecstacy")
Yersinia enterocolitica Double-stranded RNA Neuronal firing Bryostatin-1 Trail-receptor-4-Ligand (Trail) 6-hydro		Neuronal firing	Bryostatin-1	Trail-receptor-4-Ligand (Trail)	6-hydroxydopamine	MEN 17055 (disaccharide

Table. 1 A list of inducers of NF-kB

anthracycline) Monensin N-methyl-D-aspartate Mycophenic acid Nickel sulfate Nickel sulfate Nicotine	N-nitrosomorphine No-aitrosomorphine Okadaic Araid Peplomycin Photo Ester Photobletster CpG DNAs Photobletster CpG DNAs Prospholletster CpG DNAs Prospholletster CpG DNAs Prospholletster CpG DNAs Saflower polyauchartians) Querettin (high concentrations) Querettin (high concentrations) Q
hPepT1 (apical di-/tripeptide transporter transporter atalanie acid (Kainate) Leukoritien B4 Loflutamate Loflutamate Long-term potentiation (LTP)	Mixed meal ingestion (hi glucose) Monosodium urate crystals Monosodium urate crystals Monosodium urate crystals Ninic oxide Ninic oxide Olici acid Osteopontin PAF (platelat activating factor) Palmitate CSC (polysaccharide from Poria cocos) Phalimus lintus protoglycan Phalinus lintus protoglysis- intorysis-inducing factor (PIF) Regulatory RNA Regulatory RNA Regulatory RNA Regulatory RNA Regulatory RNA Saturated fatry acids Stoph derivation Stopher implants Trefl costimulatory receptor 4-1BB Trefl costimulatory receptor 4-1BB
Apoptotic Mediators Amti-Fas/Apo-1 Poly(ADP) Ribose Polymerase (PARP) Trail	Mitegens, growth factors and Bone morphogenic protein 2 Bone morphogenic protein 2 Bone morphogenic protein 4 Epidermal Growth Factor Folicle Stimulating Hormone Gastrin Gastrin GMCSF Hepatocyte Growth Factor Human Growth Hormone Human Growth Hattor 1 Lysophosphatidic acid Mullerian Inhibiting Substance Insulin-like growth factor 1 Lysophosphatidic acid Mullerian Inhibiting Substance Fustor (PEDF) Platech Activating Factor Platech Activating Factor Platech Activating Factor Platech Activating Factor Platech Activating Factor Platech Activating Factor Platech Growth Factor Platech Activating Factor Platech Activating Factor Platech Activation Factor (PEDF) Platech Activation Stophatide (L-selectin Schum Suphatide (L-selectin CF-alpha TGF-betha TGF-betha
Bucillamine metabolite SA 981 Camptothecin Celecoxib Ciprofibrate Ciprofibrate Cycloprodigiosin	IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII
Overventilation (perfused lungs) Pancreatitis Proteimuria Recorgenation Rheumatoid arthritis Senescence (keratinocytes)	Shear Stress Neucornal trimethyltin injury Uni-axial cyclic cell arteching T-cell selection Physical Stress Bild duct ligation Cyclic mechanical muscle strain Exercise Exercise Exercise PME Photosensitization Ultraviolet irradiation Ultraviolet irradiation Ultraviolet irradiation Ultraviolet irradiation Ultraviolet irradiation Ultraviolet Stress Butyl Peroxide Guatation Statistice Hydrogen Peroxide Foroxintrie Peroxynitrie Peroxynitrie Peroxynitrie Peroxynitrie
EBV: EBNA-2 EBV: LMP1 HBV: HBX HBV: HBX HBV: LHBs HBV: MHBs HCV. Core protein HCV. Core protein HCV. Saimiri: HVS13	
Bacterial or Fungal Products Apicularen A Cycloysin (Vibrio Vulnificus)	Diphosphoryl lipid A (Rhodeacer (Rhodeacer extoxina) Enterotoxin (Bateroides fragitis) Erimbria protein ATTLE (P gingirvalis) Funonisin B1 (Fusarium G(Anh) M Tetra (E coli) G(Acah) M Tetra (E coli) G(Acah) M Tetra (E coli) Glycosyhosphotiyhino falciparum falciparum falciparum Lipotoretohic acid (Lipotoretohic acid (Listeria) Membrane lipoproteins (Mycoplasma proteansa) Membrane lipoproteins (Mycoplasma proteansa) Muranyl Peptides Mycobacterium lipoaterionnannan (Lastrah) PeB (Phospholipase) (Listeria) Muranyl Peptides Mycobacterium lipoaterionnannan lipoaterion lipoaterion liboaterian lipoaterionnannan lipoaterionnan



### Nucleus

**FIGURE 1.** Schematic pathway for TNF-induced NF-kB activation and its inhibition by various natural products.

### WHAT GENES ARE REGULATED BY NF-KB?

Although initially identified in kappa chain of immunoglobulin, the NF- $\kappa$ B binding sequences have now been identified in over 400 different genes (TABLE 2). These include inflammatory cytokines (e.g., TNF, IL-1, IL-6, and chemokines), adhesion molecules, inflammatory enzymes (e.g., COX-2, 5-LOX), viral proteins, telomerase, angiogenesis proteins (VEGF), antiapoptotic proteins, and cell cycle–regulatory

	Enzymes Liver alcohol dehydrogenase Collagenase 1 Gulaathione S-transferase H+x-K+ATPase x2 Lysozyme Matrix mealloproteinaase-9 GD3-synthase Galatinase B PM-1 PKC8 Phospholipase C 81 PKC8 Phospholipase C 81 PKC8 PKC8 PKC8 PKC8 PKC8 PKC8 PKC8 PKC8
F-kB-regulated	Bradikinin B1-receptor Amiloride-sensitive sodium channel A1 adenosine receptor TRAF-1* TRAF-2* TRAF-2* TRAF-2* TRAF-2* TRAF-2* TRAF-2* TRAF-2* TRAF-2* TRAF-2* TRAF-2* TRAF-2* TRAF-1
Table. 2 A list of target genes of NF-kB-regulated	Cell adhesion moleculesBradikinin B1-receptor Amiloride-sensitive sodium chann E-selectinE-selectinEndoglinEhdoglinEhdoglinFiboneccinFiboneccinFiboneccinFiboneccinCAM-1*RARA1-1*FiboneccinRegulators of apoptosiCAM-1*TRAF-2*P-selectin, tenascin-CEX-11*DC-SIGN*Regulators of apoptosiPocsicinveEX-11*ProfectinsRAPS*AntionectinCD5 (Fas)ProfectinsNr13AntionecineCD5 (Fas)ProfectinsNr13AngioresinogenBel-2Complement factor BNr13Complement factor BNr13Complement factor BSil1/A1Depopolysaccharide binding proteinDrincesDepopolysaccharide binding proteinDrincesDerastive proteinDrince teukemia virusSAA1 and SAA2*Bovine leukemia virusTissue factor PDrince teukemia virusDerastive proteinDrince teukemia virusDerastive plasminogen activatorCytomegalovirus
Table. 2 A li	Immunoreceptors         B7.1         BR.L-1*         BR.L-1*         BR.L-1*         BR.L-1*         BR.L-1*         BR.L-1*         BR.L-1*         CCR5         CCR5         CCR5         CCR5         CD137         CD148         CD293         CD383         Fe epsilon receptor II         III-2 receptor $\sigma$ -chain         Immunoglobulin Cyl         IgG 74         MHC class I HLA-B7         MHC class I HLA-B7         MHC class I HLA-B7         MHC class I HLA-B7         Nod2         Polymeric Ig receptor $\beta$ chain         Nod2         Polymeric Ig receptor $\beta$ chain
	Cytokines/ChemokinesImmunoreceptorsCCL3*BRL-1*CCL15/LeukotactinBRL-1*CCL22CCR5CCL22CCR5CCL22CCR5CCL22CCR5CCL23CCR5CCL240CCR4Gro-1CCR4Gro-1CD40Gro-1CD40Gro-1CD40Gro-1CD40Gro-1CD40Gro-2CD41Gro-4CD40HowerL-1Feeplor antagonistImmunoglobulin cylin traL-1MHC class I HLA-B7L-1MHC class I HLA-B7L-1Polymetri I groeptorL-12Polymetri I groeptorL-13Polymetri I groeptorL-15Polymetri I groeptorL-15Polymetri I groeptor

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Gadd45β Galeetin 3 Epsilon-globin HMG-14* HMG-14* Ka faratin Laminin B2 chain Mis1 Mis1 Mis1 Mis1 Mis1 Profice glycoprotein Prograncy-specific glycoprotein Prograncy-specific antigen Stoda (calcyclin) Syndecan-4 Vimertin Stoda (calcyclin) Syndecan-4 Vimertin al-antitypsin,
Hepatitis B virus (pregenomic promoter) HIV-1 HIV-1 HIV-1 StV* JC virus StV+ StV+ StV+ StV+ StV+ StV+ StV+ StV+
Stresss-response genes Angiotensin II Cytochrome p450 gene COX.2* Ferritin H chain 12.Lipoxygenase iNOS* Mn SOD* NQOI* Phospholipase A2 Phospholipase A2 Cell surface receptors Phospholipase A2 Phospholipase A2 Phospholipase A2 Inceptor advanced glycation and products Plateta activator receptor Nu-opioid receptor Matri* Lox-1* Codl receptor CD69
T-cell receptor/CD3y       Stresss-respon         p80 TNF-receptor       Stresss-respon         complement B       Angiotensin II         complement component 3       Cytochrome 9450 gen         complement receptor 2       Feritin H chain         Peptide transporter TAP1       Displopingenase         Proteasome subunit LMP2       12-Lipoxygenase         Tapasin       Proteasone subunit LMP2         Tapasin       Protecptor 2         Peptide transporter TAP1       Displopingenase         Tapasin       MOOSD*         Bone morphogenic protein-2       Piospholipase A2         Bone morphogenic protein-2       Piospholipase A2         Bone morphage colony       RAGE- receptor for a simulating factor         Erythropoictin, mercophage colony       RAGE- receptor for a simulating factor         Envokinin-1 receptor       Nuenopeptide Y V1-receptor         Neuropeptide Y roter       Neuropeptide Y V1-receptor         Platelet actived receptor       Neuropeptide Y V1-receptor         Protenkephalin       Md1*         Vascular endothelial growth factor       CDA         Prostnekephalin       Md1*         Vascular endothelial growth factor       CDA
<ul> <li>β-Interferon</li> <li>IP-10*</li> <li>KC*</li> <li>ENA-78 (CXCL5)</li> <li>ENA-78 (CXCL6)</li> <li>Lymphotoxin α</li> <li>Lymphotoxin α</li> <li>Lymphotoxin β</li> <li>MCP-1/JE*</li> <li>TCA3*</li> <li>TCA3*</li> <li>TCA3*</li> <li>TCA3*</li> <li>TCA3*</li> <li>TCA3*</li> <li>TCA3*</li> <li>TCA3*</li> </ul>

\*CLS, C.C chemokine ligand 5; CINC-1, cytokine-induced neutrophil chemoattractarc1: CXCL 11, CXC chemokine ligand 11; ICOS, inducible co-stimulator, IP-10, IFN; gamma-inducible protein 10, KC, kupfler cells, MCP. 1, noncoyre chemoattractant protein-1, MIP, macrophage inflammatory protein, RANTES, regulated upon activation, normal T-cell expressed and secreted; TCA3, T cell activation, TRAIL, tumor necrosis factor-related approssible inflammatory protein, RANTES, regulated upon activation, normal T-cell expressed and secreted; TCA3, T cell activation, TRAIL, tumor necrosis factor-related approssible indicating ligand 11, intercellular adhesion molecule.). MadCANT, mucusal datasin cell adhesion molecule, CAM-1, vascard and secreted; TCA3, T cell activation, TRAIL, tumor necrosis factor-related approssible indice adhesion molecule indicated and secreted and secreted; TCA3, T cell activation, TRAIL, tumor necrosis factor-related approssible indice indiversed and secreted; TCA3, T cell activation, TRAIL, tumor necrosis factor-related to approssible indice adhesion molecule, MA1, Match, Multiple data cell adhesion molecule, AA, serum amyloid A proteins; COX2, opelooxygenae2, 210S, inducible intric oxide synthase, MSOD, superoxide dismutase; NOQ1, NADYPH quinone oxidoreducase 1; MA1, Multiple daty resistance mediano 1, Lox-1, learnin-like oxidareducase 1; MA1, Multiple daty resistance mediano 1, Lox-1, learnin-like oxidare daty resistance and resistance and resistance and resistance and resistance activation receptor. TRAT, TNF-receptor associated factor, IEX-11, immediate early response factor-1, LAS, Imfler avirus, SV-40, Simian virus, 90, IRF, Interferon regulatory factor, TRAT, INF-response catadytic subunit, AMH, Auti-multerian hormone, HMG-14, High mobility group 14.

genes. Besides NF- $\kappa$ B, other transcription factors may modulate the expression of these genes. Microarray analysis has added even more genes to the list of those regulated by NF- $\kappa$ B.<sup>22,23</sup>

### WHICH DISEASES ARE LINKED TO NF-KB ACTIVATION?

Constitutive NF- $\kappa$ B activation has now been shown to contribute to the pathogenesis of a large number of diseases (TABLE 3). These include cancer, diabetes, allergy, rheumatoid arthritis, Crohn's disease, cardiovascular diseases, atherosclerosis, Alzheimer's disease, muscular dystrophy, cardiac hypertrophy, catabolic disorders, hypercholesterolemia, ischemia/reperfusion, angina pectoris, acid-induced lung injury disease, renal disease, gut diseases, skin diseases, incontinentia pigmenti, appendicitis, pancreatitis, peritonitis, sepsis, silica-induced disease, sleep apnea, autoimmunity, lupus erythematosus, psychosocial stress diseases, neuropathological diseases, familial amyloid polyneuropathy, Parkinson's disease, Huntington's disease, and retinal disease. NF- $\kappa$ B activation has also been linked with the human aging process.

A constitutive NF-κB has been detected in most tumor cell types including esophageal cancer, laryngeal cancer, pharyngeal cancer, renal cancer, colon cancer, head and neck squamous carcinoma, lung cancer, bladder cancer, acute myelogenous leukemia, non-Hodgkin's lymphoma, B-cell lymphoma, adult T-cell leukemia, T-cell lymphoma, mantle cell lymphoma, multiple myeloma, acute lymphoblastic leukemia, cervical cancer, nasopharyngeal carcinoma, melanoma, thyroid cancer, liver cancer, breast cancer, ovarian cancer, and prostate cancer.<sup>24,25</sup> NF-κB can mediate transformation, proliferation, invasion, and angiogenesis of tumor cells. Mutated ras found in several tumors has been shown to activate NF-κB. Chemoresistance and radioresistance have also been linked to NF-κB activation. The *p*-glycoprotein linked to drug-resistance is also regulated by NF-κB. Similarily, COX-2 overexpressed in most tumors is also regulated by NF-κB. Cyclin D1, overexpressed by most tumors and required for G<sub>1</sub> to S transition, is also regulated by NF-κB. Similarily, VEGF and adhesion molecules required for angiogenesis and metastasis are also regulated by NF-κB.

Many inflammatory genes relevant to the pathogenesis of atherosclerosis are regulated by NF- $\kappa$ B, the activated form of which is present in atherosclerotic plaques. NF- $\kappa$ B has been shown to be activated in atherosclerosis and myocarditis, in association with angina, during transplant rejection, after ischemia/reperfusion, in congestive heart failure, in dilated cardiomyopathy, after ischemic and pharmacological preconditioning, in heat shock, in burn trauma, and in hypertrophy of isolated cardiomyocytes.

Bronchial asthma is one of the most common chronic diseases in modern society and yet, despite the availability of highly effective drugs, there is increasing evidence to suggest that its incidence is increasing. The pathogenesis of asthma involves persistent expression of a broad array of genes, which contain the  $\kappa B$  site for NF- $\kappa B$ within their promoters, suggesting that NF- $\kappa B$  plays a pivotal role in the initiation and perpetuation of allergic inflammation.

Several reports suggest that amyloid  $\beta$  peptide can activate NF- $\kappa$ B in neurons, indicating a plausible mechanism by which amyloid may act during the pathogenesis

Ageing	Acid-induced lung inury disease (COPD)	Silica-induced
Headaches	Renal Disease	Sleep apnoea
Pain	Leptospiriosis renal disease	AIDS (HIV-1)
Cardiac hypertrophy	Gut Diseases	Autoimmunity
Muscular hystrophy (type 2A)	Skin Diseaes	Lupus
Catabolic disorders	Incontinentia pigmenti	Psychosocial stress diseases
Diabetes, Type 1	Asthma	Neuropathological diseases
Diabetes, Type 2	Arthritis	Familial amyloidotic polyneuropathy, inflamm
Hypercholesterolemia	Crohns disease	neuropathy
Atherosclerosis	Ocular allergy	Parkinson disease
Heart disease	Appendicitis	Alzheimers disease
Chronic heart failure	Pancreatitis	Huntington's disease
Ischemia/reperfusion	Periodonitis	Retinal disease
Angina pectoris	Inflammatory bowel disease	Cancer
Pulmonary disease	Sepsis	

# Table. 3 A list of NF-kB-mediated diseases

	1010n T			
Cytokine & Hormones	Aged garlic extract (allicin)	Nordihydroguaiaritic acid	Glucorticoid-induced leucine zipper	Compound 26**
Interleukin-4 <sup>+</sup>	Anetholdithiolthione	Oleandrin+	protein	Cycloepoxydon
Interleukin-10	Anethole+	Orthophenanthroline	$\gamma$ -glutamylcysteine synthetase <sup>+</sup>	Cyclolinteinone
Interleukin-11	Apocynin	Parthenolide	Heat shock protein 72	Cycloprodigiosin
Interleukin-13 <sup>+</sup>	Apple juice	PDTC**	HSCO**	hycrochloride Dehydroxymethylepo
Growth hormone	Astaxanthin	Phenolic antioxidants (Hydroquinone Losartin	: Losartin	xyquinomicin
HBEGEF**	Baicalein	and tert-butyl hydroquinone)	MnSOD** <sup>+</sup>	Diamide <sup>+</sup>
hCG**	Benidipine	Phenolic antioxidants**	NDPP1 (CARD protein)	Diarylheptanoid 7-(4'-hydroxy-3'-
Luteinizing hormone <sup>+</sup>	Betulinic acid <sup>+</sup>	Phenylarsine oxide (PAO, tyrosine	NF-2 protein	methoxyphenyl)-1-phenylhept-4-en-
α-MSH**	bis-eugenol	phosphatase inhibitor)	NLS cell permeable peptides	3-one 3-ditriazine)
Somatomammotropin	Butylated hydroxyanisole		p202a**	Dimethylfumarate
VEGF**	Caffeic Acid Phenethyl Ester (3,4-	<b>Phytochemicals</b>	Pioglitazone (PPARy ligand)	Dioxin <sup>+</sup>
Estrogen	dihydroxycinnamic acid, CAPE)	Piceatannol <sup>+</sup>	Pituitary adenylate cyclase-activating	Disulfiram
Glucocorticoids	Caffeic Acid Phenethyl Ester <sup>+</sup>	PMC (2,2,5,7,8-pentamethyl-6-	polypeptide	E-73 (cycloheximide analog)
PG-15-deoxy- $\Delta(12,14)$ -PGJ(2)**	Calagualine <sup>+</sup>	hydroxychromane)	Protein-bound polysaccharide	Ecabet sodium
Prostaglandin A1	Capsaicin <sup>+</sup>	PMC**	PTEN	Epoxyquinone A monomer Fibrates
Prostaglandin E2	Camosol	Polysaccharides	Suppressors of cytokine signaling-1	Erythromycin
	Carvedilol	Pyrrolinedithiocarbamate (PDTC)	Triglyceride-rich lipoproteins	Fosfomycin
Antiinflammatory agents	Catalposide	Quercetin	Vasoactive intestinal peptide	Flunixin meglumine
Acetaminophen	Catechol Derivatives	Quercetin (low concentrations)	ZAS3 protein**	Gangliosides
Aspirin (sodium salicylate)	Cepharanthine	Red wine		Gabexate mesilate
Flurbiprofen	Conophylline	Redox factor 1	Stress	Geldanamycin
Ibuprofen	Curcumin <sup>+</sup>	Ref-1 (redox factor 1)	Carbon monoxide	Glimepiride
Leflunamide metabolite** <sup>+</sup>	Dehydroepiandrosterone	Resiniferatoxin	Electrical stimulation of vagus nerve	Glucosamine sulfate
Sulindac	DHEA-sulfate	Resveratrol	Hypothermia	Herbimycin A

## Table. 4 A list of inhibitors of NF-KB\*

	Dibenzylbutyrolactone lignans	Rg(3) (ginseng derivative)	Metals**	Hydroquinone
Cell-signaling	Diethyldithiocarbamate	Rg(3), a ginseng derivative	Nitric Oxide	4-Hydroxynonenal
inhibitors	Diferoxamine	Rocaglamides	Saline (low Na <sup>+</sup> istonic)	Hypochlorite
Atrovastat**	Dihydrolipoic Acid	Rotenone	Hyperosmolarity	Hypoethyl starch
D609**	Dilazep +	Rotenone		Isomallotochromanol
LY294002**	Dilazep + fenofibric acid	S-allyl-cysteine (SAC, garlic	Vitamins	Isomallotochromene
Quinadril**	Dimethyldithiocarbamates	compound)	BTEE**	Jesterone dimer
RO31-8220**	Dimethylsulfoxide	Sanguinarine+	Vitamin C	Kamebakaurin
SB203580**	Disulfiram	Saucerneol D and E	Vitamin D	Lactoferrin
SC236**	Ebselen	Sauchinone	Vitamin E	LDL (Extensively oxidized)
Sphondin	EGTA**	Sauchinone	Nitrosylcobalamin**	Leptomycin B
TNP-470**	$Emodin^{+}$	Silibinin <sup>+</sup>		Mevinolin, 5'-methylthioadenosine
U0126**	Ent-kaurane diterpenoids	Silymarin+	Virus derivatives	Monochloramine
	Epigallocatechin-3-gallate	Tempol	Core Protein of Hepatitis C virus <sup>+</sup>	MX781
IKK inhibitors	EPC-K1 (phosphodiester compound	Tepoxaline	EIA	Nafamostat mesilate
AS602868	of vitamin E and vitamin C)	Tepoxaline (5-(4-chlorophenyl)-N-	HIV-1 Vpu protein	N-ethyl-maleimide
BAY-117082**	Epigallocatechin-3-gallate (green tea	hydroxy-(4-methoxyphenyl) -N-	IkB-like proteins	Nicotine
BAY-117083**	polyphenols)	methyl-1H-pyrazole-3-propanamide)	K1 protein	Omega 3 fatty acids
BMS-345541	Epoxyquinol	Tert-butyl hydroquinone	Kaposi's sarcoma-associated herpesvirus	Pervanadate <sup>+</sup>
DTD**	Epoxyquinol A	Tranilast	Pertussis toxin binding protein	Petrosaspongiolide M
E3330**	Erbstatin <sup>+</sup>	Triptolide (PG490)	SspH1 and IpaH9.8**	<b>Phenethylisothiocyanate</b>
LF15-0195**	Ergolide	Uncaria tomentosa	YopJ**	Phenylarsine oxide <sup>+</sup>
MOL 294**	Ergothioneine	Ursolic acid <sup>+</sup>		Phenyl-N-tert-butylnitrone
PS1142	Ethyl Pyruvate	Vitamin C	Synthetic compounds	Phosphorylation
	Ethylene Glycol Tetraacetic Acid	Vitamin E derivatives	AS602868	Phytic acid
Protease/ Proteasome	Eugenol	Yakuchinone A and B	Decoy oligonucleotides**	Pranlukast
inhibitors	Fenofibric acid	Yakuchinone A and B	DTD**	Psychosine
ALLnL	Flavenoids (Crategus)		E3330**	Pyrithione
APNE	Flavopirido1 <sup>+</sup>	Plant extracts	Hydroquinone	Raxofelast
APNE***	Fluorochalcones	Apple	Macrolide antibiotics	Rebamipide
Boronic Acid Peptide	Gamma-glutamylcysteine synthetase	Aged garlic	MOL 294**	Rhein
BTEE	Ganoderma lucidum polysaccharides	Black raspberry	Pentoxifylline	Ribavirin
Cyclosporin A	Garcinol (from extract of Garcinia	Blueberry		Rifamides
DCIC**	indica fruit rind)	Ganoderma lucidum	Others	Rifampicin
	+ • • • • • • • • • • • • • • • • • • •			

TABLE 4 – continued.

Ginbas hilaha avtraat	Ochna macrocality harb	-	6 aminoanimezoline derivatives	DA106 0020
Ginkgo Diloda extract	OCINIA INACTOCALYX DAIL	×	o-aminoquinazonne derivatives	R0100-9920
Glutathione	PC-SPES (8 herb mixture)	ture)	6(5H)-phenanthridinone + benzamide	Sanggenon C
Glycyrrhizin	Phyllanthus amarus		7-amino-4-methylcoumarin	Serotonin derivative**
Guaianolides	Qingkailing		15-Deoxyspergualin	Siah2**
Hematein	Shuanghuanglian		ADP ribosylation inhibitors**	SLPI**
Hypericin	Stinging nettle		Amentoflavone	Statins
IRFI 042 (Vitamin E-like compound)	e compound) Tanacetum larvatum		Amrinone	Staurosporine
Iron tetrakis	Uncaria tomentosum		Anandamide	Sulfasalazine
Isoeugenol	Fungal gliotoxin		Anti-thrombin III	Surfactant protein A
KT-90**			APC0576**	Survanta
L-cysteine	Polypeptides		Artemisinin	T-614**
Lacidipine	and enzymes		Astragaloside IV	Taurine + niacine
Lazaroids	Angiopoietin-1		Atorvastatin	Tetrathiomolybdate
Lovastatin	Atrial Natriuretic Peptide	ide	Aucubin	THI 52**
Lupeol	AvrA protein (Salmonella)	(ella)	Azidothymidine	$Thalidomide^+$
Luteolin	β-amyloid protein		Benfotiamine (thiamine derivative)	Thiopental
Magnolol	β-catenin		Bisphenol A	Triflusal
Manassantins A and B	Bovine serum albumin	_	o,o'-bismyristoyl thiamine disulfide	Tyrphostin AG-126
Manganese superoxide dismutase	ismutase CaMKK**		Cacospongionolide B	Wedelolactone
Melatonin	Complement protein C5a	Sa	Capsiate	Wogonin
Mesalamine	Cytochalasin D		Caprofin	
N-acetyl-L-cysteine	D-amino acid peptide		Chitosan	
Nacyselyn	DQ 65-79**		Chromene derivatives	
Nordihvdroguaiaritic acid			Clarithromycin	

\*For mast references see http://jbcopfe.bu.edu/gilmore/nf4k/Jab/index.html
\*ADP ribosylation inhibitors, nicotinamide and 3-aminobenzamide, APC056, 54((5)-22-dimethylocyloproparecarbonyl)amino)\_24(4((5)-22-dimethylocyloproparecarbonyl)amino)\_pheoxylparidine, APNE, N-aecyl-DL-pheoxylparidine, APNE, Maceyl-DL-pheoxylparidine, APNC056, 54((5)-22-dimethylocyloproparecarbonyl)amino)\_pheoxylparidine, APNE, N-aecyl-DL-pheoylandylchenile
\*ADP ribosylation inhibitors, nicotinamide and 3-aminobenzamide, APC056, 54((5)-22-dimethylocyloproparecarbonyl)-aufonyl)-2-propeneintile, BTRE, N-barzoyl L-phylorseyl, MacCoA reactase inhibitor, A77 1736, Leftuomide metaboline; BAY117082, E3(4+methylphenyl)-aufonyl)-2-propeneintile, BTRE, N-barzoyl L-phylorseyl, Tarcoline, ATTRE, N-barzoyl L-phylorsylphenyl)-aufonyl)-2-propeneintile, BTRE, N-barzoyl L-phylorseyl, Parcoly 1, 2-phylorseyl, and 2-adio-fachylorseyphenylylchenik. DQ: 5-79, as do: 579, acid, FEG0.
The optimization of the cubation of the cubation factors for binding to their consensus sequences; DCIC, 4-4 dichloroisocoumanin, DPF, dispopoyl functorbane, DQ 5-79, acid, FEG0.
Theory and the cubation of the cubation of the cubation factors for binding to their consensus sequences; DCIC, 4-4 dichloroisocoumanin, DPI, dispopoyl functorbane, DQ 5-79, acid, FEG0.
Theory and the cubation of the cubation factors for binding to their consensus sequences; DCIC, 4-4 dichloroisocoumanin, DPI, dispopoyl functorbane, DQ 5-79, acid, FEG0.
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Theory acid, FEG2.
Theory acid, FEG1.
Theory acid, FEG2.
The

of Alzheimer's disease. Rheumatoid arthritis is a chronic inflammatory disease characterized by persistent joint swelling and progressive destruction of cartilage and bone. NF- $\kappa$ B plays an essential role in transcriptional activation of TNF and IL-1. Together they form a positive regulatory cycle that may amplify and maintain the rheumatoid disease process.

### HOW TO INHIBIT NF-KB ACTIVATION?

Because of the role of NF-κB in a wide variety of diseases, inhibitors of NF-κB activation are extensively sought (TABLE 4). Different steps in the NF-KB activation pathway are being targeted to block NF- $\kappa$ B. These include inhibitors of proteosome that mediate I $\kappa$ B $\alpha$  degradation, inhibitors of kinase (IKK), which mediate I $\kappa$ B $\alpha$ phosphorylation, decoy peptides from I $\kappa$ B $\alpha$ , IKK, and p65 proteins. The doublestranded oligodeoxynucleotides (ODNs) that possess consensus NF-KB sequence as transcription factor decoys (TFDs) also have been found to inhibit NF-KB binding to native DNA sites. Examples of proteasome blockers include peptide aldehydes such as ALLnL, LLM, Z-LLnV, and Z-LLL, lactacystine, PS-341, ubiquitin ligase inhibitors, and cyclosporine A. Several cytokines that are produced by Th2 have been found to suppress NF-KB activation. These include IL-4,<sup>26</sup> IL-13,<sup>27</sup> and IL-10.<sup>28</sup> Additionally, endocrine hormones such as HCG,<sup>29</sup> LH, MSH,<sup>30</sup> and GH<sup>31</sup> have been shown to abrogate NF- $\kappa$ B activation. Both IFN- $\alpha$  and IFN- $\beta$ , which exhibit antiviral, antiproliferative, and immunosuppressive activities, also abolish NF-KB activation.<sup>32</sup> Several phytochemicals from different plants have been identified that can suppress NF-KB activation effectively.33-46 These include curcumin (turmeric), resveratrol (red grapes), guggulsterone (guggul), ursolic acid (from holy basil), betulinic acid (birch trees), eugenol (cloves), gingerol (ginger), oleandrin (oleander), silymarin (artichoke), emodin (aloe), capsaicin (red chili), anethol (anise), and others. All these blockers of NF-KB have potential in the treatment of a wide variety of diseases. Pharmacological safety, bioavailability, and efficacy in vivo will determine their therapeutic potential in particular diseases.

### CONCLUSION

This minireview shows that NF- $\kappa$ B is an important transcription factor that is activated by a wide variety of stimuli, controls the expression of a large number of genes, mediates pathogenesis of various diseases, and can be suppressed by numerous agents. NF- $\kappa$ B activation, however, is required for the proper function of the immune system. Proliferation of T cells and B cells, activation of macrophages, proliferation and survival of dendritic cells, and activation of T cells are dependent on NF- $\kappa$ B activation. Some recent evidence, however, indicates that while NF- $\kappa$ B1 mediates an inflammatory response, NF- $\kappa$ B2 mediates an immune response.<sup>47</sup> This suggests that suppression of the NF- $\kappa$ B1 pathway that controls inflammation may have less effect on the immune system. This remains to be determined. That NF- $\kappa$ B activation has been linked with most diseases is not too surprising considering that as many as 98% of all diseases are proinflammatory. Thus, the thesis that NF- $\kappa$ B is a "smoke-detector" that is activated by cigarette smoke<sup>48</sup> or a "stress-signal" is quite appropriate.

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