Transcription Factor NF-κB

A Sensor for Smoke and Stress Signals

KWANG SEOK AHN AND BHARAT B. AGGARWAL

Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030, USA

ABSTRACT: Nuclear factor-kappa B (NF-κB) 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-κB 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-κB 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-κB 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-κB 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-κB?

Nuclear transcription factor κB (NF-κB) 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.[1] NF-κB 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-κB family members have been identified and cloned: NF-κB1 (p50/p105), NF-κB2 (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 IκBs, the intracellular inhibitor for NF-κB. Two different NF-κB activation pathways have been identified, a canonical pathway initiated by NF-κB1 (p50/p105) and a noncanonical pathway initiated by NF-κB2

Address for correspondence: Bharat B. Aggarwal, Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas M. D. Anderson Cancer Center, Box 143, 1515 Holcombe Boulevard, Houston, TX 77030. Voice: 713-792-3503/6459; fax: 713-794-1613. aggarwal@mdanderson.org

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(p52/p100). Before the NF-κB complex is translocated into the nucleus, NF-κB1 and NF-κB2 are cleaved to the active p50 and p52 subunits, respectively.

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

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

WHAT ACTIVATES NF-κB?

Extensive research in the last two decades has shown that a large number of stimuli can activate NF-κB (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-κB activation suggests that it can be used as a "smoke-detector" or "stress-sensor."

The mechanisms by which these diverse stimuli activate NF-κB are not identical. Perhaps the best understood of these pathways is the tumor necrosis factor (TNF)-induced NF-κB activation pathway (FIG. 1). The sequential recruitment of TNFR, TRADD, TRAF2, RIP, and IKK leads to TNF-induced NF-κB activation.[2] Recent work from our laboratory has implicated ras,[3] syk,[4] and β-GSK[5] in TNF-induced NF-κB activation. Others have implicated AKT,[6] MEK3,[7] and FAK.[8] TNF-induced NF-κB activation is mediated through the production of reactive oxygen species as SOD[9] and γ-GCS[10] inhibited the activation. Numerous studies have indicated that NF-κB activated by several agents, however, differs from that of TNF.[11,12] For example, we have shown that NF-κB activated by pervanadate[13,14] and hydrogen peroxide[12] differs from that activated by TNF. Others have shown that activation of NF-κB by hypoxia,[15] UV,[16] γ-radiation,[17] X-rays,[18] ds RNA,[19] erythropoietin,[20] and hepatitis C virus[21] differs significantly from that activated by TNF. Although activation of NF-κB by most agents requires the activation of IκBα kinase (IKK), activation of NF-κB by UV, X-ray, hypoxia, pervanadate, erythropoietin, H_2O_2, and hepatitis C virus (NS5A) has been shown to be IKK-independent.

Table. 1 A list of inducers of NF-κB

Bacterial & Fungi
Anaplasma phagocytophilum
Angiostrongylus cantonensis
Bacteroides forsythus
Bartonella henselae
Bordetella pertussis
Chlamydia pneumoniae
Ehrlichia chaffeensis
EPEC, enterophathogenic E. coli
Fusobacterium nucleatum
Gardnerella vaginalis
Helicobacter pylori
Lactobacilli
Listeria monocytogenes
Mycoplasma fermentans
Mycobacteria tuberculosis
Neisseria gonorrhoeae
Neisseria meningiditis
Porphyromonas gingivalis
Prevotella intermedia
Pseudomonas aerogenosa
Rhodococcus equi
Rickettsia rickettsii
Salmonella dublin
Salmonella typhimurium
Shigella flexneri
Staphyllococcus aureus
Streptococci (group A)
Streptococcus (group B)
Streptomyces californicus (fungus)
Trichomonas vaginalis
Ureaplasma urealyticum
Yersinia enterocolitica
Staphylococcus enterotoxin A and B (super antigen)
Toxic Shock Syndrome Toxin 1
Wogonin (Scutellaria baicalensis)

Viruses
Adenovirus
Cytomegalovirus
Epstein-Barr Virus (EBV)
Hepatitis B Virus
Herpes Virus Saimiri
Human Herpesvirus 6
HIV-1
Herpex Simplex Virus -1
HTLV-I
Influenza Virus
Measles Virus
Molony Murine Leukemia Virus
mRNA (in vitro transcribed)
Newcastle disease virus
Respiratory Syncytial Virus
Rhinovirus
Sendai paramyxovirus
Sindbis Virus
Vaccinia Virus Akara
West Nile Flavavirus

Viral products
Adenovirus 5: E1A
Adenovirus: E3/19K
African Swine Fever Virus: IAP
Antibody to Dengue Virus nonstructural protein 1
CMV: ie1
Double-stranded RNA
THANK
TNFα
TNFβ
TWEAK (TNF-like weak inducer of apoptotis)

Physiological (Stress) Conditions
Acute lung injury/respiratory distress syndrome
Adhesion
Angina pectoris
Antiphospholipid antibodies
Appendicitis
Asthma
Butter and Walnut diet
Cecal ligatin and puncture (mouse)
Crohn's disease/ulcerative colitis
Corneal epidemic keratoconjunctivitis
Coronary artery by-pass
Depolarization
Hemorrhage
Hypercholesterolemia
Hyperglycemia
Hyperhomocysteinemia
Hyperosmotic Shock
Hyperoxia
Ischemia (transient, focal)
Ischemic preconditioning
Liver Regeneration
Human labor (childbirth)
Mechanical Ventilation (in vitro)
Muscle disuse
Muscular Dystrophy (type 2A)
Neuronal firing

Environmental Hazards
Arsenic
3,3',4,4'-tetrachlorobiphenyl (PCB77)
Benzo[a]pyrene diol epoxide
Chromium
Cigarette smoke
Cigarette smoke condensate
Cobalt
Crocidolite asbestos fibers
Dicamba (herbicide, peroxisome proliferator)
Diesal exhaust particles
Gliadin (from wheat)
House dust mite
Dust particles
Fear-potentiated startle response
Iron
Lead
Lead chromate
Manganese
Nickel
Noise
Oily fly ash
Silica Particles
Wood smoke
Zymosan (yeast cell wall product)

Therapeutically used drugs
ABR-25757 (oxo-quinoline-3-carboxamide)
2-(1-adamantylamino)-6-methylpyridine (AdAMP)
1-b-D-Arabinofuranosyl-cytosine (ara-C))
Anthralin
Azidothymidine (AZT)
Baicalein
Bleomycin
Bryostatin-1
Maleylated Bovine Serum Albumin
Modified (Oxídized)LDL
Neurotrophin Receptor proteolytic fragments
Non-amyloid beta component of Alzheimer's disease

Overexpressed Proteins
CFTR
Erythropoietin-Receptor
Hematopoietic progenitor kinase 1
Ig heavy chain
MHC Class I

Receptor Ligands
Antigen (IgM-Ligand)
BAFF (B cell-activating factor)
Beta-D-glucan ligand
CD11b/CD18-Ligand (Complement)
CD28-Ligand (B7-1)
CD2-Ligand
CD35-Ligand (Complement)
CD3-Ligand
CD40-Ligand
CD43-Ligand
CD4-Ligand (gp120)
CD66a-Ligand
M3 Cholinergic receptor agonist
Fc-2a-Receptor-Ligand (IgG2a)
Flt-1-Ligand
Heat shock protein 60 (HSP60)
Ly6A/E-Ligand
N-CAM
PGG-Glucan (Betafectin)
Sphingosine 1-phosphate
Trail-receptor-1-Lignad (Trail)
Trail-receptor-2-Ligand (Trail)
Trail-receptor-4-Ligand (Trail)
Activin A
Adenosine
Adrenomedullin
AILb-A (from Aeginetia indica)
Albumin
Allergin
Alloxan
Amino acid analogs
Anaphylatoxin C3a
Anaphylatoxin C5a
Angiotensin II
Antiphospholipid antibodies
Areca nut extract
Baicalin (plant compound)
Basic calcium phosphate crystals
Bronchoalveolar lavage fluid
Bradykinin
Brusatol
beta-carotene
Catalase
C2-Ceramide (N-acetyl-sphingosine)
Cerulein
Chelidonium majus extract
Collagen lattice
Collagen Type I
Cryptdins
Cysteinyl leukotrines
Deoxycholic acid (bile acid)
Des-Arg10-kallidin (B1 receptor agonist)
1,25-dihydroxycholecalciferol
Double-stranded polynucleotides
f-Met-Leu-Phe
Fibrinogen
Free fatty acids
Heat shock protein 25 (Hspb1)
Heat shock protein 60 (HSP 60)
Hemoglobin
Homocysteine
Hyaluronan
12(R)-Hydroxyeicosatrienoic acid
6-hydroxydopamine
Uremic toxins
Very Low density Lipoproteins (VLDL)
Violacein
Vitamin D_3

Chemical Agents
2-Deoxyglucose
Adriamycin
Alumnum
Anisomycin
Benzyl isothiocyanate
Bisperoxovanadium (bpV)
phosphotyrosyl phosphatase inhibitors
Brefeldin A
Cadmium
Calchicine
Calcium Ionophores
Calyculin A
Ceramide-beta-galactose
2-chloroethyl ethyl sulfide (mustard analog)
Cobalt chloride
Con A
Cycloheximide
Cyclopiazonic Acid
Diquat
2,4-dinitrofluorobenzene
Ethanol
Ferrocene
Forskolin
Gadolinium chloride
Glass fibers
HDAC inhibitors (sodium butyrate and trichostatin A)
Linoleic acid
L-NMA
Lysophosphatidic acid
Malondialdehyde
MDMA ("Ecstacy")
MEN 17055 (disaccharide

Bacterial or Fungal Products
Apicularen A
CpG
Cytolysin (Vibrio vulnificus)
Diphosphoryl lipid A (Rhodobacter sphaeroides)
Enterotoxin (Bateroides fragilis)
Exotoxin B
Fimbria protein ATTLE (P gingivalis)
Fumonisin B1 (Fusarium verticillioides)
G(Anh) M Tetra (E coli)
Glycosylphosphatidylinositols (Plasmodium falciparum)
Lipoprotein LpK (Mycobacterioum leprae)
Lipoteichoic acid (Listeria)
Lipopolysaccharide (LPS)
Membrane lipoproteins (Mycoplasma fermentans)
Membrane lipoproteins (Mycoplasma penetrans)
Muramyl Peptides
Mycobacterium lipoarabinomannan
PlcA (Phospholipase) (Listeria)
PlcB (Phospholipase) (Listeria)
Porins (Gram negative bacteria)
Porin 1B (Gonoccocus)

EBV: EBNA-2
EBV: LMP1
HBV: HBx
HBV: LHBs
HBV: MHBst
HCV: Core protein
Herpes Saimiri: HVS13
Herpes Saimiri:StpC
HIV-1: gp160
HIV-1: Nef
HIV-1: p9 (9 aa peptide)
HIV-1: Tat
HTLV-I: Tax
HTLV-II: Tax
Influenza Virus: Hemagglutinin
Parvovirus B19: NSI
SV40: small T-antigen

Eukaryotic parasites
Leishmania (lipophosphglycan)
Phospholipomannan (C. albicans)
Pneumocystis
Theileria parva
Trypanoplasma borreli

Cytokines and Cytokine Receptors
CD30
Salivary cystatins (SA1 and SA2)
IL-1
IL-2
IL-12
IL-15
IL-17
IL-18
LIF
p43
Pentraxin-3
S100B

Overventilation (perfused lungs)
Pancreatitis
Proteinuria
Reoxygenation
Rheumatoid arthritis
Senescence (keratinocytes)
Shear Stress
Neuoronal trimethyltin injury
Uni-axial cyclic cell stretching
T-cell selection

Physical Stress
Bile duct ligation
Cyclic mechanical muscle strain
Exercise
Gamma Radiation
Heavy ion irradiation
Laminar shear stress
PPME Photosensitization
Ultraviolet irradiation (UV-A, B, C)
Mechanical lung ventilation
Obesity
Wounding combined with HeNe irradiation
Wounding combined with thermal irradiation

Oxidative Stress
Butyl Peroxide
Cerulein
Glutathione
Hydrogen Peroxide
Ozone
Peroxynitrite
Pervanadate
Reoxygenation

Bucillamine metabolite SA 981
Camptothecin
Celecoxib
Ciprofibrate
Cisplatin
Cycloprodigiosin
Dacarbazine
Daio-Orengedeokuto
Daunomycin
Daunorubicin
Diazoxide
5,6-dimethylxanthenone-4-acetic acid
Doxorubicin
Etoposide
Flavone-8-acetic acid
Haloperidol
Kunbi-Boshin-Hangam-Tang
Lithium
Methamphetamine
Mitoxantrone
Norepinephrine
Olitipraz
Phenobarbital
Protocatechuic acid (from herb radix Salviae miltiorrhizae)
SN38 (metabolite of CPT-11)
Tamoxifen
Taxol (Paclitaxel)
Vinblastine
Vincristine
WR1065

Modified Proteins
Advanced glycated end products (AGEs)
Amyloid Protein Fragment (bA4)
Anti-PR3
Glycosylated oxyhaemaglobin

Apoptotic Mediators
Anti-Fas/Apo-1
Poly(ADP) Ribose Polymerase (PARP)
Trail

Mitogens, growth factors and hormones
Bone morphogenic protein 2
Bone morphogenic protein 4
Cortical Releasing Hormone
Epidermal Growth Factor
Folicle Stimulating Hormone
Gastrin
GMCSF
Hepatocyte Growth Factor
Human Growth Hormone
Insulin
Insulin-like growth factor 1
Lysophosphatidic acid
M-CSF
Mullerian Inhibiting Substance
Nerve Growth Factor
Pigment epithelium-derived factor (PEDF)
Platelet Activating Factor (PAF)
Platelet-Derived Growth Factor
Plant steroids (diosgenin, hecogenin, tigogenin)
Prostatin
All-trans retinoic acid
RET/PTC3 Fusion oncoprotein
S100B
Serum
Sulphatide (L-selectin crosslinker)
TGF-alpha
TGF-beta2

Physiological Mediators
Acrp30/adiponectin

hPepT1 (apical di-/tripeptide transporter
Kaianic acid (Kainate)
Leukotriene B4
L-Glutamate
Long-term potentiation (LTP)
Lysophosphatidylcholine (LysoPC)
Mixed meal ingestion (hi glucose)
Monosodium urate crystals
Neuormelanin
Neutrophil elastase
Nitric oxide
NS-398 (high dose)
Oleic acid
Osteopontin
PAF (platelet activating factor)
Palmitate
PCSC (polysaccharide from Poria cocos)
Phellinus linteus proteoglycan
Platelet type arachidonate 12-lipoxygenase
Polysaccharides of Poria cocos
Potassium
Prolactin N-terminal fragment (16K PRL)
Proteolysis-inducing factor (PIF)
Regulatory RNA
Rev-erbalpha
S100B
Saturated fatty acids
Sleep deprivation
St John's Wort (hyperforin)
Streptozotocin
Substance P
Tauroursodeoxycholic acid (TUDCA)
T-cell costimulatory receptor 4-1BB
Thioredoxin
Thrombin
Titanium and copper implants
Trypsin (SLIGRL)
Tuberous sclerosis complex

anthracycline)
Monensin
N-methyl-D-aspartate
Mycophenolic acid
Nafenopin
Nickel sulfate
Nicotine
N-nitrosomorphine
Nocodazol
Okadaic Acid
Peplomycin
PHA
Phorbol ester
Phosphodiester CpG DNAs
Podophyllotoxin
Prostratin (a phorbol ester)
Pyrogallol
Quercetin (high concentrations)
Quinolinic acid
Saflower polysaccharides
Sanglifehrin A
Staurosporine
Thapsigargin
Transglutaminase 2
Tunicamycin
Vinblastine
WF10WY-14 643 (peroxisome proliferator)

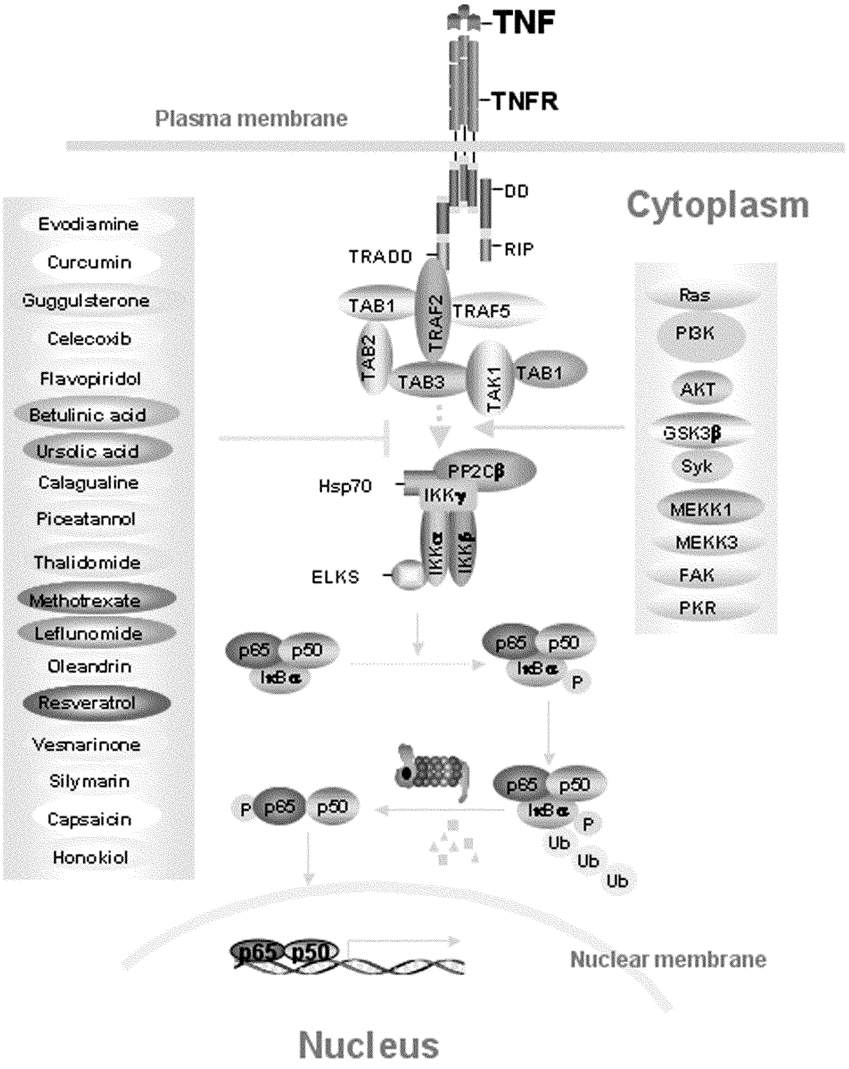

FIGURE 1. Schematic pathway for TNF-induced NF-kB activation and its inhibition by various natural products.

WHAT GENES ARE REGULATED BY NF-κB?

Although initially identified in kappa chain of immunoglobulin, the NF-κB 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

Table. 2 A list of target genes of NF-κB-regulated

Cytokines/Chemokines	Immunoreceptors	Cell adhesion molecules	Bradikinin B1-receptor	Enzymes
CCL5*	B7.1	E-selectin	Amiloride-sensitive sodium channel	Liver alcohol dehydrogenase
CCL15/Leukotactin	BRL-1*	Endoglin	A1 adenosine receptor	Collagenase 1
CCL22	CCR5	Fibronectin		Glutathione S-transferase
CCL28	CCR7	ICAM-1*	**Regulators of apoptosis**	Hyaluronan synthase
CINC-1*	CD137	MadCAM-1*	TRAF-1*	H+-K+ATPase α2
CXCL 11*	CD154	P-selectin, tenascin-C	TRAF-2*	Lysozyme
Eotaxin	CD40	VCAM-1*	IEX-1L*	Matrix metalloproteinaase-9
Fractalkine	CD40 ligand	DC-SIGN*	IAPs*	GD3-synthase
Gro a-g	CD48		Fas-ligand	Gelatinase B
Gro-1	CD83	**Acute phase response**	CD95 (Fas)	PIM-1
ICOS*	Fc epsilon receptor II	**proteins**	c-FLIP	PKCδ
IFN-g	IL-2 receptor α-chain	Angiotensinogen	Nr13	Phospholipase C δ1
IL-1α	Immunoglobulin Cγ1	β-defensin-2	Caspase-11	Serpin 2A
IL-1β	IgG γ4	C4b binding protein	Bcl-2	Transglutaminase
IL-1 receptor antagonist	Immunoglobulin epsilon heavy chain	Complement factor B	Bcl-x_L	TIRT*
IL-2	Immunoglobulin k light chain	Complement factor C4	Bfl1/A1	
IL-6	Invariant chain I1	C-reactive protein		
IL-8	MHC class I (H-2Kb)	Lipopolysaccharide binding protein	**Viruses**	**Miscellaneous**
IL-9	MHC Class I HLA-B7	Pentraxin PTX3	Adenovirus (E3 region)	α-1 acid glycoprotein
IL-10	β2-microglobulin	SAA1 and SAA2*	Avian leukosis virus	Apolipoprotein C III
IL-11	Nod2	Tissue factor-1	Bovine leukemia virus	AMH*
IL-12 (p40)	Polymeric Ig receptor	Urokinase-type plasminogen activator	Cytomegalovirus	Cyclin D1
IL-13	T-cell receptor β chain		Epstein-Barr virus (Wp promoter)	Factor VIII
IL-15				

β-Interferon
IP-10*
KC*
ENA-78 (CXCL5)
GCP-2 (CXCL6)
Lymphotoxin α
Lymphotoxin β
MCP-1/JE*
MIP-1α,β*
MIP-2
MIP-3α
mob-1
Neutrophil activating peptide-78
RANTES*
TCA3*
TNFα
TNFβ
TRAIL*
TFF3*

T-cell receptor/CD3γ
p80 TNF-receptor
Complement B
Complement component 3
Complement receptor 2
Proteasome subunit LMP2
Peptide transporter TAP1
Tapasin

Growth Factors

Bone morphogenic protein-2
Granulocyte colony stimulating factor
Granulocyte macrophage colony stimulating factor
Erythropoietin, macrophage colony stimulating factor (M-CSF)
Neurokinin-1 receptor
Hepatocyte growth factor
Platelet-derived growth factor B chain
Proenkephalin
Vascular endothelial growth factor

Stresss-response genes

Angiotensin II
Cytochrome p450 gene
COX-2*
Ferritin H chain
12-Lipoxygenase
iNOS*
Mn SOD*
NQO1*
Phospholipase A2

Cell surface receptors

RAGE- receptor for advanced glycation end products
Platelet activator receptor-1
Neuropeptide Y Y1-receptor
Mu-opioid receptor
Mdr1*
Lox-1*
Gal1 receptor
CD69

Hepatitis B virus (pregenomic promoter)
HIV-1
HSV*
JC virus
Human papillomavirus type 16
SIV*
SV-40*

Transcription/ growth control factors

A20
Androgen receptor
c-myb
c-myc
IRF-1*
IRF-2
IRF-4
IRF-7
Rel/NF-κB proteins (p52/p100, p50/p105, c-Rel, and RelB)
IκB proteins (IκBα, IκBβ, Bcl-3, JunB, Stat5a, WT1, p53, Ras)

Gadd45β
Galectin 3
Epsilon-globin
HMG-14*
K3 keratin
Laminin B2 chain
Mts1
MUC-2
Perforin
Pregnancy-specific glycoprotein
mCGM3
Prostate-specific antigen
S100A6 (calcyclin)
Syndecan-4
Vimentin
Wilm's tumor suppressor gene
a1-antitrypsin,

*CCL5, C-C chemokine ligand 5; CINC-1, cytokine-induced neutrophil chemoattractant-1; CXCL 11, CXC chemokine ligand 11; ICOS, inducible co-stimulator; IP-10, IFN-gamma-inducible protein 10; KC, kupffer cells; MCP-1, monocyte 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 apoptosis-inducing ligand; TFF3, trefoil factor 3; ICAM-1, intercellular adhesion molecule-1; MadCAM-1, mucosal addressin cell adhesion molecule; VCAM-1, vascular cell adhesion molecule; DC-SIGN, dendritic cell surface C-type lectin. SAA, serum amyloid A proteins; COX-2, cyclooxygenase-2; iNOS, inducible nitric oxide synthase; Mn SOD, superoxide dismutase; NQO1, NAD(P)H quinone oxidoreductase 1; Mdr1, Multiple drug resistance mediator 1; Lox-1, lectin-like oxidized low-density lipoprotein receptor-1; TRAF, TNF-receptor associated factor; IEX-1L, immediate early response factor-1; IAPs, Inhibitor of apoptosis; HSV, Herpes simplex virus; SIV, Simian immunodeficiency virus; SV-40, Simian virus 40; IRF, Interferon regulatory factor; TERT, Telomerase catalytic subunit; AMH, Anti-mullerian hormone; HMG-14, High mobility group 14

genes**.** Besides NF-κB, 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-κB.[22,23]

WHICH DISEASES ARE LINKED TO NF-κB ACTIVATION?

Constitutive NF-κB 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-κB 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.[24,25] 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_1 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-κB, the activated form of which is present in atherosclerotic plaques. NF-κB 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 κB site for NF-κB within their promoters, suggesting that NF-κB plays a pivotal role in the initiation and perpetuation of allergic inflammation.

Several reports suggest that amyloid β peptide can activate NF-κB in neurons, indicating a plausible mechanism by which amyloid may act during the pathogenesis

Table. 3 A list of NF-κB-mediated diseases

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 neuropathy
Hypercholesterolemia	Crohns disease	
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. 4 A list of inhibitors of NF-κB*

Cytokine & Hormones	Aged garlic extract (allicin)	Nordihydroguaiaritic acid	Glucorticoid-induced leucine zipper protein	Compound 26**
Interleukin-4+	Anetholdithiolthione	Oleandrin+		Cycloepoxydon
Interleukin-10	Anethole+	Orthophenanthroline	γ-glutamylcysteine synthetase+	Cyclolinteinone
Interleukin-11	Apocynin	Parthenolide	Heat shock protein 72	Cycloprodigiosin
Interleukin-13+	Apple juice	PDTC**	HSCO**	hycrochloride Dehydroxymethylepo
Growth hormone	Astaxanthin	Phenolic antioxidants (Hydroquinone	Losartin	xyquinomicin
HBEGEF**	Baicalein	and tert-butyl hydroquinone)	MnSOD**+	Diamide+
hCG**	Benidipine	Phenolic antioxidants**	NDPP1 (CARD protein)	Diarylheptanoid 7-(4'-hydroxy-3'-
Luteinizing hormone+	Betulinic acid+	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-	**Phytochemicals**	Pioglitazone (PPARγ ligand)	Dioxin+
Estrogen	dihydroxycinnamic acid, CAPE)	Piceatannol+	Pituitary adenylate cyclase-activating	Disulfiram
Glucocorticoids	Caffeic Acid Phenethyl Ester+	PMC (2,2,5,7,8-pentamethyl-6-	polypeptide	E-73 (cycloheximide analog)
PG-15-deoxy-Δ(12,14)-PGJ(2)**	Calagualine+	hydroxychromane)	Protein-bound polysaccharide	Ecabet sodium
Prostaglandin A1	Capsaicin+	PMC**	PTEN	Epoxyquinone A monomer Fibrates
Prostaglandin E2	Carnosol	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+	Ref-1 (redox factor 1)	Carbon monoxide	Glimepiride
Leflunamide metabolite**+	Dehydroepiandrosterone	Resiniferatoxin+	Electrical stimulation of vagus nerve	Glucosamine sulfate
Sulindac	DHEA-sulfate	Resveratrol+	Hypothermia	Herbimycin A

TABLE 4 — *continued.*

Cell-signaling inhibitors
Atrovastat**
D609**
LY294002**
Quinadril**
RO31-8220**
SB203580**
SC236**
Sphondin
TNP-470**
U0126**

IKK inhibitors
AS602868
BAY-117082**
BAY-117083**
BMS-345541
DTD**
E3330**
LF15-0195**
MOL 294**
PS1142

Protease/ Proteasome inhibitors
ALLnL
APNE
APNE**+
Boronic Acid Peptide
BTEE
Cyclosporin A
DCIC**
Deoxyspergualin
Dibenzylbutyrolactone lignans
Diethyldithiocarbamate
Diferoxamine
Dihydrolipoic Acid
Dilazep +
Dilazep + fenofibric acid
Dimethyldithiocarbamates
Dimethylsulfoxide
Disulfiram
Ebselen
EGTA**
Emodin+
Ent-kaurane diterpenoids
Epigallocatechin-3-gallate
EPC-K1 (phosphodiester compound of vitamin E and vitamin C)
Epigallocatechin-3-gallate (green tea polyphenols)
Epoxyquinol
Epoxyquinol A
Erbstatin+
Ergolide
Ergothioneine
Ethyl Pyruvate
Ethylene Glycol Tetraacetic Acid
Eugenol
Fenofibric acid
Flavenoids (Crategus)
Flavopiridol+
Fluorochalcones
Gamma-glutamylcysteine synthetase
Ganoderma lucidum polysaccharides
Garcinol (from extract of Garcinia indica fruit rind)
Genistein+
Rg(3) (ginseng derivative)
Rg(3), a ginseng derivative
Rocaglamides
Rotenone
Rotenone
S-allyl-cysteine (SAC, garlic compound)
Sanguinarine+
Saucerneol D and E
Sauchinone
Sauchinone
Silibinin+
Silymarin+
Tempol
Tepoxaline
Tepoxaline (5-(4-chlorophenyl)-N-hydroxy-(4-methoxyphenyl) -N-methyl-1H-pyrazole-3-propanamide)
Tert-butyl hydroquinone
Tranilast
Triptolide (PG490)
Uncaria tomentosa
Ursolic acid+
Vitamin C
Vitamin E derivatives
Yakuchinone A and B
Yakuchinone A and B

Plant extracts
Apple
Aged garlic
Black raspberry
Blueberry
Ganoderma lucidum
Ginkgo biloba
Metals**
Nitric Oxide
Saline (low Na^+ istonic)
Hyperosmolarity

Vitamins
BTEE**
Vitamin C
Vitamin D
Vitamin E
Nitrosylcobalamin**

Virus derivatives
Core Protein of Hepatitis C virus+
E1A
HIV-1 Vpu protein
IκB-like proteins
K1 protein
Kaposi's sarcoma-associated herpesvirus
Pertussis toxin binding protein
SspH1 and IpaH9.8**
YopJ**

Synthetic compounds
AS602868
Decoy oligonucleotides**
DTD**
E3330**
Hydroquinone
Macrolide antibiotics
MOL 294**
Pentoxifylline

Others
Adenosine+
Hydroquinone
4-Hydroxynonenal
Hypochlorite
Hypoethyl starch
Isomallotochromanol
Isomallotochromene
Jesterone dimer
Kamebakaurin
Lactoferrin
LDL (Extensively oxidized)
Leptomycin B
Mevinolin, 5'-methylthioadenosine
Monochloramine
MX781
Nafamostat mesilate
N-ethyl-maleimide
Nicotine
Omega 3 fatty acids
Pervanadate+
Petrosaspongiolide M
Phenethylisothiocyanate
Phenylarsine oxide+
Phenyl-N-tert-butylnitrone
Phosphorylation
Phytic acid
Pranlukast
Psychosine
Pyrithione
Raxofelast
Rebamipide
Rhein
Ribavirin
Rifamides
Rifampicin
Rolipram

TABLE 4 — *continued.*

DFP**
FK506**
Lactacystine, b-lactone
LLM**
MG101**
MG115**
MG132**
Pefabloc
Peptide Aldehydes
PS-341**
TLCK**
TPCK**
Ubiquitin Ligase Inhibitors
Z-LLL
Z-LLnV

Anti-oxidants
β-lapachone[+]
α-lipoic acid
α-tocopherol
15-deoxyspergualine
23-hydroxyursolic acid
α-torphryl acetate
α-torphryl succinate
Ginkgo biloba extract
Glutathione
Glycyrrhizin
Guaianolides
Hematein
Hypericin
IRFI 042 (Vitamin E-like compound)
Iron tetrakis
Isoeugenol
KT-90**
L-cysteine
Lacidipine
Lazaroids
Lovastatin
Lupeol
Luteolin
Magnolol
Manassantins A and B
Manganese superoxide dismutase
Melatonin
Mesalamine
N-acetyl-L-cysteine
Nacyselyn
Nordihydroguaiaritic acid
Ochna macrocalyx bark
PC-SPES (8 herb mixture)
Phyllanthus amarus
Qingkailing
Shuanghuanglian
Stinging nettle
Tanacetum larvatum
Uncaria tomentosum
Fungal gliotoxin

Polypeptides and enzymes
Angiopoietin-1
Atrial Natriuretic Peptide
AvrA protein (Salmonella)
β-amyloid protein
β-catenin
Bovine serum albumin
CaMKK**
Complement protein C5a
Cytochalasin D
D-amino acid peptide
DQ 65-79**
6-aminoquinazoline derivatives
6(5H)-phenanthridinone + benzamide
7-amino-4-methylcoumarin
15-Deoxyspergualin
ADP ribosylation inhibitors**
Amentoflavone
Amrinone
Anandamide
Anti-thrombin III
APC0576**
Artemisinin
Astragaloside IV
Atorvastatin
Aucubin
Azidothymidine
Benfotiamine (thiamine derivative)
Bisphenol A
o,o'-bismyristoyl thiamine disulfide
Cacospongionolide B
Capsiate
Caprofin
Chitosan
Chromene derivatives
Clarithromycin
Ro106-9920
Sanggenon C
Serotonin derivative**
Siah2**
SLPI**
Statins
Staurosporine
Sulfasalazine
Surfactant protein A
Survanta
T-614**
Taurine + niacine
Tetrathiomolybdate
THI 52**
Thalidomide[+]
Thiopental
Triflusal
Tyrphostin AG-126
Wedelolactone
Wogonin

*For most references see http://people.bu.edu/gilmore/nf-kb/lab/index.html

** ADP ribosylation inhibitors, nicotinamide and 3-aminobenzamide; APC0576, 5-(((5)-2,2-dimethylcyclopropanecarbonyl)amino)-2-(4-(((5)-2,2-dimethylcyclopropanecarbonyl)amino)-pheoxy)pyridine; APNE, N-acetyl-DL-phenylalanine-b-naphthylester; Atrovastat , HMG-CoA reductase inhibitor; A77 1726, Leflunomide metabolite; BAY117082, E3((4-methylphenyl)-sulfonyl)-2-propenenitrile; BAY117083, E3((4-t-butylphenyl)-sulfonyl)-2-propenenitrile; BTEE, N-benzoyl L-tyrosine-ethylester; CaMKK, Calcium/calmodulin-dependent kinase kinase; Compound 26, 2-amino-3-cyano-4-aryl-6-(2-hydroxy-phenyl)pryridine analog; D609, phosphatidylcholine-phospholipase C inhibitor; Decoy oligonucleotides, synthetic decoys which "compete" with transcription factors for binding to their consensus sequences; DCIC, 3,4-dichloroisocoumarin; DFP, diisopropyl fluorophosphate; DQ 65-79, aa 65-79 of the α helix of the α-chain of the class II HLA molecule DQA03011; DTD, (4,10-dichloropyrido [5,6:4,5] thieno[3,2-d':3,2- d]-1, 2; E3330, (2E)-3-[5-(2,3-Dimethoxy-6-methyl-1,4-benzoquinoyl)]-2-nonyl-2-propenoic acid; EGTA, Ethylene Glycol Tetraacetic Acid; FK506, Tarcolimuc; HBEGEF, Heparin-binding EGF-like GF; hCG, human choriogonadotropin; HSCO, Hepatoma Substrated-cDNA library clone one; KT-90, synthetic derivative of morphine; LF15-0195, analog of 15-deoxyspergualine; LLM, N-acetyl-leucinyl-leucynil-methional; LY294002, wortmannin, PI3-kinase inhibitor; Metals, examples are chromium, cadmium, gold, lead, mercury, zinc, arsenic, and titanium;MG101, also ALLnL, N-acetyl-leucinyl-leucinyl-norleucinal; MG115, also Z-LLnV, carbobenzoxyl-leucinyl-leucynil-norvalinal; MG132, also Z-LLL, carbobenzoxyl-leucinyl-leucynil-leucynal; MOL294, methyl(4R/S)-4-hydroxy-4-[(5S,8S)/(5R,8R))-8-methyl-1,2-diox-2-phenyl-2,5,5,8-tetrahydro-1H[1,2,4]triazolo[1,2-9]-pyridazin-5-yl]-2-butynoate; MnSOD, Mangenese superoxide dismutase; α-MSH, alpha-Melanocyte stimulating hormone; Nitrosylcobalamin, vitamin B12 analog; p202a, IFN- inducible protein; PDTC, Pyrrolnedithiocarbamate; PG-15-deoxy-Δ(12,14)-PGJ(2),Prostaglandin 15-deoxy-Delta(12,14)-PGJ(2); Phenolic antioxidants,example is Hydroquinone; PMC, (2,2,5,7,8-pentamethyl-6-hydroxychromane); PS341, Velcade, bortezolimb; Quinadril, ACE inhibitor; RO31-8220,PKC inhibitor; SB203580, p38 MAPK inhibitor; SC236, COX-2 inhibitor; Serotonin derivative, N-(p-coumaroyl) serotonin; Siah2, Seven in abstentia homolog2; SLPI, Secretory leukocyte protease inhibitor; SspH1 and IpaH9.8, Leucine-rich effector proteins of Salmonella & Shigella; T-614, methanesulfoanilide anti-arthritis inhibitor; THI 52, 1-naphthylethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline; TLCK, N-a-tosyl-L-lysine chloromethyl ketone; TNP-470, angiogenesis inhibitor; TPCK, N-a-tosyl-L-phenylalanine chloromethyl ketone; U0126, MEK inhibitor; VEGF, vascular endotheliail growth factor; YopJ, encoded by Yersinia pseudotuberculosis; ZAS3 protein, zinc finger protein which binds NF-κB site.

[+] Investigated in author's laboratory.

of Alzheimer's disease. Rheumatoid arthritis is a chronic inflammatory disease characterized by persistent joint swelling and progressive destruction of cartilage and bone. NF-κB 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-κB 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-κB activation pathway are being targeted to block NF-κB. These include inhibitors of proteosome that mediate IκBα degradation, inhibitors of kinase (IKK), which mediate IκBα phosphorylation, decoy peptides from IκBα, IKK, and p65 proteins. The double-stranded oligodeoxynucleotides (ODNs) that possess consensus NF-κB sequence as transcription factor decoys (TFDs) also have been found to inhibit NF-κB 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-κB activation. These include IL-4,[26] IL-13,[27] and IL-10.[28] Additionally, endocrine hormones such as HCG,[29] LH, MSH,[30] and GH[31] have been shown to abrogate NF-κB activation. Both IFN-α and IFN-β, which exhibit antiviral, antiproliferative, and immunosuppressive activities, also abolish NF-κB activation.[32] Several phytochemicals from different plants have been identified that can suppress NF-κB 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-κB 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-κB 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-κB 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-κB activation. Some recent evidence, however, indicates that while NF-κB1 mediates an inflammatory response, NF-κB2 mediates an immune response.[47] This suggests that suppression of the NF-κB1 pathway that controls inflammation may have less effect on the immune system. This remains to be determined. That NF-κB 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-κB is a "smoke-detector" that is activated by cigarette smoke[48] or a "stress-signal" is quite appropriate.

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