CHAPTER 6

NF-κB and Immune Cell Effector Functions

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Abstract

Initially identified as a constitutive nuclear factor of kappa light chain immunoglobulin in B lymphocytes (NF-κB), the NF-κB transcription factor family now consists of 5 mammalian members (p50/NF-κB1, p52/NF-κB2, p65/RelA, c-Rel, and RelB). Individual knockouts of each NF-κB subunit in mice have shown that NF-κB is functionally expressed in nearly every tissue and cell type. The best documented roles for NF-κB lie in their ability to modulate the development, activation, and effector functions of immune cells. NF-κB participates in both innate and adaptive immunity through regulation of target genes including anti-apoptotic molecules, cell cycle regulators, cytokines, surface receptors, and various other immune modulators. This chapter will focus on the contribution of each NF-κB member to immune cell differentiation and effector function, particularly with regard to macrophages, dendritic cells, T lymphocytes, and B lymphocytes.

Brief Overview of the Immune System

The primary purpose of the vertebrate immune system is to protect the host from infection by foreign pathogens such as bacteria, viruses, and parasites. Distinct immune cell types carry out two main branches of host immunity, namely the innate and adaptive arms of immune regulation. However components of the innate system also play an important part in shaping the adaptive system. Here we review key elements of the immune system that will be relevant to this chapter.

Immune responses are initiated by host cells which recognize foreign antigens as potentially harmful substances in the body. Innate responses are typically generated against microbial antigens through recognition of invariable patterns expressed on molecules produced by pathogens. To identify these antigens, phagocytes such as macrophages and neutrophils bear pattern-recognition receptors (PRR) on their cell surface. The breadth of antigenic responses induced upon recognition by PRRs is restricted however, as only a limited number of fixed structures are effectively detected. As a consequence, the adaptive immune system has evolved to allow more specific recognition of pathogenic antigens, and entails use of antigen-specific receptors to identify these unique epitopes. Antigen-specific receptors are found only on the surface of lymphocytes, and are generated through genetic recombination to produce receptors bearing variable regions that can recognize a potentially infinite number of epitopes. This complex strategy invites a perplexing dilemma as to how the immune system distinguishes "foreign" versus "self" antigens. Mechanisms must therefore be in place to spare the host from
attacking its own tissues. To avoid harmful autoimmune responses, nature has evolved a fail-safe method to remove self-reactive lymphocytes via a process termed negative selection. Negative selection ensures that only nonself-reactive lymphocytes are allowed to populate peripheral lymphocyte pools in the body.

As it stands, the immune system is prepared to guard against foreign invasion and has developed similar methods for the surveillance of abnormal cell growth (i.e., tumors). Modern medicine, not surprisingly, is developing approaches to manipulate these mechanisms for combating cancer, or conversely to enable organ graft tolerance by suppressing undesirable immune reactions. Failure or dysregulation of the immune system therefore has multiple health implications including the development of immunodeficiency, tumorigenesis, hypersensitivity, graft rejection, or autoimmune disease. An understanding of how the immune system operates holds tremendous potential for the treatment of these and many other serious conditions.

**NF-κB and Innate Immunity**

Innate and adaptive immunity comprise two important aspects of host defense against microbial infection. Innate immunity occurs through phagocytosis of pathogenic material and secretion of anti-microbial or inflammatory mediators by cells such as macrophages and neutrophils. This response typically occurs within minutes or hours of infection. Phagocytes recognize pathogens through several forms of pattern-recognition receptors, including mannose receptors, scavenger receptors, and the more recently identified family of Toll-like receptors (TLRs). Recognition by these receptors leads to (1) enhanced phagocytic activity, (2) production of anti-microbial products such as nitric oxide (NO), defensins, and proteolytic enzymes, (3) production of anti-inflammatory cytokines such as TNF-α, IL-1, and IL-6, (4) production of chemokines or trafficking and adhesion molecules, and (5) expression of costimulatory molecules.

Notably, signaling through all members of the TLR family converge upon the activation of NF-κB through shared signaling pathways (see chapter on Receptor and Adaptor Signaling). Multiple studies support the role of NF-κB in the production of inflammatory mediators that control innate immune responses against bacterial infection. NF-κB induced expression of NO synthase (iNOS) for instance, has been well-documented and highlights one of the key pathways involved in respiratory NO production. Subsequent studies in NF-κB knockout mice have shown that deletion of p65 and c-Rel decreases production of iNOS, as well as the expression of TNF-α, IL-1, and IL-6 in macrophages. These reports implicate NF-κB in the regulation of inflammatory cytokines and the respiratory burst in phagocytes. Other studies in mice lacking p50 illustrate the physiological significance of NF-κB-mediated host defense where an inability to clear L. monocytogenes and greater susceptibility to infection with S. pneumoniae is seen. The observed immunodeficiencies are attributed to a hyporesponsive reaction to bacterial lipopolysaccharide (LPS) through a TLR4-dependent recognition pathway. These data suggest that intact NF-κB protein is essential for TLR signaling during activation of macrophages and neutrophils in the clearance of bacteria.

Corroborating these findings is a recent report on a human subject experiencing a recurrent bacterial infection. The study showed that leukocytes derived from the patient displayed profound hyporesponsiveness to LPS and IL-1 concurrent with diminished downstream NF-κB activation. Evidence suggests that the patient carried specific mutations in the IRAK-4 molecule, a kinase downstream of the TLR4 and IL-1R pathways that is required for NF-κB activation (see chapter on Receptors and Adaptors for NF-κB Signaling). Thus, studies such as this support the notion that regulation of inflammatory cytokines, chemokines, and costimulatory molecules by NF-κB is critical to phagocyte activation, maturation, trafficking to inflamed tissues, as well as the ability to present pathogenic antigens to infiltrating T lymphocytes. NF-κB therefore constitutes an important aspect of frontline defense during infection.