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Activators and target genes of Rel/NF-κB transcription factors

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The vertebrate transcription factor NF-κB is induced by over 150 different stimuli. Active NF-κB, in turn, participates in the control of transcription of over 150 target genes. Because a large variety of bacteria and viruses activate NF-κB and because the transcription factor regulates the expression of inflammatory cytokines, chemokines, immunoreceptors, and cell adhesion molecules, NF-κB has often been termed a 'central mediator of the human immune response'. This article contains a complete listing of all NF-κB inducers and target genes described to date. The collected data argue that NF-κB functions more generally as a central regulator of stress responses. In addition, NF-κB activation blocks apoptosis in several cell types. Coupling stress responsiveness and anti-apoptotic pathways through the use of a common transcription factor may result in increased cell survival following stress insults.

Keywords: NF-κB; Rel; transcription factors; immune response; stress response; ER overload

NF-κB, a central mediator of the human immune response

The Rel/NF-κB family of eukaryotic transcription factors is comprised of several structurally-related proteins that form homodimers and heterodimers (Chen and Ghosh, 1999, this issue). In vertebrates, this family includes p50/p105, p52/p100, RelA (p65), c-Rel and RelB. These dimers bind to a set of related 10 bp DNA sites, collectively called κB sites, to regulate the expression of many genes. In most cells, Rel/NF-κB transcription complexes are present in a latent, inactive state in the cytoplasm where they are bound to an inhibitor (IκB). As described below, many stimuli can rapidly activate these transcription complexes by freeing them from their inhibitor and enabling them to translocate to the nuclues. The most common Rel/NF-κB dimer in mammals contains p50-RelA and is specifically called NF-κB. For the purposes of this review, NF-κB will be used to refer any induced complex that can be translocated from the cytoplasm to the nucleus and can bind to κB sites.

The transcription factor NF-κB has often been called a 'central mediator of the human immune response'. How was such a reputation established and is it justified? A summary of all stimuli that are known to activate NF-κB (Table 1) and a compilation of its many target genes (Table 2) may provide an answer.

In many cell types, nuclear NF-κB activity is induced by exposure to a wide variety of bacteria or bacterial products (Table 1). Likewise, a host of viruses or their proteins activate NF-κB (Table 1). Bacterial and viral infection certainly present situations where an adequate immune response is vital. That human cells respond to so many different organisms by activating the same transcription factor, NF-κB, is one reason for its reputation as a 'central switch'. Moreover, homozygous disruption in mice of the genes encoding certain members of the Rel/NF-κB family, including those encoding c-Rel, p50 and RelB, leads to defects in the immune response to certain pathogens (Gerondakis *et al*., 1999, this issue).

The active NF-κB transcription factor promotes the expression of over 150 target genes (Table 2). The majority of proteins encoded by NF-κB target genes participate in the host immune response. These include, for example, 27 different cytokines and chemokines, as well as receptors required for immune recognition, such as MHC molecules, proteins involved in antigen presentation and receptors required for neutrophil adhesion and transmigration across blood vessel walls (Table 2). These target genes alone would merit NF-κB the designation as a 'central mediator of the immune response'.

Many viruses that induce NF-κB activity also harbor NF-κB binding sites in their viral promoters (Table 2). Therefore, it seems likely that a virus would gain a selective advantage from the acquisition of a κB site in its promoter. If the transcription factor is induced either directly through viral infection or indirectly by the ensuing immune response (via inflammatory cytokines, for example), the κB site-containing viral promoter will be transactivated, resulting in enhanced viral transcription. Thus, the organism's own sword is turned against itself. The presence of a κB site in the HIV-1 promoter may have led to the activation of viral replication that was observed during trials in which IL-2 was used to stimulate T-cell replication in HIV-1-infected patients (Kovacs *et al*., 1995). A low level of NF-κB activation is perhaps part of the mechanism by which some viruses, such as EBV, HSV, CMV or HIV-1, maintain their chronic infections.

A compilation of the many pathogens that induce NF-κB and a look at the function of its various target genes certainly validate the reputation this transcription factor has gained as an important regulator of the immune response. Moreover, the fact that viruses often use this protein to their advantage argues that NF-κB activity exerted an evolutionary pressure on these pathogens.

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Table 1 Inducers of NF-κB activity

Condition	*Reference*
Bacteria	
EPEC, enterophathogenic *E. coli*	Savkovic *et al*., 1997
Gardnerella vaginalis	Hashemi *et al*., 1999
Helicobacter pylori	Münzenmaier *et al*., 1997
Lactobacilli	Klebanoff *et al*., 1999
Listeria monocytogenes	Hauf *et al*., 1994
Micoplasma fermentans	Marie *et al*., 1999
Mycobacteria tuberculosis	Zhang *et al*., 1994
Neisseria gonorrhoeae	Naumann *et al*., 1997
Rickettsia rickettsii	Sporn *et al*., 1997
Salmonella dublin	Eaves-Pyles *et al*., 1999
Salmonella typhimurium	Hobbie *et al*., 1997
Shigella flexneri	Dyer *et al*., 199
Staphyllococcus aureus	Busam *et al*., 1992
Bacterial Products	
Diphosphoryl lipid A (*Rhodobacter sphaeroides*)	Lawrence *et al*., 1995
Exotoxin B	Busam *et al*., 1992
G(Anh) M Tetra	Dokter *et al*., 1994
Lipoteichoic acid (*Listeria*)	Hauf *et al*., 1997
Lipopolysaccharide (LPS)	Sen and Baltimore, 1986a
membrane lipoproteins (*Micoplasma fermentans*)	Garcia *et al*., 1998; Rawadi *et al*., 1999
Muramyl Peptides	Schreck *et al*., 1992
PlcA (Phospholipase) (*Listeria*)	Hauf *et al*., 1997
PlcB (Phospholipase) (*Listeria*)	Hauf *et al*., 1997
Staphylococcus enterotoxin A and B (super antigen)	Trede *et al*., 1993; Busam *et al*., 1992
Toxic Shock Syndrome Toxin 1	Trede *et al*., 1993
Viruses	
Adenovirus	Shurman *et al*., 1989
Cytomegalovirus	Sambucetti *et al*., 1989
Epstein-Barr Virus (EBV)	Hammarskjöld and Simurda, 1992
Hepatitis B Virus	Siddiqui *et al*., 1989
Herpes Virus Saimiri	Yao *et al*., 1995
Human Herpesvirus 6	Ensoli *et al*., 1989
HIV-1	Bachelerie *et al*., 1991
Herpex Simplex Virus -1	Gimble *et al*., 1988
HTLV-I	Leung and Nabel, 1988; Ballard *et al*., 1988
Influenza Virus	Ronni *et al*., 1997
Measles Virus	Harcourt *et al*., 1999
Molony Murine Leukemia Virus	Pak and Faller, 1996
Newcastle disease virus	Ten *et al*., 1993
Respiratory Syncytial Virus	Mastronarde *et al*., 1996; Garofalo *et al*., 1996
Rhinovirus	Zhu *et al*., 1996a; Zhu *et al*., 1996b
Sendai paramyxo virus	Hiscott *et al*., 1989
Sindbis Virus	Lin *et al*., 1995a
Viral Products	
Adenovirus 5: E1A	Shurman *et al*., 1989
Adenovirus: E3/19K	Pahl *et al*., 1996
CMV: ie1	Sambucetti *et al*., 1989
Double-stranded RNA	Visvanathan and Goodbourn, 1989
EBV: EBNA-2	Scala *et al*., 1993
EBV: LMP	Hammarskjöld and Simurda, 1992
HBV: HBx	Twu *et al*., 1989
HBV: LHBs	Hildt *et al*., 1996
HBV: $MHBs^t$	Meyer *et al*., 1992
HCV: Core protein	You *et al*., 1999
Herpes Saimiri: HVS13	Yao *et al*., 1995
HIV-1: gp160	Chirmule *et al*., 1994
HIV-1: Tat	Westendorp *et al*., 1994
HTLV-I: Tax1	Ballard *et al*., 1988; Leung and Nabel, 1988
HTLV-II: Tax2	Tanaka *et al*., 1996
Influenza Virus: Hemagglutinin	Pahl and Baeuerle, 1995a
Parvovirus B19: NSI	Moffatt *et al*., 1996
Eukaryotic parasite	
Theileria parva	Ivanov *et al*., 1989
(Inflammatory) Cytokines	
IL-1	Osborn *et al*., 1989
IL-2	Hazan *et al*., 1990
IL-12	Grohmann *et al*., 1998
IL-15	McDonald *et al*., 1998
IL-17	Shalom-Barak *et al*., 1998
IL-18	Matsumoto *et al*., 1997
LIF	Gruss *et al*., 1992
THANK	Mukhopadhyay *et al*., 1999
TNFα	Osborn *et al*., 1989; Israël et al., 1989a
TNFβ	Messer *et al*., 1990
Physiological (Stress) Conditions	
Adhesion	Lin *et al*., 1995b
Depolarization	Kaltschmidt *et al*., 1995
Hemorrhage	Shenkar *et al*., 1996; Shenkar and Abraham, 1997
Hyperglycemia	Yerneni *et al*., 1999
Hyperosmotic Shock	Courtois *et al*., 1997
Hyperoxia	Shea *et al*., 1996
Ischemia (transient, focal)	Gabriel *et al*., 1999; Li *et al*., 1999
Liver Regeneration	Tewari *et al*., 1992; Cressman *et al*., 1994
Mechanical Ventilation (*in vitro*)	Pugin *et al*., 1998
Reoxygenation	Rupec and Baeuerle, 1995
Shear Stress	Lan *et al*., 1994
T-cell Selection	Moore *et al*., 1995
Physical Stress	
PPME Photosensitization	Legrand-Poels *et al*., 1995
Ultraviolet irradiation (UV-A, B, C)	Stein *et al*., 1989
Wounding combined with HeNe irradiation	Haas *et al*., 1998
γ Radiation	Brach *et al*., 1991a
Oxidative Stress	
Butyl Peroxide	Munroe *et al*., 1995
Hydrogen Peroxide	Schreck *et al*., 1991
Ozone	Haddad *et al*., 1996
Pervanadate	Imbert *et al*., 1996
Reoxygenation	Rupec and Baeuerle, 1995
Environmental Hazards	
3,3',4,4'-tetrachlorobiphenyl (PCB77)	Hennig *et al*., 1999
Chromium	Ye *et al*., 1995
Cigarette Smoke	Nishikawa *et al*., 1999
Cobalt	Goebeler *et al*., 1995
Crocidolite asbesstos fibres	Janssen et al., 1995
Dicamba (herbicide, peroxisome proliferator)	Espandiari *et al*., 1998
Lead	Ramesh *et al*., 1999
Nickel	Goebeler *et al*., 1995
Silica Particles	Chen *et al*., 1995
Therapeutically used drugs	
1-b-D-Arabinofuranosyl-cytosine (ara-C)	Strum *et al*., 1994
Anthralin	Schmidt *et al*., 1996
Azidothymidine (AZT)	Kurata, 1994
Camptothecin	Piret and Piette, 1996
Ciprofibrate	Li *et al*., 1996a
Cisplatin	Nie *et al*., 1998
Daunomycin	Das and White, 1997; Hellin *et al*., 1998
Daunorubicin	Wang *et al*., 1996
Doxorubicin	Das and White, 1997
Etoposide	Bessho *et al*., 1994
Haloperidol	Post *et al*., 1998
Methamphetamine	Asanuma and Cadet, 1998
Phenobarbital	Li *et al*., 1996b
Tamoxifen	Ferlini *et al*., 1999

Table 1 continued

Condition	*Reference*
Taxol (Paclitaxel)	Hwang and Ding, 1995
Vinblastine	Rosette and Karin, 1995a
Vincristine	Das and White, 1997
Modified Proteins	
Advanced glycated end products (AGEs)	Yan *et al*., 1994; Wautier *et al*., 1994
Amyloid Protein Fragment (βA4)	Behl *et al*., 1994
Maleylated BSA	Misra *et al*., 1996
Modified (Oxidized)LDL	Rajavashisth *et al*., 1995; Andalibi *et al., 1993*
Overexpressed Proteins (ER Overload)	
CFTR	Knorre and Pahl, unpublished observation
Erythropoietin-Receptor	Knorre and Pahl, unpublished observation
Ig heavy chain	Pahl and Baeuerle, 1995b
MHC Class I	Pahl and Baeuerle, 1995b
Receptor Ligands	
Antigen (IgM-Ligand)	Marcuzzi *et al*., 1989
CD11b/CD18-Ligand (Complement)	Thieblemont *et al*., 1995
CD28-Ligand (B7-1)	Verweij *et al*., 1991
CD2-Ligand	Bressler *et al*., 1991
CD35-Ligand (Complement)	Thieblemont *et al*., 1995
CD3-Ligand	Tong-Starksen *et al*., 1989
CD40-Ligand	Berberich *et al*., 1994
CD4-Ligand (gp120)	Chirmule *et al*., 1994
Fc-2a-Receptor-Ligand (IgG2a)	Muroi *et al*., 1994
Flt-1-Ligand	Reikerstorfer *et al*., 1995
Ly6A/E-Ligand	Ivanov *et al*., 1994
N-CAM	Krushel *et al*., 1999
Trail-receptor-1-Ligand (Trail)	Schneider *et al*., 1997
Trail-receptor-2-Ligand (Trail)	Schneider *et al*., 1997
Trail-receptor-4-Ligand (Trail)	Degli-Esposti *et al*., 1997
Apoptotic Mediators	
Anti-Fas/Apo-1	Rensing-Ehl *et al*., 1995
Trail	Schneider *et al*., 1997
Mitogens, growth factors and hormones	
Bone morphogenic protein 2	Mohan *et al*., 1998
Bone morphogenic protein 4	Mohan *et al*., 1998
Folicle Stimulating Hormone	Delfino and Walker, 1998
Human Growth Hormone	Shen *et al*., 1997
Insulin	Bertrand *et al*., 1995
M-CSF	Brach *et al*., 1991b
Nerve Growth Factor	Wood, 1995; Carter *et al*., 1996
Platelet-Derived Growth Factor	Olashaw *et al*., 1992
Serum	Baldwin *et al*., 1991
TGF-α	Lee *et al*., 1995
Physiological Mediators	
12(R)-Hydroxyeicosatrienoic acid	Laniado-Schwartzman *et al*., 1994
Amino acid analogs	Kretz-Remy *et al*., 1998
Anaphylatoxin C3a	Pan, 1998
Anaphylatoxin C5a	Pan, 1998
Angiotensin II	Li and Brasier, 1996
Basic calcium phosphate crystals	McCarthy *et al*., 1998
Bradikinin	Pan *et al*., 1996
C2-Ceramide (N-acetyl-sphingosine)	Andrieu *et al*., 1995
Cerulein	Gukovsky *et al*., 1998; Steinle *et al*., 1999
Collagen lattice	Xu *et al*., 1998
Collagen Type I	Lee *et al*., 1995
Des-Arg10-kallidin (B1 receptor agonist)	Schanstra *et al*., 1998
Double-stranded polynucleotides	Suzuki *et al*., 1999
f-Met-Leu-Phe	Browning *et al*., 1997
Heat shock protein 60 (HSP 60)	Kol *et al*., 1999
Hemoglobin	Simoni *et al*., 1998
Hyaluronan	Noble *et al*., 1996
Kaianic acid (Kainate)	Kaltschmidt *et al*., 1995
Leukotriene B4	Brach *et al*., 1992
L-Glutamate	Guerrini *et al*., 1995
Lysophosphatidylcholine (LysoPC)	Zhu *et al*., 1997
PAF (platelet activating factor)	Smith and Shearer, 1994; Mutoh *et al*., 1994
Potassium	Kaltschmidt *et al*., 1995
Thrombin	Mari *et al*., 1994
Chemical Agents	
2-Deoxyglucose	Pahl and Baeuerle, 1995b
Anisomycin	Sen and Baltimore, 1986a
Brefeldin A	Pahl and Baeuerle, 1995b
Calchicine	Rosette and Karin, 1995a
Calcium Ionophores	Novak *et al*., 1990
Calyculin A	Suzuki *et al*., 1994
Cobalt chloride	Sultana *et al*., 1999
Con A	Rattner *et al*., 1991
Cycloheximide	Sen and Baltimore, 1986a
Cyclopiazonic Acid	Pahl *et al*., 1996
Forskolin	Delfino and Walker, 1998
Glass fibres	Ye *et al*., 1999
Linoleic acid	Hennig *et al*., 1996
L-NMA	Peng *et al*., 1995
Lysophosphatidic acid	Shahrestanifar *et al*., 1999
Monensin	Pahl and Baeuerle unpublished observation
N-methyl-D-aspartate	Guerrini *et al*., 1995
Nocodazol	Rosette and Karin, 1995a
Okadaic Acid	Thevenin *et al*., 1991
PHA	Sen and Baltimore, 1986b
Phorbol ester	Sen and Baltimore, 1986a
Podophyllotoxin	Rosette and Karin, 1995a
Pyrogallol	Adcock *et al*., 1994
Quinolinic acid	Qin *et al*., 1998
Thapsigargin	Pahl *et al*., 1996
Tunicamycin	Pahl and Baeuerle, 1995b
Vinblastine	Rosette and Karin, 1995a

Where possible, the first publication to report the data is given as a reference

NF-κB, a central regulator of the stress response

NF-κB, however, is involved in the control of transcription of many genes whose functions extend beyond the immediate immune response. For example, NF-κB also regulates the transcription of many acute phase proteins (Table 2). Similarly, there are many activators of NF-κB that are not bacterial and viral pathogens. Therefore, rather than being a central mediator of the immune response, NF-κB perhaps more generally represents a regulator of stress responses. NF-κB activity, for instance, is induced during various physiological stress conditions such as ischemia/reperfusion, liver regeneration and hemorrhagic shock (Table 1). Physical stress in the form of irradiation as well as oxidative stress to cells also induce NF-κB (Table 1). In this context, it appears evolutionarily beneficial that a large variety of stress response genes, such as the inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), are in turn activated by NF-κB (Table 2). Again, NF-κB relays the information of an imminent stress and at the same time enacts a response by promoting the transcription of genes whose products alleviate the stress condition.

Besides physiological stress situations, the human body is exposed to environmental hazards and therapeutic drugs, which can also exert a stress. Indeed, NF-κB is activated both by environmental stresses, such as heavy metals or cigarette smoke, and

Table 2 Target genes of NF-κB

Gene	*Function*	*Reference*
Cytokines/Chemokines and their modulators		
CINC	Cytokine-induced neutrophil chemoattractant	Blackwell *et al*., 1994; Ohtsuka *et al*., 1996
*CXCL 11	Chemokine ligand for CXCR3	Tensen *et al*., 1999
Eotaxin	β Chemokine, eosinphil-specific	Hein *et al*., 1997
Gro α-γ	Melanoma growth stimulating activity	Anisowicz *et al*., 1991
IFN-γ	Interferon	Sica *et al*., 1992; Sica *et al*., 1997
IL-1α	Interleukin-1α	Mori and Prager, 1996
IL-1β	Interleukin-1β	Hiscott *et al*., 1993
IL-1-receptor antagonist	Inhibitor of IL-1 activity	Smith *et al*., 1994
IL-2	Interleukin-2	Serfling *et al*., 1989; Hoyos *et al*., 1989; Lai *et al*., 1995
IL-6	Interleukin-6, inflammatory cytokine	Libermann and Baltimore, 1990; Shimizu *et al*., 1990
IL-8	Interleukin-8, α-chemokine	Kunsch and Rosen, 1993
*IL-9	Interleukin-9	Zhu *et al*., 1996a
IL-11	Interleukin-11	Bitko *et al*., 1997
IL-12 (p40)	Interleukin-12	Murphy *et al*., 1995
*IL-15	Interleukin-15	Azimi *et al*., 1998
β-Interferon	Interferon	Hiscott *et al*., 1989; Lenardo *et al*., 1989
IP-10	α Chemokine	Ohmori and Hamilton, 1993
KC	α Chemokine	Ohmori *et al*., 1995
Lymphotoxin α		Worm *et al*., 1998
Lymphotoxin β	Anchors TNF to cell surface	Kuprash *et al*., 1996
MCP-1/JE	Macrophage chemotactic protein, β Chemokine	Ueda *et al*., 1994
MIP-1α,β	Macrophage inflammatory protein-1, β Chemokine	Grove and Plumbi, 1993; Widmer *et al*., 1993
MIP-2	Macrophage inflammatory protein-1, β Chemokine	Widmer *et al*., 1993
RANTES	Regulated upon Activation Normal T lymphocyte Expressed and Secreted, β Chemokine	Moriuchi *et al*., 1997
TCA3, T-cell activation gene 3	T-cell activation gene 3, β Chemokine	Oh and Metcalfe, 1994
TNFα	Tumor necrosis factor α	Shakhov *et al*., 1990; Collart *et al*., 1990
TNFβ	Tumor necrosis factor β	Paul *et al*., 1990; Messer *et al*., 1990
Immunoreceptors		
B7.1 (CD80)	Co-stimulation of T cells via CD28 binding	Fong *et al*., 1996; Zhao *et al*., 1996
BRL-1	B-cell homing receptor	Wolf *et al*., 1998
CCR5	Chemokine receptor	Liu *et al*., 1998
CD48	Antigen of stimulated lymphocytes	Klaman and Thorley-Lawson, 1995
F_c epsilon receptor II (CD23)	Receptor for IgE	Richards and Katz, 1997
IL-2 receptor α-chain	IL-2 receptor subunit	Ballard *et al*., 1988
Immunoglobulin Cgamma1	IgG heavy chaini	Lin and Stavnezer, 1996
Immunoglobulin ε heavy chain	IgE heavy chain	Iciek *et al*., 1997
Immunoglobulin κ light chain	Antibody light chain	Sen and Baltimore, 1986b
Invariant Chain I_I	Antigen presentation	Pessara and Koch, 1990
MHC class I (H-2K^b)	Mouse histocompatibility antigen	Israël *et al*., 1989a; Israël *et al*., 1989b
MHC Class I HLA-B7	Mouse histocompatibility antigen	Johnson and Pober, 1994
β2 Microglobulin	Binds MHC class I	Israël *et al*., 1989a; Israël *et al*., 1989b
T-cell receptor β chain	T-cell receptor subunit	Jamieson *et al*., 1989
*TNF-Receptor, p75/80	High-affinity TNF receptor	Santee and Owen-Schaub, 1996
Proteins involved in antigen presentation		
Proteasome Subunit LMP2	Subunit of 26S proteasome, cysteine protease	Wright *et al*., 1995
Peptide Transporter TAP1	Peptide transporter for ER	Wright *et al*., 1995
Cell adhesion molecules		
ELAM-1	E-selectin, endothelial cell leukocyte adhesion molecule	Whelan *et al*., 1991
ICAM-1	Intracellular adhesion molecule-1	van de Stolpe *et al*., 1994
MadCAM-1	Mucosal addressin cell adhesion molecule	Takeuchi and Baichwal, 1995
P-selectin	Platelet adhesion receptor	Pan and McEver, 1995
Tenascin-C	ECM protein controls cell attachment and migration, cell growth	Mettouchi *et al*., 1997
VCAM-1	Vascular cell adhesion molecule	Iademarco *et al*., 1992
Acute phase proteins		
Angiotensinogen	Angiotensin precursor, regulates blood pressure	Brasier *et al*., 1990; Ron *et al*., 1990
C4b binding protein	Complement binding protein	Moffat and Tack, 1992
Complement factor B	Complement factor	Nonaka and Huang, 1990
Complement Factor C4	Activates extrinsic pathway of complement activation	Yu *et al*., 1989
C-reactive protein	Pentraxin	Zhang *et al*., 1995
Lipopolysaccharide binding protein	Binds to LPS receptor (CD14) with LPS	Schumann, 1995
Pentraxin PTX3	Pentraxin	Basile *et al*., 1997
Serum amyloid A precursor	Serum component	Edbrooke *et al*., 1991; Li and Liao, 1991
Tissue factor-1	Activates extrinsic pathway of complement activation	Mackman *et al*., 1991
Urokinase-type Plasminogen activator	Activates fibrinogen for fibrin clot lysis	Novak *et al*., 1991
Stress response genes		
Angiotensin II	Peptide hormone	Brasier *et al*., 1990

continued

Table 2 continued

Gene	*Function*	*Reference*
COX-2	Cyclooxygenase, prostaglandin endoperoxide synthase	Yamamoto *et al*., 1995
Ferritin H chain	Iron storage protein	Kwak *et al*., 1995
*5-Lipoxygenase	Arachidonic acid metabolic enzyme, leukotriene synthesis	Chopra *et al*., 1992
12-Lipoxygenase	Arachidonic acid metabolic enzyme	Arakawa *et al*., 1995
inducible NO-Synthase	NO synthesis	Geller *et al*., 1993
Mn SOD	Superoxide dismutase	Das *et al*., 1995
NAD(P)H quinone oxidoreductase (DT-diaphorase)	Bioreductive enzyme	Yao and O'Dwyer, 1995
Phospholipase A2	Fatty acid metabolism	Morri *et al*., 1994
Cell-surface receptors		
A1 adenosine receptor	Pleiotropic physiological effects	Nie *et al*., 1998
Bradikinin B1-Receptor	Pleiotropic physiological effects	Ni *et al*., 1998
*CD23	Cell-surface molecule	Tinnell *et al*., 1998
CD69	Lectin mainly on activated T cells	Lopez-Cabrera *et al*., 1995
Gal1 Receptor	Galanine receptor, neuroendocrine peptide	Lorimer *et al*., 1997
Lox-1	Receptor for Oxidized low density lipoprotein	Nagase *et al*., 1998
Mdr1	Multiple drug resistance mediator (P-glycoprotein)	Zhou and Kuo, 1997
Neuropeptide Y Y1-receptor	Pleiotropic physiological effects	Musso *et al*., 1997
PAF receptor 1	Platelet activator receptor	Mutoh *et al*., 1994
RAGE- receptor for advanced glycation end products	Receptor for Advanced Glycation End products	Li and Schmidt, 1997
Regulators of apoptosis		
Bfl1/A1	Pro-survival Bcl-2 homologue	Grumont *et al*., 1999; Zong *et al*., 1999
Bcl-xL	Pro-survival Bcl-2 homologue	Chen *et al*., 1999; Lee *et al*., 1999b
Nr13	Pro-survival Bcl-2 homologue	Lee *et al*., 1999
cCD95 (Fas)	Pro-apoptotic receptor	Chan *et al*., 1999
Fas-Ligand	Inducer of apoptosis	Matsui *et al*., 1998
IAPs	Inhibitors of Apoptosis	You *et al*., 1997; Stehlik *et al*., 1998
IEX-1L	Immediate early gene	Wu *et al*., 1998
Growth factors and their modulators		
G-CSF	Granulocyte Colony Stimulating Factor	Nishizawa and Nagata, 1990
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor	Schreck and Baeuerle, 1990
*IGFBP-1	Insulin-like growth factor binding protein-1	Lang *et al*., 1999
IGFBP-2	insulin-like growth factor binding protein-2	Cazals *et al*., 1999
M-CSF (CSF-1)	Macrophage Colony Stimulating Factor	Brach *et al*., 1991b
PDGF B chain	Platelet-Derived Growth Factor	Khachigian *et al*., 1995
Proenkephalin	Hormone	Rattner *et al*., 1991
*Thrombospondin	Matrix glycoprotein t	Adolph *et al*., 1997
VEGF C	Vascular Endothelial Growth Factor	Chilov *et al*., 1997
Early response genes		
p22/PRG1	Rat homology of IEX	Schafer *et al*., 1998*
p62	Non-proteasomal multi-ubiquitin chain binding protein	Vadlamudi and Shin, 1998
Transcription factors		
A20	TNF-inducible zinc finger	Krikos *et al*., 1992
c-*myb*	Proto-oncogene	Toth *et al*., 1995
c-*myc*	Proto-oncogene	Duyao *et al*., 1992
c-*rel*	Proto-oncogene	Hannink and Temin, 1990
IRF-1	Interferon regulatory factor-1	Harada *et al*., 1994
IRF-2	Interferon regulatory factor-2	Harada *et al*., 1994
IκBα	Inhibitor of Rel/NF-κB	Haskill *et al*., 1991; Sun *et al*., 1993; deMartin *et al*., 1993
*jun*B	Proto-oncogene	Brown *et al*., 1995
nfkb2	NF-κB p100 precursor	Lombardi *et al*., 1995
nfkb1	NF-κB p105 precursor	Ten *et al*., 1992
p53	Tumor suppressor	Wu and Lozano, 1994
Viruses		
Adenovirus (E3 region)	Adenovirus	Williams *et al., 1990*
Avian Leukosis Virus	Causes avian leukosis	Bowers *et al*., 1996
Bovine Leukemia Virus	Causes bovine leukemia	Brooks *et al*., 1995
CMV	Cytomegalovirus	Sambucetti *et al*., 1989
EBV (Wp promoter)	Epstein-Barr virus	Sugano *et al*., 1997
HIV-1	Human immunodeficiency virus	Nabel and Baltimore, 1987; Griffin *et al*., 1989
HSV	Herpes simplex virus	Rong *et al*., 1992
JC Virus	Polyoma virus	Ranganathan and Khalili, 1993
Measles virus	Causes measles	Harcourt *et al*., 1999
SIV	Simian immunodeficiency virus	Bellas *et al*., 1993
SV-40	Simian virus 40	Kanno *et al*., 1989
Enzymes		
*Ceramide glycosyl transferase	Glycosphingolipid	Ichikawa *et al*., 1998
Collagenase 1	Matrix metalloproteinase	Vincenti *et al*., 1998

continued

Table 2 continued

Gene	*Function*	*Reference*
*Dihydrodiol dehydrogenase	Oxidoreductase, oxidation of trans-hydodiols	Ciaccio *et al*., 1996
*GAD67	Glutamic acid decarboxylase	Szabo *et al*., 1996
Gelatinase B	Matrix metalloproteinase	He, 1996
GSTP1-1	Glutathione transferase	Xia *et al*., 1996*
Glucosel-6-phosphate dehydrogenase	Hexose monophosphate	Garcia-Nogales *et al*., 1999
* HO-1	Hemeoxygenase	Lavrovsky *et al*., 1994
Hyaluronan synthase	Synthesizes hyaluronic acid	Ohkawa *et al*., 1999
Lysozyme	Hydrolyzes bacterial cell walls	Phi van, 1996
*PTGIS, prostaglandin synthase	Prostaglandin synthase	Yokoyama *et al*., 1996
Transglutaminase	Forms isopeptide bonds	Mirza *et al*., 1997
*Xanthine Oxidase	Oxidative metabolism of purines	Xu *et al*., 1996
Miscellaneous		
alpha-1 acid glycoprotein	Serum protein	Mejdoubi *et al*., 1999
Apolipoprotein C III	Apoprotein of HDL	Gruber *et al*., 1994
*Biglycan	Connective tissue proteoglycan	Ungefroren and Krull, 1996
Cyclin D1	Cell-cycle regulation	Guttridge *et al*., 1999; Hinz *et al*., 1999
*Cyclin D3	Cell-cycle regulation	Wang *et al*., 1996b
Factor VIII	Hemostasis	Figueiredo and Brownlee, 1995
Galectin 3	β-galactosidase-binding lectin	Hsu *et al*., 1996
HMG14	High mobility group 14	Walker and Enrietto, 1996
K3 Keratin	Intermediate filament protein	Wu *et al*., 1994
Laminin B2 Chain	Basement membrane protein	Richardson *et al*., 1995
Mts1	Multiple tumor suppressor	Tulchinsky *et al*., 1997
*Pax8	Paired box gene	Okladnova *et al*., 1997
*UCP-2	Uncoupling protein-2	Lee *et al*., 1999a
Vimentin	Intermediate filament protein	Lilienbaum *et al*., 1990
Wilm s Tumor Supressor Gene	Tumor suppressor	Dehbi *et al*., 1998
α1-antitrypsin	Protease inhibitor	Ray *et al*., 1995

Where possible, the first publication to report the data is given as a reference. *Genes contain NF-κB binding sites in their promoter/enhancer regions, but further experiments are required to prove their functionality

by therapeutic drugs, including various chemotherapeutic agents (Table 1). One may speculate that the activators and the target genes of this multifunctional transcription factor have co-evolved. While environmental stresses and xenobiotics activate NF-κB, its target genes include many cell surface receptors, among them the *mdr-1* gene, which encodes the multiple drug resistance mediator. Likewise, while modified proteins such as advanced glycated end products (AGEs) induce NF-κB (Table 1), the AGE receptor (RAGE) is an NF-κB target gene (Table 2).

Another recently recognized cellular stress has been termed the ER-Overload Response (Pahl and Baeuerle, 1997a, 1997b; Pahl, 1999). ER-overload arises from an accumulation of proteins within the endoplasmic reticulum (ER). It can occur under a variety of circumstances:

(1) a sudden increase in the production of proteins which enter the ER, for example during viral infection;
(2) drugs which interfere with ER function thereby leading to protein accumulation in the organelle;
(3) production of mutant proteins, which cannot fold correctly and thus accumulate in the ER; and
(4) an overproduction of wild-type proteins, for example during transient transfection experiments, which overwhelm the ER folding/processing machinery and therefore also accumulate in the organelle (Table 1).

Agents eliciting the ER-Overload Response thus appear under various categories in Table 1.

Cellular stress can result in the most drastic form of cellular self defense, namely programmed cell death or apoptosis. It is now clear that NF-κB can exert both pro- and anti-apoptotic effects in different cells types (Barkett and Gilmore, 1999, this issue). The observation that several stimuli, among them tumor necrosis factor a (TNFα) and binding to the IgM receptor (or cross linking of the receptor with antibodies), can lead both to NF-κB activation (Table 1) and to apoptosis (Laster *et al*., 1988; Hasbold and Klaus, 1990) suggested that NF-κB induction was pro-apoptotic. Furthermore, both cross-linking of the Fas-receptor by anti-Fas antibodies and binding of the Trail receptors 1 and 2 stimulate NF-κB (Table 1). Moreover, both the Fas-receptor and its ligand are encoded by NF-κB target genes (Table 2). However, cells derived from RelA knockout mice are more susceptible to apoptosis induced by various agents, including TNFα (Beg and Baltimore, 1996; Van Antwerp *et al*., 1996; Wang *et al*., 1996a). Likewise, binding of the Trail receptor-4 induces NF-κB but prevents Trail-mediated apoptosis (Degli-Esposti *et al*., 1997), and inhibition of NF-κB restores drug-induced apoptosis sensitivity to certain drug-resistant primary leukemic cells and leukemic cell lines (Jeremias *et al*., 1998). These data, together with the identification of pro-survival *bcl-2* homologs, Bfl1/A1, Bcl-x_L and Nr13, and inhibitors of apoptosis (IAPs) as NF-κB target genes (Table 2), suggest that NF-κB activation is anti-apoptotic in several cell types.

Consistent with a pro-surivival activity for NF-κB, several mitogens and growth factors stimulate NF-κB (Table 1) or are induced by NF-κB (Table 2). Some of these mitogens, such as M-CSF and PDGF, appear to act via an autocrine loop: they activate NF-κB which in turn stimulates transcription of the growth factor

gene. Because mitogens and growth factors stimulate NF-κB activity it is logical that several early response genes are also regulated by this transcription factor (Table 2). Thus, in addition to immune modulation and the more general stress response, NF-κB appears to promote cell survival. Teleologically speaking, it may 'make sense' to couple a stress response factor to anti-apoptotic pathways. This central coordinator evokes an effective response against the stress and ensures that the cell does not succumb in the process.

Many physiological mediators that bear no apparent connection to stress responses also activate NF-κB (Table 1). Among these mediators are several, such as PAF and Bradikinin, that activate NF-κB and whose receptors are NF-κB target genes (Table 2). Perhaps these mediators are released under conditions which have not been recognized or categorized as 'stress'. This, however, is only a question of definition.

Of the many chemical agents that induce NF-κB activity (Table 1), most elicit stress of some sort. Cycloheximide, for example, inhibits protein synthesis, while tunicamycin, brefeldin A, 2-deoxyglucose and monensin disrupt ER function, thereby eliciting ER-overload. Nocodazol, calchicine, podophyllotoxin and vinblastin interfere with microtubule function (Rosette and Karin, 1995). Systematic screening of chemical libraries would surely unearth a plethora of additional agents that induce NF-κB, perhaps by interfering with vital cell functions, thereby causing stress.

In addition to the response genes already discussed, NF-κB activation leads to the transcriptional induction of various transcription factor genes, some themselves members of the Rel/NF-κB/IκB family. In this way, NF-κB limits its own activation, in that NF-κB activation results in the new synthesis of its inhibitor IκB (Table 2). Newly-synthesized IκB can enter the nucleus and dislodge active NF-κB from its DNA binding site (Zabel and Baeuerle, 1990, Zabel *et al*., 1993). Thus, in most cell types, NF-κB activation is transient. However, because NF-κB can induce the transcription of other transcription factors, for instance the proto-oncogene c-*myc* and the tumor suppressor *p53*, an initial NF-κB activation may indirectly induce the transcription of many more genes than the identified 150 targets.

Thus, a more detailed look at inducers and targets of NF-κB suggests that this transcription factor is more than a mediator of the immune response. It appears that NF-κB is activated and induces responses to various forms of cell stress and should therefore more generally be termed a 'central mediator of human stress response'. In this context it is interesting to note that certain well-studied stress situations, such as heat shock and the unfolded protein response, do not activate NF-κB. NF-κB activity, therefore, appears reserved for select but widely varied stresses.

New roles for NF-κB?

There are many NF-κB target genes whose properties and function defy classification (listed under Enzymes and Miscellaneous in Table 2). Several of these target genes, such as vimentin, laminin, collagenase and gelatinase, appear to involve NF-κB in the regulation of cell structure and micro-environment. Such an adaptation response may also serve to reduce cell stress, however, more data are required to evaluate a role for NF-κB in these processes. Likewise, the observations that NF-κB regulates transcription of the cyclin D1 gene (Guttridge *et al*., 1999; Hinz *et al*., 1999) and may also participate in cyclin D3 gene transcription (Wang *et al*., 1996b) are very intriguing. If NF-κB controls cyclin transcription, this would implicate NF-κB in cell-cycle progression. However, more data are required to substantiate this idea.

Specificity of the NF-κB response

NF-κB participates in the transcription of over 150 target genes. Are all activated when NF-κB is induced? How can this transcription factor maintain any selectivity or specificity?

For NF-κB activation the selectivity resides mainly in the cell type targeted. Not all cell types respond equally to a given stimulus, either because they lack the cognate receptor or because they lack the required signal transduction molecules (discussed in Karin, 1999, this issue). Thus, not every stimulus listed in Table 1 will activate NF-κB in every cell type examined.

Several different mechanisms confer selectivity on the transcriptional response to NF-κB activation. These include:

(1) the combinatorial response of promoter/enhancer regions, and
(2) The selective activation and binding of individual Rel/NF-κB proteins.

The combinatorial response

The promoter/enhancer regions of most genes contain more than one transcription factor response element. Therefore, more than one transcription factor is usually required to induce effective transcription of a given gene. For the target genes listed in Table 2, NF-κB activity is necessary for efficient transcription. Thus, mutation of the κB site abrogates transcription of these promoters. However, NF-κB may not be sufficient for full transcription, as other transcription factors are also required. This combinatorial regulation of transcription provides specificity to a given response. While a given stimulus may activate NF-κB, if it fails to activate additional transcription factors, the target gene will not be transcribed fully.

We have demonstrated such selectivity using stably transfected cell lines, which express a chimeric p50/VP16 protein. In this fusion protein, the p50 DNA-binding domain confers specific binding to κB sites, while the HSV VP16 transactivation domain provides potent transcriptional activation. Expression of the p50/VP16 protein was placed under the control of a tetracycline repressable promoter in CMS-5 fibroblast cells. While induction of p50/VP16 was sufficient to activate transcription of the GM-CSF gene in these cells, transcription of the NF-κB target genes IL-1, IL-2 and IL-6 was not induced (Meerpohl and Pahl, unpublished observations). Thus, despite the almost overwhelming number of NF-κB target genes, the individual gene is selectively activated under specific circumstances.

Selective activation of Rel/NF-κB family members

The various members of the Rel/NF-κB family differ in their preference for specific DNA-binding sites (Kunsch *et al*., 1992). Using random oligonucleotides and a DNA-binding assay, Kunsch *et al*. (1992) selected optimal DNA-binding sites for p50, RelA and c-Rel, as homodimers. The preferred binding site differs for each homodimer. Not surprisingly, such specificity is also seen *in vivo*. For example, several NF-κB target genes have been reported to contain binding sites that preferentially bound by RelA homodimers (e.g., ICAM-1 (Ledebur and Parks, 1995) and IL-4 (Casolaro *et al*., 1995)).

Thus, the availability of different Rel/NF-κB hetero- and homodimers, whose synthesis and activation may be controlled by distinct signal transduction pathways, provides an additional level of selectivity in NF-κB-mediated gene transcription.

Demonstration of NF-κB activation and discovery of target genes

The simplest and most reliable assay to demonstrate NF-κB activation is the electrophoretic mobility shift assay (EMSA, (Müller *et al*., 1997)). When combined with the appropriate controls, i.e. unstimulated control cells, as well as competition and supershift assays, the EMSA is both sensitive and accurate. Transient transfection experiments using a κB site-driven reporter gene are also frequently used. The appropriate controls include either a reporter gene lacking the κB sites, or, even better, a reporter gene preceded by mutated κB sites. Inhibition of reporter gene expression by co-transfection of an expression vector for the NF-κB inhibitor IκB provides an additional confirmation of specificity. All of the inducers listed in Table 1 have been demonstrated to activate NF-κB using one of these assays.

What makes a gene an NF-κB target gene? Not all genes listed in Table 2 are *bona fide* NF-κB target genes. That is, genes in Table 2 preceded by an asterisk merely contain a putative NF-κB binding site in their promoter/enhancer region. To establish that a gene is truly regulated by NF-κB, the following experiments must be performed:

(1) NF-κB binding to the putative DNA site must be shown in an EMSA, preferably using cell extracts from a tissue which usually expresses the gene under investigation, and

(2) the promoter/enhancer region must be cloned in front of a reporter gene and functional importance of the κB site must be demonstrated by mutagenesis.

These two experiments are required before a gene can be considered an NF-κB target. However, these data can be misleading if, for example, NF-κB can bind to a DNA sequence, but this site or adjacent sequences are occupied by other proteins *in vivo*. In such a scenario, NF-κB would bind the isolated site *in vitro* in an EMSA. Mutation of this site would result in a loss of function in reporter gene assays, but only because binding of the adjacent unidentified protein is lost. Therefore, for final proof of NF-κB involvement, *in vivo* DNA footprinting of the κB site should be performed. This, however, has not been done for the majority of the target genes listed in Table 2. Nevertheless, the vast majority of these genes are expected to be true NF-κB target genes. Moreover, it is likely that cDNA microarray technologies and genomic sequencing will identify many other NF-κB target genes.

Summary

This article lists and categorizes the known inducers and target genes of the pleiotropic transcription factor NF-κB known to date. Compilation of these data reveals that the vast majority of NF-κB inducing agents or conditions represent a form of stress to cells. In response, many NF-κB target genes function to alleviate cell stress. In addition, NF-κB has recently been shown to inhibit apoptosis in several cell types. Therefore, NF-κB may act as a central integrator of stress responses and cell survival pathways. The rapid rate at which new NF-κB inducers and target genes are being identified suggests that this transcription factor may coordinate additional cellular functions.

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