Chapter 3
Potential Role of Nuclear Factor κB in Cardiovascular Disease: An Update

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ABSTRACT

Lung and Cardiovascular disease creating a major health burden in developed countries and primary cause of deaths. Although treatments have progressed, the development of novel treatments for patients with cardiovascular diseases remains a major research goal. Despite modern advances in pharmacological and interventional cardiology, cardiovascular disease still remains a leading cause of morbidity and mortality in all over the world. The nuclear factor (NF)-κB super family of transcription factors has been implicated in the regulation of immune cell maturation, cell survival, and inflammation in many cell types, including cardiac myocytes. Recent studies have shown that NF-κB is cardioprotective during acute hypoxia and reperfusion injury. NF-kB regulates the gene expression of major pro-inflammatory cytokines (TNF-a, IL-b), chemokines [macrophage inflammatory protein (MIP-2), cytokine-induced neutrophil chemoattractant (CINC)], and adhesion molecules (ICAM-1, E selectin) (2), all of which play a major role in lung injury. However, prolonged activation of NF-κB appears to be detrimental and promotes heart failure by eliciting signals that trigger chronic inflammation through enhanced elaboration of cytokines. In this review, we summarize progresses in understanding the NF-kB pathway in lung and cardio-vascular disease development as well as in modulating NF-kB for prevention and therapy.

INTRODUCTION

Over the past few years, the transcription factor nuclear factor (NF)-kB and the proteins that regulate it have emerged as an importance signaling system in human physiology and in an increasing number of disease pathogenesis. Ranjan Sen and David Baltimore (Sen & Baltimore, 1986) identified a DNA-binding factor that has since been found to be ancient and evolutionarily conserved and to be linked to many biological pathways. It influences cellular development, innate and adaptive immune responses,

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the induction of inflammatory mediators and wound repair, and, when dysregulated, can lead to various forms of cancer, autoimmunity and chronic inflammatory syndromes this factor is NF-κB (Baltomore, 1986, Pages 705-716).The NF-κB family controls multiple processes, including immunity, inflammation, cell survival, differentiation and proliferation, and regulates cellular responses to stress, hypoxia, stretch and ischemia (Evans etal, 2010). It is therefore not surprising that NF-κB has been shown to influence numerous cardiovascular diseases including atherosclerosis, myocardial ischaemia/reperfusion injury, ischaemic preconditioning, vein graft disease, cardiac hypertrophy and heart failure (Hopkins, Ouchi, Shibata & Walsh, 2007). The function of NF-κB is largely dictated by the genes that it targets for transcription and varies according to stimulus and cell type (Morgan & Liu, 2011,page 103–115). Thus NF-κB has divergent functions and can protect cardiovascular tissues from injury or contribute to pathogenesis depending on the cellular and physiological context. The present book chapter will focus on recent studies on the function of NF-κB in the lung and cardiovascular system.

Nuclear Factor-κB Signaling

NFκB comprises a family of transcription factors first described as B-lymphocyte-specific nuclear proteins, essential for transcription of immunoglobulin kappa (κ) light chains. Mammalian cells contain five NFκB subunits—relA (p65), relB, c-rel, p50 and p52, that exist in an inactive form in the cytoplasm bound to three inhibitory proteins (IκBα, IκBβ and IκBε) (Evans etal, 2010). In most cell types, NF-kB proteins are sequestered in the cytoplasmic compartment, associated with members of the inhibitor of kB (IkB) family (IkBa, IkBb and IkBe). In response to multiple stimuli such as inflammatory cytokines, bacterial lipopolysaccharide (LPS), viral infection or stress, IkBs are phosphorylated on two critical serine residues. This modification triggers their ubiquitination and destruction via the proteasome degradation machinery. As a consequence, free NF-kB enters the nucleus and activates transcription of a variety of genes participating in immune and inflammatory responses, cell adhesion, growth control and regulation of apoptosis (Ghosh et al, 2009, Jones et al, 2003, Tiruppathi et al, 2014).

Pro-inflammatory cytokines produced by macrophages, T cells and other immunologic cells exert their actions on target cells by transactivating NF-kB (Karin & Ben, 2000, page 621–663). These cells express receptors for the pro-inflammatory cytokines, IL-1b and TNF-a, and they also contain the IKK complex that is crucial for signal transduction. Cells such as leukocytes, vascular endothelial and smooth muscle cells, cardiomyocytes and fibroblasts therefore respond to pro-inflammatory cytokines by NF-kB activation (Ghosh et al 2004; Baeuerle et al, 1998; Baldwin et al, 1996; Maniatis et al, 1995). Also, NF-kB activation induces the expression of pro-inflammatory cytokines in a positive feedback loop.

The NF-kB pathway is used not only by pro-inflammatory cytokines but also by microbial products. In particular, endotoxins of gram-negative bacteria signal through NF-kB after ligation of their LPS moieties to receptors of the Toll-like receptor (TLR) family. TLR/NFkB– mediated response to bacteria has been a key mechanism through evolution for the protection of multicellular organisms against pathogenic invaders (Maniatis et al, 1995; Janeway et al, 1997)

NF-kB in Acute Lung Injury (ALI)

Acute lung injury (ALI) and its more severe manifestation, acute respiratory distress syndrome (ARDS), are characterized by acute inflammation that affects the function of the gas exchange surface of the lung.