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

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OUTLINE

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

- Polyomavirididae family
  - BKV
    - Viral nephritis and nephropathy
      - Hirsch H et al. The Lancet 2003
  - JCV
    - Viral encephalopathy
  - Simian virus SV40
    - Hemorrhagic cystitis
BKV genome (Dunlop Strain) 5153bp

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

BK viruia 10-50%

BK viremia 10-20%

BKVAN 5-10%

Graft loss 0-5%

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 silencing
  - 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
Cytokines Effect on BKV Infection

[Bar chart showing different cytokines and their effects on BKV infection. The x-axis represents different cytokines: Control, IFN-γ, TFG-β, IL-1β, IL-6, IL-4, and EGF. The y-axis represents the total cell amount in percentage.]
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IL-1β has Dose-dependent Suppressive Effect on BKV Replication

<table>
<thead>
<tr>
<th>LT-Ag</th>
<th>VP1</th>
<th>Tubulin</th>
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<tbody>
<tr>
<td>BKV</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>IL-1β (ng/ml)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
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RESULT

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IL-1β Reduces BKV TAg Transcripts in Time-dependent Manner
IL-1β Reduces BKV TAg Transcripts in Dose-dependent Manner
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TAK1 siRNA Reduces the Inhibitory Effect of IL-1β

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<th>IL-1β (ng/ml)</th>
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<tbody>
<tr>
<td>Mock</td>
<td>–</td>
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<tr>
<td>siTAK 50 nM</td>
<td>+</td>
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NF-κB Inhibitor Attenuates the Inhibitory Effect of IL-1β

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<tr>
<td>BKV</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>IL-1β (ng/ml)</td>
<td>−  −  −  –</td>
<td>–  −  −  −  −  −  −  +</td>
</tr>
<tr>
<td>NF-kBi (nM)</td>
<td>0  0.5  0  0.5  0  0.5  0  0.5</td>
<td>+  +  +  +</td>
</tr>
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</table>
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