Signal transduction through nuclear factor kappa B in ischemia-reperfusion and heart failure

Abstract Ischemic heart disease is the major cause of morbidity and mortality in the Western world, with chronic heart failure as one complication. Ischemia-reperfusion injury may induce cardiomyocyte cell death by necrosis or apoptosis. The heart can be adapted to tolerate an ischemic event by preceding brief episodes of ischemia and reperfusion, called preconditioning. Innate immunity has the latest years surfaced as important for the development of cardiovascular pathology as well as for myocardial protection. Nuclear factor kappa B (NFκB) is a redox sensitive transcription factor which contributes to the regulation of innate and adaptive immunity. NFκB regulates a battery of inflammatory genes, and has been indicated to play a role in the development of numerous pathological states. Activation of NFκB induces gene programs leading to transcription of factors which promote inflammation, among them leukocyte adhesion molecules, cytokines such as tumor necrosis factor alpha, and chemokines, but may in some situations also promote tissue remodelling, the resolution of inflammation, and transcription of some few substances with possible antiinflammatory effects. The present paper reviews the basic regulation of NFκB, and the possible role of NFκB activation in ischemia-reperfusion injury, in adaptation to ischemia-reperfusion injury, and in chronic heart failure.

Key words Nuclear factor kappa B – preconditioning – signal transduction – toll-like receptors

Introduction

Innate immunity is the process of our first line defence against invading microorganisms (1, 2, 10, 46). Although this was previously believed to be a non-specific response characterized by cellular engulfment and digestion of foreign substances, it is now recognized that the innate immunity response not only has a considerable specificity and capability to discriminate between pathogens and self, but that it also may be a prerequisite for triggering adaptive immunity (1, 10, 46). Adaptive immunity is mediated by clonally distributed B-cells and T-cells, and is characterized by high specificity and memory. Nuclear factor kappa B (NFκB) is a transcription factor with a crucial influence on the regulation of innate and adaptive immunity (6, 15, 29, 42, 71). NFκB is activated by bacterial and viral products, and regulates central genes in the immune response such as proinflammatory cytokines, chemokines, leukocyte adhesion molecules, and inflammatory enzymes (6, 15, 29, 42, 71).

Chronic heart failure is a major health care problem. Although the background for heart failure may be diverse and include, among others, valve disease and...
idiopathic cardiomyopathy, ischemic heart disease is the most common background. Heart failure is clinically manifest as pump failure, and although the prognosis has improved with the use of angiotensin converting enzyme inhibitors and beta-adrenergic blockers, there is still a large need for improved treatment. At a molecular level heart failure is characterized by activation of fetal gene programs, apoptosis, hypertrophy, remodeling, and activation of the immunosystem with overexpression of NFκB-regulated inflammatory genes such as tumor necrosis factor alpha (TNFα), interleukin 1beta (IL-1β), and inducible nitric oxide synthase (iNOS) (19, 23–27, 32, 34). However, although NFκB activation in some situations of heart disease such as ischemia-reperfusion injury appears to be detrimental to the heart, in other situations it may be advantageous such as in the process whereby the heart adapts to ischemia known as preconditioning (71). Nevertheless, NFκB may play a beneficial role for the resolution of inflammation, in tissue remodeling, and it regulates several antiapoptotic genes (38, 51, 53, 71). The present paper reviews the role of NFκB in ischemia-reperfusion injury, ischemic preconditioning, and heart failure.

The NFκB dimer

Recent reviews in depth describe the regulation of NFκB activation and its consequences within the cell at a cellular and molecular level (6, 15, 29, 42, 71). Briefly, NFκB can be activated by reactive oxygen intermediates, hypoxia/anoxia, hyperoxia, cytokines, protein kinase C activators, MAP kinase activators, bacterial or viral products, such as lipopolysaccharide, dsRNA, or the human T-cell leukemia virus type 1 Tax protein, and by UV radiation. NFκB regulates genes involved in both innate and adaptive immunity, among them proinflammatory cytokines, chemokines, leukocyte adhesion molecules, and inflammatory enzymes (6, 15, 29, 42, 71). The NFκB family consists of the members p50, p52, p65 (RelA), c-Rel, and RelB which form various homo- and heterodimers, where the most common active form is the p50 or p52/RelA heterodimer. NFκB dimers in resting cells reside in the cytoplasm in an inactive form bound to inhibitory proteins known as IκB. At least six IκB proteins are involved in controlling the activity of the NFκB dimer (6, 15, 29, 42, 71). IκBα and IκBβ, the two stimulus-regulatory proteins of NFκB, have two N-terminal serine residues that are phosphorylated in response to diverse stimuli. The phosphorylated IκBs are then ubiquitinated and proteolytically degraded. This process activates NFκB, which translocates to the nucleus and binds to promoter or enhancer regions of specific genes, initiating transcription (6, 15, 29, 42, 71).

NFκB activation by IκB kinases

A critical step in the activation of NFκB is the phosphorylation of IκBs by a multimeric complex referred to as the IκB kinase (IKK) complex (16). The IKK complex consists of two catalytic subunits (IKK1/IKKa and IKK2/IKKβ) (20, 48), the NFκB essential modulator alternatively referred to as NEMO (75), IKKγ (60), IKK-associated protein (53), or FIP-3 (43). NEMO is not itself a kinase, but mediates crucial protein-protein interactions, possibly with upstream activators of the kinase complex (60, 75). Activation of the IKK complex is mediated via phosphorylation of either IKKa or IKKβ by the upstream kinases including NFκB inducing kinase (NIK) and MEKK1 of the MAP3K family (35, 43, 44, 59). IκB is then recruited into the IKK complex through phosphorylation of serine residues. Recently, another IKK complex has been suggested containing an IκB kinase referred to as IKKε (58). In addition, a lipopolysaccharide-inducible IκB kinase, IKKi, has also been identified (63). IKKε can be induced in immune cells in response to LPS and the proinflammatory cytokines TNFα, IL-1β and IL-6, and IKKε phosphorylates TRAF1 and c-Jun N-terminal kinase (57).

Toll-like receptors in NFκB signaling

Toll receptors were first identified as an essential molecule for embryonic patterning in Drosophila, and discovered as a key to antifungal immunity (40). Toll receptors are transmembrane proteins which are evolutionary conserved between insects and humans. In humans a homologous family of Toll-like receptors (TLR) consisting of more than 10 members have been identified (1, 10, 46). The cytoplasmatic portion of TLR are linked to the IL-1 receptors based on the similarity (designated the Toll-IL-1R or TIR domain), while the extracellular portions are different. Thus, the intracellular downstream signaling from TLR is similar, using the adaptor protein MyD88 to phosphorylate IR-associated protein kinase (IRAK) when the ligand is bound to the IL-1R. Phosphorylated IRAK dissociates from the receptor complex and associated with TNF receptor-activated factor 6 (TRAF6), resulting in the activation of two different pathways: the c-Jun N-terminal kinase and the p38 mitogen activated protein kinase of the mitogen activated protein kinase family, and NFκB. TLR were first described in immune cells, but since then have also been discovered in endothelial cells, myocytes, adipocytes, and intestinal epithelial cells (1, 10, 46). TLR serve as so-called pattern-recognition receptors, recognizing pathogen associated molecular patterns which are shared by large groups of microorganisms. The different subfamily members recognize different products; for instance, TLR 4 recognizes...