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MINIREVIEW

Host-Pathogen Interactions: Subversion and Utilization of the NF-κB Pathway during Infection

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The NF-κB family of transcription factors is a group of evolutionarily conserved proteins which are important in regulation of the immune system. These transcription factors are involved in the development of accessory cell and lymphocyte populations and expression of numerous proteins involved in innate and adaptive immunity (12, 23, 32, 48, 55, 79). Invasion of a host by a pathogen is frequently associated with the activation of NF-κB, which coordinates various aspects of immune function required for resistance to infection. The importance of NF-κB in resistance to infection is perhaps best illustrated by studies in which mice deficient in different NF-κB family members were shown to be susceptible to a variety of viral, bacterial, and parasitic infections (Table 1) (4, 9, 10, 20, 25, 27, 47a, 76, 80, 89; D. Artis, K. Speirs, J. C. Caamano, C. A. Hunter, and P. Scott, submitted for publication). However, the focus of this article is to review the strategies utilized by some microbes to interfere with the activation of NF-κB in order to evade the immune response. In addition, we shall discuss how some pathogens have managed to exploit these transcription factors to optimize their replication and survival. Examination of the ways in which pathogens interact with the NF-κB system provides an insight into the complex interactions between host and pathogen.

REGULATION AND ACTIVATION OF NF-κB

The events which lead to the activation of NF-κB represent one of the best-characterized signaling pathways. The five NF-κB family members include NF-κB1 (p50), NF-κB2 (p52), Rel A (p65), Rel B, and c-Rel. These proteins pair to form homo- and heterodimers that are sequestered in the cytoplasm by the inhibitor-kappa B (IκB) proteins, which contain a tail of ankyrin repeats that are important in binding to NF-κB family members (15). Interestingly, the NF-κB1 and NF-κB2 genes produce proteins of 105 and 100 kDa (p105 and p100), respectively, which are cleaved to give rise to NF-κB1 and NF-κB2. However, these precursors are similar to the IκB proteins in that they contain a tail of ankyrin repeats which folds back on itself to mask the nuclear localization signal (45). A variety of signaling pathways lead to the phosphorylation and degradation of IκB proteins, which reveal the nuclear localization signal of the NF-κB protein and so allow nuclear translocation of NF-κB dimers. Though numerous stimuli which lead to the activation of NF-κB exist, some of the best characterized are microbial products. Thus, the binding of molecules such as lipopolysaccharide (LPS), bacterial DNA, peptidoglycans, and parasite mucins to Toll-like receptors results in the activation of NF-κB, which is important in the initiation of innate responses (31, 43, 65, 66, 85, 94). In addition, signaling through many cytokine receptors and the T- and B-cell receptors as well as costimulatory molecules results in the activation of NF-κB (5, 42, 49). Each of these pathways involves distinct scaffolding and signaling proteins, including MyD88, serine/threonine kinases (IRAK), TRAF proteins, MAP3Ks (NIK), and the IKK signalosome complex (33, 38). These diverse signaling pathways converge at the level of phosphorylation of IκB and its degradation to allow nuclear localization of NF-κB. However, depending on the stimulus and the cell type, different homo- and heterodimers may be activated. Once in the nucleus, NF-κB is involved in the increased transcription of IκB proteins, which provides a feedback mechanism to limit NF-κB activity (13, 18), as well as the regulation of numerous genes involved in immune function. Thus, many cytokines (gamma interferon [IFN-γ], interleukin-12 [IL-12]), receptors (CD25), and adhesion molecules (intercellular adhesion molecule 1 [ICAM-1], vascular cell adhesion molecule [VCAM]), as well as proteins involved in cell proliferation and survival, have NF-κB binding sites in their promoters, and molecular studies have correlated many of these sites and specific NF-κB members with gene expression (14, 22, 30, 37, 39, 42, 53, 63, 78, 93). In addition, NF-κB has an important role in regulating the expression of antiapoptotic proteins and affecting the susceptibility of cells to apoptosis (26, 40, 88, 90, 95). As discussed below, the role of NF-κB in determining susceptibility to apoptosis has been used by many pathogens to either promote or prevent cell death.

PATHOGENS THAT INHIBIT NF-κB ACTIVATION

The ability of pathogens to interfere with the development of immune responses associated with antimicrobial immunity provides a strong survival advantage to the pathogen. It is now recognized that microorganisms have targeted several parts of the NF-κB pathway, allowing them to interfere with the transcription of immune response genes. These pathogens can be broadly characterized according to the specific part of the signaling pathway targeted, the first of which are those that

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TABLE 1. NF-κB-deficient mice and infection

Deficiency	Increased susceptibility to:	Characteristic(s) of response
NF-κB1	*L. monocytogenes*	Decreased antibody production
	S. pneumoniae	Decreased proliferation
	L. major[a]	Decreased IFN-γ
NF-κB2	*L. monocytogenes*	Decreased antibody production
	T. gondii	Decreased proliferation
	L. major	Decreased macrophage function
		Increased IL-2 and GM-CSF[b]
		Increased apoptosis
RelB	Lymphocytic choriomeningitis virus	Decreased antibody production
	L. monoctytogenes	Increased inflammatory response
	T. gondii	Decreased IFN-γ
c-Rel	*L. monocytogenes*	Decreased antibody production
	S. pneumoniae	Decreased proliferation
	T. gondii	Decreased IL-2, IL-12, IFN-γ
	L. major	Decreased macrophage response
	Influenza virus	

[a] *L. major*, *Leishmania major*.
[b] GM-CSF, granulocyte macrophage colony-stimulating factor.

inhibit the pathway proximal to the phosphorylation and degradation of IκB. An example of this is provided by vaccinia virus, which produces A52R, a viral homologue of MyD88, the scaffolding protein necessary for IL-1/IL-18- and TLR4-mediated activation of NF-κB. This virally derived protein acts as a dominant-negative form of MyD88 and antagonizes MyD88-dependent activation of NF-κB (7) (Fig. 1, step 1). Thus, the virus is able to abrogate IL-1-mediated signaling, which is important for resistance to vaccinia (2, 81).

The gram-negative extracellular bacteria *Yersinia pestis*, *Yersinia pseudotuberculosis*, and *Yersinia enterocolitica* use a type III secretion system to inject virulence factors into target host cells. These pathogens typically target macrophages but can also affect epithelial cells, fibroblasts, and lymphocytes by producing proteins which directly inhibit kinase activation within the target cell. The injection of virulence factors known as *Yersinia* outer proteins (Yop) has been found to interfere with a variety of signaling pathways. Thus, YopJ of *Y. pseudotuberculosis* targets mitogen-activated protein (MAP) kinase kinases, which are upstream of IκB phosphorylation (58), and it appears that related proteins in a variety of *Yersinia* species, such as *Y. pestis*, use similar mechanisms to disrupt NF-κB activation (Fig. 1, step 2). It has also been shown that YopJ may act as a cysteine protease and target ubiquitin-like molecules to disrupt the degradation of regulatory proteins (59). The same group showed that YopJ can abrogate conjugation of SUMO-1, a ubiquitin-like molecule, to target proteins (59). Since it has been proposed that MAP3Ks may be modified by ubiquitination, it is thought that these kinases may be targeted by YopJ. Studies with *Y. enterocolitica* have shown that this pathogen can prevent phosphorylation and degradation of IκB in macrophages, and this is associated with decreased production of tumor necrosis factor alpha (TNF-α) and increased susceptibility to apoptosis (70). Subsequent studies revealed that YopP of *Y. enterocolitica* can bind to IKKβ to prevent activation of NF-κB and cause apoptosis in macrophages (71, 72). In T and B cells, YopH, a tyrosine phosphatase found in *Y. pseudotuberculosis*, has been shown to block all antigen-specific receptor signaling by inhibiting phosphorylation of proteins early in the pathway (92). Since signaling through these receptors activates NF-κB, this virulence factor is likely able to inhibit NF-κB-mediated transcription of cytokines after antigen-specific T-cell receptor cross-linking. Furthermore, it is thought that the inhibition of NF-κB activation not only limits the ability of these lymphocytes to produce cytokines but may also promote their apoptosis and so inhibit activation of the immune system (69).

The ability to interfere with the degradation of IκB is another strategy employed by some pathogens to inhibit activation of NF-κB. Although the exact mechanism is still unclear, it is has been shown that the measles virus is able to prevent phosphorylation of IκBα in neuronal cells (Fig. 1, step 3), which effectively shuts down NF-κB-dependent expression of antiviral beta interferon and HLA class I molecules (16). Other pathogens are able to disrupt degradation of IκB even if the proximal signaling pathways are intact and phosphorylation of IκBα is successful. For example, cowpox virus, raccoonpox virus, and certain strains of vaccinia virus can prevent degradation of phosphorylated IκBα (57) (Fig. 1, step 5). It has been proposed that this inhibition may be the result of dephosphorylation of IκB or interference with degradation after phosphorylation. Similarly, the human immunodeficiency virus (HIV) has employed a variety of ways to manipulate NF-κB activation. Beta-transducin repeat-containing protein, β-TrCP, is part of a ubiquitin ligase complex and is required for the ubiquitination of IκB and the subsequent degradation of phosphorylated IκB proteins. The HIV type 1 (HIV-1) Vpu protein competitively inhibits β-TrCP-dependent degradation of IκB,

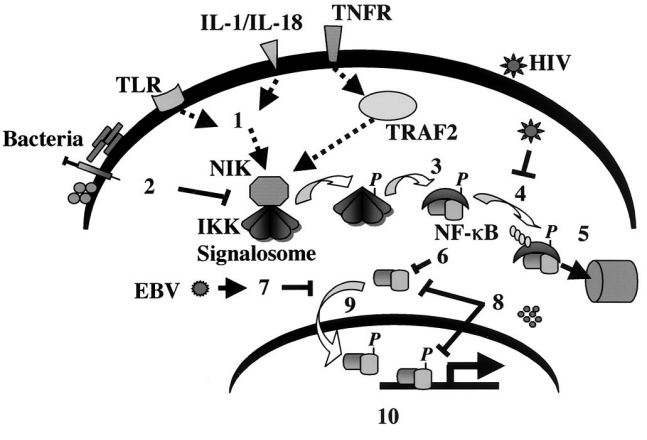

FIG. 1. Pathogen-mediated inhibition of the NF-κB pathway. 1, virally derived vaccinia protein, A52R, acts as a dominant-negative form of MyD88; 2, *Yersinia* Yop proteins interfere with MAP3K and IKKβ to prevent phosphorylation of IκBα and UPEC virulence factors interfere with MAP kinase activity; 3, measles virus prevents phosphorylation of IκBα; 4, *Salmonella* and HIV-1 Vpu protein inhibit ubiquitination of phosphorylated IκBα; 5, orthopoxviruses can either dephosphorylate IκBα or inhibit degradation of the phosphorylated protein; 6, an ASFV-derived protein acts as an IκB-like molecule to inhibit NF-κB translocation to the nucleus; 7, EBV-derived ZEBRA protein binds to p65; 8, soluble toxin from *M. ulcerans* may prevent phosphorylation of p65 and/or binding of NF-κB to DNA; 9, *T. gondii* prevents nuclear translocation of NF-κB; 10, *S. mansoni* disrupts NF-κB binding to DNA in the nucleus.

thus keeping NF-κB sequestered in the cytoplasm and resulting in inhibition of NF-κB activity in T cells (1, 6) (Fig. 1, step 4).

Species of extremely pathogenic bacteria have also been shown to block degradation of IκBα and so abrogate nuclear localization of NF-κB. When uropathogenic *Escherichia coli* (UPEC), the most common cause of urinary tract infections, is cultured with a urothelial cell line, it increases the stability of IκBα, prevents its degradation, and blocks NF-κB-dependent expression of antiapoptotic proteins, resulting in increased apoptosis (36). In addition, there is evidence that this pathogen may be able to inhibit MAP kinase signaling through either a contact-dependent mechanism or through the use of soluble factors (36) (Fig. 1, step 2). Since apoptotic cells are shed during urination, apoptosis during UPEC infection is usually considered a host defense strategy to clear bacteria (54). However, the ability of UPEC to invade bladder epithelial cells suggests that this inhibition of NF-κB activation decreases inflammation and may allow the pathogen more time to be internalized by urothelial cells where they remain safe from the immune system and a source of recurrent infection (36, 47).

In contrast to pathogenic microorganisms, avirulent species of the intracellular bacteria *Salmonella* are able to delay an immune response by shutting down NF-κB signaling in host epithelial cells as they colonize mucosal tissues. Inhibition of NF-κB by *Salmonella* also occurs through the regulation of IκBα ubiquitination either by reducing IκB association with β-TrCP or by increasing de-ubiquitinating activity (56) (Fig. 1, step 4). Since epithelial cells in the lining of the intestine have an intimate relationship with intraepithelial lymphocytes, which sample and monitor the constant flow of antigen present in the mucosa, the inhibition of NF-κB is thought to allow colonization of epithelial monolayers by the nonpathogenic strains *Salmonella enterica* serovar Typhimurium *phoP*^{c} and *S. enterica* serovar Pullorum without inducing the inflammation seen during invasion with the more virulent strains of this species (56).

Some pathogens are able to interfere with NF-κB activation downstream from the degradation of IκB. The African swine fever virus (ASFV), which typically targets macrophages, makes a viral protein, A238L, which is a homologue of IκB. A238L (also referred to as ASFV-IκB) contains ankyrin repeats and can bind to NF-κB following degradation of host IκB and so inhibits nuclear localization of dimers (64) (Fig. 1, step 6). This inhibition may explain why disease caused by ASFV is often fatal to the animal. Another pathogen, Epstein-Barr virus (EBV), has been shown to target B, T, and epithelial cells. However, NF-κB activation is affected in distinctly different ways depending on the specific cell type. In infected T cells, the viral protein, ZEBRA, can bind to RelA and inhibit NF-κB activity, thus rendering infected T cells susceptible to apoptosis (17) (Fig. 1, step 7). This inhibition of NF-κB most likely blocks transcription of antiapoptotic proteins, allowing the virus to suppress the immune response through the selective killing of activated T cells.

Some pathogenic bacteria also interfere with the ability of NF-κB dimers to translocate into the nucleus. Thus, the extracellular bacterium *Mycobacterium ulcerans* has been shown to inhibit NF-κB activation in T cells and monocytes (60). Since there is no evidence that IκBα degradation is compromised during infection, it is speculated that a soluble toxin produced by the bacteria may either block phosphorylation of RelA, which has been shown to be required for nuclear translocation of RelA (44), or directly interfere with the ability of NF-κB to bind DNA (Fig. 1, step 8). Consequently, this inhibition leads to decreased T-cell and monocyte functions (60).

Several parasites have also developed strategies to interfere with NF-κB activation and so decrease the immune response to allow parasite survival. Recent studies have reported that invasion of macrophages by the protozoan parasite *Toxoplasma gondii* results in the degradation of IκB but does not lead to the nuclear translocation of NF-κB (8, 77). Moreover, this parasite appears to actively inhibit the ability of other inflammatory stimuli to induce the translocation of NF-κB to the nucleus (8, 77) (Fig. 1, step 9). The functional consequences of these events are that infected cells are unable to produce proinflammatory cytokines such as IL-12 and TNF-α that are essential for resistance to *T. gondii*. Thus, the ability of *T. gondii* to inhibit activation of NF-κB may delay the development of protective immunity and allow *T. gondii* to replicate and disseminate within the infected host before the development of a strong cell-mediated immune response.

Another pathogen capable of interfering with NF-κB signaling is the helminth *Schistosoma mansoni*. This parasite has a developmental stage, the schistosomula, which migrates through the lungs, and protective immunity is directed against this migratory stage. In vitro studies have reported that an excretory-secretory product of schistosomula can inhibit the formation of the protein complex necessary for transcription at the κB binding sites of the E-selectin promoter and so downregulates lung endothelial cell expression of adhesion molecules (86) (Fig. 1, step 10). This effect may allow the schistosomula to inhibit the recruitment of inflammatory cells to the lungs as they migrate through this tissue and so allow the schistosomula to evade the effector arm of the immune system.

PATHOGENS THAT UTILIZE NF-κB

As mentioned previously, the activation of NF-κB in response to microbial stimuli is normally associated with the initiation of protective immunity. However, some pathogens have taken advantage of the NF-κB system to enhance their own replication, survival, and dissemination within the host. EBV is one example of how pathogens can either inhibit NF-κB activation or, alternatively, promote activation of these transcription factors in a different cell type. While the ability of EBV to inhibit NF-κB activity promotes apoptosis of activated T cells (discussed above) the viral transformation of B cells and the development of lymphoproliferative disease is associated with sustained NF-κB activation (11). Other viruses such as human T-cell leukemia virus (HTLV) are also able to transform cells through the sustained activation of NF-κB. It has been shown that the HTLV-encoded Tax oncoprotein facilitates the phosphorylation and degradation of the NF-κB2 precursor p100 to the transcriptionally active form of p52 by not only activating IKK but also physically associating with p100 (91). The functional consequence of these events may be increased expression of antiapoptotic molecules which facilitate the transformation of these cells.

This approach to transforming infected cells is not restricted

to viruses. *Theileria parva* is a parasite which infects the lymphocytes of cattle, causing a lymphoproliferative disorder. The schizont stage of *Theileria* mediates continuous degradation of IκB proteins which results in sustained activation of NF-κB and promotes proliferation of infected cells and resistance to apoptosis (28, 61). The mechanism by which *T. parva* achieves activation of NF-κB has yet to be elucidated. However, since parasite replication at this stage of development is dependent on the proliferation of the infected lymphocytes, this strategy is essential for the success of this pathogen.

Another approach used by microbes is to activate NF-κB to try to prevent the death of infected cells in order to allow the pathogen the opportunity to replicate. Perhaps the best example is provided by encephalomyocarditis virus, which requires the activation of NF-κB1 to prevent apoptosis of infected cells. This was shown by studies in which animals deficient for NF-κB1 were more resistant to encephalomyocarditis virus infection, and infected cells from these animals underwent rapid apoptosis (74, 76). Studies with *E. coli* also illustrate this principal. When macrophages deficient in their ability to activate NF-κB were cocultured with *E. coli* or bacterial products, they underwent rapid apoptosis (35). These data suggest that macrophages have an apoptotic pathway that can be induced by bacteria but is antagonized by activation of NF-κB. Likewise, studies done on *Chlamydia pneumoniae* have shown that infection of a human monocytic cell line with this bacteria is able to induce activation of NF-κB and was associated with increased survival of infected cells (87). Thus, it is likely that intracellular pathogens which can activate NF-κB and inhibit apoptosis would enhance survival of infected cells and provide an opportunity for increased replication.

As mentioned earlier, the ability of HIV to interfere with NF-κB signaling is associated with an inhibition of the immune response. However, earlier studies demonstrated that the replication of this virus is dependent on NF-κB. Thus, the binding of NF-κB at the enhancer region of the long terminal repeat promotes viral replication and survival (68). More recently, it has been shown that the 5′-untranslated leader region of HIV contains binding sites for NF-κB (3), and it is thought that the 5′-untranslated leader region can work independently as well as in concert with the long terminal repeat to enhance viral replication. It is known that the HIV Tat protein can induce activation of NF-κB by using the T-cell-specific tyrosine kinase $p56^{lck}$ (46). However, this also enhances NF-κB binding to κB binding sites within the FasL promoter of $CD4^+$ T cells, resulting in FasL expression (41). This upregulation of FasL ultimately makes $CD4^+$ T cells more susceptible to cell death. Thus, although HIV has developed a sophisticated strategy to enlist the nuclear machinery of $CD4^+$ T cells to promote viral replication, it contributes to the loss of T-cell-mediated immunity and susceptibility of the host to opportunistic infections.

For many pathogens, the manipulation and exacerbation of the inflammatory response serves to increase recruitment and flow of monocytes to and from the local site of infection, which can result in increased spread of the pathogen throughout the host. It is proposed that this mechanism allows bacteria such as *Listeria monocytogenes* to invade monocytes that have been recruited to the site of infection and thus to spread to other tissues, contributing to the establishment of a systemic infection (24). It is likely that many other bacteria use this same mechanism, and this is supported by evidence that the ability to activate NF-κB results in increased expression of adhesion molecules and chemokines associated with trafficking. For example, *C. pneumoniae* causes an NF-κB-mediated increase in MCP-1 by human endothelial cells (50). Furthermore, the bacterium *L. monocytogenes* may promote an inflammatory response by inducing NF-κB with the virulence factor listeriolysin O (LLO). In vivo injection of purified LLO, which during a natural infection is secreted by *L. monocytogenes*, has been shown to induce NF-κB-mediated transcription of the chemokine IL-8 and expression of adhesion molecules in endothelial cells (34). In contrast to the less pathogenic strains of *Salmonella* discussed above, the virulent species *S. enterica* serovar Typhimurium, the causative agent of typhoid fever, employs this strategy by strongly inducing a proinflammatory response via NF-κB activation in macrophages (67). In vitro studies have shown that the ability of the gram-negative bacterium *Bartonella henselae* to stimulate human endothelial cells to produce inflammatory molecules and increase expression of adhesion molecules is dependent on NF-κB. It is thought that the activation of NF-κB occurs independently of bacterial LPS and instead is triggered by an outer membrane protein (OMP) of *B. henselae* (21). Similarly, "blebs" containing LPS and OMP shed from *Neisseria gonorrhoeae* promote NF-κB-dependent upregulation of the carcinoembryonic antigen-related cellular adhesion molecule (CEACAM) in vitro (52), which mediates bacterial binding to endothelial cells. This mechanism allows bacterial colonization and, by up-regulating CEACAM on other cell types, can facilitate phagocytosis to achieve cellular invasion (52).

Increased activation of NF-κB can also contribute to the development of tissue damage and so provide a strategy for the pathogen to contaminate the environment. *Shigella flexneri*, a gram-negative intracellular bacterium, activates NF-κB as it invades M cells, macrophages, and epithelial cells in the gut. It is proposed that LPS from this intracellular bacterium triggers sustained activation of NF-κB through the ligation of an intracellular pattern recognition receptor (62). It is thought that this persistent NF-κB activation and production of proinflammatory mediators may lead to disruption of the epithelial layer for easier invasion of bacteria, ultimately leading to severe diarrhea in the host, environmental contamination, and spread of infection from person to person. Likewise, *Helicobacter pylori* causes gastric inflammation when it interacts with epithelial cells and gut monocytes during colonization. This bacterium uses a type IV secretion system enabling it to translocate bacterial proteins into the target cell and activate NF-κB. It is thought that bacterial factors may directly target p21-activated kinase 1 (PAK1), resulting in phosphorylation of NIK by PAK1 (19). Phosphorylation of NIK leads to phosphorylation of the IKK signalosome responsible for IκB phosphorylation and NF-κB activation. While it is unclear how this may provide a survival advantage for this bacterium, it is the existence of a specific strategy for activating NF-κB which supports the hypothesis that NF-κB activation enhances the life cycle of this bacterium (51).

The ability of schizonts of *Plasmodium falciparum*, the causative agent of malaria, to activate NF-κB in host vascular endothelium is thought to contribute to parasite survival. During infection, a parasite-derived glycosylphosphatidylinositol

toxin activates tyrosine kinase as well as protein kinase C pathways (83, 84), which result in the activation of NF-κB and the subsequent expression of the adhesion molecules ICAM-1, VCAM-1, and E-selectin (73). This increased expression of adhesion molecules, which serve as ligands for parasite molecules (29, 75, 82), enhances the ability of infected cells to stick to vascular endothelium. These parasite-induced events allow infected cells to sequester in capillaries and so avoid the antiparasite effector mechanisms present in the spleen.

FINAL COMMENTS

The immune system has evolved a variety of receptors to recognize invading microorganisms which result in patterns of gene expression associated with the development and maintenance of an immune response. Downstream of many of these receptors are complex signaling pathways which converge on the activation of NF-κB. The fact that many different pathogens have evolved diverse strategies to evade or manipulate this pathway likely reflects the selective pressure that this system places on the evolution of pathogens. In turn, the evolving pathogen is probably responsible in part for the diversification of this system as the immune system has evolved to consist of multiple pathways and NF-κB family members which are involved in the NF-κB-mediated regulation of gene expression. The development of strategies to interfere with activation of NF-κB provides an obvious selective advantage to invading microorganisms, but what is sometimes less clear is whether the activation of NF-κB in response to infection benefits the host or the pathogen. One of the main challenges in this field of research is to try to understand the functional consequences of NF-κB activation and how it affects the host-pathogen interaction.

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