HKU AIDS Research Institute Discovers a New Immune Pathway Critical to Treatment of Gut Inflammation in HIV-1 Infection

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Speakers

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HIV / AIDS

- Human Immunodeficiency virus type 1 (HIV-1) causes AIDS
- Infects primarily CD4 T lymphocytes, integrates into the host genome and establishes chronic infection
- Diminishing CD4 T cell count over years
- Immune dysfunction
- Prone to opportunistic infections and other diseases such as gut enteropathy
- Highly active antiretroviral therapy (HAART) can prolong a patient’s life
- No vaccine to date
- New understanding and therapy is required
Early HIV-1 infection

- Gut inflammation
- CD4 depletion
- Inflammatory cytokines
- Viral replication
- Viral setpoint

Difficulty to study

- Rare samples
- Window period <30 days
- Non-human models
Identification of Δ42PD1

- Isoform of PD-1 (Molecular Therapy 2013)
- Expressed on a subset of T cells = γδ-T
- γδ-T comprise of 1-10% of peripheral blood lymphocytes
- Important in maintenance and activating immune response
- Readily migratory
High Δ42PD1+γδ-T cells in acute HIV-1 patients

Plasma cytokines

TNF-α, IL-6, IL-1β, IFN-α = pro-inflammatory cytokines
Δ42PD1+γδ-T cells are gut-homing

Acute HIV-1 patients

Humanized mice model – transfer of labelled cells

Detection of HIV-induced labelled γδ-T cells in small intestines
Δ42PD1+γδ-T cells causes gut inflammation

Small intestines after transfer

Inflammation
- Villous blunting
- Vacuolization
- Epithelial layer detachment
- Mucosal ulceration
- Disintegration of lamina propria
**Δ42PD1-TLR4 interaction**

**Protein-protein binding**

- Protein-protein binding curve showing $K_D = 6.82 \mu M$
  - Different concentrations of TLR4/MD2 (μM): 44.1, 14.7, 4.9, 1.64, 0.49

**Cell experiments**

- Diagram of TLR4 and Δ42PD1 with IL-6 production

**Microscopy**

- Microscopy image of Δ42PD1 and TLR4

**Bar graph**

- Comparison of IL-6 production with different treatments:
  - IsoAb, Anti-Δ42PD1, Anti-TLR4, DMSO, CLI-095, Y6-T only, Untreated, sΔ42PD1, LPS

- Co-DC and DC conditions
Blocking Δ42PD1-TLR4 pathway prevents gut inflammation

CLI-095 = TLR4 inhibitor
HIV-1 infection

“Cytokine storm”

Inflammation
- Epithelial damage
- Villi shortening

Pro-inflammatory Cytokines

TLR4
Δ42PD1

Vδ2
CD103
CCR9
Δ42PD1

Small intestine villi

Summary
Conclusions

• Discovered a new Δ42PD1-TLR4 pathway important to understand early HIV-1 infection
• Generated an antibody to block it and prevent gut inflammation
• May be applicable to other mucosal inflammatory diseases
• Develop the antibody for clinical use
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Q & A Session