IL-1β Inhibits BKV Replication in Human Renal Proximal Tubular Cells

2010 Aug. 14th

Wei-Hung Weng
Dept. of Medicine, Chang Gung University
Advisor | Ya-Chung Tian M.D., Ph.D.
Dept. of Nephrology, Chang Gung Memorial Hospital

OUTLINE

- Background knowledge of BK virus (BKV)
- Materials / Methods
- Results
- Conclusions

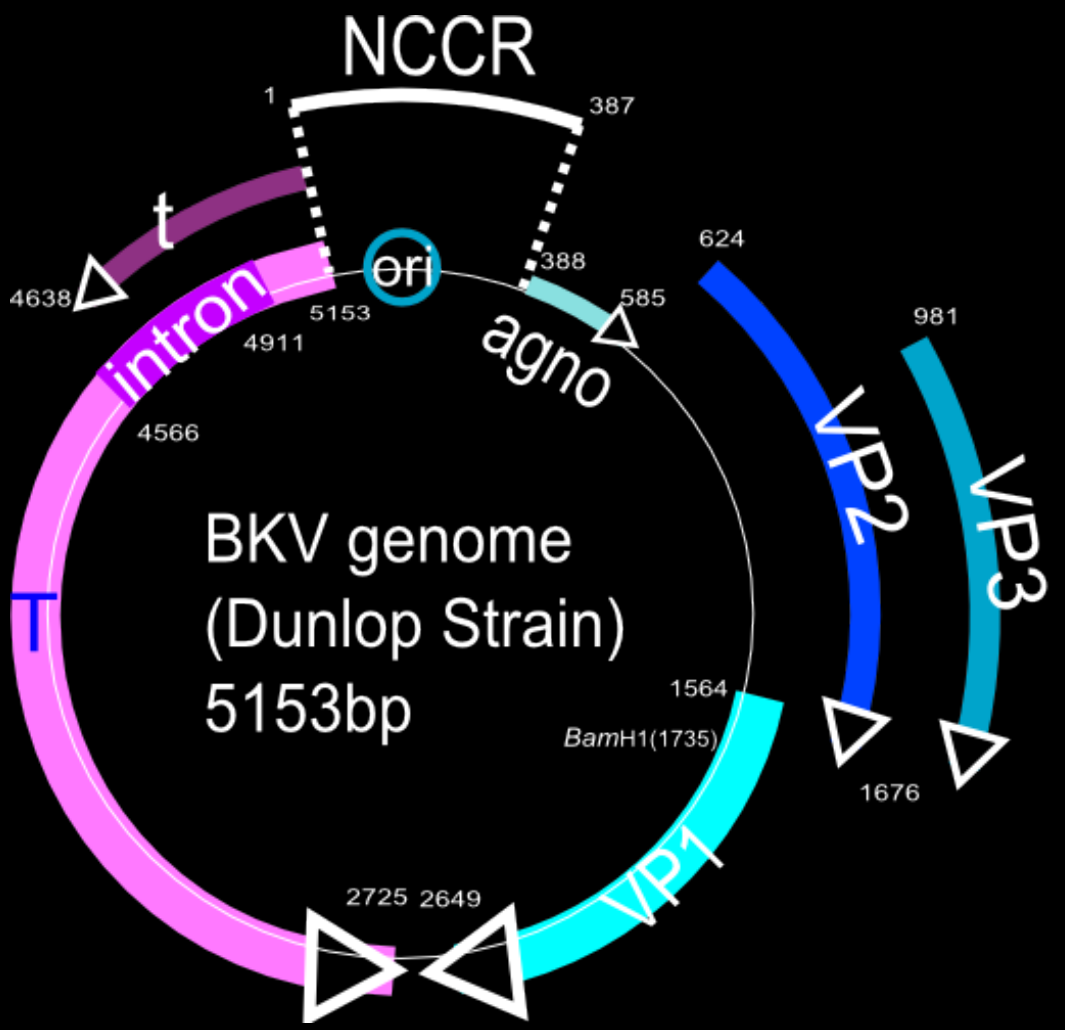
INTRODUCTION

- Polyomaviridae family
  - BKV
    - Viral nephritis and nephropathy

Hirsch H et al. The Lancet 2003

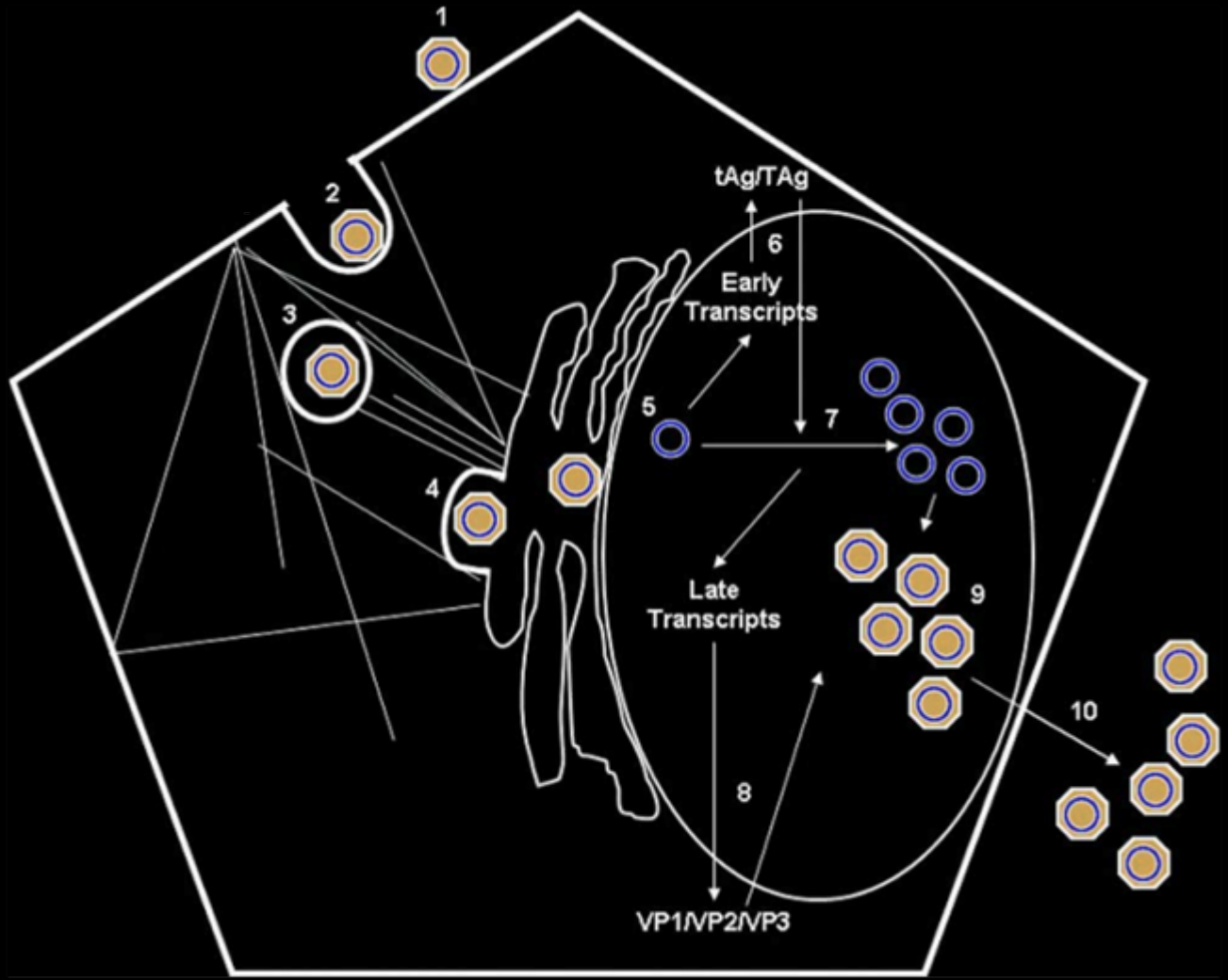
  - JCV
    - Viral encephalopathy
  - Simian virus SV40
    - Hemorrhagic cystitis

Structure



Adapted from CUBITT Christopher L., *Advances in Experimental Medicine and Biology* 577, (2006)

Life Cycle



Adapted from Abend J., *Cytokine-mediated Regulation of BK virus Replication*, (2008)

BKV Infection

- Almost 90% people has exposed to BKV in childhood

Kean, Rao et al. 2009

- Infects and replicates rapidly in the kidney tubular epithelial cells, uroepithelial cells (Renourinary tract)

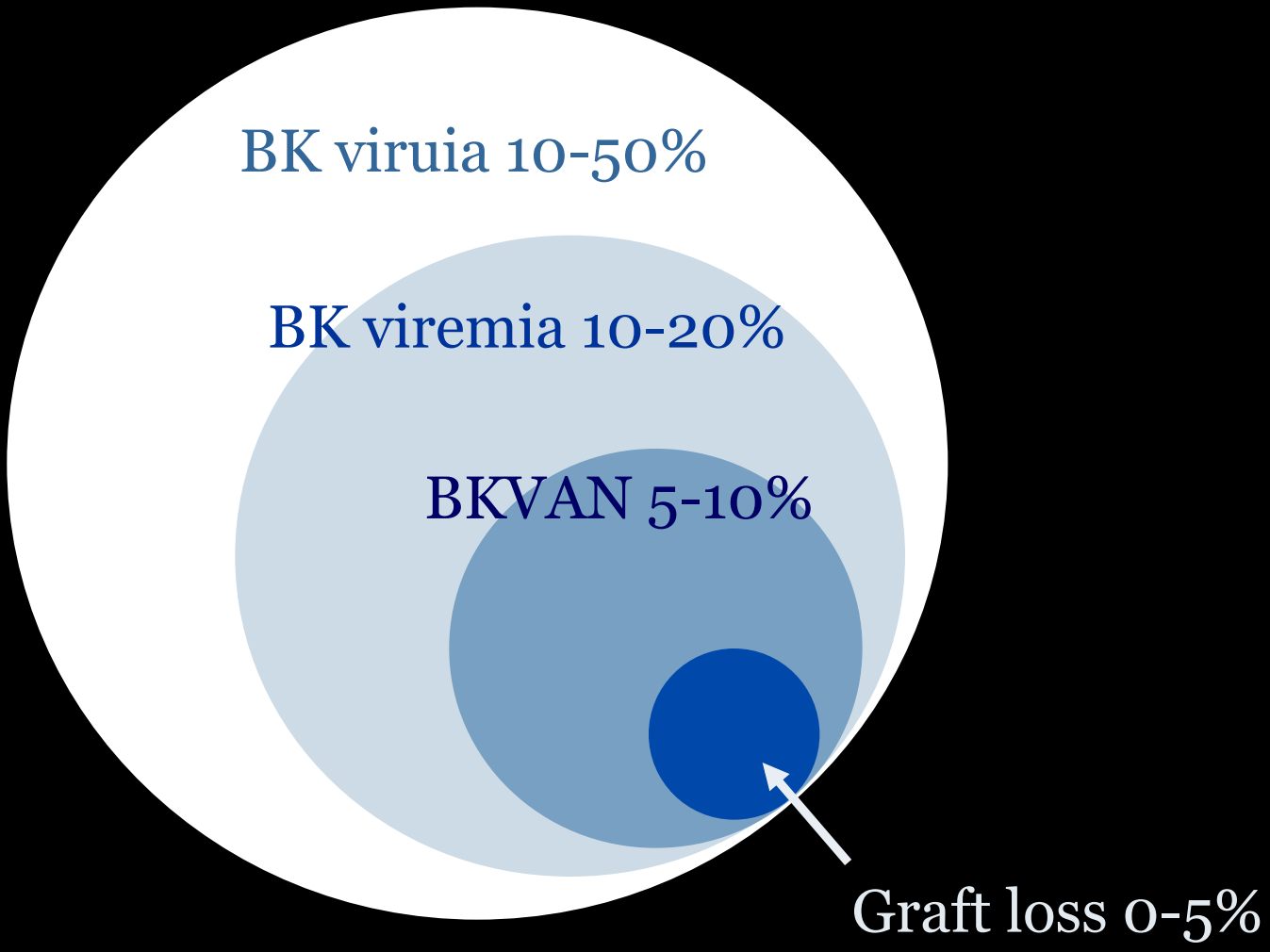
- Primary BKV infection is subclinical or unspecific, poorly characterized

BKV Infection

- Host over-immunosuppression causes BKV reactivation
  - Organ transplant patients
  - Autoimmune disease patients (ex: SLE)

- BKV-associated nephropathy (BKVAN) is often caused by BKV reactivation
  - Graft function loss in 50% of renal transplant patients with BKVAN within 1 year

Vasudev B et al. Kidney Int, 2005.



Hariharan S Am J Transplant, 2005

Cytokines Effect on BKV Infection

- Host cells
  - Human renal proximal tubular cells (HK-2 cells)
- IFN-γ
  - Suppressive effect for BKV
- IL-6 / TGF-β / TNF-α/ IL-15 / MCP-1 / RANTES

Abend, Low et al. 2007

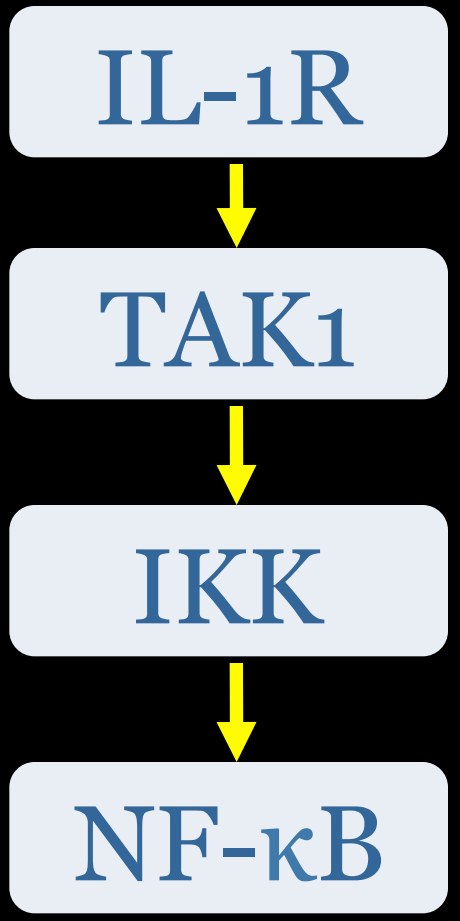
- IL-1β
  - Promote reactivation of CMV and HBV

Cook, Trgovcich et al. 2006, Chen et al. 2006, Zhang et al. 2004

  - No research for BKV infection

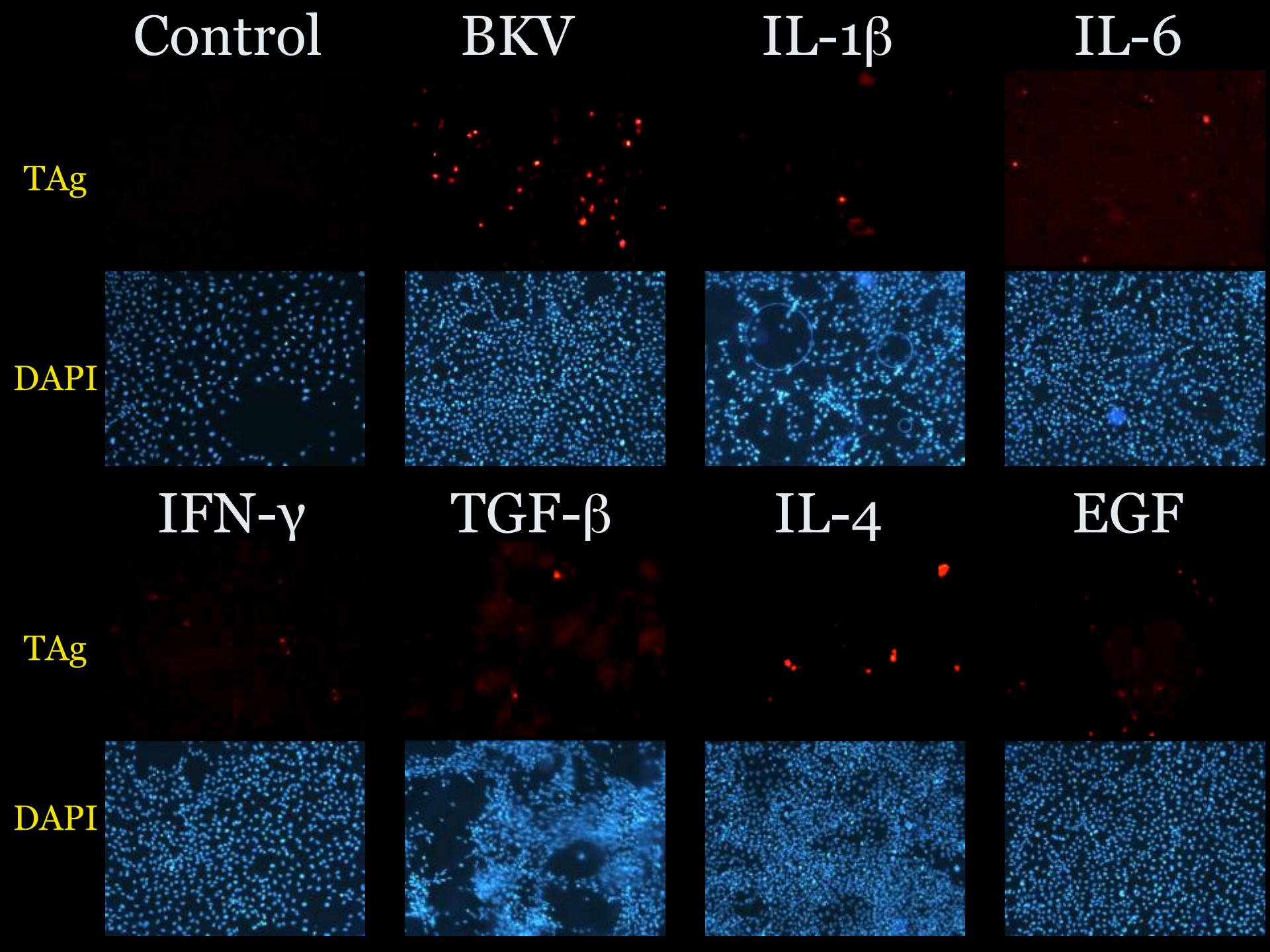
METHODS (*in vitro* study)

- Evaluation of protein expression
  - Immunofluorescent stain
  - Western blotting
- Evaluation of gene transcripts
  - Real-time PCR
- Gene sliencing
  - siRNA

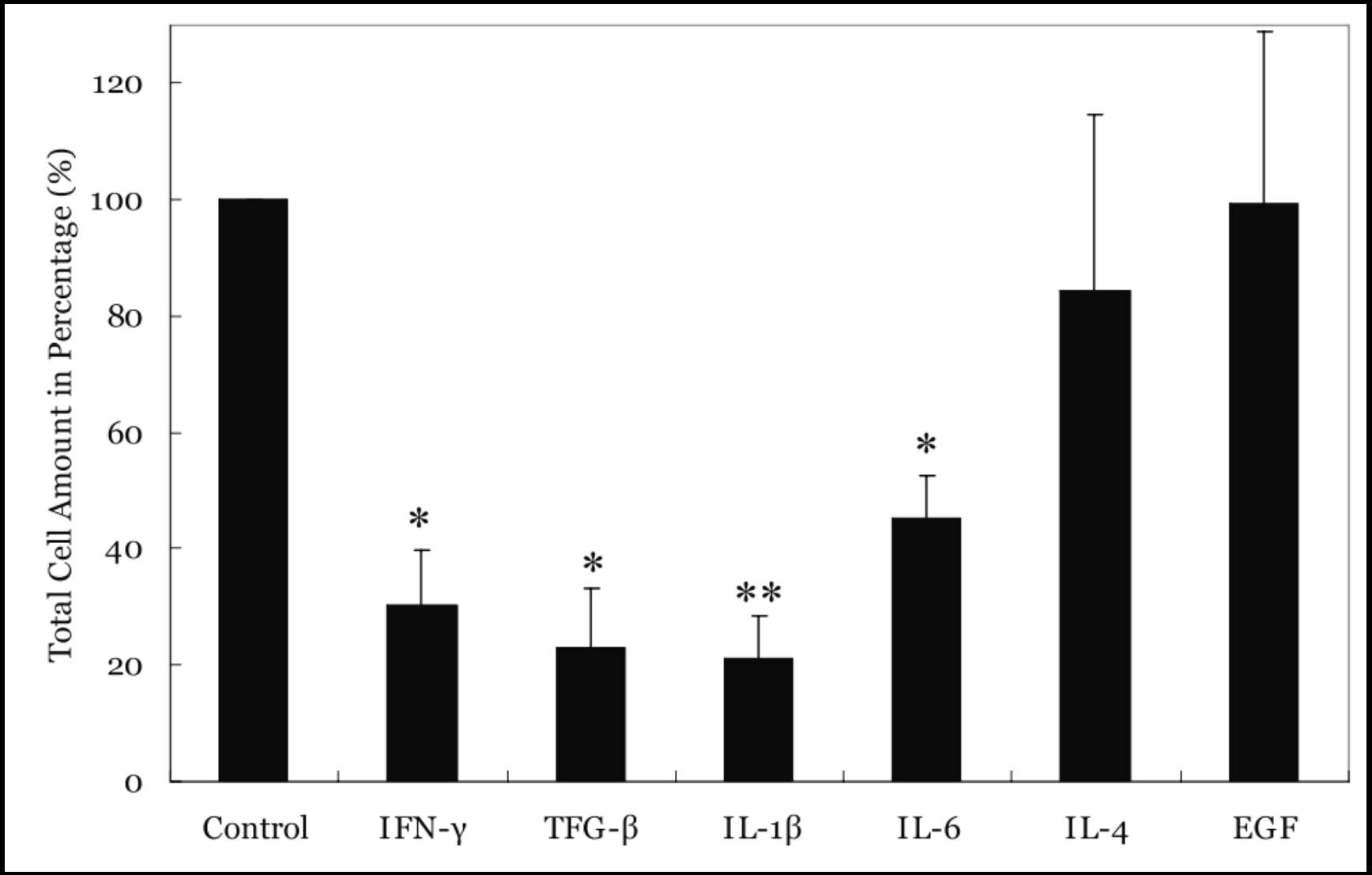


RESULT

- BKV infects renal proximal tubular cells, HK2 cells
- IL-1β reduces BKV protein expression in dose-dependent manner
- IL-1β reduces BKV gene transcription in time and dose-dependent manners
- TAK1 and NF-κB are indispensable for IL-1β-mediated suppression


Control
BKV
IL-1β
IL-6
TAg
DAPI
IFN-γ
TGF-β
IL-4
EGF
TAg
DAPI

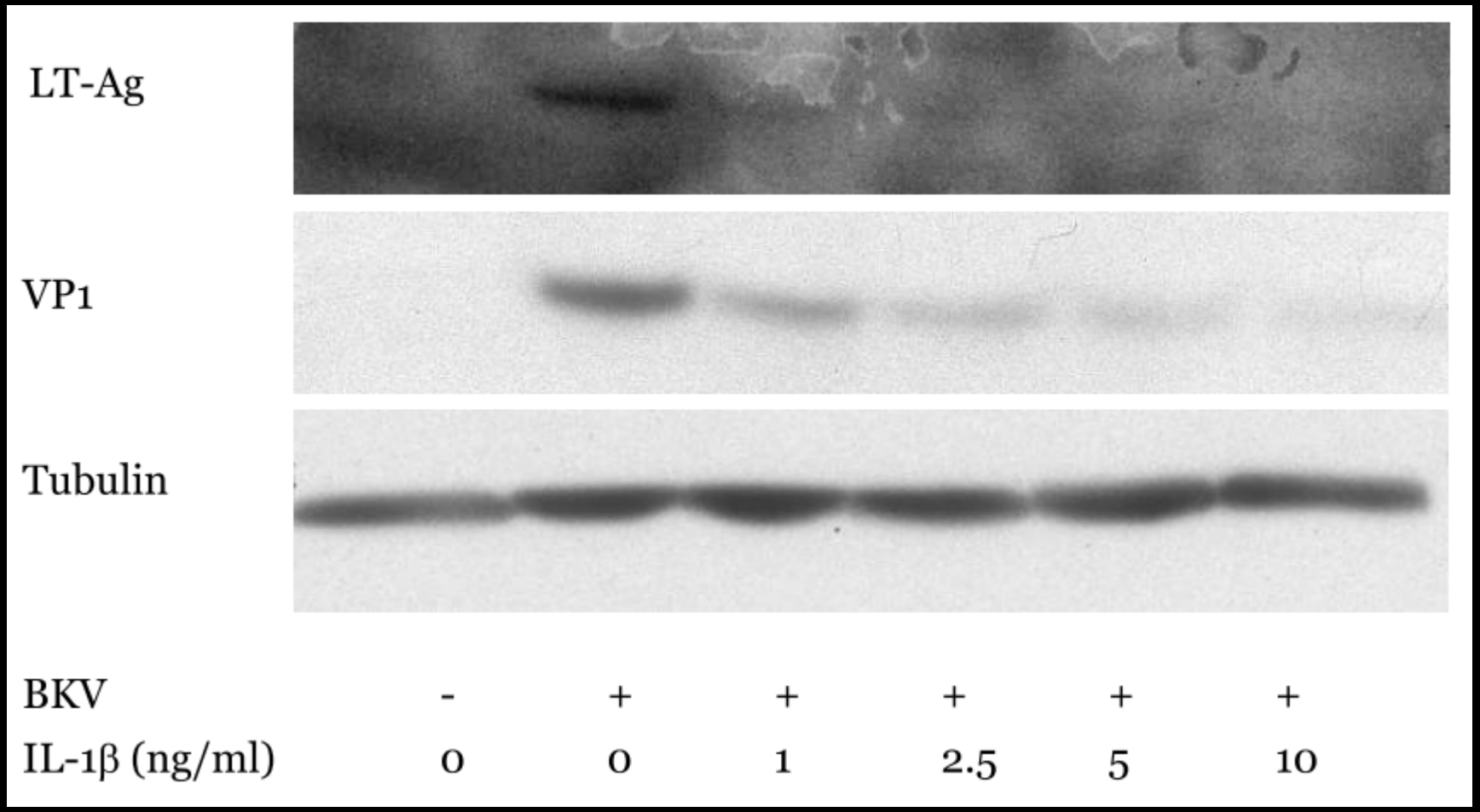
Cytokines Effect on BKV Infection



RESULT

- BKV infects renal proximal tubular cells, HK2 cells
- IL-1β reduces BKV protein expression in dose-dependent manner
- IL-1β reduces BKV gene transcription in time and dose-dependent manners
- TAK1 and NF-κB are indispensable for IL-1β-mediated suppression

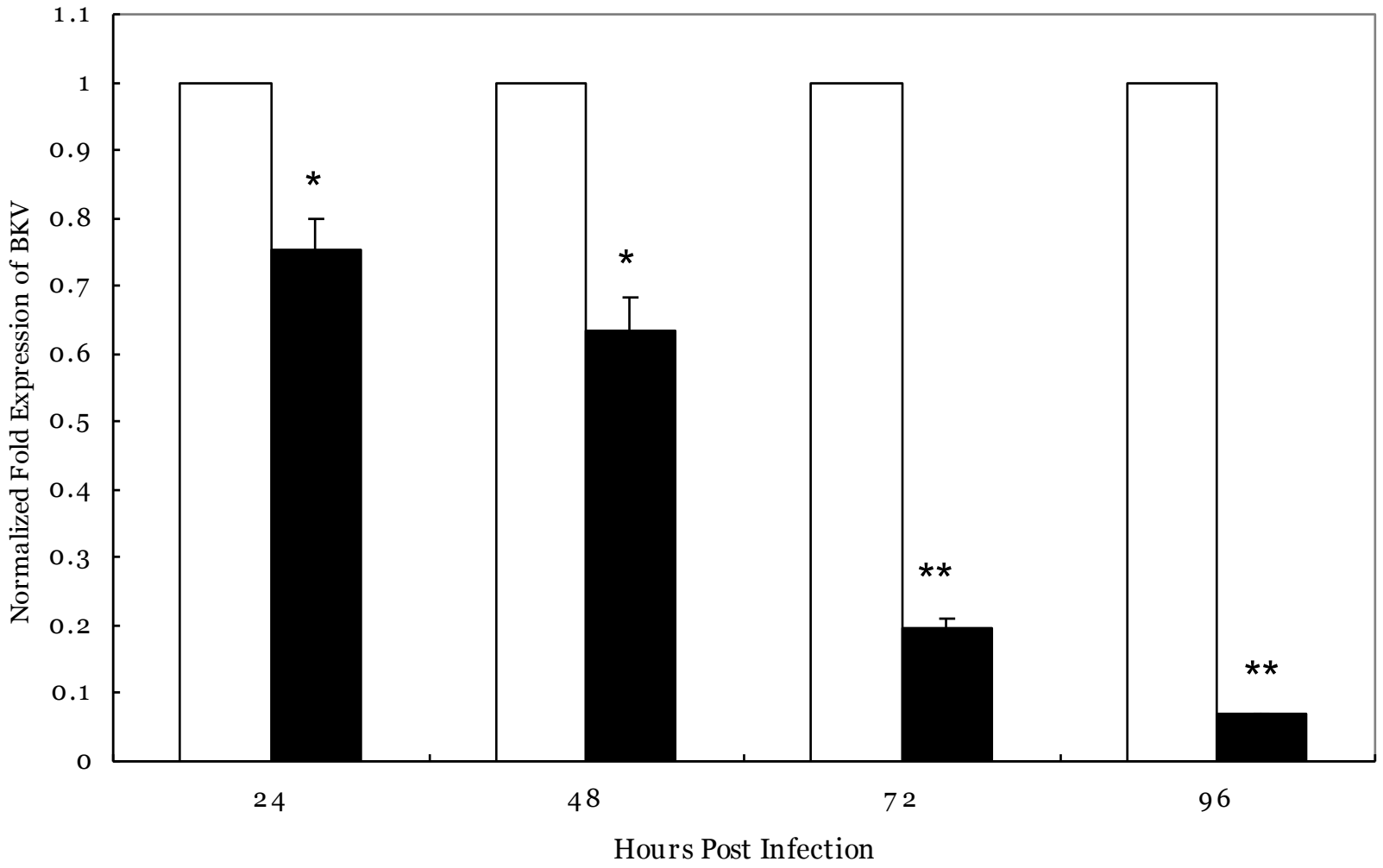
IL-1β has Dose-dependent Suppressive Effect on BKV Replication



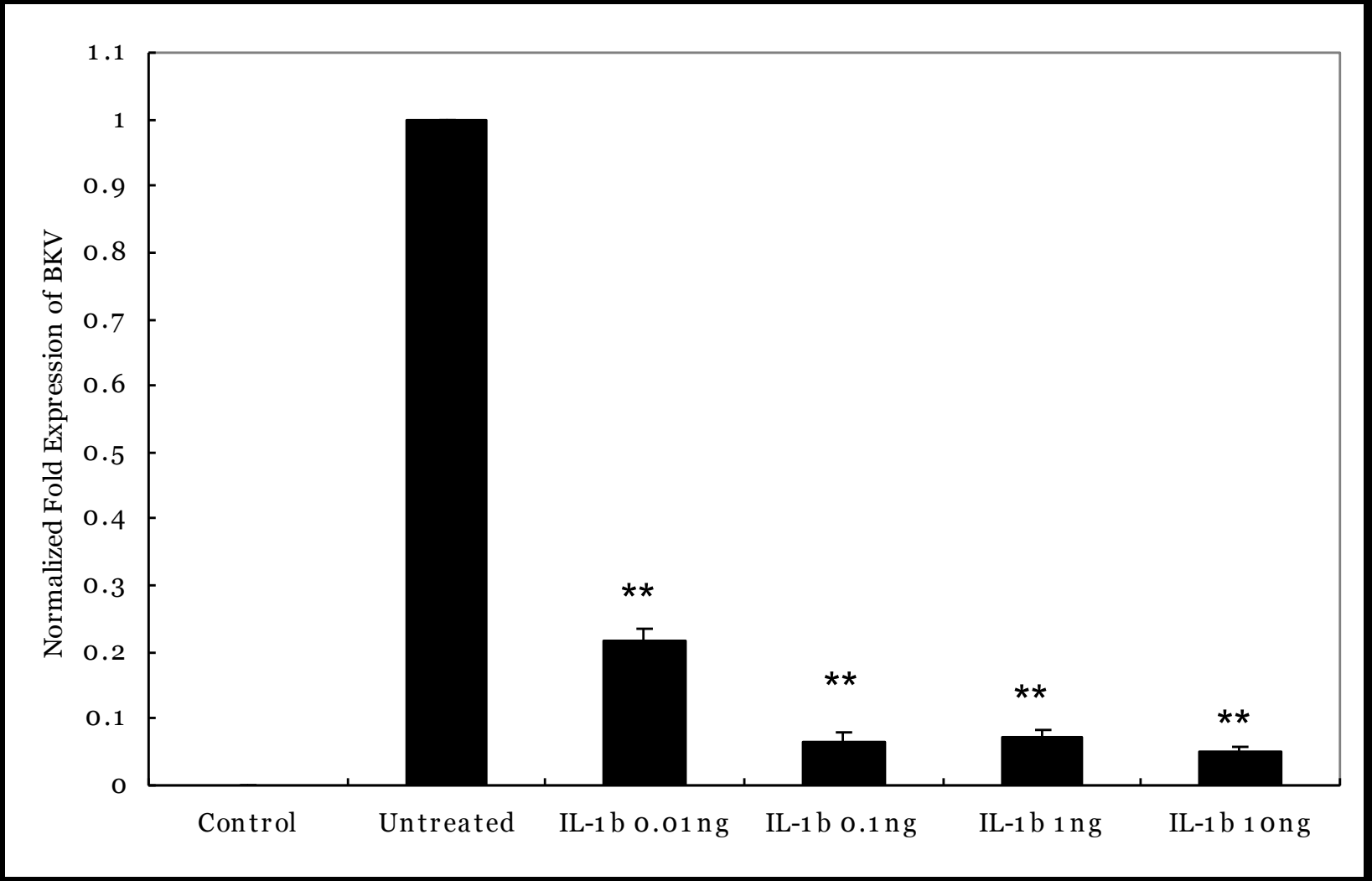
RESULT

- BKV infects renal proximal tubular cells, HK2 cells
- IL-1β reduces BKV protein expression in dose-dependent manner
- IL-1β reduces BKV gene transcription in time and dose-dependent manners
- TAK1 and NF-κB are indispensable for IL-1β-mediated suppression

IL-1β Reduces BKV TAg Transcripts in Time-dependent Manner



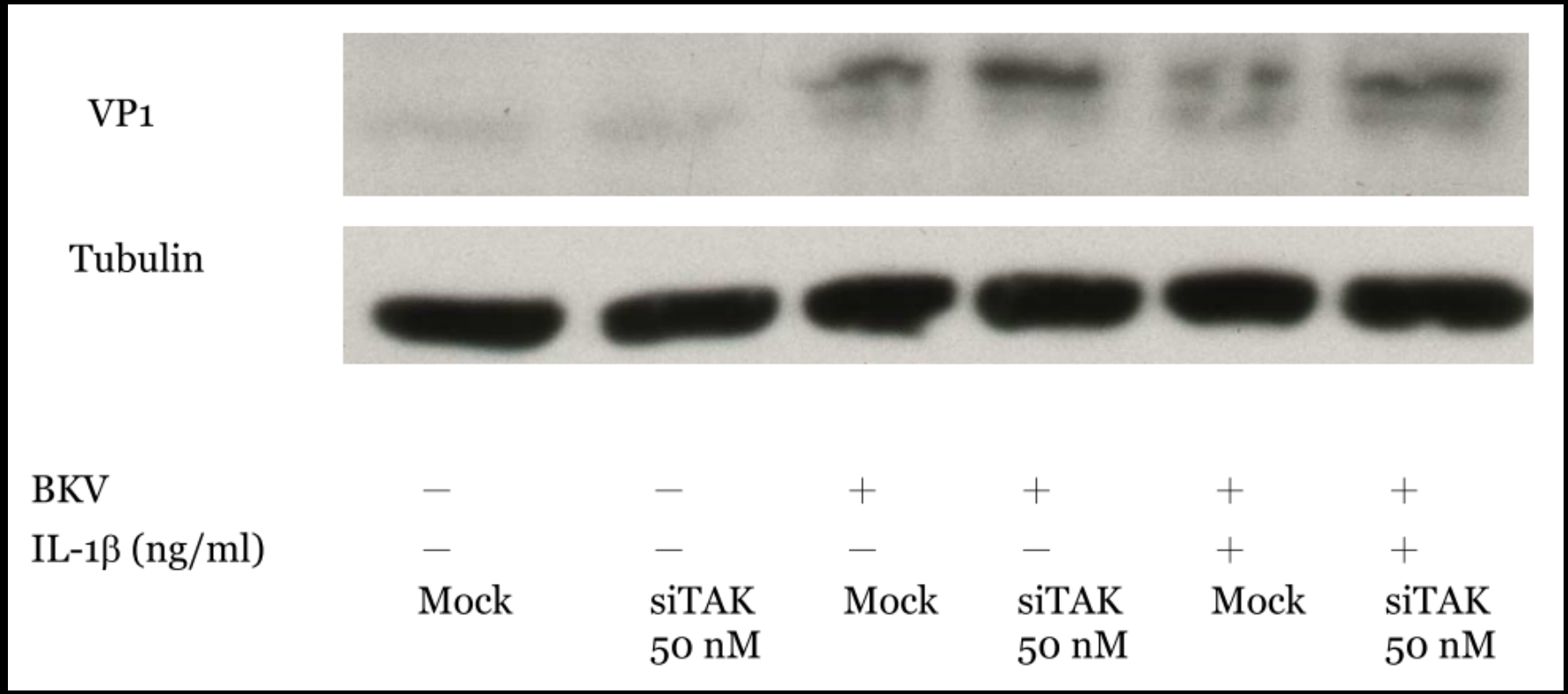
IL-1β Reduces BKV TAg Transcripts in Dose-dependent Manner



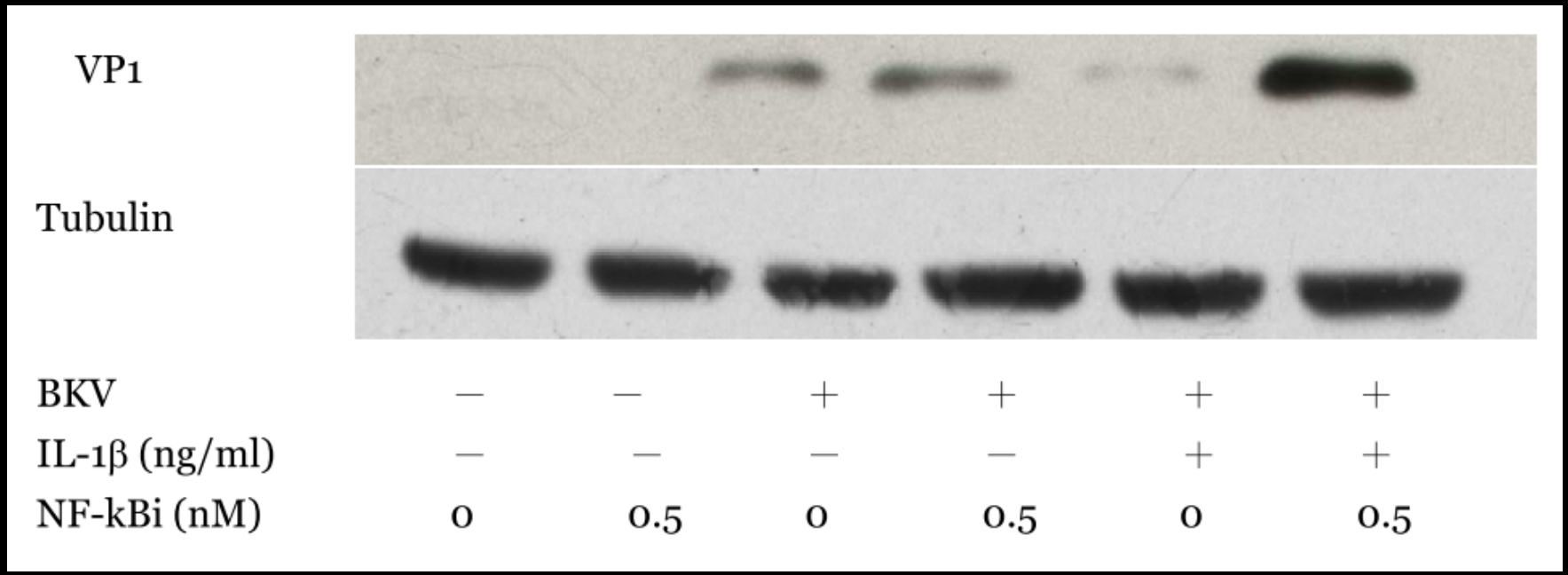
RESULT

- BKV infects renal proximal tubular cells, HK2 cells
- IL-1β reduces BKV protein expression in dose-dependent manner
- IL-1β reduces BKV gene transcription in time and dose-dependent manners
- TAK1 and NF-κB are indispensable for IL-1β-mediated suppression

TAK1 siRNA Reduces the Inhibitory Effect of IL-1β



NF-κB Inhibitor Attenuates the Inhibitory Effect of IL-1β



CONCLUSIONS

- BKV can infect renal proximal tubular cells
- IL-1β reduces BKV TAg and VP1 protein expression in dose-dependent manner
- IL-1β reduces BKV TAg transcription in time- and dose-dependent manners
- TAK1-NF-κB signaling pathway is indispensable for IL-1β-mediated suppression

→ IL-1β has suppressive effect on BKV replication in human renal proximal tubular cells via TAK1-NF-κB signaling pathway