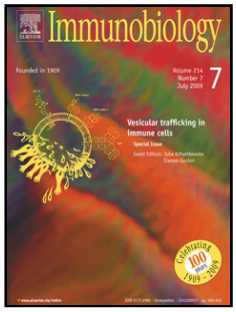
Accepted Manuscript



Title: The effect of IκK-16 on lipopolysaccharide-induced impaired monocytes

Authors: Norman Galbraith, Stephen Manek, Samuel Walker, Campbell Bishop, Jane V. Carter, Meredith Cahill, Sarah A. Gardner, Hiram C. Polk, Susan Galandiuk

PII: S0171-2985(17)30186-9
DOI: https://doi.org/10.1016/j.imbio.2017.10.045
Reference: IMBIO 51685

To appear in:

Received date: 21-8-2017
Accepted date: 19-10-2017

Please cite this article as: { https://doi.org/

<remove picture pageno 1><remove picture pageno 1>Immunobiology

<AT>The effect of IκK-16 on lipopolysaccharide-induced impaired monocytes

<AU>Norman Galbraith, MBChB, MSc <Deg>PhD</Deg>, MRCS[a], Stephen Manek, BS[a], Samuel Walker, BS[a], Campbell Bishop, BS[a], Jane V. Carter, MBChB <Deg>PhD</Deg>, MRCS[a], Meredith Cahill[a], Sarah A. Gardner, BS[a], Hiram C. Polk, Jr., MD[a,b] ##Email##hcpolk01@exchange.louisville.edu##/Email##, Susan Galandiuk, MD[a]
<AU>
<AFF>[a]From the Price Institute of Surgical Research, Hiram C. Polk, Jr., M.D. Department of Surgery, University of Louisville School of Medicine.
<PA>[b]Corresponding author at: The Hiram C. Polk, Jr., M.D. Department of Surgery University of Louisville School of Medicine, Louisville, KY 40292, USA. Tel.: (502) 852-1897; Fax: (502) 852-8915.

<remove picture pageno 1>A B S T R A C T

This study focuses on impaired monocyte function, which occurs in some patients after trauma, major elective surgery, or sepsis. This monocyte impairment increases the risk of secondary infection and death. We aimed to determine the influence IκK-16 had on monocytes using an ex-vivo model of human monocyte impairment. We included the effects of the well-studied comparators interferon-gamma (IFN-γ) and granulocyte-macrophage colony-stimulating factor (GM-CSF) on impaired monocytes. Primary human monocytes were stimulated with 10 ng/mL of lipopolysaccharide (LPS) for 16 h and then challenged with 100 ng/mL LPS to assess the monocyte inflammatory response. Treatment regimens, consisting of either IκK-16, IFN-γ, or GM-CSF, were administered to impaired monocytes near the time of initial LPS stimulation. Stimulation with 10 ng/mL LPS initially promoted a pro-inflammatory response but subsequently impaired production of both tumor necrosis factor-α (TNF-α) and interleukin-10 (IL-10) and decreased HLA-DR expression. IκK-16 treatment attenuated TNF-α production and programmed death-ligand 1 (PD-L1) expression and increased IL-10 and CD14 expression. IFN-γ treatment increased TNF-α production as well as PD-L1 and HLA-DR expression. In conclusion, limiting early inflammation with IκK-16 suppresses TNF-α production and PD-L1 expression but enhances IL-10 production and preserves CD14 expression for potential future exposure to infective stimuli.

<KWD>Abbreviations: DAMPs, danger-associated molecular patterns; ELISA, enzyme-linked immunosorbent assay; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN-γ, interferon-gamma; IL-10, interleukin-10; IκK, inhibitor of kappa B kinase; LPS, lipopolysaccharide; MFI, mean fluorescence intensity; PAMPs, pathogen-associated molecular patterns; PD-L1, programmed death-ligand 1; TNF-α, tumor necrosis factor-alpha

<KWD>Keywords:
Endotoxin tolerance
Monocyte
Sepsis
IκK-16
PD-L1