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SCIENCE DIRECT
Microbes and Infection 8 (2006) 1151–1156
Microbes and Infection
www.elsevier.com/locate/micinf

Forum in immunology

Lessons learned from molecular defects in nuclear factor κB dependent signaling

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Available online 19 January 2006

Abstract

Nuclear factor (NF) κB is a ubiquitously expressed transcription factor that plays critical roles in normal development and inflammation. Characterization of naturally occurring defects in signaling pathways leading to activation of NFκB, complemented by mouse knockout models, has demonstrated the vital role of NFκB in normal host defense.

Keywords: NFκB; Immunodeficiency; Toll-like receptor

1. Introduction

Effective protection from invading pathogens requires the ability of the immune system to detect diverse classes of organisms, including viruses, bacteria, fungi, and parasites. Optimal function of host defenses requires an intact innate and adaptive immune system. The innate immune system includes germline-encoded receptors, including Toll-like receptors (TLRs) and nucleotide oligomerization domain receptors (NODs) that detect a limited number of pathogen-associated molecular patterns (PAMPs). PAMPs represent molecules (lipopolysaccharide, lipoproteins, dsRNA) that are essential for the survival of an organism and, therefore, are relatively invariant. In addition, soluble factors, such as complement proteins, mannose binding lectin, and C-reactive protein are components of the innate immune system. Adaptive immunity, on the other hand, involves the generation of antigen specific T-cell receptors and immunoglobulins through recombination and somatic hypermutation, resulting in an enormous repertoire of specificities against invading pathogens. Over the past decade it has become apparent that the innate and adaptive immune systems are interdependent. Defects in either system are associated with significant morbidity and mortality in human patients. At a molecular level, the innate and adaptive immune systems are known to share common signaling pathways. Perhaps one of the best examples of shared signaling pathways includes the activation of the nuclear factor of κ light polypeptide gene enhancer in B cells (NFκB) [1]. NFκB is expressed ubiquitously and is a regulator of numerous cellular processes. In the present review, we will discuss mutations involving components of the NFκB signal transduction pathway demonstrated to affect human health and development.

Naturally occurring mutations in human genes encoding proteins involved in regulation of the NFκB pathway have demonstrated the essential role of NFκB in normal host defense [2–5]. Analysis of the function of NFκB has revealed its role as a master regulator of gene transcription in development as well in activation of innate and adaptive immunity. The signaling pathways leading to activation of NFκB have been the subject of several recent excellent reviews and will be discussed only briefly here [6–8]. In mammals, NFκB consists of five family members (p65/Rel A, Rel-B, c-Rel, p50/NFkB1, and

Abbreviations: EDA-ID, ectodermal dysplasia associated with immunodeficiency; PAMP, pathogen-associated molecular pattern; NFκB, nuclear factor κB; TLR, Toll-like receptor.

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doi:10.1016/j.micinf.2005.10.030

p52/NFkB2). The IκB family consists of seven members, including IκBα, IκBβ, IκBγ, IκBε, Bcl-3, and the precursor proteins p105 and p100. The p105 and p100 proteins are proteolytically processed into p50/NFκB1 and p52/NFκB2, respectively. The biological significance of NFκB activation has been confirmed in mouse models in which knockout of IKKβ or p65/Rel A results in embryonic lethality [9,10]. This phenotype is rescued by crossing onto a TNFRI$^{-/-}$ background which prevents tumor necrosis factor (TNF) α-induced apoptosis in the fetal liver. Knockout models of individual genes of the NFκB family result in susceptibility to certain bacterial infections and defects in lymphoid organogenesis (discussed below). In humans, IKKγ (also known as NEMO, *N*FκB *E*ssential *Mo*difier) is encoded on the X chromosome. Complete loss of function of IKKγ in males results in embryonic lethality, whereas the hemizygous condition in females results in the dermatologic condition known as incontientia pigmenti. Hypomorphic mutations in IKKγ can result in defects in the development of the ectoderm, known as ectodermal dysplasia, which can also be associated with immunodeficiency in males [11].

Presently, two distinct signaling pathways leading to NFκB activation have been characterized, referred to as the classical and alternative NFκB pathways [7]. In the classical NFκB pathway, activation by numerous stimuli, including TNFR1, TNFR2, T-cell receptor, B cell receptor, interleukin (IL)-1, IL-18, and TLRs, results in the association of adapter proteins with the cytoplasmic domain of the receptors and activation of proteins kinases, ultimately resulting in the activation of NFκB and NFκB-dependent gene transcription. In the classical pathway, NFκB is activated through the assembly of a multimeric complex consisting of the protein kinases IKKα, IKKβ, and the regulatory subunit IKKγ. It is believed that oligomerization of IKKγ is required for optimal activation of IKKβ. Activation of IKKβ has been shown to be necessary and sufficient to phosphorylate IκBα on Ser32 and Ser 36 and IκBβ on Ser19 and Ser23 [6,7]. Phosphorylation of IκB leads to its ubiquitination and degradation, allowing NFκB dimers to translocate into the nucleus where they activate gene transcription. An alternative NFκB pathway has been shown to be activated by LTβ, CD40, and BAFFR [10,12–14]. This pathway activates the protein kinase NIK, leading to activation of IKKα, which results in the phosphorylation and proteolytic processing of p100, generating p52/RelB heterodimers.

2. Lessons from NFκB knockout mice

The NFκB transcription factor family has been implicated in a wide variety of cellular processes including cell division, cell survival and cell differentiation. Extensive studies in murine transgenic and gene knockout models have been a valuable tool to study the role of NFκB mediated transcription in all these cellular processes (for a detailed review see [15]). Although NFκB is important in a lot of cellular processes, a common feature of most of the mice with a deletion of a single NFκB component is impaired immune function (for recent review see [16]). This can lead to enhanced inflammation contributing to the pathology observed in inflammatory bowel disease, psoriasis and asthma. In addition, it can lead to severe defects in the host defense against various pathogens. We do not aim to give a complete overview of the role of all known components of the NFκB pathway in immune function, but we will illustrate its importance by discussing some examples related to host defense against pathogens.

2.1. The role of NFκB activation in the host defense

Recognition of PAMPs via TLRs is a crucial step in the host defense (Table 1). Ligation of various TLRs leads to NFκB activation resulting in the induction of TNFα, IL6, and many other pro-inflammatory cytokines and chemokines which are crucial to initiate an inflammatory response. Various mice with a deletion of a single gene in the NFκB activation pathway have been generated and these studies have shown that NFκB activation is essential for the development of the host defense against bacteria, parasites, and viruses. Mice with defects in *nfkb1* are highly susceptible to infection with bacteria such as *Listeria monocytogenes*, *Streptococcus pneumoniae* [17], and parasites such as *Leishmania major* [18]. In addition deletion of *c-rel* leads to impaired defense against influenza virus infection. Surprisingly, knockout of *c-rel* can also lead to normal or even enhanced resistance to other pathogens. For example susceptibility of *nfkb1* knockout mice to *Haemophilus influenza* is not affected while they exhibit enhanced resistance to encephalomyocarditis virus [17]. The latter findings illustrate the fact that there is a high level of redundancy in pathways that mediate host defense. Sometimes impaired host defense can be attributed to the fact that the NFκB pathway is also involved in the development of lymphoid organs. Mice with a deletion *nfkb2*, whose expression is restricted to epithelial cells and hematopoietic organs, display a disruption of splenic and lymph-node architecture [19].

2.2. The role of NFκB activation in adaptive immunity

NFκB activation is not only necessary for activation of innate immunity to control microbial pathogens but also development of adaptive immune responses. Although B- and T-cell numbers are usually normal in mice with a deletion of a single component of the NFκB pathway, indicating that no obvious defects in hematopoiesis are present, proliferation, maturation and activation are often impaired. For instance isotype

Table 1
Known natural and synthetic ligands of human Toll-like receptors (TLR)

TLR	Ligands
TLR1, 2	Tri-acylated lipopeptides, LTA, PAM3CSK4, PGN, Zymosan
TLR2, 6	Di-acylated lipopeptides, MALP-2, Zymosan, LTA
TLR3	dsRNA, CMV, influenza A, poly IC
TLR4	LPS
TLR5	Flagellin
TLR7	Imidazoquinolone
TLR8	ssRNA (G-U rich), Imidazoquinolone
TLR9	Unmethylated CpG DNA, CMV, HSV, malarial protein

LTA, lipoteichoic acid; PGN, peptidoglycan; dsRNA, double-stranded RNA; LPS, lipopolysaccharide; ssRNA, single-stranded RNA; CMV, cytomegalovirus; HSV, herpesvirus.