Nuclear Factor-κB: Central Regulator in Ocular Surface Inflammation and Diseases

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ABSTRACT The nuclear factor-κB (NF-κB) is a key transcription factor pathway that is responsible for many key biological processes, such as inflammation, apoptosis, stress response, corneal wound healing, angiogenesis, and lymphangiogenesis. Numerous recent studies have investigated NF-κB in the context of ocular surface disorders, including chemical injury, ultraviolet radiation-induced injury, microbial infections, allergic eye diseases, dry eye, pterygium, and corneal graft rejection. The purpose this article is to summarize key findings with regard to the pathways regulating NF-κB and processes governed by the NF-κB pathway. In the innate defense system, NF-κB is involved in signaling from the toll-like receptors 2, 3, 4, 5 and 7, which are expressed in conjunctival, limbal, and corneal epithelial cells. These determine the ocular responses to infections, such as those caused by *Pseudomonas aeruginosa, Staphylococcus aureus*, adenovirus, and herpes simplex-1 virus. Natural angiogenic inhibitors enhance NF-κB, and this may occur through the mitogen-activated protein kinases and peroxisome proliferator-activated receptor γ. In alkali injury, inhibition of NF-κB can reduce corneal angiogenesis, suggesting a possible therapeutic strategy. The evaluation of NF-κB inhibitors in diseases is also discussed, including emodin, besifloxacin, BOL-303242-X (mapracorat), thymosin-β4, epigallocatechin gallate, Perilla frutescens leaf extract and IKKβ-targeting short interfering RNA.

KEY WORDS angiogenesis, apoptosis, inflammation, NF-κB, signal transduction, transcription factors, wound healing

I. INTRODUCTION TO NUCLEAR FACTOR-κB (NF-κB) PATHWAY IN THE OCULAR SURFACE

NF-κB is a ubiquitous transcription factor that, through target genes, regulates key processes such as inflammation, apoptosis, stress response, wound healing, angiogenesis, and lymphangiogenesis.[1] NF-κB/Rel proteins consist of p50 (originating from p105 or NF-κB1), p52 (derived from p100 or NF-κB2), c-Rel, RelB, and p65 (RelA). The p65, the most commonly studied member, interacts with NF-κB inhibitor protein (IκB) in the cell cytoplasm. Upon activation by various types of pathological or physiological stimulation, IκB is phosphorylated and degraded. The p65 then translocates to the cellular nucleus, regulating transcription of NF-κB target genes.[1]

It is well known that NF-κB regulation is cell- and tissue-specific.[2] Because of the unique anatomical and physiological requirements of the cornea and the special immunological microenvironment of the ocular surface, inflammatory processes in the ocular surface can have sequelae and outcomes very different from those in other parts of the body.[3] NF-κB plays an important role in the development of the cornea and conjunctiva.[4,5] IκB kinase (**IKK**)α, upstream of IκB, is essential for differentiation of corneal and conjunctival epithelium.[4] More importantly, immunological and inflammatory pathways regulating NF-κB and its downstream processes (Figure 1, Table 1) can potentially be exploited in the treatment of human ocular surface diseases (Figure 2).[1]

There has been an increase in the number of studies on NF-κB in the context of the ocular surface in recent years, including its involvement in chemical injury, ultraviolet (**UV**) radiation-induced injury, microbial infections, allergic eye diseases, dry eye, pterygium, and corneal graft rejection. The purpose of this article is to summarize key findings of NF-κB research in the ocular surface and its related cell types. This includes three main categories: regulation of the ocular surface innate immunity, regulation of ocular

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OUTLINE

Abbreviations

AGE	Advanced glycation end products
CCL	Chemokine (C-C motif) ligand
COX	Cyclo-oxygenase
ds	Double-stranded
EGCG	Epigallocatechin gallate
ERK	Extracellular signal-regulated kinase
Fn-14	Fibroblast growth factor inducible 14
hBD	Human beta defensin
HCEC	Human conjunctival epithelial cell
HSV	Herpes simplex virus
ICAM	Intercellular adhesions molecule
IFN	Interferon
IKK	NF-κB inhibitor protein (IκB)-kinase
IL	Interleukin
iNOS	Inducible nitric oxide synthase
IP-10	IFN-induced protein of 10 kDa
I-TAC	IFN-inducible T-cell alpha-chemoattractant
IκB	NF-κB inhibitor protein
JNK	c-Jun N-terminal kinase
LPS	Liposaccharide
MCP	Monocyte chemoattractant protein
MIG	Monokine induced by IFN- γ
MMP	Matrix metalloproteinase
MnSOD	Manganese superoxide dismutase
NF-κB	Nuclear factor-κB
PAMP	Pathogen-associated molecular pattern
PI3K	Phosphoinositide 3-kinase
poly(I:C)	Polyinosinic-polycytidylic acid
RANKL	Receptor activator of NF-κB ligand
RANTES	Regulated on Activation, Normal T Expressed and Secreted
TGF	Transforming growth factor
TLR	Toll-like receptor
TNF	Tumor necrosis factor
TRAF	TNF receptor-associated factor
TWEAK	TNF-like weak inducer of apoptosis
UV	Ultraviole
VCAM	Vascular cell adhesion protein
VEGF	Vascular endothelial growth factor

surface angiogenesis and wound healing response, and regulation of inflammatory response against stress. We also describe recent drugs used in ocular surface intervention via NF-κB targeting.

II. REGULATION OF OCULAR SURFACE INNATE IMMUNITY

Microbial infections, such as bacterial, viral, and fungal keratitis, are common and devastating sight-threatening conditions in the eye.[6] The innate immunity is the first line of defense against microbes, and the toll-like receptors (**TLR**) form a family of pattern recognition receptors that play an important role in innate host defense in the ocular surface.[7-9] These receptors initiate a rapid host innate immune response to microbial components, known as pathogen-associated molecular patterns (**PAMP**s), which determine the outcome of many infections.[7-9]

A. Bacterial Infections

1. Gram-negative Bacterial Keratitis

One of the most commonly encountered clinical conditions is contact lens wear-associated Gram-negative bacterial cornea ulcers, such as those caused by *Pseudomonas aeruginosa*.[6] Hypoxic conditions created by contact lens wear facilitate internalization of *P. aeruginosa* via its cellular receptor, the cystic fibrosis transmembrane conductance channel.[10] This internalization, as well as hypoxia alone, results in elevated NF-κB activation via nuclear translocation and a worsening of inflammation consequently leading to corneal destruction. The use of an NF-κB inhibitor, kamebakaurin, can block the *P. aeruginosa*-induced rise in cytokines, namely interleukin (**IL**)-6, -8 and tumor necrosis factor (**TNF**)-α, reducing the severity of inflammation.[11]

In the cornea, the neuropeptide substance P is a potent immunoregulator, and C57BL/6 mice injected intraperitoneally with substance P showed worsening of *P. aeruginosa*-induced corneal perforation. Both transcript and protein levels of NF-κB were elevated, along with increased neutrophils and bacteria counts in the cornea. The authors