Preface

The NF-κB pathway brought mammalian signal transduction into the modern era, allowing the analysis of cell signaling to become inclusive and holistic. Prior to its definition, biologists had focused on receptor-proximal events, largely through study of receptor tyrosine kinases and G-protein-coupled receptors or the study of isolated protein kinases. The gaping hole in our understanding at that point was the connection to the nucleus. It was clear that many of the physiological effects of receptor signaling were achieved by altering gene expression, but how signals were transduced from the plasma membrane to the nucleus was by-and-large a mystery. The elucidation of NF-κB signaling in all of its molecular glory provided a new paradigm for understanding how receptor signaling can elicit transcriptional responses in mammalian cells. Even more importantly, NF-κB helped transform the study of cell signaling from dealing with cultured cells to consideration of whole animal systems.

As David Baltimore points out in his introduction, NF-κB was born rather innocently in a search for transcriptional regulators of the immunoglobulin locus. At the time, this effort was directed towards understanding the orchestrated changes in gene expression that take place during lymphocyte development. However, by following their noses, scientists in the Baltimore lab soon realized that the nuclear accumulation of the NF-κB DNA binding proteins could be induced by a number of extracellular stimuli and set out to understand how this molecular connection was made. The discovery that NF-κB exists in a latent form in the cytoplasm and translocates to the nucleus in response to various stimuli changed the way mammalian signal transduction was conceptualized.

What followed was a breathtaking explosion of research that uncovered pivotal roles for NF-κB in a host of biological processes critical for normal physiology of animals and their ability to counter stress, disease, and infection. As Jules Hoffman discusses, NF-κB emerged early in animal evolution as an important regulator of development and as a defense mechanism against invading pathogens, themes that have been embellished in vertebrate evolution. Although mammals no longer count on NF-κB in the control of general development and morphogenesis, they use it to signal downstream of a host of receptors, many of which are members of extended gene families to control responses to stress, infection, and injury.

This collection includes reviews of the molecular mechanisms by which NF-κB transcription factors are activated and exert their function in the nucleus, as well as reviews that summarize certain realms of biology that are particularly influenced by NF-κB signaling. Ingrid Wertz and Vishva Dixit focus on the mechanisms whereby receptors that detect antigens, inflammatory cytokines, and foreign organisms utilize protein–protein interactions and the ubiquitin system to engage IκB kinase (IKK) to initiate NF-κB signaling. The structure of IKK complex components and the elaborate regulation of its protein kinase activity are described by Alain Israël in his contribution. Andrea Oeckinghaus and Sankar Ghosh summarize the process by which IκBs sequester NF-κB in a latent state in the cytoplasm and how IKK action relieves this inhibition. Ynon Ben-Neriah and colleagues discuss the role of ubiquitination in the regulated degradation of the IκBs. The Rel-homology DNA binding domains of NF-κB transcription factors are discussed in structural detail by Tom Huxford and Goury Ghosh. The various NF-κB heterodimers have distinct target genes, as discussed by Ranjan Sen and Steve Smale, and can be altered in their transcription regulatory activities by post-translational modifications and association with co-factors, as discussed by
Fengyi Wan and Mike Lenardo. Chromatin structure further shapes the transcriptional output of NF-κB dimers, as reviewed by Gioacchino Natoli. The overall biological output of NF-κB signaling must be viewed from a systems biology perspective, as argued by Ellen O’Dea and Alex Hoffmann, whereas Steve Gerondakis and Uli Siebenlist recount the manifold ways in which NF-κB signaling controls lymphocyte differentiation, activation, and function in vivo. Equally important is the regulation of innate immunity and inflammatory responses, as presented by both Toby Lawrence and Michael Karin. Inflammation can promote cancer development, and Michael Karin outlines the compelling evidence for the critical pathogenic role played by NF-κB signaling in this process. Not surprisingly, cancers of many varieties accumulate genetic lesions that subvert NF-κB signaling to protect against cell death and promote proliferation, offering many possible avenues for therapy, as discussed by Lou Staudt. Barbara and Christian Kaltschmidt remind us that without NF-κB in our neurons, we would suffer learning disabilities and memory loss and would gain little from reading collections like this!

Twenty-four years after the discovery of mammalian NF-κB and more than 25,000 publications later, there remain mysteries and challenges in the NF-κB field. The contribution by Tao Lu and George Stark demonstrates that unbiased genetic screens continue to yield new regulators of NF-κB, so it will be years before we have a complete parts list for this system and a full understanding of its working. Given the dysregulation of NF-κB in inflammatory and autoimmune diseases, as well as in cancer, it is imperative that precise methods to manipulate NF-κB are developed. This will be a challenge given the baroque regulation of the NF-κB signaling system and its diverse biological functions, but one that can be met by building on the strong edifice of knowledge presented in this volume.

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Index

A
Act1 (NF-κB activator 1), 256–257
Activated B-cell-like (ABC) DLBCL
cancer therapies and, 158–159, 160
involvement in cancer development, 170–171
oncogenic activation of NF-κB
activation of NF-κB pathway, 140
biological consequences of NF-κB
signaling, 141
chronic ABC receptor signaling, 144–146
engagement of the CARD11 module, 141–143
genetic alterations deregulating NF-κB in,
146–147
influence of NF-κB signaling on, 141
oncogenic CARD11 mutations, 143–144
Anhidrotic ectodermal dysplasia (EDA-ID), 59
Ankyrin repeat domain (ARD), 40
Aryl hydrocarbon receptor (AhR), 26–27
Ataxia telangiectasia mutated (ATM), 135
Azoxymethane (AOM), 172

B
β-catenin, 27–28, 66, 67, 68, 69, 75, 172
B-cell chronic lymphocytic leukemia, 170
B-cells. See Lymphocyte development and function
and NF-κB
Bcl3, 11, 42–43
Binding activity. See Specification of DNA binding
activity of NF-κB complexes
B lymphocytes. See Lymphocyte development and
function and NF-κB
Bortezomib, 74–75, 159
β-TRCP
IKB recognition by, 68–69
interference, 159
regulation, 67–68

C
CAC (colitis-associated cancer), 172–174
Cactus, 224. See also Immune response of Drosophila
and NF-κB
Cancer. See Inflammation and cancer link and
NF-κB; Oncogenic activation of NF-κB
CaP (prostrate cancer), 176–179
CARD11/BCL10/MALT1 (CBM) signaling complex
engagement of in ABC DLBCL, 141–143
oncogenic mutations, 143–144, 146–147
relationship with marginal zone B-cell
differentiation, 149
role in B-cell lymphoma, 170–171
targeting of specific cancer pathways and,
159–160
CD40 system for noncanonical NF-κB signaling,
90–91
CD4 and DC9 thymocytes, 197–199
CD79, 144–146
Cdk9 (cyclin-dependent kinase 9), 28
Chromatin organization and control of NF-κB-
dependent transcriptional responses
classes of regulated genes, 118–120
complexity of inflammatory transcriptional
responses, 117–118
concluding remarks and future studies, 125
genetic dissection of chromatin remodeling
events
absence of IκBδ, 121
chromatin remodeling, 120
regulatory layers, 120–121
steps in the gene activation process, 121
molecular bases of differential chromatin
accessibility, 122–124
transcription factors’ locating of relevant
binding sites in the genome, 124–125
Colitis-associated cancer (CAC), 172–174
c-Rel, 7
de novo synthesis, 109
NF-κB pathway in inflammation and, 185
post-translational modifications of Rel
proteins, 24–25
selectivity of mechanisms used, 104–106
target gene selectivity, 102–104
Cyclin-dependent kinase 9 (Cdk9), 28
CYLD, 152, 153f, 154, 155–156

D
Dasatinib, 160
DEN (diethylnitrosamine), 174–176
Deubiquitinases (DUBs), 69, 83–84
Dextrane sulfate sodium (DSS), 172
Diethylamino-nitrosamine (DEN), 174–176
Dimer generation regulation
dimerization process, 129
equilibrium states, 129–131
stimulus-responsive alterations, 131, 132f
DNA binding in NF-κB. See Specification of
DNA binding activity of NF-κB complexes
Dorsal-related immunity factor (DIF), 223–224.
See also Immune response of Drosophila
and NF-κB
DP thymocytes, 197–199
Drosophila. See Immune response of Drosophila
and NF-κB
DSS (dextrane sulfate sodium), 172
E3 ubiquitin ligase, 66–67
EBV (Epstein-Barr virus), 148–149, 171
EDA-ID (anhidrotic ectodermal dysplasia), 59
ELKS protein, 60
Epithelial cancers
CYLD as a tumor suppressor, 155–156
unconventional IKKs and, 156–158
Epithelial cells, thymic, 202–204
Epstein-Barr virus (EBV), 148–149, 171
F-box protein (FBP), 66–67
FBXL11, 259–260
Forward genetics and regulators of NF-κB
approaches to study of NF-κB
cDNA library expression, 256–257
chemical mutagenesis, 255–256
insertional mutagenesis (see Insertional
mutagenesis in forward genetics studies)
concluding remarks and future studies, 260–262
mammalian cells in tissue culture and, 253
selection system to identify mutants, 253–254
GABAergic interneurons, 243
γ-aminobutyric acid (GABA), 240
Ganciclovir (GCV), 254. See also Forward genetics
and regulators of NF-κB
Germinal center B-cell-like (GBC) DLBCL
involvement in cancer development, 170–171
oncogenic activation of NF-κB, 140, 141, 145,
146–148, 159, 160
Glia and NF-κB in the nervous system, 247
Glutamate, 240
Hepatocellular carcinoma (HCC), 174–176
Hodgkin lymphoma, 148–149
Hodgkin Reed-Sternberg (HRS), 148
Hsp70, 60
Hsp90, 60, 158
Hypothalamus and NF-κB in the nervous system,
244–246
IκB kinase (IKK) complex, 7
activation cascade in prostate cancer, 176–179
activation of catalytic subunits, 52–54
catalytic subunits, 51
epithelial cancers and, 156–158
function, 12
IKKa and IKKB, 51
IKKq and NF-κB pathway in inflammation,
187–189
IKKβ-based cancer therapies, 179–180
IKKβ inhibitors and NF-κB link between
inflammation and cancer, 172–174
IKKβ inhibitors and therapy of NF-κB-driven
cancers, 158–159
IKKβ inhibitors anti-inflammatory roles, 186
mice knockout experiments, 60–61
NEMO/IKKγ regulatory subunit
canonical pathway and, 54
function, 51–52, 54–55
hypomorphic mutations results, 59
interferon regulatory factor signaling
pathways and, 57
loss of function mutations results, 58–59
polyubiquitination role, 57
post-translational modifications, 57–58
ubiquitin binding, 55–57
vFLIP and, 54
NF-κB signaling module and
catalytic subunit domain organization,
43–44
complex oligomerization, 45
distinct activation pathways, 45
emerging structure of NEMO/IκKγ, 45–46
introduction to, 43
NEMO/IκKγ domain organization,
44–45
physiological significance, 12, 13f
probability of other components, 59–60
regulation of binding activity and, 21–23
Inflammation and the NF-κB pathway (continued)
canonical pathway (continued)
tissue-specific role, 185–186
TNFα and IL-1 signaling, 185
summary, 189–190
Insertional mutagenesis in forward genetics studies
information about p65 and TAB3 from retroviral, 257, 258f
transposon-mediated, to discover short RIP, 257, 259
VBM technique to discover FBXL11, 259–260
Interferon regulatory factor (IRF) signaling pathways, 57
IP (incontinentia pigmenti), 58–59
ITAMs (immunoreceptor tyrosine-based activation motifs), 91–92
Kruppel-associated box (KRAB), 259
Kupffer cells, 174–176

L
Lamina propria macrophages, 172
Learning and NF-κB, 239–240, 242–244. See also Nervous system and NF-κB
Lipopolysaccharide (LPS)
IKK complex and, 45, 53, 55
IL1R1/TLR4 and, 88–89
induction of NF-κB, 2
NF-κB induction by, 109, 120–121, 134
Liver apoptosis, 60
Lymphocyte development and function and NF-κB
B-cell activation and, 205–207
B-cell division and, 207–208
cell-autonomous roles of NF-κB
DP and SP thymocytes, 197–199
early lymphocyte progenitors, 193–196
immature (bone marrow) B cells and negative selection, 197
mature and marginal zone B cells, 200–202
NF-κB in thymic epithelial cells, 202–204
nonconventional T cells, 199–200
pre-antigen receptor expression and, 196
small (late) pre-B cells, 196–197
concluding remarks and future studies, 214
control of activated B-cell survival, 208–209
effector T-cell differentiation and, 213–214
isotype switching, 209–210
stromal cells and establishment of secondary lymphoid organs, 204–205
T-cell activation and, 210
T-cell proliferation and, 210–211
T-cell survival and, 212–213
Lymphocyte-predominant Hodgkin lymphoma, 149
Lymphoma and NF-κB, 140, 148–151, 170–172

M
MALT (mucosa-associated lymphoid tissue), 149–151, 160
Marginal zone B cells (MZB), 149, 200–202
Medullary thymic epithelial cells (mTECs), 203–204
Memory and NF-κB, 242–244. See also Nervous system and NF-κB
Mi2/Nurd, 120
MLN4924, 159
mTECs (medullary thymic epithelial cells), 203–204
Mucosa-associated lymphoid tissue (MALT), 149–151, 160
Multiple myeloma (MM), 74–75, 152–155, 171
MZB (marginal zone B cells), 149, 200–202

N
NEDD8, 159
NEMO/IKKγ regulatory subunit
canonical pathway and, 54
definition of IKK and, 128
domain organization, 44–46
emerging structure of, 45–46
function, 51–52, 54–55
hypomorphic mutations results, 59
interferon regulatory factor signaling pathways and, 57
loss of function mutations results, 58–59
polyubiquitination role, 57
post-translational modifications, 57–58
ubiquitin binding, 55–57
vFLIP and, 54
Nervous system and NF-κB
biochemical/cellular concept of memory, 240
defining learning, 239–240
glia, 247
hypothalamus, 244–246
learning and memory and, 242–244
neural stem cells, 248
neurons and, 240, 242
neuroprotection, 246–247
NF-κB’s role in the cellular context of, 241f
pain and, 247–248
Neural stem cells, 248
NF-κB
cellular response to stimuli (see Selectivity of the NF-κB response)
dimers’ physiological role, 9
discovery of, 1–2
IkB proteins (see IkB proteins)
IKK complex (see IkB kinase (IKK) complex)
immune response of Drosophila and (see
Immune response of Drosophila and
NF-κB)
inhibition of IkB (see IkB proteins,
ubiquitination and degradation)
involvement in cancer development (see
Inflammation and cancer link and NF-κB;
Oncogenic activation of NF-κB)
lymphocytes and (see Lymphocyte development
and function and NF-κB)
post-translational modifications, 12–14
protein binding activity (see Specification of DNA
binding activity of NF-κB complexes)
signaling and (see Regulatory logic of the NF-κB
signaling system; Signaling by
ubiquitination; Signaling module)
stimuli and κB-dependent target genes, 6–7
termination of the NF-κB response, 14–15
transcriptional control (see Specification of DNA
binding activity of NF-κB complexes)
transcriptional responses (see Chromatin
organization and control of NF-κB-
dependent transcriptional responses)
transcription factor family, 7–9
NF-κB essential modulator. See NEMO/IKKγ
regulatory subunit
NF-κB inducing kinase (NIK), 128, 160–161, 171
NOD2, 93–95
Nucleotide-binding domain leucine-rich repeat
(NLR), 93
Nucleotide-binding oligomerization domain
(NOD), 93

O
Oncogenic activation of NF-κB
ABC DLBCL
activation of NF-κB pathway, 140
biological consequences of NF-κB signaling,
141
chronic ABC receptor signaling, 144–146
engagement of the CARD11 module, 141–143
 genetic alterations deregulating NF-κB in,
 146–147
influence of NF-κB signaling on, 141
oncogenic CARD11 mutations, 143–144
epithelial cancers
CYLD as a tumor suppressor, 155–156
unconventional IKKs and, 156–158
GCB DLBCL, 147–148
Hodgkin lymphoma, 148–149
MALT lymphoma, 149–151
multiple myeloma, 152–155
NF-κB’s role in the initiation and promotion of
cancer, 139–140
primary mediastinal B-cell lymphoma, 140, 148
therapy of NF-κB-driven cancers
βTrCP interference, 159
chronic ABC receptor signaling, 160
IKKβ inhibitors, 158–159
NIK targeting, 160–161
proteasome inhibitor bortezomib, 159
strategies targeting specific upstream
pathways, 159–161

P
p100, 23, 42, 71–72
p100/52 (NF-κB2), 7, 10–11
p105, 23, 42, 71–72
p105/p50, 7, 10–11
p50 and p52, 106
p50/p65 heterodimers, 7
p65 (RelA), 7, 13–14, 15, 242
Pain and NF-κB in the nervous system, 247–248
Peptidoglycan recognition proteins (PGRPs),
225–227, 230–231
Pirk, 232
Primary mediastinal B-cell lymphoma (PMBL),
140, 148
Prostrate cancer (CaP), 176–179

R
Receptor-interacting protein kinase 1 (RIP1), 259
Regulatory logic of the NF-κB signaling system
concluding remarks and future studies, 137
integrating signals that control IkB
inflammatory signals and developmental
signals cross talk, 136
ribotoxic stresses and inflammatory signals
cross talk, 136
integrating signals that control NF-κB synthesis
and IkB degradation, 137
molecular components of the
system, 127–128
regulation of activity via IkB
process description, 131–133
signaling in response to cellular stresses, 135
signaling in response to developmental
signals, 134–135
signaling in response to inflammatory signals,
133–134
Regulatory logic of the NF-κB signaling system (continued)
duration of activation, 107f
de novo c-Rel synthesis, 109
IκB-dependent export, 106–108
cytokine signaling, 43–44
mechanisms that mediate signaling cross talk
NF-κB dimerization, 37–38
NF-κB recognition of κB DNA, 38–40
Rel homology region structure, 36–37
Recruitment of κB DNA, 36–37
Signaling by ubiquitination
concluding remarks and future studies, 95–96
introduction to NF-κB signaling, 81–82
ubiquitin/proteasome system
CD40 system for noncanonical signaling, 90–91
components and pathways, 82t, 83–86
IL1R1/TLR4, 88–89
inactivation of NF-κB signaling, 85
NF-κB activation by intracellular stimuli, 93–95
polyubiquitination and IκK activation, 84–85
system description, 82–84
TCR antigen receptor, 91–93
TNFR1, 86–88
Signal transduction module
dimerization, 37–38
IκB
classical sequence and structure, 40–41
IκBα dynamics, 41–42
interactions with NF-κB, 41
introduction to, 40
nonclassical proteins, 42
nuclear proteins, 42–43
proteins ubiquitination and degradation
role in pathway, 72–74
IKK
catalytic subunit domain organization, 43–44
complex oligomerization, 45
distinct activation pathways, 45
emerging structure of NEMO/IKKγ, 45–46
introduction to, 43
NEMO/IKKγ domain organization, 44–45
introduction to, 35–36
mechanisms that mediate signaling cross talk
(see Regulatory logic of the NF-κB signaling system)
NF-κB dimerization, 37–38
introduction to, 35–36
recognition of κB DNA, 38–40
Rel homology region structure, 36–37
recognition of κB DNA, 38–40
Rel homology region structure, 36–37
Specification of DNA binding activity of NF-κB complexes
concluding remarks and future studies, 30–31
function, 20
IκB proteins and regulation of binding activity, 20–24
integral non-Rel subunits in NF-κB complexes, 28–30
post-translational modifications of Rel proteins, 24–26
regulatory effects of Rel-associating proteins, 27–28
Rel subunit-associating proteins, 20, 26–28
SP thymocytes, 197–199
STAT3 transcription factor
forward genetics and NF-κB and, 261
NF-κB role in inflammation and cancer and, 172–174, 175f, 176–178, 179
NF-κB signaling in ABC DLBCL and, 141
Stromal cells and establishment of secondary lymphoid organs, 204–205

T
TAD (transcription activation domain), 20
TAK1 activation of the JNK branch, 232
T-cells. See Lymphocyte development and function and NF-κB
TCR antigen receptor, 91–93
Thymocytes, DP and SP, 197–199
TIR domains, 227
T lymphocytes. See Lymphocyte development and function and NF-κB
TNFα, 185
TNFR1, 86–88
TNF receptor associated protein with a death domain (TRADD), 86–87

Toll signaling cascade activation
fungal or yeast glucans and, 227
immune response of Drosophila and NF-κB, 224–225
interaction with death domains, 227–228
kinetics of, 228–229
peptidoglycan recognition proteins, 225–227
response to microbial infections, 229–230
TRAF2, 90–91
TRAMP mouse, 176–177
Transcription activation domain (TAD), 20

U
Ubiquitin/proteasome system (UPS), 82–84.
See also Signaling by ubiquitination

V
Validation-based insertional mutagenesis (VBIM), 259
vFLIP, 54

Z
Zeocin (Zeo), 254. See also Forward genetics and regulators of NF-κB