

NF- κ B in allograft rejection

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ABSTRACT: Nuclear factor-kappa B (NF- κ B) as an essential transcription factor in the control of expression of the cytokine-induced genes in immune and inflammatory responses regulates cytokines in allograft rejection. In this review, we summarize the general properties of NF- κ B and the principal findings to shed new light on transplantation.

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Key words: NF- κ B; allograft rejection

Introduction

Nuclear factor-kappa B (NF- κ B) has attracted great interest of researchers since its first report in 1986.^[1] It is an essential transcription factor in control of expression of the cytokine-induced genes involved in immune and inflammatory responses as well as cell growth, differentiation, development, and death.^[2–4] Studies^[2,3,5] have shown that inhibiting NF- κ B will be a potential approach in treating inflammatory diseases, auto-immune diseases, and transplant rejection. In this review, we briefly summarize the general properties of NF- κ B and the major findings that have shed new light on transplantation.

The role of NF- κ B in gene regulation

NF- κ B is a DNA binding protein complex that is usually present in the cytoplasm as an inactive complex. I- κ B, an associated protein, renders this complex inactive by shielding the nuclear localization signal (NLS). Upon I- κ B phosphorylation and its subsequent degradation, the heterodimeric NF- κ B complex translocates to the nucleus,^[3,6] where it binds to specific DNA sequences in the promoter

region of several genes and up-regulates their transcription. Facilitated nuclear import is a receptor-mediated process involving NLS-binding proteins, called karyoperins, which reside in the cytoplasm and the nuclear pore.

NF- κ B can be activated within minutes by a variety of stimuli. As to transplantation, the common stimuli include ischemia/reperfusion, allograft antigens, and cytokines such as TNF- α and IL-1.^[2]

Extensive studies have shown that more than 100 genes are regulated by the transcriptional factor NF- κ B and most of them participate in allograft rejection (Table).

NF- κ B in allograft rejection

The important procedures of allograft rejection include EC activation, recipient T cells activation, and maturation of dendritic cells.

NF- κ B and EC activation

One important step in transplanted organ damage is mediated by ischemia/reperfusion (I/R) injury. Ischemia/reperfusion injury after transplantation may result in significant pathological changes in the transplanted organ. Although the causes of reperfusion injury have not been elucidated, existing evidence suggests that there is a multifactorial pathway. It is dependent on up-regulation of adhesion molecules which plays a critical role in the development of reperfusion injury. After reperfusion, reactive oxygen substrate (ROS) is released from

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Table. NF- κ B-inducible proteins involved in transplantation

Type	Role in transplantation and cytokines
Cytokines/growth factors	Lymphocyte activation and cell growth differentiation IL-1 α and β ; IL-2, -3, -6, -12 TNF- α ; LT- α ; IFN- β G-CSF; M-CSF; GM-CSF
Cytokine receptors	T cell activation IL-2R α ; TCR- α β
Chemokines	Lymphocyte infiltration IL-8; MIP-1 α ; MCP-1
Stress proteins	Activate complementary pathway SAA Complement factors B C3 C4 α -acid glycoprotein B β ; CRP
Cell adhesion molecules	Cell adhesion and T cell activation ICAM-1; VCAM-1; MAdCAM-1 E-selectin
Immunoregulatory molecules	Antigen presentation I κ g; MHC class I and II; TCR α and β β 2-microglobulin; Ii; TAP1
Enzymes	Inflammatory damage iNOS; COX-2

Abbreviations; B β ; B factor; CRP; C reactive protein; G-CSF; granulocyte colony-stimulating factor; GM-CSF; granulocyte-macrophage colony-stimulating factor; ICAM-1; intercellular adhesion molecule 1; iCOX-2; inducible cyclooxygenase-2; IFN- β ; interferon- β ; I κ g; immunoglobulin κ light chain; Ii; invariant chain; IL; interleukin; IL-2R α ; IL-2 receptor α -chain; iNOS; inducible nitric oxide synthase; LT- α ; lymphotoxin- α ; MAdCAM-1; mucosal addressin cell adhesion molecule 1; MCP-1; macrophage chemotactic protein 1; M-CSF; macrophage colony-stimulating factor; MHC; major histocompatibility complex; MIP-1 α ; macrophage inflammatory protein 1 α ; SAA; serum amyloid A protein; TAP1; transporter associated with antigen processing 1; TCR; T cell receptor; TNF- α ; tumor necrosis factor- α ; VCAM-1; vascular cell adhesion molecule 1.^[2,3,7-10]

the ischemic tissue. Then the ROS up-regulates endothelial cell surface proteins such as cellular adhesion molecules including ICAM-1, VCAM-1, E-selectin and P-selectin.^[10,11] The increase of adhesion molecules on the endothelial surface promotes binding of neutrophils and transendothelial migration of inflammatory cells to the damaged site.^[12] Transcriptional activation of genes encoding adhesion molecules is tightly regulated by the transcription factor NF- κ B.^[2,13,14]

It has been demonstrated that oxidative stress increases NF- κ B activity.^[15,16] Reperfusion and subsequent reoxygenation of an allograft induce the re-

lease of both reactive oxygen species (i.e., oxidative stress) and TNF- α from the endothelium,^[6] resulting in NF- κ B-mediated transcription of genes encoding inflammatory chemokines, including monocyte chemoattractant protein-1, cytokines, and cell adhesion molecules.^[17,18]

The role of ICAM-1 in reperfusion injury has been extensively studied. ICAM-1 binds to its ligand LFA-1 on neutrophils and promotes neutrophils binding to the endothelium.^[19] Blockage of ICAM-1, either with monoclonal antibodies or with antisense oligodeoxynucleotides, has been shown to decrease reperfusion injury.^[19,20]

NF- κ B and T cell activation

As reported by Albert,^[21] T cell activation requires three signals; triggering of the T cell antigen receptor, mediated by the TCR/MHC complex; costimulation by CD28/B7 and CD40/CD40L; and signal from cytokines such as IL-2 and IFN- γ . Activated T cells can secrete cytokines such as interleukin-2 (IL-2) and tumor necrosis factor- α (TNF- α),^[22] which activate T cells further and induce apoptosis of allograft cells. The cells can also secrete chemokines such as IL-8, MCP-1 and MIP-1. Activation of T cells also needs increased IL-2R for propagating the IL-2 signal.

Previous studies have shown that NF- κ B activation in T cells is necessary for acute rejection of vascularized cardiac allograft in vitro and in vivo.^[23]

NF- κ B and dendritic cells maturation

Another important cell involving rejection is dendritic cell (DC). DC plays a critical role in the initiation and regulation of immune responses and is instrumental in the induction and maintenance of tolerance.^[24] The ability of DC to induce immunity or tolerance appears to be related to its state of functional maturation. The classic mature DC expresses high levels of MHC class II and costimulatory molecules and stimulates vigorous Th1 responses. In contrast, DC with tolerogenic properties expresses a low level of costimulatory molecules and induces antigen-specific hypo-responsiveness by triggering T cell apoptosis.^[25] Moreover, blockage of costimulation markedly enhances the capacity of

DC to induce T cell apoptosis.^[26] However, tolerance has not been achieved because of late maturation/activation of DC with up-regulation of costimulatory molecules upon encountering a host microenvironment rich in proinflammatory mediators.

DC maturation and function are associated with NF- κ B-dependent gene transcription. Activation of DC by LPS results in up-regulation of CD80, CD86, and inducible nitric oxide synthase (iNOS) gene expression through increased NF- κ B-dependent transcription.^[2,27-29] Potent immunosuppressive drug cyclosporin A (CsA) is verified for the function of inhibition of costimulatory molecule expression of DC by interfering with nuclear translocation of NF- κ B.^[30] Another article^[31] also demonstrated that short oligodeoxynucleotides (ODN) with consensus NF- κ B binding sites can specifically inhibit the NF- κ B activity and maintain DC in tolerogenic state for inducing antigen-specific tolerance.

NF- κ B-targeted therapies in transplantation

Inhibiting the activity of NF- κ B has been used to treat diseases such as asthma, rheumatoid arthritis, inflammatory bowel disease, and cancer,^[32] but the outcome should be evaluated further in transplantation. The identification of NF- κ B as a key factor for the pathogenesis of allograft rejection suggests that NF- κ B-targeted therapeutics might be effective in transplantation. A variety of drugs can inhibit the activation of NF- κ B.^[33] Corticosteroids, a traditional immunosuppressant, used in transplantation for anti-rejection routinely are probably mediated by activating the glucocorticoid receptors which can interfere the binding between NF- κ B and the specific DNA promoter. Then the NF- κ B target genes are inhibited.^[34] Other immunosuppressants such as cyclosporin specifically target the IL-2 expression via inhibiting the calcium-dependent phosphatase calcineurin and consequently inhibiting translocation of NF- κ B.^[10] Some nonsteroidal anti-inflammatory drugs (NSAID) such as aspirin appear to act as a competitive inhibitor of IKK- β . Other anti-inflammatory drugs like sulfasalazine may block nuclear translocation of NF- κ B by inhibiting

I- κ B α degradation. These drugs, however, are not specific, and require relatively high concentrations to achieve an effective NF- κ B inhibition. Although successful outcome has been obtained with sulfasalazine in treating chronic graft-versus-host disease after allogeneic bone marrow transplantation,^[35] the side-effects of NSAID limit their use.

Some researchers have inhibited the activation of NF- κ B by transferring domain negative I κ B α gene, encoding non-degradable I κ B α protein.^[23] The allograft rejection is reduced significantly. Another method to inhibit NF- κ B is to inject κ B decoy oligonucleotides, which contain a sequence corresponding to the consensus sequence of κ B binding site.^[36,37] Although marked outcomes are obtained, further investigations are needed for clinical use.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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