Modulation of NF-κB signalling by microbial pathogens

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Abstract | The nuclear factor-κB (NF-κB) family of transcription factors plays a central part in the host response to infection by microbial pathogens, by orchestrating the innate and acquired host immune responses. The NF-κB proteins are activated by diverse signalling pathways that originate from many different cellular receptors and sensors. Many successful pathogens have acquired sophisticated mechanisms to regulate the NF-κB signalling pathways by deploying subversive proteins or hijacking the host signalling molecules. Here, we describe the mechanisms by which viruses and bacteria micromanage the host NF-κB signalling circuitry to favour the continued survival of the pathogen.

The nuclear factor-κB (NF-κB) family of transcription factors regulates the expression of hundreds of genes that are associated with diverse cellular processes, such as proliferation, differentiation and death, as well as innate and adaptive immune responses. The mammalian NF-κB proteins are members of the Rel domain-containing protein family: RELA (also known as p65), RELB, c-REL, the NF-κB p105 subunit (also known as NF-κB1; which is cleaved into the p50 subunit) and the NF-κB p100 subunit (also known as NF-κB2; which is cleaved into the p52 subunit); these proteins can homodimerize or heterodimerize through their conserved Rel homology domain to mediate gene transcription[1,2]. NF-κB proteins are activated by a variety of diverse extracellular or intracellular stimuli, including microbial pathogens and pathogen-associated molecular patterns (PAMPs)[3]. The NF-κB signalling pathway is an attractive target for exploitation by microbial pathogens in order to modulate host cell events, as activation of NF-κB is such a rapid response. Cytoplasmic NF-κB complexes are transferred to the nucleus within minutes after exposure to a pathogen or PAMPs, even in the absence of *de novo* protein synthesis, and induce the expression of a broad spectrum of antimicrobial pro-inflammatory cellular response genes[4,5]. The central role of these transcription factors in pathogen defence is highlighted by the fact that the NF-κB signalling cascade is probably the most frequently targeted intracellular pathway for subversion by anti-immune modulators that are encoded by a wide spectrum of microbial pathogens[4]. In this Review, we describe some of the recent advances in our understanding of the various mechanisms used by pathogens to modulate NF-κB signalling.

Signalling targets upstream of NF-κB

NF-κB proteins are tightly regulated in both the cytoplasm and the nucleus[6]. Under normal physiological conditions, NF-κB complexes remain inactive in the cytoplasm through a direct interaction with proteins of the inhibitor of NF-κB (IκB) family, including IκBα, IκBβ and IκBε (also known as NF-κBIα, NF-κBIβ and NF-κBIε, respectively); IκB proteins mask the nuclear localization domains in the NF-κB complex, thus retaining the transcription complex in the cytoplasm. In response to diverse stimuli, various cellular immune receptors (such as Toll-like receptors (TLRs)) and cytokine receptors (such as the interleukin-1 receptors (IL-1Rs), TNF receptors (TNFRs) and other TNFR-like receptors) can rapidly activate the NF-κB complex following the appropriate pro-inflammatory stimulation. This activation is mediated by a signalling cascade that uses multiple adaptors (including TNFR-associated factors (TRAFs), myeloid differentiation primary response protein 88 (MYD88) and TIR domain-containing adaptor protein (TIRAP)), as well as intermediate transducing molecules and kinases (including IL-1R-associated kinases (IRAKs), receptor-interacting proteins (RIPs; also known as RIPKs) and NF-κB-inducing kinase (NIK; also known as MAP3K14)), to eventually lead to degradation of the inhibitory protein IκBα, thus liberating the NF-κB complexes for transport to the nucleus, where they undergo further layers of regulation[7] (FIG. 1).

The receptor-mediated signalling events converge on the same core components of the NF-κB activation apparatus: the IκB kinase (IKK) complex, which is composed of two catalytic subunits, IKKα and IKKβ, and a regulatory subunit, NEMO (NF-κB essential modulator;

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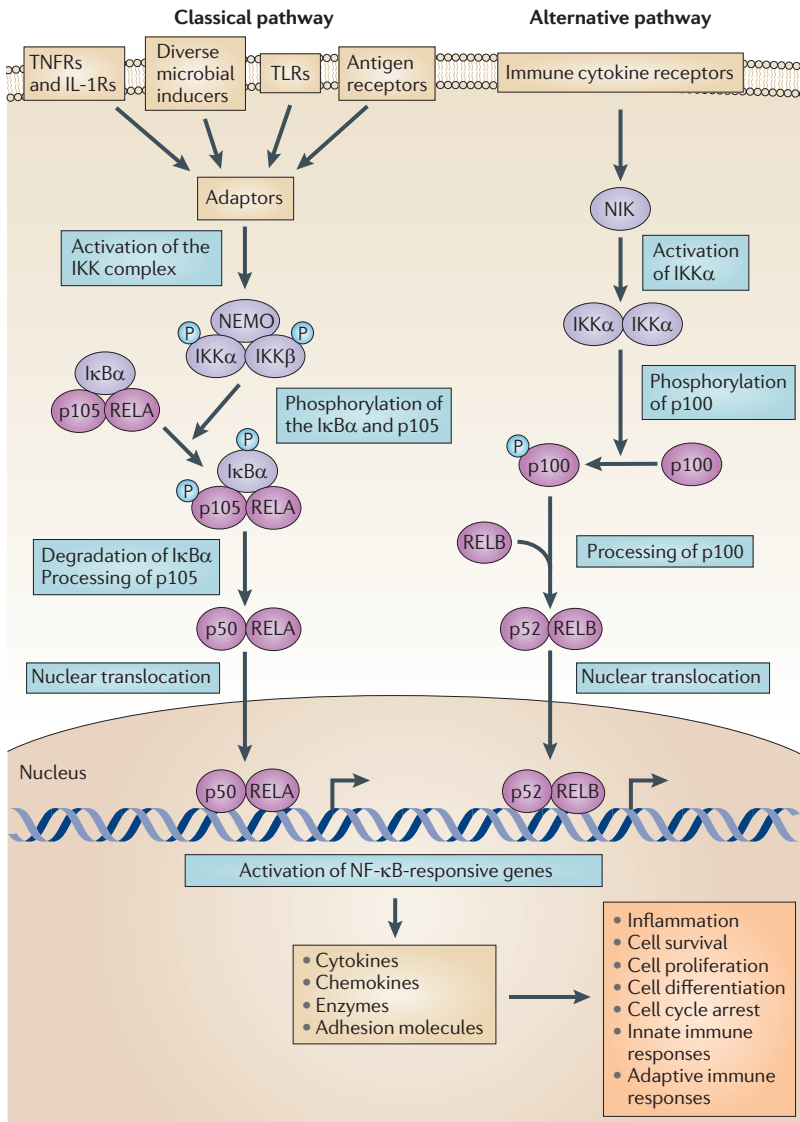
Figure 1 | **The classical and alternative NF-κB signalling pathways use a wide variety of signals to control a diverse set of cellular responses.** Protein levels and activity of signalling molecules can be regulated through post-translational modifications such as phosphorylation, ubiquitylation and acetylation. The activation of nuclear factor-κB (NF-κB) ultimately results in the transcription of genes that encode pro-inflammatory factors and factors that influence cell proliferation. IκBα, NF-κB inhibitor-α (also known as NF-κBIα); IKK, IκB kinase; IL-1R, interleukin-1 receptor; NEMO, NF-κB essential modulator (also known as IKKγ); NIK, NF-κB-inducing kinase (also known as MAP3K14); TLR, Toll-like receptor; TNFR, TNF receptor.

also known as IKKγ)[8,9]. Activation of the IKK complex induces phosphorylation of IκBα, followed by ubiquityl-ation by a specific cullin-RING ubiquitin ligase (CRL) family SCF^{βTRCP} complex, which contains SKP1 (S phase kinase-associated protein 1), cullin 1 and the F-box protein βTRCP as substrate adaptor; this SCF^{βTRCP} complex specifically recognizes and degrades IκBα that is phosphorylated on Ser32 and Ser36. As well as processing IκBα, the ubiquitylation–proteasome path-way is important for the processing of NF-κB subunits p105 and p100 to p50 and p52, respectively[10]. In addi-tion to the IKK complex, members of the IKK family of

kinases — including IKKi (inducible IKK; also known as IKKε) and TBK1 (TANK-binding kinase 1) — can activate the NF-κB pathway in response to microbial infection[11]. TBK1 interacts with TANK, a TRAF-binding protein that activates NF-κB by modulating the func-tion of TRAF2 and that also interacts with IKKi. TBK1 enhances the enzymatic activity of IKKβ by direct phos-phorylation, and thus contributes to NF-κB activation[12]. Because of the essential role of IKKs and IκBα in the activation and regulation of NF-κB signalling, these pro-teins (or their post-translational modifications) are often targeted directly by microbial pathogens to control the host immune responses.

The NF-κB pathway is classified as either classi-cal (canonical) or alternative (non-canonical) on the basis of the IKK subunits that get activated by upstream kinases[13,14] (FIG. 1). In the classical pathway (for exam-ple, triggered by TNFR1 signalling), IKKβ and NEMO become activated by adaptors (such as TRAFs) and then phosphorylate p105 and IκBα to release the prototypi-cal heterodimer p50–RELA. In the alternative pathway (for example, triggered by lymphotoxin-β receptor), IKKα is activated by NIK and then phosphorylates p100, which is subsequently cleaved to form p52. p52 then forms a heterodimer with RELB and translocates to the nucleus. This alternative pathway is triggered by a subset of tumour necrosis factor (TNF) family members, including CD40, lymphotoxin-β, B cell-activating factor (BAFF), receptor activator of NF-κB ligand (RANKL) and TNF-related weak inducer of apoptosis (TWEAK). By contrast, inflammatory cytokines, genotoxic stress, antigens and TLR stimulation tend to activate the clas-sical pathway. Both the classical and alternative pathways are modulated by microbial pathogens, as the two path-ways induce coordinated immune responses following diverse infections.

Outcome of NF-κB activation

Activation of NF-κB is considered to be the central initiating cellular event of host responses to invasion by microbial pathogens. The presence of a functional NF-κB signalling cascade in the horseshoe crab, a species that is known as a 'living fossil', suggests that the pro-teins involved are the evolutionarily conserved immune defence molecules[15], and highlights the central role of NF-κB in upregulating the expression of genes encod-ing chemokines, cytokines, adhesion molecules (such as intercellular adhesion molecule 1 (ICAM1)), enzymes that produce secondary inflammatory mediators, and inhibi-tors of apoptosis. These molecules are key components of the innate immune response to invading microorgan-isms and are required for the migration of inflammatory and phagocytic cells to the site of infection, where NF-κB has been activated. The activated phagocytic cells kill, ingest and degrade microbial pathogens and eventually present the antigens to T cells after they re-migrate to secondary lymphoid organs. The secreted cytokines, including TNF and IL-1β, also start a feedback loop for a second phase of NF-κB activation that continues the induction of robust immune responses. The cellular pattern recognition receptors (PRRs) such as TLRs,

Table 1 | **Role of individual NF-κB members in the response to microbial pathogens**

NF-κB protein*	Expression in tissue or cells	Functions	Role in the immune response
p105 (NF-κB1)	Ubiquitous	• Innate and adaptive immunity • Proliferation of B cells and T cells	• Protection against pathogens such as *Listeria monocytogenes*, *Streptococcus pneumoniae*, *Leishmania major* and *Trichuris muris*, and against *Escherichia coli*-induced pneumonia
p100 (NF-κB2)	Highest levels in haematopoietic tissues	• Development of secondary lymphoid structures • B cell maturation • Normal T cell and antigen-presenting-cell function	• Major role in the T cell-mediated immune response against lymphocytic choriomeningitis virus , veisicular stomatitus virus and the parasite *Toxoplasma gondii* • Protection against *L. monocytogenes* and *T. muris*
RELA (p65)	Ubiquitous	• Essential for the expression of pro-inflammatory cytokines such as TNF and IL-6 • Transactivation of microRNA genes • Deletion causes embryonic lethality in mice	• Crucial for early IFNβ expression and resistance to replication of RNA viruses • Induction of the epithelial cell immune response against *Cryptosporidium parvum* • Induction of the pulmonary innate immune response against pathogens • Protection against *L. major* infection • Cell-specific protection against intracellular parasites
RELB	Highest levels in the thymus, lymph nodes and Peyer's patches	• Formation of secondary lymphoid structures • Regulation of immune cell development • Local immunity	• Protection against influenzavirus A • Innate and adaptive immunity to *T. gondii*, and to *L. monocytogenes* and other bacteria
c-REL	Highest levels in lymphocytes, monocytes and erythrocytes, but also expressed in the epidermis	• Essential for the normal function of B cells, T cells, macrophages and dendritic cells	• Increased susceptibility to *L. major* and *T. gondii*

IFNβ, interferon-β; IL-6, interleukin-6; TNF, tumour necrosis factor. *Alternative names are given in brackets.

RIG-I-like receptors (RLRs) and NOD-like receptors (NLRs), which all sense microbial pathogens and PAMPs, use distinct signalling pathways that eventually converge to activate NF-κB[16], leading to the production of inflammatory mediators.

The initiation of innate immune events is important in host resistance to many different types of pathogens prior to the activation of adaptive immune responses, which are also mediated by NF-κB. In addition, NF-κB plays a part in the suppression of apoptosis induced by bacterial components such as lipopolysaccharide. The importance of NF-κB in protection against pathogens is also supported by the fact that NF-κB complexes are abundantly expressed in myeloid cells, which are mostly dedicated to innate immunity. The importance of members of the NF-κB family in both the immune response against pathogens and the development and function of other immune cells has been demonstrated by sequentially knocking down the expression levels of these proteins[17]. Mice lacking different NF-κB family members become susceptible to various viral, bacterial and parasitic infections (TABLE 1). In addition, IKK and IKK-related kinases also play an important part in regulating antimicrobial responses[11,18]. As a result, pathogens have developed various mechanisms to alter the activation of NF-κB. Here, we focus on the mechanisms by which viruses and bacteria modulate NF-κB activation.

Modulation of NF-κB by viruses
NF-κB-dependent genes are important for regulating cellular processes such as apoptosis, inflammation and immune responses, and so many viruses have acquired diverse strategies to regulate NF-κB signalling[19]. Some viruses regulate NF-κB in a biphasic manner to optimize viral replication in the infected cells during different phases of the viral life cycle. For example, some viruses (such as the gammaherpesviruses Kaposi's sarcoma-associated herpesvirus (KSHV) and Epstein–Barr virus (EBV)) activate NF-κB during latency, whereas they tend to suppress NF-κB signalling during the lytic cycle[20]. By contrast, viruses such as Sindbis virus, dengue virus and reoviruses activate NF-κB to facilitate the induction of apoptosis, which increases viral spread via phagocytic myeloid cells. However, more often, viruses inhibit NF-κB primarily to dampen host inflammatory and immune responses, often by encoding multiple proteins that target the pathways at multiple levels[21–23]. Larger DNA viruses, such as poxviruses, frequently deploy several proteins to regulate NF-κB in cultured cells in a seemingly redundant manner, whereas smaller RNA viruses may encode only a single protein that has multiple roles in regulating NF-κB. TABLES 2,3 list some of the NF-κB modulators that are derived from viruses.

Activation of NF-κB by viruses
Some viruses have evolved mechanisms to pro-actively stimulate NF-κB activation[19,21,24]. Viruses such as HIV-1, human T-lymphotrophic virus 1 (HTLV-1), hepatitis B virus (HBV), hepatitis C virus (HCV), rotaviruses, influenza viruses and respiratory syncytial viruses (RSVs) activate NF-κB to promote viral replication and to pre-empt virus-induced apoptosis (FIG. 2). These viral genomes all possess strategic gene promoters with NF-κB-binding sites and, thus, activated NF-κB is crucial for viral gene

Table 2 | **Activation of the NF-κB signalling pathway by viral proteins**

Virus	Viral protein	Mechanism of modulation	Host targets	Refs
African swine fever virus	A224L (an IAP)	Activates NF-κB	TRAF2	61
Bovine foamy virus	BTas	Activates the IKK complex for the activation of NF-κB	IKKα and IKKβ	40
Epstein–Barr virus	gp350	Activates NF-κB	CD21 and TLR2	41
	LMP1 (through CTAR1 and CTAR2)	Activates NIK and IKKα (CTAR1), and activates IKKβ and NEMO (CTAR2)	TRAF2 and TRAF3 (CTAR1 targets), and TRAF6, TRADD and RIP1 (CTAR2 targets)	47,154
Hepatitis B virus	HBx	Enhances the transcriptional activity of NF-κB	RELA	59
Hepatitis C virus	Core and NS3	Activates NF-κB using TNFR1 and TLRs	Unknown	60
Herpes simplex viruses	ICP4 and ICP27	Phosphorylates RELA	Unknown	64
	UL37	Activates NF-κB	TRAF6	63
	Glycoprotein D	Activates NF-κB using HVEA	Unknown	62
Herpesvirus saimiri	StpA11 and StpC	Activate TRAF2 and TRAF6 for the activation of NF-κB	TRAF2 and TRAF6	52,53
Herpesvirus ateles	Tio	Activates the IKK complex using TRAF6	TRAF6	54
HIV-1	Tat, Vpr and Nef	Activate NF-κB	Unknown	30,32,33
Human T-lymphotrophic virus 1	Tax1	Activates the IKK complex for the activation of NF-κB	NEMO	34
Kaposi's sarcoma-associated herpesvirus	vFLIP	Activates the NF-κB pathway	NEMO	48
	K15	Induces TRAF2-dependent NF-κB activation	TRAF2	155
Murine gammaherpesvirus 68	RTA	Activates RTA using the activated IKK complex, to trigger lytic replication	Unknown	55
Respiratory syncytial viruses	Unknown	Activates both the classical and alternative NF-κB pathways	Unknown	26
	M2-1	Induces nuclear translocation of RELA	RELA	29
	F protein	Activates NF-κB	Unknown	28

CTAR, carboxy-terminal activation region; gp350, glycoprotein 350; HVEA, herpesvirus entry mediator A; IAP, inhibitor of apoptosis; IKK, IκB kinase; LMP1, latent membrane protein 1; NEMO, NF-κB essential modulator (also known as IKKγ); NF-κB, nuclear factor-κB; NIK, NF-κB-inducing kinase (also known as MAP3K14); RIP1, receptor-interacting protein 1 (also known as RIPK1); RTA, replication and transciption activator; Stp, *Saimiri* transformation-associated protein; TLR, Toll-like receptor; TNFR1, TNF receptor 1; TRAF, TNFR-associated factor.

expression, replication and spread. Infections with RSVs, the causative agents of acute respiratory diseases such as bronchiolitis and pneumonia, are associated with excessive inflammation caused by the release of NF-κB-regulated pro-inflammatory cytokines and chemokines by airway epithelial cells[25]. This occurs because the infection induces a persistent activation of both classical and alternative NF-κB pathways[25]. The classical NF-κB pathway is activated by the host superoxide-generating enzyme NOX2-containing NADPH oxidase, which phosphorylates IκBα and RELA in airway epithelial cells via RIG-I (also known as DDX58), TRAF6 and IKKβ[26]. However, the alternative NF-κB pathway is activated by the kinases NIK and IKKα, leading to the nuclear translocation of p52–RELB[27]. This suggests that the redox modification mediated by RSVs might have multiple upstream targets that then lead to the activation of both NF-κB pathways. Two of the RSV proteins, fusion glycoprotein F and M2-1, have been shown to activate NF-κB-mediated cytokine induction in monocytic cells[28,29].

The HIV-1 proteins Tat, Vpr and Nef activate the NF-κB pathway by exploiting multiple mechanisms. Tat, a transcriptional activator, induces transcription of cytokines such as IL-10, IL-6 and TNF in monocytes or macrophages; these cytokines promote HIV-1 replication at early stages of infection[30]. Tat also increases the DNA-binding activity of NF-κB complexes by promoting acetylation of p50 via the CREBBP–p300 complex[31]. However, recent studies have demonstrated that Tat also can inhibit NF-κB activation, as discussed below. Vpr, a viral late protein, and Nef, a viral early protein, enhance virion infectivity and increase viral replication. These viral proteins can activate the NF-κB pathway when added exogenously and stimulate the transcription of HIV-1 genes in promonocytic cells and primary macrophages[32,33].

Many oncogenic viruses activate NF-κB to facilitate transformation of infected cells. In most cases, virus-encoded oncoproteins are directly involved in this activation process. Among the oncoproteins identified so far, the mechanisms of persistent NF-κB activation by Tax1 from HTLV-1 and Tax2 from HTLV-2 during T cell leukaemia are well established[34,35]. Tax1 primarily activates the IKK complex by directly interacting with the non-catalytic subunit, NEMO[36]. In addition, Tax1 modulates the activity of kinases that activate the IKK

complex, such as MEK kinase 1 (MEKK1; also known as MAP3K1), NIK and TGFβ-activated kinase 1 (TAK1; also known as MAP3K7) (REF. 37). Recently, it was demonstrated that Tax1 sequesters the activated IKK complex in lipid rafts through its interaction with NEMO, providing an optimal microenvironment for kinase activation and thus allowing constitutive activation of the NF-κB pathway[38]. Unlike Tax2, Tax1 also modulates the alternative NF-κB pathway by upregulating IKKα in T cells, thereby inducing the processing of p100 (REF. 39). Another member of the *Retroviridae*, bovine foamy virus (BFV), activates the classical and alternative NF-κB pathways using the viral transactivator BTas, which interacts with IKKα and IKKβ and persistently activates NF-κB[40].

EBV, a human gammaherpesvirus that causes multiple types of cancer, is a strong inducer of NF-κB activation. During the early phase of infection, the binding of EBV glycoprotein gp350 (or its alternative isoform, gp250) to the cellular receptors CD21 (also known as CR2) and TLR2 causes persistent activation of the classical NF-κB pathway[41]. At later stages of EBV infection, B cells are immortalized, in part owing to the activation of NF-κB by viral latent membrane protein 1 (LMP1), which mimics a constitutively activated TNFR[42]. LMP1 activates both the alternative and the classical NF-κB pathways using its carboxy-terminal activation region 1 (CTAR1) and CTAR2, respectively[43,44]. CTAR2 interacts with TRAF6, TRADD and RIP1, which activate IKKβ and NEMO[45], thus activating the classical NF-κB pathway, whereas CTAR1 interacts with TRAF2 and TRAF3, which activate NIK and IKKα, thus activating the alternative pathway[46]; in fact, the identification of these signalling molecules using LMP1 led to the identification of the alternative NF-κB pathway. However, recent studies suggest that additional mechanisms are involved in LMP1-mediated activation of NF-κB[47].

Similarly to EBV, KSHV, another human oncogenic gammaherpesvirus, establishes latent infection by activating NF-κB. The K13 protein, known as vFLIP, is one of the proteins that regulates the latency of KSHV. vFLIP interacts with NEMO in the IKK complex to activate classical NF-κB signalling[48]. In addition, vFLIP blocks KSHV lytic replication by antagonizing the KSHV lytic genes, including RTA (replication and transcription activator) and vGPCR, by binding to their promoters[49]. Moreover, activation of NF-κB by vFLIP suppresses the host AP1 pathway, which is essential for KSHV lytic replication[50], and upregulates the expression of miR-146a, which suppresses the expression of CXCR4, a CXC-chemokine receptor for stromal-derived factor 1 (SDF1; also known as CXCL12); the suppression of CXCR4 may enhance the spread of KSHV-infected endothelial cells[51]. Thus, vFLIP has multiple roles in the regulation of cellular gene expression in order to maintain the fine balance between latency and lytic replication.

Some gammaherpesviruses that cause lymphoma in New World primates harbour several oncoproteins that activate NF-κB and transform human T cells. The oncoproteins *Saimiri* transformation-associated protein C (StpC) and StpA11 of herpesvirus saimiri induce TRAF2

and TRAF6 and activate both NF-κB pathways[52–54]. Tio, an oncoprotein from herpesvirus ateles (a virus that causes T cell malignancies in primates), also activates both NF-κB pathways using TRAF6 to activate the IKK complex[54].

Some viruses modulate the kinases associated with the NF-κB pathway to promote transcription of their own genes. Murine gammaherpesvirus 68 (MuHV-68), which establishes long-term latent infection in the mouse spleen, initiates lytic replication using its RTA protein (encoded by ORF50) in latently infected cells. MuHV-68 activates IKKβ in a MAVS (mitochondrial antiviral-signalling protein)-dependent manner through phosphorylation of RTA, to promote the lytic replication cycle[55], although a previous study reported that the NF-κB pathway is dispensable for MuHV-68 lytic replication[56]. HBV, which causes hepatocellular carcinoma (the most common form of liver cancer in adults), can persistently activate NF-κB using the transcriptional transactivator protein HBx (also known as protein X)[57]. Several mechanisms have been proposed for the induction of NF-κB target genes by HBx, including direct targeting of the NF-κB components and, as an indirect route, activation of cellular kinases that induce transcription of cellular genes containing κB elements (sequences to which NF-κB binds) in their promoters[58]. A complex consisting of HBx and RELA can activate the gene encoding metastasis-associated protein 1 (MTA1), which is a master chromatin modifier, and can regulate cancer progression, indicating the importance of NF-κB upregulation[59]. HCV, which causes acute and chronic hepatitis, also persistently activates NF-κB, leading to liver cirrhosis and hepatocellular carcinoma. The core and NS3 proteins of HCV activate NF-κB by activating TNFR1 and TLRs[60]. Apart from using oncoproteins, viruses use homologues of cellular anti-apoptotic proteins as a survival strategy; for example, the African swine fever virus (ASFV) inhibitor of apoptosis (IAP), A224L, can activate NF-κB using TRAF2 and IKKβ, and can thus prevent apoptosis[61].

Other viruses, such as herpes simplex virus (HSV) spp. and HIV-1, activate NF-κB in a biphasic manner for viral infection and replication. The early phase of NF-κB activation happens independently of viral replication, whereas the second phase requires viral gene expression. In the case of HSV, the early phase of NF-κB activation is mediated by envelope glycoprotein D and involves the host protein herpesvirus entry mediator A (HVEA)[62] and the viral tegument protein UL37, which binds to TRAF6 during entry[63]. After entry, the HSV immediate–early proteins ICP4 and ICP27 start the second phase of NF-κB activation in a TLR-independent manner[64].

Suppression of receptors and NF-κB adaptors

Viruses suppress NF-κB activation to dampen the host immune responses and, in some cases, to maintain latency. Multiple virus-encoded proteins have been identified that inhibit NF-κB activation by targeting the inducer ligands, receptors or sensors that activate innate responses, the downstream adaptor molecules in

Table 3 | **Inhibition of the NF-κB signalling pathway by viral proteins**

Virus	Viral factor	Mechanisms of modulation	Host targets	Refs
Adenoviruses	E3 10.4 kDa protein and E3 14.5 kDa protein	Inhibit activation of the IKK complex by TNF	Unknown	156
African swine fever virus	A238L (a viral homologue of IκBα)	Interacts with RELA and downregulates NF-κB	RELA	88
Borna disease virus	P protein	Inhibits the kinase activity of TBK1	TBK1	157
Bovine viral diarrhoea virus	NS5A	Inhibits TNF and poly I:C induced NF-κB activation	NIBP	70
Classical swine fever virus	Npro	Interacts with IκBα and inhibits NF-κB function	IκBα	90
Cowpox virus	CP77	Interacts with RELA and blocks TNF-induced activation of NF-κB	RELA	96
	ORF006	Inhibits NF-κB by interaction with p105	p105	158
Coxsackieviruses	Protease 3C	Cleaves IκBα and inhibits NF-κB function	IκBα	89
Epstein–Barr virus	EBNA1	Inhibits phosphorylation of the IKK complex	Unknown	74
Hantaan virus	N protein	Interacts with importin-α and blocks nuclear translocation of NF-κB	Importin-α	99
Hepatitis C virus	NS3–NS4A	Cleaves TRIF and MAVS, and blocks activation of NF-κB	TRIF and MAVS	67,68
	NS5A	Inhibits TRAF2- and TLR-mediated activation of NF-κB	TRAF2 and MYD88	159
	NS5B	Inhibits TRAF2- and IKK-induced activation of NF-κB	IKKα	71
	Core	Inhibits IKK-mediated activation of NF-κB	IKKβ	72
Herpes simplex viruses	ICP27	Stabilizes IκBα by blocking its phosphorylation and ubiquitylation	IκBα	66
	ICP0	Reduces TLR2-mediated activation of NF-κB	MYD88	65
Human adenovirus 12	E1A	Prevents the phosphorylation of RELA and p50 by PKAc	RELA and p50	100,101
Human cytomegalovirus	M45	Binds to RIP1 and inhibits NF-κB signalling	RIP1	160
	IE86	Blocks binding of NF-κB to genes	Unknown	102
	Late gene product	Inhibits TNF- and IL-1β-mediated activation of the IKK complex	Unknown	103,104
HIV-1	Vpu	Blocks proteasome-dependent degradation of IκBα	βTRCP	92
	Tat (extracellular)	Inhibits lipopolysaccharide-induced activation of NF-κB	Unknown	94
Human papillomaviruses	E7	Inhibits activity of the IKK complex and phosphorylation of IκBα	IKK complex	161

these pathways, or the kinases that activate the NF-κB pathways (FIG. 3). As mentioned above, some viruses (for example, HSV spp.), maintain a delicate balance between activation and suppression of NF-κB in order to maintain long-term persistence. Activation of NF-κB is required to start the infection and viral replication; however, NF-κB signalling also promotes the expression of inflammatory cytokines, and several viral proteins — the immediate–early proteins of HSV, for example — block NF-κB activation at a later stage to ensure a smooth progression of infection. The HSV immediate–early protein ICP0, an E3 ubiquitin ligase, reduces TLR2-mediated inflammatory responses against the virus by inducing degradation of the adaptor protein MYD88 (REF. 65), whereas ICP27, another immediate–early protein, represses NF-κB function by stabilizing IκBα through blockade of its phosphorylation and ubiquitylation[66]. This suggests that bifunctional viral proteins such as ICP27, which activate as well as suppress NF-κB, have complex regulatory duties that function to maintain a delicate balance between advantageous and deleterious host responses.

HCV establishes persistent intra-hepatic infection using multiple proteins to either activate NF-κB and stimulate viral replication, or inhibit NF-κB and suppress the expression of its target host defence genes. The NS3–NS4A protease of HCV causes proteolysis of TRIF (TIR domain-containing adaptor inducing IFNβ; also known as TICAM1), an adaptor protein used by TLR3 and MAVS, and this proteolysis inhibits NF-κB and interferon regulatory factor 3 (IRF3)[67,68]. Another HCV protein, phosphoprotein NS5A, interacts with MYD88 and TRAF2 in macrophage cell lines and inhibits the TLR2-, TLR4-, TLR7- and TLR9-mediated activation of NF-κB[69]. However, NS5A from bovine viral diarrhoea virus, a member of the *Flaviviridae* that is closely related to HCV, modulates host immune responses by interaction with NIK- and IKKβ-binding protein (NIBP; also known as TRAPPC9) in LB9.K cells[70], suggesting that related viral immunomodulatory molecules might have multiple cellular targets to regulate NF-κB in different ways, depending on the host. Among the other HCV proteins, NS5B and the core proteins interact with IKKs and inhibit activation of the IKK complex[71,72].

Table 3 (cont.) | **Inhibition of the NF-κB signalling pathway by viral proteins**

Virus	Viral factor	Mechanisms of modulation	Host targets	Refs
Kaposi's sarcoma-associated virus	MicroRNAs	Regulates IκBα	Unknown	109
Molluscum contagiosum virus	MC159	Prevents the degradation of IκBβ	TRAF2	84
	MC160	Reduces the kinase activity of the IKK complex, reduces the activation of TRAF2, NIK and MYD88, and inhibits pro-caspase 8-mediated activation of NF-κB	HSP90 and pro-caspase 8	86,162
Myxoma virus	M013	Inhibits NF-κB by interaction with p105	p105	98
Parapoxviruses	ORF024	Inhibits phosphorylation of the IKK complex	Unknown	87
Poliovirus	Protease 3C	Cleaves RELA	RELA	95
Reovirus strain T3 Abney	S1 gene segment	Inhibits NF-κB and induces apoptosis	Unknown	107
Rotaviruses	NSP1	Degrades βTRCP and inactivates the E3 ligase complex to stabilize IκBα	βTRCP	93
SARS-coronavirus	M protein	Inhibits TNF-induced activation of NF-κB	IKKβ	73
Vaccinia virus	A46R	Sequesters multiple TIR-domain containing adaptor molecules	MYD88, MAL, TRIF and TRAM1	77
	A52R	Inhibits IRAK2- and TRAF6-dependent activation of NF-κB via TLRs	IRAK2 and TRAF6	76
	B14	Inhibits phosphorylation of IκBα	IKKβ	80
	E3L	Inhibits NF-κB	Unknown	83
	K1L	Inhibits degradation of IκBα	Unknown	82,163
	M2L	Inhibits ERK2 phosphorylation, and activation of NF-κB	Unknown	164
	N1L	Inhibits TRAF6-induced activation of NF-κB	TBK1	79
Varicella-zoster virus	Unknown	Inhibits NF-κB	Unknown	165
Variola virus	G1R	Inhibits NF-κB by interacting with p105	p105	97
West Nile virus	NS1	Blocks TLR3-mediated activation of NF-κB and IRF3	Unknown	108

ERK2, extracellular signal-regulated kinase 2 (also known as MAPK1); HSP90, heat shock protein 90; IκB, NF-κB inhibitor (also known as NF-κBI); IKK, IκB kinase; IL-1β, interleukin-1β; IRAK2, IL-1R-associated kinase 2; IRF3, interferon regulatory factor 3; MAL, myelin and lymphocyte protein; MAVS, mitochondrial antiviral-signalling protein; M protein, membrane protein; MYD88, myeloid differentiation primary response protein 88; NF-κB, nuclear factor-κB; NIBP, NIK- and IKKβ-binding protein (also known as TRAPPC9); NIK, NF-κB-inducing kinase (also known as MAP3K14); Npro, amino-terminal protease; N protein, nucleocapsid protein; PKAc, catalytic subunit of protein kinase A enzymes; poly I:C, polyinosinic:polycytidylic acid; P protein, phosphor protein; RIP1, receptor-interacting protein 1 (also known as RIPK1); TBK1, TANK-binding kinase 1; TLR, Toll-like receptor; TNF, tumour necrosis factor; TRAF, TNFR-associated factor; TRAM1, thyroid hormone receptor activator molecule 1 (also known as NCOA3); TRIF, TIR domain-containing adaptor inducing IFNβ (also known as TICAM1).

Viruses frequently target IKKs to mediate NF-κB inhibition, as diverse signalling pathways converge on these kinases. SARS coronavirus (SARS-CoV), which causes life-threatening atypical pneumonia, modulates signalling through IKK and subsequently interrupts NF-κB activation via viral membrane (M) protein[73]. M protein physically interacts with IKKβ, thereby suppressing TNF-induced activation of NF-κB and the subsequent expression of cyclooxygenase 2, an enzyme that is known to have an antiviral function[73]. In a similar manner, the EBV protein EBNA1 inhibits phosphorylation of IKKα–IKKβ to suppress the classical NF-κB pathway in carcinoma cells[74].

Members of the *Poxviridae*, a large family of DNA viruses, modulate NF-κB function through multiple proteins that target diverse NF-κB signalling molecules, including the IKK complex[75]. Vaccinia virus (VACV), the prototypical orthopoxvirus, encodes a remarkable NF-κB tool kit that includes multiple inhibitory proteins — such as A46R, A52R, B14, K1L M2L and N1L — all of which block activation of the IKK complex and inhibit degradation of IκBα, albeit using diverse mechanisms[76–79]. Among

these, B14 inhibits NF-κB by directly targeting IKKβ of the IKK complex[80]. Interestingly, the B14 counterpart in the attenuated virus modified virus Ankara (MVA), encoded by ORF183 and lacking six amino acids that are present in α-helix 6 of B14, cannot inhibit NF-κB activation[81]; as a result, MVA infection activates NF-κB, whereas VACV infection inhibits NF-κB very quickly after activating it. The VACV proteins E3L, K1L and N1L use multiple targets, as they all block both NF-κB and antiviral pathways[82,83]. Molluscum contagiosum virus (MOCV) protein MC159 is a vFLIP that inhibits FAS-mediated apoptosis and TNF-induced late activation of NF-κB. However, transgenic expression of this protein in mice instead enhanced NF-κB-mediated immune responses[84,85]. Another MOCV protein, MC160, inhibits NF-κB activation using multiple mechanisms[86]. ORF024 of the parapoxviruses encodes a unique protein that modulates the NF-κB induction pathway. In the absence of this gene, the virus replicates normally in primary OFTu cells, but induces higher expression of NF-κB-regulated chemokines and other pro-inflammatory host genes than the wild-type virus[87]. The ORF024 protein
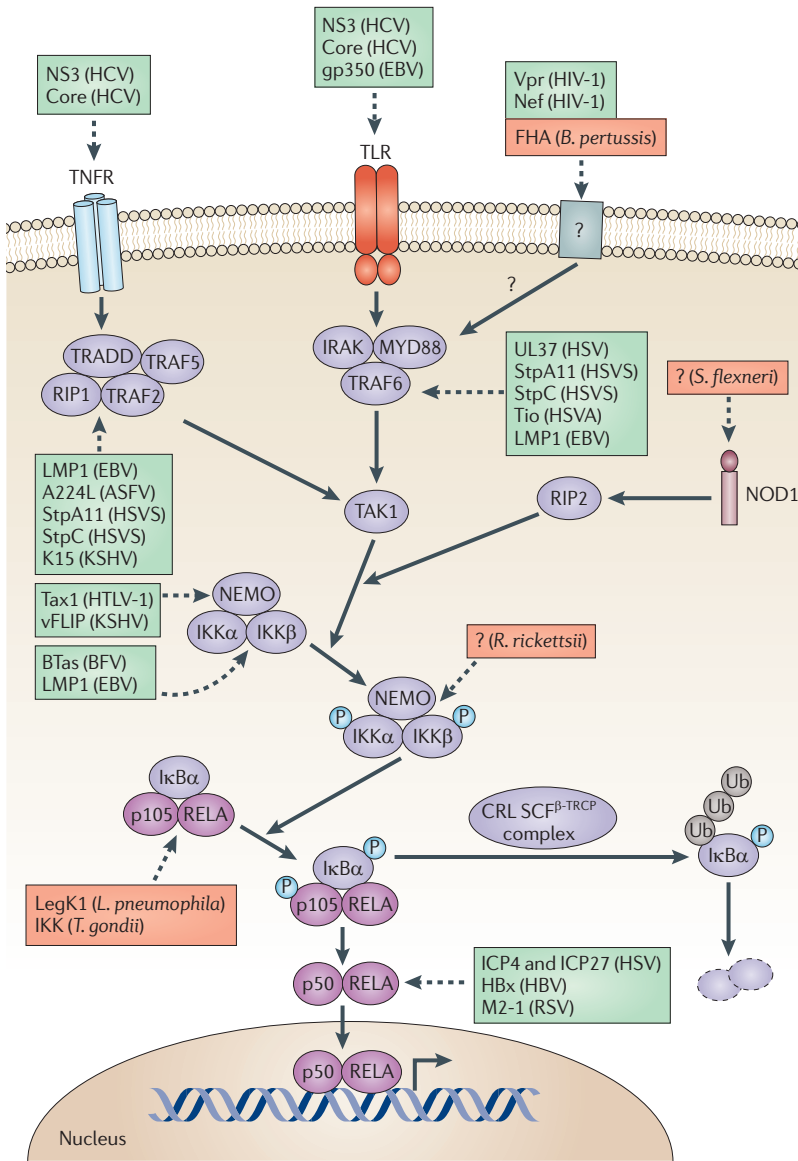
Figure 2 | **Activation of NF-κB signalling pathways by microbial pathogens.** A diagrammatic representation of the nuclear factor-κB (NF-κB) pathways that are induced by various receptors, microbial pathogens and pathogen-derived proteins. See main text for details. Virus-encoded proteins are in green boxes, and bacterium- and parasite-encoded proteins are in orange boxes. ASFV, African swine fever virus; BFV, bovine foamy virus; *B. pertussis*, *Bordetella pertussis*; CRL, cullin-RING ubiquitin ligase; EBV, Epstein–Barr virus; FHA, filamentous haemagglutinin; gp350, glycoprotein 350; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; HSVA, herpesvirus ateles; HSVS, herpesvirus saimiri; HTLV-1, human T cell leukaemia virus 1; IκBα, NF-κB inhibitor-α (also known as NF-κBIα); IKK, IκB kinase; IRAK, IL-1R-associated kinase; KSHV, Kaposi's sarcoma-associated herpesvirus; LMP1, latent membrane protein 1; *L. pneumophila*, *Legionalla pneumophila*; MYD 88, myeloid differentiation primary response protein 88; NEMO, NF-κB essential modulator (also known as IKKγ); RIP1, receptor-interacting protein 1 (also known as RIPK1); *R. rickettsii*, *Rickettsia rickettsii*; RSV, respiratory syncytial virus; SCF^{βTRCP}, SKP1, cullin 1 and F-box protein βTRCP; *S. flexneri*, *Shigella flexneri*; Stp, *Saimiri* transformation-associated protein; TAK1, TGFβ-activated kinase 1; *T. gondii*, *Toxoplama gondii*; TLR, Toll-like receptor; TNFR, TNF receptor; TRAF, TNFR-associated factor; Ub, ubiquitin.

expressed by itself decreased phosphorylation of IKK and the downstream activation of the NF-κB pathway, suggesting that this viral protein targets upstream kinases that phosphorylate IKK.

Targeting NF-κB and its cellular inhibitors

Viruses can also regulate the function of NF-κB complexes through proteins that either directly interact with the nuclear factors themselves or control the cellular regulators of these factors. This indirect regulation includes inhibition of IκBα degradation, of dimer complex formation among the NF-κB members, of nuclear translocation or of binding to the targeted cellular gene promoters (FIG. 3). Some viruses encode homologues of cellular NF-κB signalling molecules, and these homologues act as dominant negatives of the cellular proteins. For example, ASFV encodes a homologue of IκBα, A238L, which interacts with cellular RELA and thus suppresses the activation of NF-κB complexes[88]. Furthermore, virus-encoded proteases can cleave IκBα and NF-κB subunits to render them non-functional. The human coxsackievirus B3 protease 3C cleaves IκBα to create an amino-terminal fragment that interacts with RELA and translocates with it to the nucleus, where the complex therefore remains inactive[89]. This blockade of NF-κB activation induces apoptosis of infected cells. Another protease, amino-terminal protease (Npro) from classical swine fever virus, also interacts with IκBα and modulates NF-κB function[90].

Some viral proteins block NF-κB activation by preventing the degradation of IκBα. For example, HIV-1 modulates IκBα function in order to maintain long-term infection. The Vpu protein of HIV-1 blocks proteasome-dependent degradation of IκBα by binding to βTRCP in the E3 ubiquitin ligase complex that is involved in the regulated degradation of IκBα[91,92]. Thus, HIV-1 induces apoptosis of infected T cells by reducing the expression of NF-κB-dependent cellular anti-apoptotic factors such as BCL-X$_L$ and TRAF1 The rotaviral non-structural protein NSP1 induces proteasome-dependent degradation of βTRCP to stabilize IκBα and inhibit NF-κB[93]. Another HIV-1 protein, Tat, also inhibits degradation of IκBα and nuclear translocation of RELA [94]. This modulation of immune responses by Tat at late stages may provide a favourable environment for both HIV-1 and other opportunistic microorganisms. However, at early stages of infection, Tat instead activates NF-κB.

Some virus-encoded proteases can cleave NF-κB itself. For example, the poliovirus protease 3C cleaves RELA at the later stages of infection and thereby suppresses NF-κB activation[95]. Other virus-encoded proteins instead regulate the nuclear translocation of RELA. The cowpox virus ankyrin repeat domain-containing host range protein CP77 directly targets RELA and blocks its translocation to the nucleus to inhibit NF-κB[96]. Several other poxviral proteins suppress NF-κB function by preventing the degradation of the precursor molecule p105 (REFS 75,97,98). Hantaan virus, a member of the *Bunyaviridae*, uses its nucleocapsid (N) protein to block the nuclear translocation of RELA by interacting with importin-α proteins, which are nuclear transport proteins used by the NF-κB proteins to translocate to the nucleus[99]. The E1A protein from human adenovirus 12 associates with RELA and prevents PKAc, the catalytic subunit of protein kinase A enzymes, from phosphorylating RELA at Ser276; this then downregulates
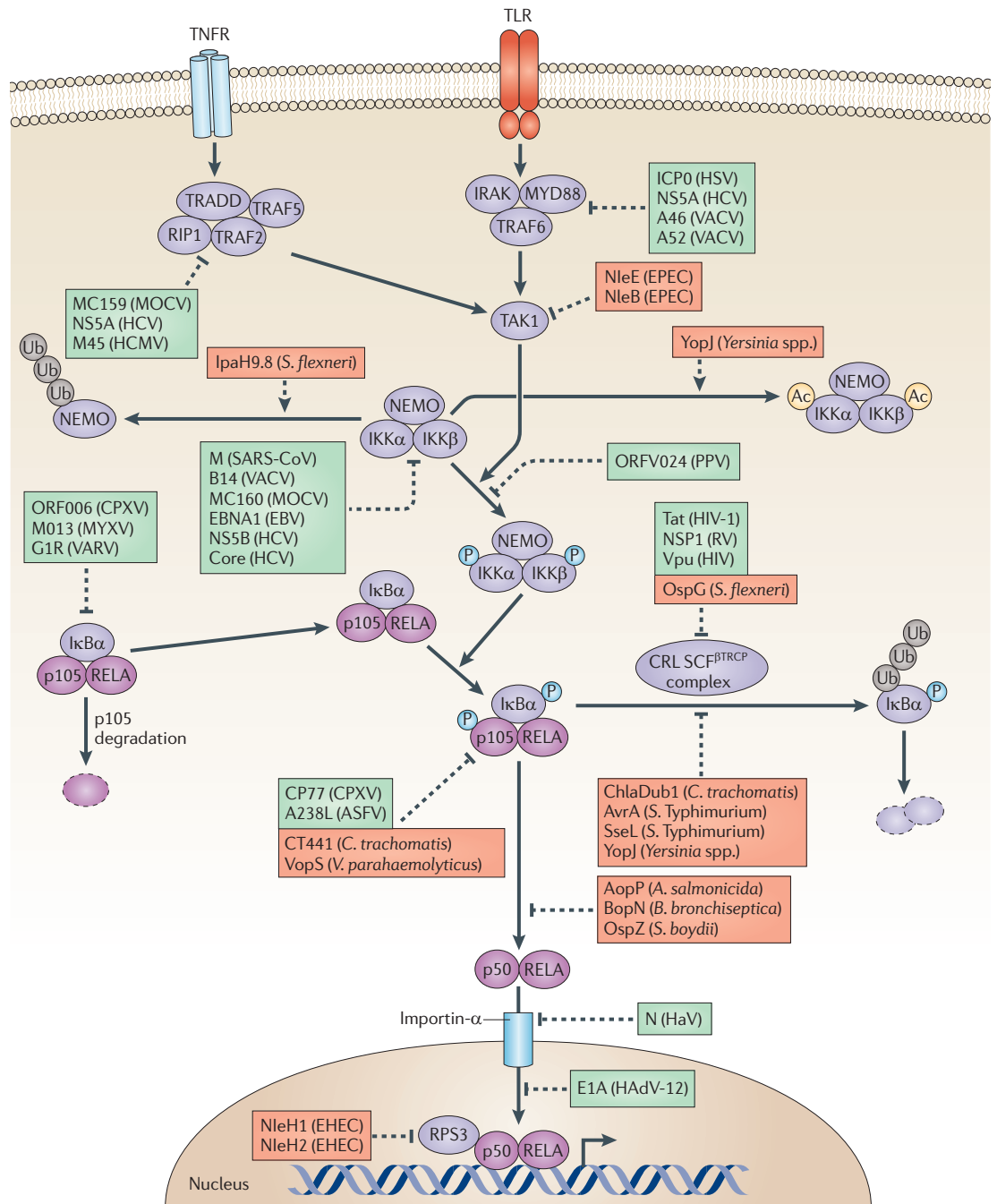
Figure 3 | **Inhibition of NF-κB signalling pathways by microbial pathogens.** A diagrammatic representation of the nuclear factor-κB (NF-κB) pathways, showing the signalling molecules that are targeted by microbial pathogen-derived proteins for inhibition of the NF-κB pathways. See main text for details. Virus-encoded proteins are in green boxes, and bacterium-encoded proteins are in orange boxes. Ac, acetyl group; *A. salmonicida, Aeromonas salmonicida*; ASFV, African swine fever virus; *B. bronchiseptica, Bordetella bronchiseptica*; ChlaDub1, *Chlamydia* deubiquitylase and deneddylase; CPXV, cowpox virus; CRL, cullin-RING ubiquitin ligase; *C. trachomatis, Chlamydia trachomatis*; EBV, Epstein–Barr virus; EHEC, enterohaemorrhagic *Escherichia coli*; EPEC, enteropathogenic *E. coli*; HAdV-12, human adenovirus 12; HaV, hantaan virus; HCMV, human cytomegalovirus; HCV, hepatitis C virus; HSV, herpes simplex virus; IκBα, NF-κB inhibitor-α (also known as NF-κBIα); IKK, IκB kinase; IRAK, IL-1R-associated kinase; M, membrane protein; MOCV, molluscum contagiosum virus; MYD88, myeloid differentiation primary response protein 88; MYXV, myxoma virus; N, nucleocapsid protein; NEMO, NF-κB essential modulator (also known as IKKγ); PPV, parapoxvirus; RIP1, receptor-interacting protein 1 (also known as RIPK1); RPS3, 40S ribosomal protein S3; RV, rotavirus; SARS-CoV, SARS coronavirus; *S. boydii, Shigella boydii*; SCF^βTRCP, SKP1, cullin 1 and F-box protein βTRCP; *S. flexneri, Shigella flexneri*; S. Typhimurium, *Salmonella enterica* subsp. *enterica* serovar Typhimurium; TAK1, TGFβ-activated kinase 1; TLR, Toll-like receptor; TNFR, TNF receptor; TRAF, TNFR-associated factor; Ub, ubiquitin; VACV, vaccinia virus; VARV, variola virus; *V. parahaemolyticus, Vibrio parahaemolyticus*.

transcription of the genes encoding major histocompatibility complex (MHC) class I molecules[100]. Similarly, E1A binds to p50 and prevents its phosphorylation at Ser337 by PKAc[101].

Other mechanisms of NF-κB modulation

Human cytomegalovirus (HCMV) modulates the NF-κB pathway at every stage of the viral life cycle, either by activation or inhibition. NF-κB is activated during the viral entry process, whereas HCMV successfully inhibits the NF-κB pathway after the initial infection. HCMV immediate–early protein IE86 inhibits binding of NF-κB to the promoters of interferon-β (IFNβ), cytokines and chemokines in response to TNF stimulation or virus infection[102]. However, IE86 does not block the nuclear translocation of NF-κB or directly interact with the subunits, suggesting that the protein might target host factors required for the transcriptional activity of NF-κB. HCMV can also inhibit the activation of the NF-κB pathway that is induced by TNF and IL-1β at later times post-infection, by inhibiting IKK activation using a late viral gene product[103,104]. An HCMV-encoded homologue of human IL-10 also inhibits NF-κB activation[105]. Like HCMV, reoviruses also modulate NF-κB in a manner that promotes the viral life cycle in the infected host. For example, reovirus 3 strain Dearing activates NF-κB to induce NF-κB-dependent apoptosis[106]. However, another strain of reovirus 3 (strain Abney) inhibits NF-κB at a later stage of infection to promote induction of apoptosis in HEK293 and primary cardiac myocytes. Infection of cells with this strain inhibits activation of NF-κB by external stimuli, an effect that requires the T3 S1 gene segment, which is also responsible for regulating apoptosis[107].

For many virus-encoded proteins (TABLES 2,3), the cellular targets are still unknown. For example, the West Nile virus protein NS1 inhibits TLR3-mediated activation of the NF-κB pathway by blocking nuclear translocation of RELA and IRF3 in order to suppress the production of IL-6 and IFNβ[108]. KSHV-encoded miRNAs, which are expressed during viral latency and in Kaposi's sarcoma tumours, modulate cellular gene functions and are thought to play a part in the pathogenesis of KSHV-induced malignancies. Recently, it has been demonstrated that the deletion of 14 miRNA clusters from KSHV reduced virus-induced NF-κB activation and enhanced lytic induction, as KSHV miRNAs activate NF-κB and induce enhanced expression of RTA and major capsid protein[109].

Modulation of NF-κB by bacteria

Bacterial proteins that directly interact with the NF-κB signalling pathway. Bacteria generally encode a larger repertoire of proteins than viruses, and many of these proteins are also predicted to have host modulatory functions[110]. Like viruses, bacteria modulate the NF-κB signalling pathway by either activation or inhibition, according to the requirement for the life cycle of the individual pathogen[111]. Individual bacteria often encode and deploy multiple effector proteins for regulation of the NF-κB signalling pathway. Recent studies suggest

that functional redundancy exists among the effector proteins from a single strain of bacteria[112]. TABLE 4 lists some of the documented NF-κB modulators from bacteria and other microbial pathogens. Although the known bacteria-derived effector molecules that modulate the NF-κB pathway are not structurally related to the viral modulators, in many cases they target the same cellular signalling molecules (FIGS 2,3). For example, viral and bacterial effector molecules target the same IKK complex, as well as IκBα, to inhibit the NF-κB pathway (FIG. 3). By contrast, structurally related bacterial effector molecules often have diverse cellular targets for the regulation of NF-κB function.

Unlike viruses, bacterial pathogens use secretion systems, which are multicomponent complexes that translocate virulence factors to the extracellular space or the cytosol of target eukaryotic cells. These secretion systems are grouped into seven classes (type I to type VII) according to their protein composition and their mechanism of function[113]. Together, these secretion systems transport hundreds of virulence factors and effector proteins, but only a few of these have been characterized in detail. The known effector proteins that modulate host innate immune responses associated with the NF-κB signalling pathway are primarily delivered by the type III secretion system (T3SS), as found in *Salmonella* spp. and *Yersinia* spp., or by the type IV secretion system (T4SS), as found in *Bartonella* spp. Type III effector proteins from *Yersinia* spp., known as Yops, counteract multiple signalling pathways that are activated in the infected host cells[114]. For example, YopJ (also known as YopP in *Yersinia enterocolitica*) inhibits NF-κB signalling to block the production of pro-inflammatory cytokines. However, multiple mechanisms of action were described for YopJ, as it has several protein targets in the NF-κB pathway. YopJ was identified as a cysteine protease that also has deubiquitylating and desumoylating activity; it removes polyubiquitin chains from IκBα and therefore inhibits proteasomal degradation of the protein[115]. YopJ can also remove ubiquitin chains from TRAF6 to inhibit TLR-mediated activation of NF-κB signalling[116]. In addition, it acts as an acetyltransferase that acetylates serine and threonine residues in the activation loops of IKKα and IKKβ, thereby blocking phosphorylation and activation of the IKK complex by upstream kinases[117,118]. *Aeromonas salmonicida* encodes AopP, a type III effector protein that is related to YopJ. Secretion of this effector prevents the nuclear translocation of RELA, but the direct host target of AopP is unknown. It does not inhibit the phosphorylation of IκBα, suggesting that AopP might prevent degradation of IκBα using a similar mechanism to that used by YopJ[119]. Thus, YopJ (variants of which are encoded by multiple Gram-negative bacterial species) has acquired several mechanisms of inhibiting the NF-κB signalling pathway.

Owing to the importance of the NF-κB signalling pathway in many crucial cellular processes, cells have developed multiple mechanisms to regulate the function of this pathway. One negative regulatory mechanism is deubiquitylation of signalling molecules that activate the IKK complex, by deubiquitylase enzymes such as CYLD

Table 4 | **Bacteria and parasite proteins that modulate NF-κB signalling**

Species	Protein	Mechanisms of modulation	Host targets	Refs
Aeromonas salmonicida	AopP	Inhibits nuclear translocation of RELA	Unknown	119
Bordetella bronchiseptica	BopN	Blocks nuclear translocation of RELA, but promotes nuclear translocation of p50 for IL-10 expression	Unknown	148
Bordetella pertusis	FHA	Activates NF-κB at early stages of infection, but inhibits NF-κB during late stages of infection	Unknown	142
Chlamydia pneumoniae	CP0236	Sequesters ACT1	ACT1	139
Chlamydia trachomatis	ChlaDub1	Binds IκBα and inhibit its ubiquitylation and degradation	IκBα	138
	CT441	Cleaves RELA	RELA	137
Enterohaemorrhagic *Escherichia coli* serogroup 0111	Unknown	Inhibits nuclear translocation of RELA	Unknown	128
Enteropathogenic *E. coli*	NleE	Blocks phosphorylation and activation of IKKβ and the nuclear translocation of c-REL	TAK1 and c-REL	130,131
E. coli 0157:H7 str. EDL9883	NleH1 and NleH2	Inhibit the transcriptional activity of NF-κB	RPS3	127
E. coli K1	OmpA	Inhibits the NF-κB pathway via ERK1–ERK2 and p38 MAPK	Unknown	133
Lactobacillus reuteri	Unknown	Inhibits degradation of IκBα and nuclear translocation of RELA	Unknown	145
Legionella pneumophila	LegK1	Directly activates NF-κB signalling by phosphorylation of the IκB family of inhibitors	Unknown	140
Pseudomonas aeruginosa	*N*-(3-oxo-dodecanoyl) homoserine lactone (also known as C12)	Modulates the function of the IKK complex	Unknown	134
Salmonella enterica subsp. *enterica* serovar Typhimurium	AvrA	Deubiquitylates IκBα and blocks its degradation	IκBα	122
	SseL	Inhibits ubiquitylation and degradation of IκBα	IκBα	125
Shigella boydii	OspZ	Blocks nuclear translocation of RELA	Unknown	131
Shigella flexneri	IpaH9.8	Degrades NEMO by ubiquitylation	NEMO and ABIN1	132
	Unknown	Activates the NOD1-dependent RIP2–IKKβ–NF-κB signalling pathway	Unknown	143
	OspG	Inhibits ubiquitin-mediated degradation of phosphorylated IκBα	Ubiquitin-conjugating enzymes (E2s) and UBCH5	126
Theileria annulata	Unknown	Hijacks signalling through the IKK complex	Unknown	166
Toxoplasma gondii	IKK	Phosphorylates IκBα and activates NF-κB	IκBα	151
Vibrio parahaemolyticus	VopS (encoded by the locus VP1686)	Interacts with RELA and suppresses activation of NF-κB	RELA	135
	VopA	Acetylates MAPK and inhibits MAPK signalling	MAPK	167
Yersinia spp.	YopJ (also known as YopP in *Yersinia enterocolitica*)	Inhibits activation of the IKK complex and degradation of IκBα	IKKα–IKKβ and IκBα	115,117

ACT1, NF-κB activator (also known as CIKS); ChlaDub1, *Chlamydia* deubiquitylase and deneddylaase; ERK1, extracellular signal-regulated kinase 1 (also known as MAPK3); ERK2, extracellular signal-regulated kinase 2 (also known as MAPK1); FHA, filamentous haemagglutinin; IκBα, NF-κB inhibitor-α (also known as NF-κBIα); IKK, IκB kinase; IL-10, interleukin-10; MAPK, mitogen-activated protein kinase; NEMO, NF-κB essential modulator (also known as IKKγ); NF-κB, nuclear factor-κB; RIP2, receptor-interacting protein 2 (also known as RIPK2); RPS3, 40S ribosomal protein S3; TAK1, TGFβ-activated kinase.

and zinc finger protein A20 (also known as TNFAIP3) (REFS 120,121). Several bacteria have co-opted this mechanism using virulence factors that deubiquitylate NF-κB signalling molecules. The type III effector protein AvrA of *Salmonella enterica* subsp. *enterica* serovar Typhimurium str. PhoP[c], a non-pathogenic strain, is a deubiquitylase that is closely related to YopJ and that inhibits the NF-κB pathway by removing ubiquitin from

IκBα and from β-catenin, a negative regulator of the pro-inflammatory NF-κB pathway in epithelial cells[122,123]. Another *S.* Typhimurium type III effector protein, SseL (encoded in *Salmonella* pathogenicity island 2), also possesses a deubiquitylase activity that inhibits degradation of IκBα[124,125]. *S.* Typhimurium lacking SseL causes increased NF-κB activation in macrophages as a result of ubiquitin-mediated degradation of IκBα.

Several bacterial proteins can inhibit the degradation of IκBα by targeting the cellular ubiquitin machinery. The *Shigella flexneri* T3SS effector OspG can modulate the host NF-κB function by blocking the degradation of phosphorylated IκBα, and thus blocking NF-κB activation, in response to TNF stimulation in and *S. flexneri* infection of epithelial cells[126]. OspG is a serine/threonine kinase that binds to various ubiquitylated ubiquitin-conjugating enzymes (E2s), including UBCH5 (also known as UBE2D1), to prevent ubiquitylation of phosphorylated IκBα[126]. NleH1 and NleH2 from *Escherichia coli* O157:H7 str. EDL9883, an enterohaemorrhagic *E. coli* (EHEC) strain, have a high level of sequence similarity with OspG but have different targets from OspG. NleH1 and NleH2 lack the ability to block IκBα degradation, but instead interact with the human 40S ribosomal protein S3 (RPS3), a subunit of NF-κB complexes that regulates NF-κB-dependent transcription[127]. This suggests that the bacterial effectors that regulate the NF-κB pathway have many different targets and substrates. The existence of multiple NF-κB inhibitors was observed in EHEC serogroup 0111, which encodes a homologue of OspG. Surprisingly, EHEC serogroup 0111 lacking OspG inhibited RELA transfer to the nucleus in response to TNF, suggesting that additional modulators from T3SS are present in this EHEC serogroup[128].

Enteropathogenic *E. coli* (EPEC) can either activate or suppress NF-κB through T3SS-dependent translocation of effectors and T3SS-independent mechanisms, presumably by activation of TLRs[129]. The T3SS effector proteins NleE and NleB can inhibit NF-κB activation by inhibiting IκBα phosphorylation[130]; NleE and NleB block the phosphorylation and activation of IKKβ by targeting upstream molecules, such as TAK1 (REF. 130). Furthermore, NleE can block nuclear translocation of c-REL, but not of p50 or the transcription factors STAT1 and STAT2, indicating that the block in nuclear translocation is specific for c-REL (REF. 131). OspZ, the NleE homologue from *S. flexneri* 6 and *Shigella boydii*, also blocks nuclear translocation of RELA in response to TNF-mediated activation of NF-κB. Another *S. flexneri* effector protein, IpaH9.8, possesses E3 ligase activity and inhibits the NF-κB pathway through a unique mechanism: it interacts with the IKK regulatory subunit NEMO and with ABIN1 (also known as TNIP1), a ubiquitin-binding adaptor protein, to promote the ABIN1-dependent polyubiquitylation of NEMO. Subsequent degradation of NEMO inhibits the activation of NF-κB and thus downregulates the host inflammatory responses[132].

E. coli K1 suppresses the production of pro-inflammatory cytokines from infected monocytes. However, in the absence of OmpA, the bacterium activates the NF-κB pathway via the extracellular signal-regulated kinase 1 (ERK1; also known as MAPK3)–ERK2 (also known as MAPK1) and the mitogen-activated protein kinase p38 (also known as MAPK14) pathways, resulting in the production of pro-inflammatory cytokines and chemokines[133]. Therefore, OmpA may target a kinase common to these pathways[133]. Opportunistic pathogens such as

Pseudomonas aeruginosa synthesize a small molecule called *N*-(3-oxo-dodecanoyl) homoserine lactone (also known as C12), which inhibits the regulation of NF-κB functions in activated mammalian cells[134]. Modulation of IKK and inhibition of NF-κB signalling by C12 attenuates TLR4-dependent innate immune responses to promote persistent infection.

Like their viral counterpart proteins, bacterial effectors can inhibit the function of NF-κB transcription factors through direct interaction or proteolysis. *Vibrio parahaemolyticus* secretes the T3SS1-dependent effector protein VopS (encoded by the locus VP1686) into the cytosol of macrophages, and this then induces DNA fragmentation. Vops directly interacts with RELA to inhibit the DNA-binding activity of NF-κB, causing apoptosis of the infected macrophages[135]. The intracellular bacterial pathogen *Chlamydia trachomatis*, which infects human eyes and the urogenital tract, has acquired multiple mechanisms to modulate NF-κB function[136]. The *C. trachomatis* protein encoded by the locus CT441 (a Tsp-like protease) inhibits the nuclear translocation and function of NF-κB by cleaving RELA, and also inhibits NF-κB by regulating ubiquitin-mediated protein degradation[137]. *Chlamydia* deubiquitylase and deneddylase (ChlaDub1) binds IκBα and blocks its ubiquitylation and degradation, allowing *C. trachomatis* to evade the NF-κB-mediated host inflammatory response[138]. *Chlamydia pneumoniae*, which lacks ChlaDub1, uses an inclusion-specific protein (encoded by the locus CP0236) to sequester NF-κB activator (ACT1; also known as CIKS) and, thus, regulate NF-κB[139].

Other bacterial proteins that affect NF-κB

Bacterial effector proteins can also activate the NF-κB pathway as a strategy of immune modulation (FIG. 2). *Legionella pneumophila*, which infects lung macrophages and causes Legionnaire's disease, activates NF-κB signalling in a T4SS-dependent manner. Using an NF-κB-specific luciferase reporter activation assay, LegK1 was identified as a potential activator of NF-κB signalling. LegK1, a eukaryotic-like serine/threonine kinase, potently and specifically activates host NF-κB signalling by directly phosphorylating IκBα and other members of the IκB family of inhibitors, as well as p100 (REF. 140). Thus, LegK1 bypasses the requirement for host IKKs and upstream kinases, such as TRAF2, TRAF6, TAK1, NIK and MEKK3, in the activation of both classical and alternative NF-κB pathways. *Rickettsia rickettsii*, an obligate intracellular bacterial pathogen, activates IKKα and IKKβ to drive NF-κB activation in human endothelial cells[141]. *Bordetella pertussis* produces filamentous haemagglutinin (FHA), a cell-associated secreted adhesin that can induce early activation of the NF-κB pathway and cause the secretion of NF-κB-regulated inflammatory cytokines; however, longer exposure to this adhesin inhibits NF-κB activation, suggesting that there are complex temporal dynamics involved in the regulation of the innate response pathways[142].

Like viruses, bacterial pathogens modulate host signalling to maintain a delicate balance between

the cell death and survival pathways. For example, although infection of non-myeloid cells by *S. flexneri* induces inflammatory responses and activates anti-apoptotic pathways through the rapid activation of the NOD1-dependent RIP2–IKKβ–NF-κB signalling pathway, the bacterium can also induce apoptotic and necrotic cell death[143]. Thus, a balance between the induction of the apoptotic and anti-apoptotic pathways dictates the fate of the infected cell.

The intestinal microbiota of mammals and other metazoans maintain a homeostatic balance with the host immune system. Recent studies suggest that NF-κB signalling plays a crucial part in maintaining this host–bacteria symbiosis[144]. The host has adapted several mechanisms to distinguish between commensals and foreign pathogens, and exercises a delicate balance between tolerance and immunity. For example, in the intestine the expression pattern and localization of PRRs and the activation of NF-κB pathways have an important role in maintaining homeostasis[144]. Some commensal bacteria produce proteins that suppress immune activation; for example, *Lactobacillus reuteri*, a beneficial organism that is exploited for probiotics, can downregulate NF-κB-dependent host proteins that mediate cell proliferation and survival[145]. This species blocks nuclear translocation of RELA by preventing the degradation of IκBα in response to TNF stimulation[145], although, as shown by a recent study using the commensal intestinal bacterium *Lactobacillus plantarum*, changes in host cell gene expression can depend on the bacterial growth phase[146]. On the other hand, the effects of probiotics in the prevention or treatment of diarrhoea caused by infection with enteric pathogens (for example, *Saccharomyces boulardii*) are thought to be mediated by immune modulation and the release of pro-inflammatory cytokines that are regulated by NF-κB[147]. This suggests that the commensals could compete with invading pathogens and enhance host defences.

Bacteria can also exploit indirect mechanisms to shut off the NF-κB-dependent host inflammatory responses. *Bordetella* spp. exploit the anti-inflammatory cytokine IL-10 to suppress the host immune system. The *Bordetella bronchiseptica* T3SS effector BopN translocates to the nucleus of the host cell, where it induces the production of IL-10 and downregulates MAPKs. In addition, BopN blocks nuclear translocation of RELA but promotes nuclear translocation of p50 to selectively activate IL-10 expression[148]. This supports previous observations that *B. bronchiseptica* uses its T3SS to suppress NF-κB in order to inhibit the induction of innate immune genes such as β-defensins[149]. The virulence factor LcrV of *Yersinia* spp. also enhances the production of IL-10 via an association with TLR6 (REF. 150).

Similarly to viruses and bacteria, parasites have acquired diverse mechanisms to modulate the host innate immune responses controlled by NF-κB. For example, the intracellular parasite *Toxoplasma gondii* increases the level of phosphorylated IκBα in the infected host through the parasite kinase IKK to activate NF-κB and thereby prolong the survival of host cells[151,152].

Concluding remarks

NF-κB plays a vital part in the early stages of the host response against diverse pathogens; thus, during the course of evolution microbial pathogens have collectively acquired an impressive repertoire of molecules that target almost every aspect of the NF-κB signalling pathway. These pathogen-derived countermeasures have been selected to maintain a delicate balance between the activation and inhibition of the NF-κB pathway as a survival strategy, and this supervening control has to be exercised throughout the time that the pathogen lives within the host. In fact, single pathogens frequently deploy multiple strategies to modulate the NF-κB circuitry, but it is still a mystery why individual pathogens often need to express so many seemingly redundant regulators of the same pathway (for example, VACV encodes six known distinct NF-κB regulators, and that number is still growing). It is also clear that diverse microbial pathogens have evolved, in parallel, the ability to manipulate common cellular targets to modulate the NF-κB pathway. In fact, the pathogen-derived effector molecules themselves are remarkably diverse. With the continuing identification of ever more cellular mechanisms that regulate NF-κB, it would not be surprising if at least some successful pathogens were shown to subvert these newly found regulatory mechanisms for their benefit. Furthermore, the identification of new pathogen-derived molecules that target NF-κB will undoubtedly increase our appreciation of the most effective ways to manipulate NF-κB therapeutically in uninfected hosts.

The receptors that trigger NF-κB are activated not only by pathogens but also by various molecules that are produced by the host, and the uncontrolled activation of NF-κB is associated with multiple inflammatory diseases, progressing syndromes of autoimmunity, and human cancers. Although the cause-and-effect relationships of NF-κB activation in cancerous tissues are not completely understood, aberrant activation of kinase pathways that feed into the IKK proteins can constitutively activate NF-κB and contribute to the progression of various malignancies[153]. It is not accidental that the major chemical and physical carcinogens that have been implicated in the promotion of cancer can also frequently activate NF-κB. Newer drugs that inhibit NF-κB by targeting upstream kinases in the pathway, and the IKK proteins, have shown promise as anticancer therapeutics in preclinical studies. However, it is worth remembering that successful pathogens are still Mother Nature's master drug chemists, and pathogen-derived molecules themselves (or derivatives of these molecules), such as bioactive peptides, may be developed as both anticancer and anti-inflammatory therapeutics in the future. Newer generations of drugs are needed to treat those immune diseases and cancers that depend on NF-κB-mediated inflammatory support. Indeed, the 'right' druggable cellular targets have probably already been identified and targeted for exploitation by nature's successful microbial pathogens.

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