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Immunosuppressive effects of HHV-6 and HHV-7: clinical importance

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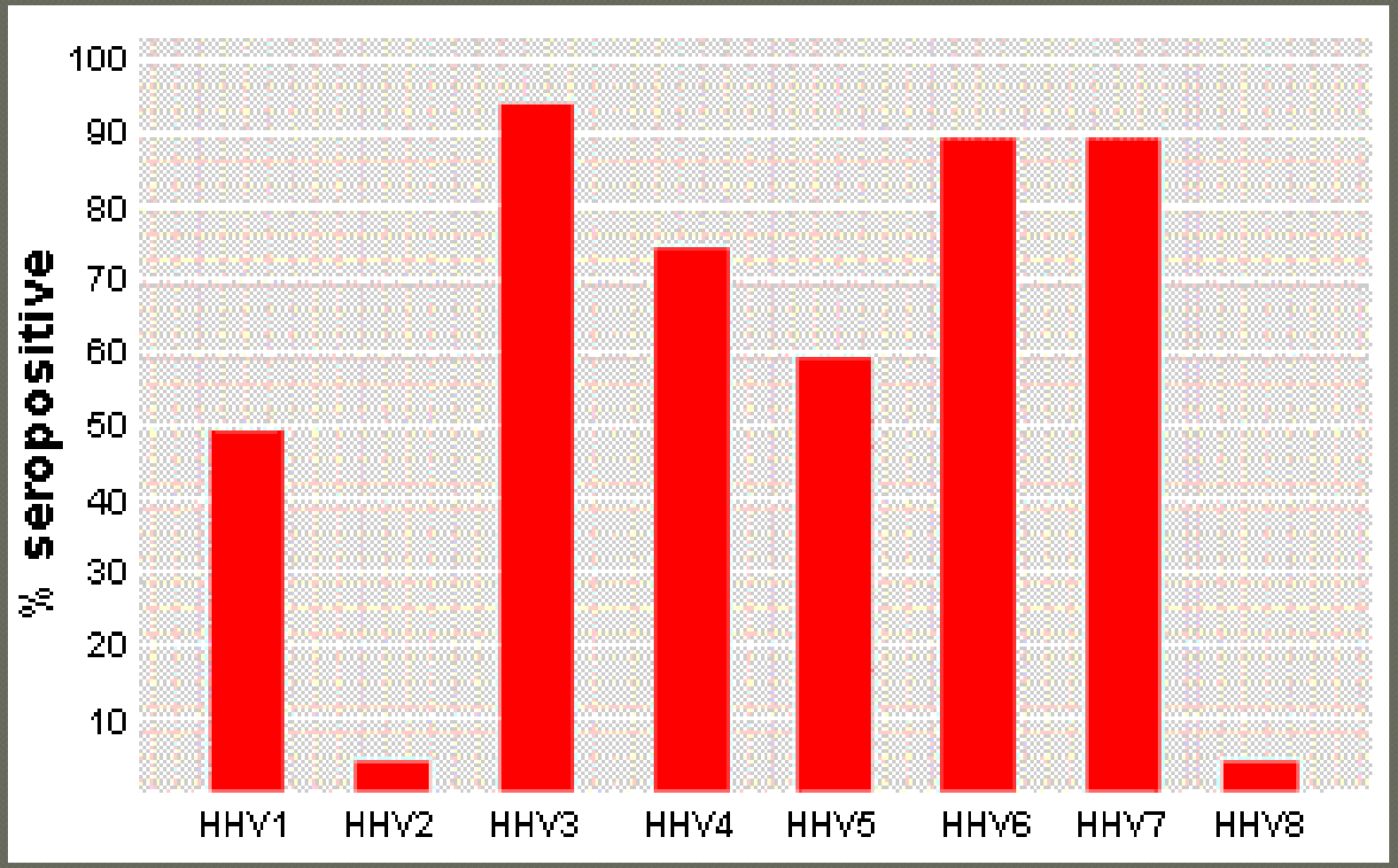
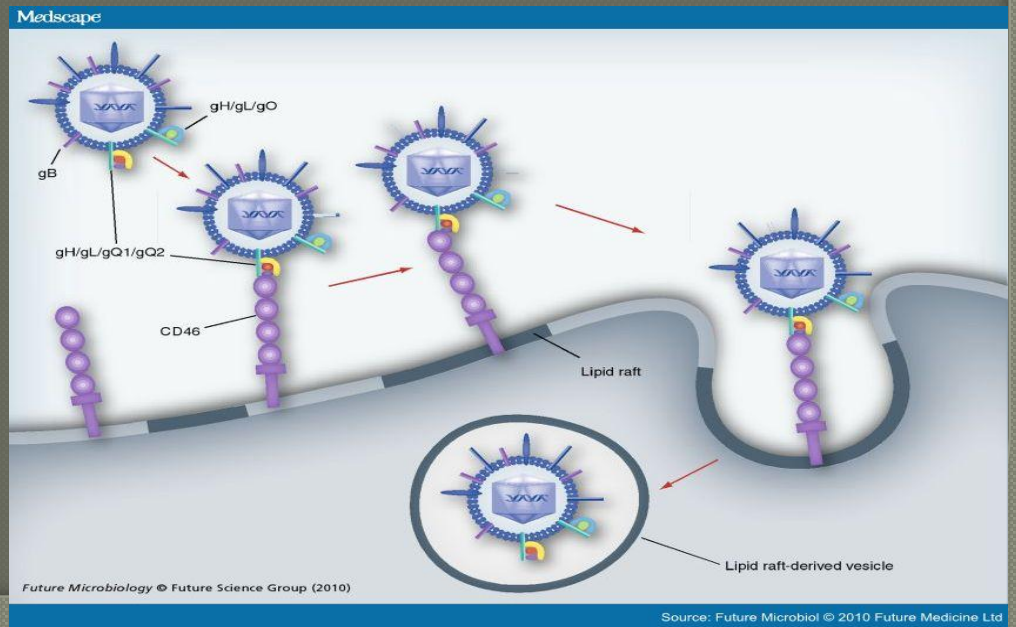
HHV seroprevalence (Hall1997)



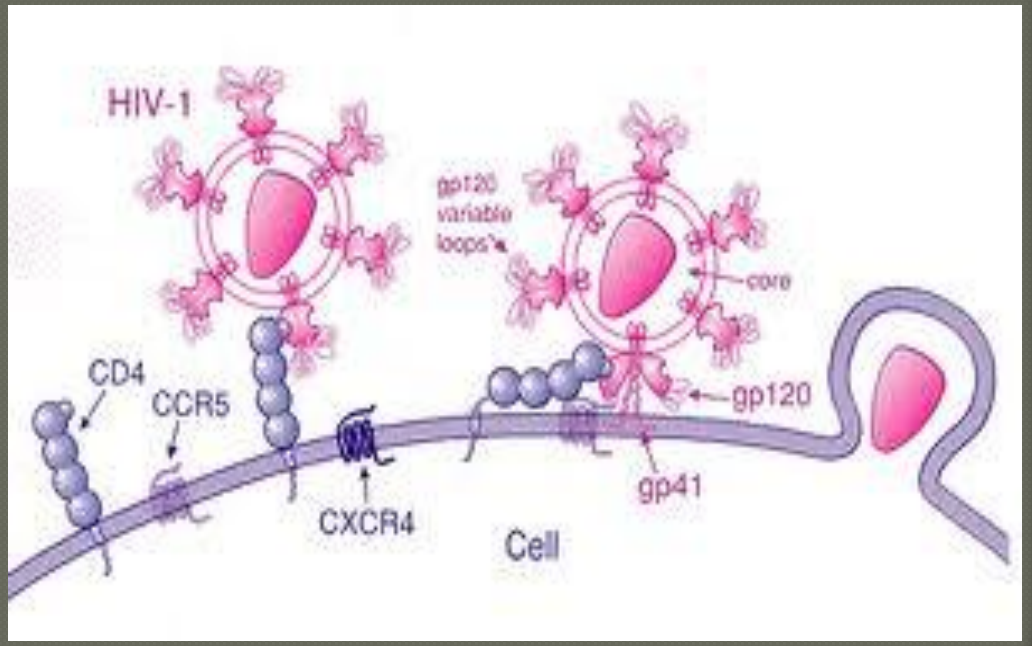
HHV-6

- Both the A and B variants enter the cell through interaction with CD46 (type I glycoprotein acting as regulator of complement activation, expressed on the surface of all nuclear cells)



HHV-7

- Primary infects T cells and uses CD4 as a cellular receptor (Lusso 1994)



HHV-6 *in vitro*

(Soderberg-Naucler 1997,Inoue 1997, Santoro 1999, Ljungman 2000, Dockrell 2002, Boech 2003)

- Depletion of CD4 T ly *via* direct infecton of intrathymic progenitors and induction of apoptosis
- Mediation of apoptosis in HHV-6 uninfected T cells
- Upregulation of NK cytotoxicity
- Suppressive effect on bone marrow monnonuclear cells – clinical correlation is found in evidence that HHV-6 reactivation may delay platelet engraftment and cause neutropenia in SCT recipients

Principal mechanisms of immunomodulation by HHV-6

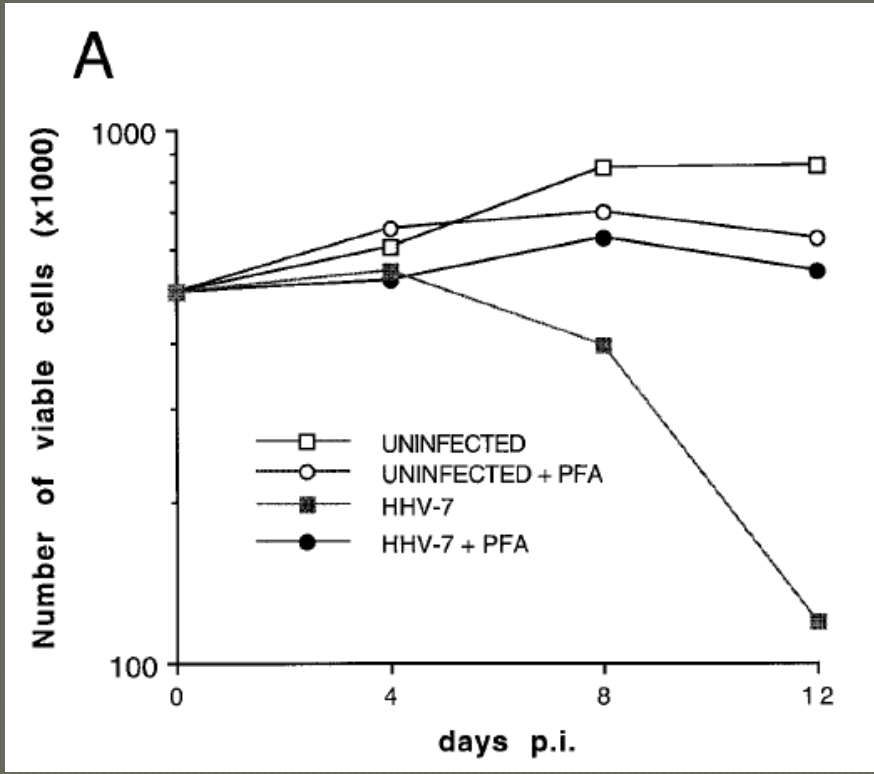
(Lusso 2006)

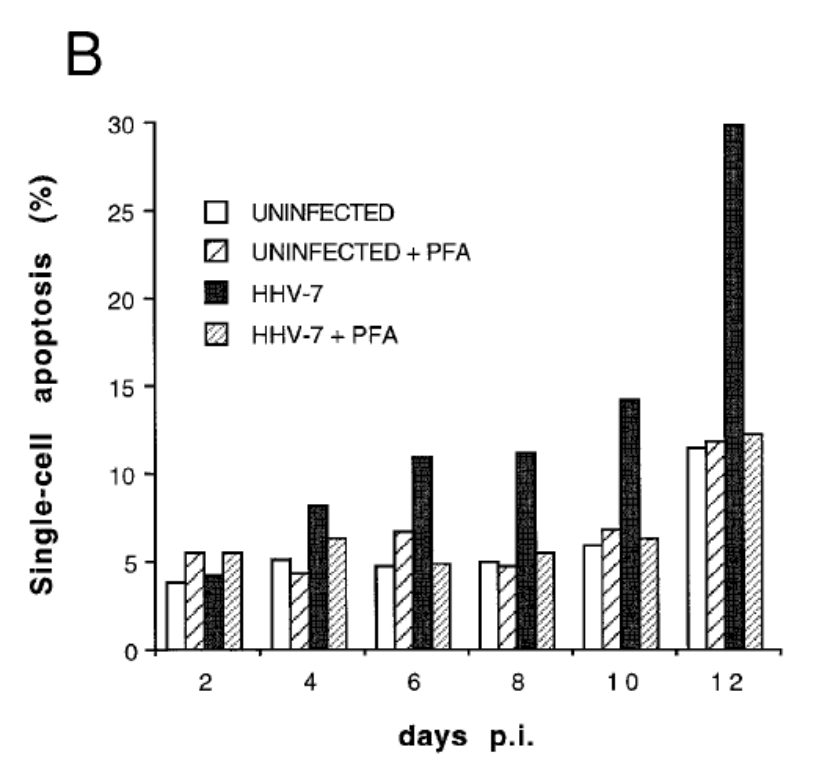
- Lytic infection of CD4+, CD8+, γδ T, NK
- Phenotypic and functional impairment of APC
- Suppression of IL-12 secretion by Mf and DC
- Suppression of IL-2 secretion
- Induction of inflammatory and immunosuppressive CK and chemokines (IFN-alpha, IL-1 beta, IL-10, IL-15, TNF-alpha, RANTES)
- Expression of viral chemokines and chemokines receptors
- Downmodulation of CD3 cell receptor complex
- *De novo* induction of CD4
- Downregulation of CD46
- Induction of Treg type I cells
- Synergy with HIV-1

Effect of cell-free HHV-7 inoculation on primary CD4+ T cells (Secchiera 1997)

A total n of viable cells

B % of apoptosis





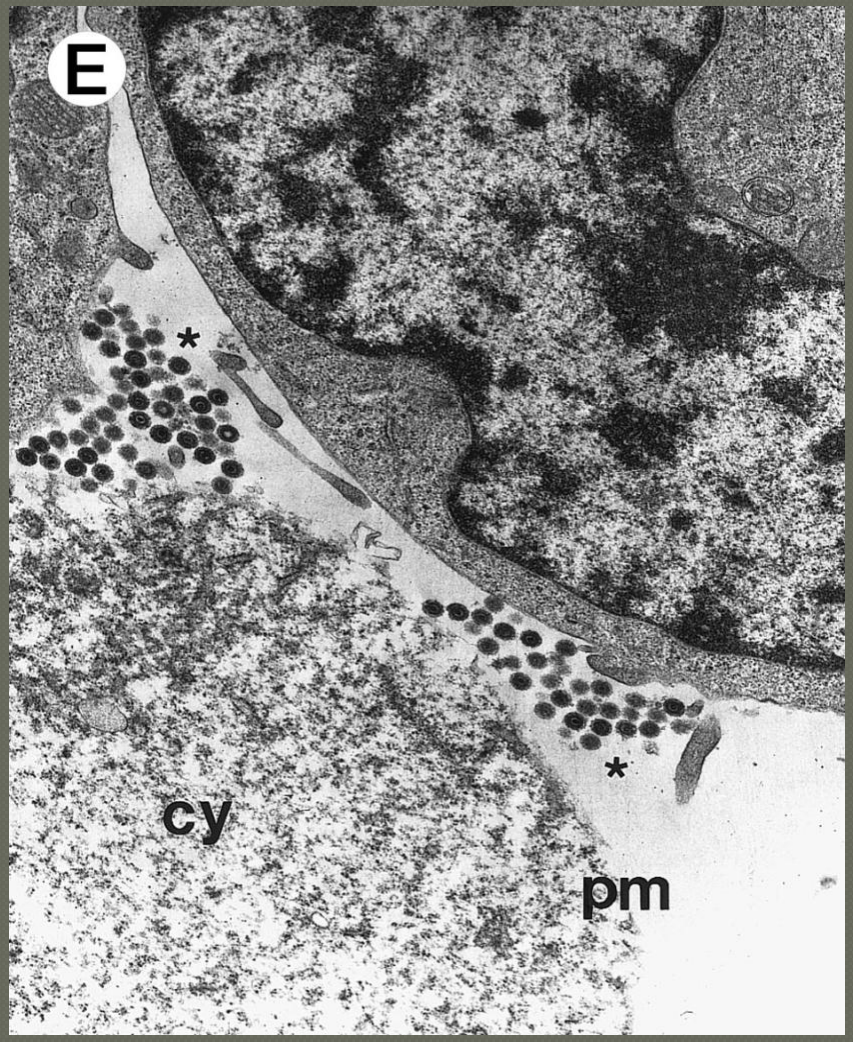
Evaluation of the Ultrastructural Features of HHV-7 Induced Syncytia in SupT1 Cell Cultures (Secchiero 1997)

- Total no. of syncytia examined 100
  - Normal 36/100
  - Necrotic 60/100
  - Apoptotic 4/100

The samples examined by transmission electron microscopy were obtained from two separate experiments and different (6 to 8) days pi.

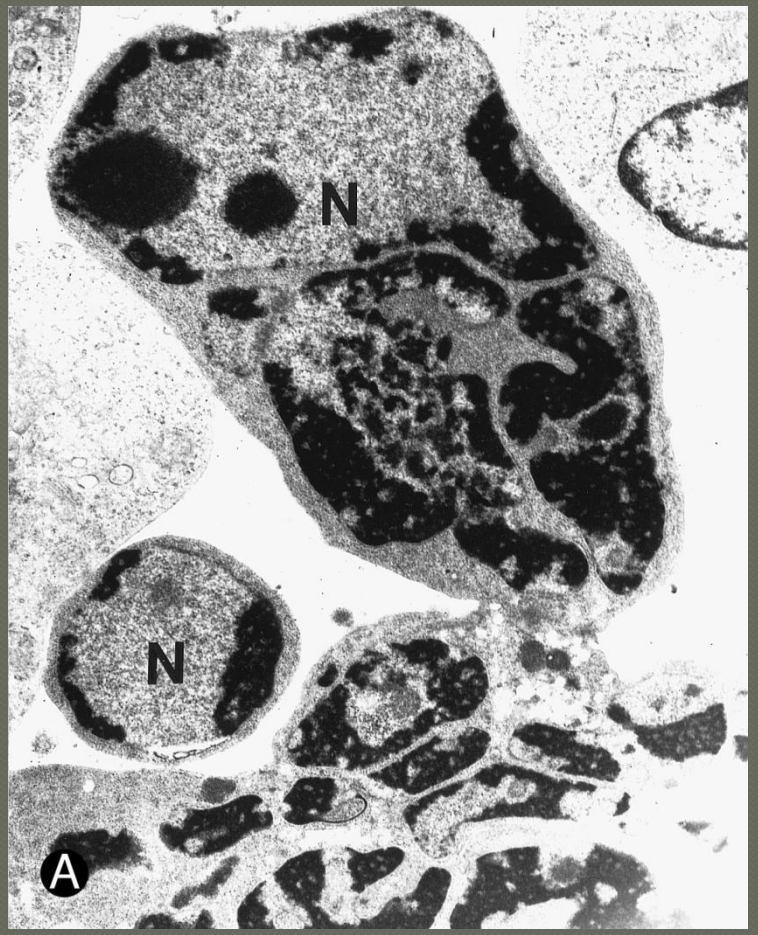
Particular of syncitium in late stage of necrosis releasing mature virions (Secchiera 1997)

HHV-7 infected SupT1 cell culture



2 apoptotic nuclei in cells that do not show viral particles (Secchiera 1997)

Apoptotic HHV-7 infected SupT1 cell



HHV-7 could induce

- formation of necrotic synccytia and apoptosis in target cells (infected and uninfected)
- disregulation of CK production

T cell depletion and functional alterations → insufficience of cellular immune response

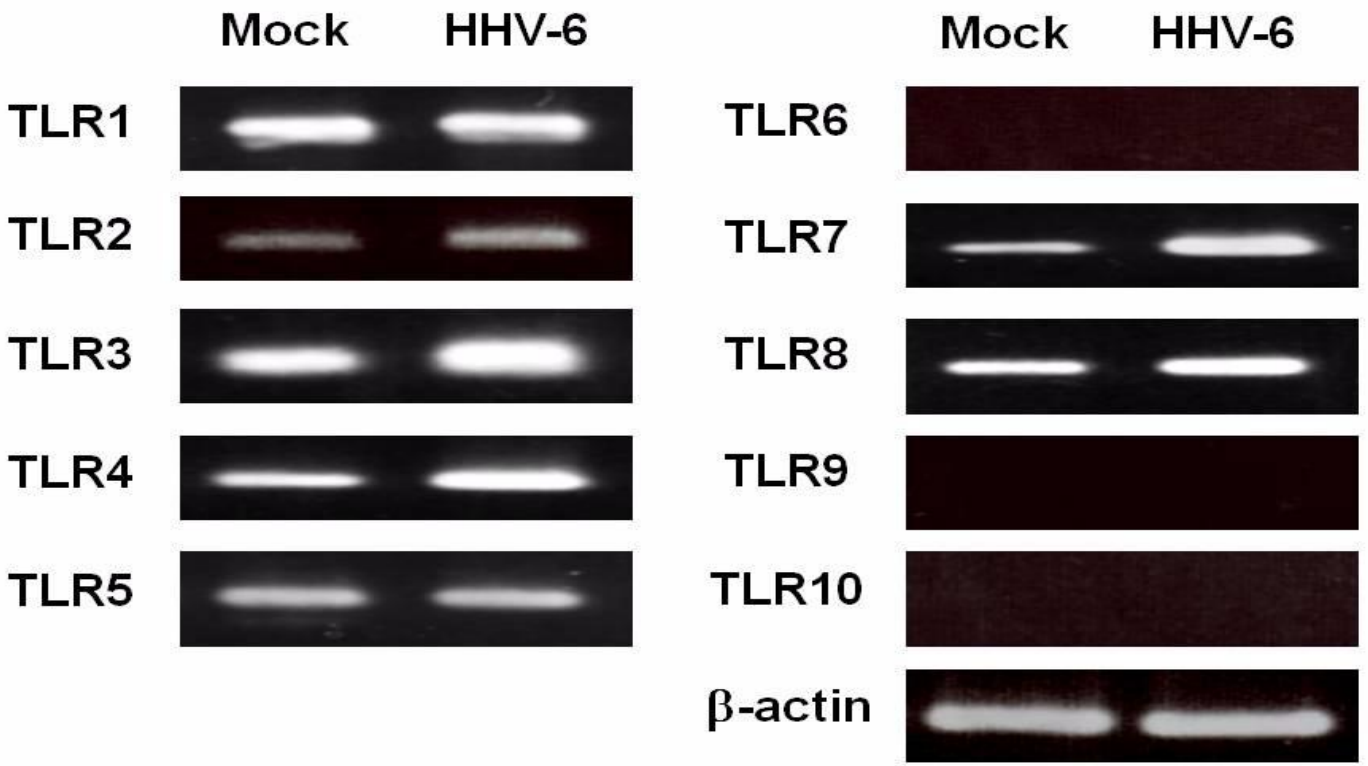
1997 in vitro HHV-7

- HHV-7–mediated CPE on CD4+ T cells might comprise additional mechanisms, besides the induction of necrotic lysis.
- … future investigations have not clarified these mechanisms…especially in the context of clinical importance…

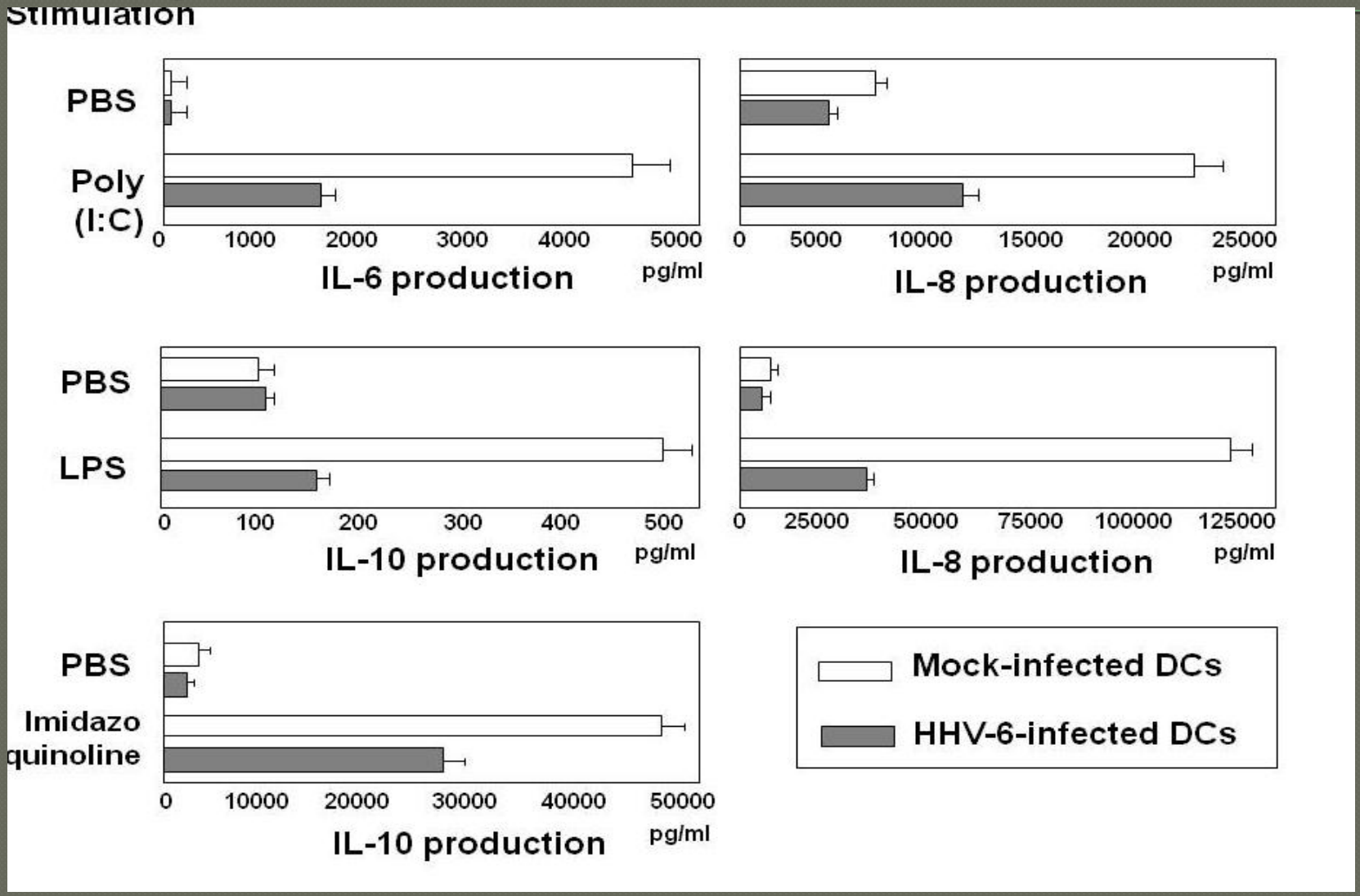
HHV-7clinical importance

- There is little evidence that the virus causes clinically significant lytic infection exists
- HHV-7 has been implicated in organ graft rejection
- The effect on the outcome of SCT remains unknown

RT-PCR analysis of TLR in mRNA in mock-infected and HHV-6 infected DCs (Murakami 2010)



Downregulation of CK production by stimulation with TLR ligand in DCs after infection with HHV-6 (Murakami 2010)



Clinical importance

- Intracellular signaling pathway through TLR system is esenssential for recognition of various pathogens and generation of innate immune response - disruption of TLR-mediated signaling may contribute virus escape from immunosurveillance → deviation of the clinical course of the disease

HIV/AIDS and HHV (Bovenzi 2003)

- HHV-6 DNA was detected in 35% of KS biopsy specimens and in the plasma of two out of 48 AIDS patients (both of whom had KS and CMV-D)

- HHV-6 and CMV may contribute to the pathogenesis of KS by

  inducing the release of cytokines (TNF-alpha, IL-1, IL-6, IFN-gamma) → cytokines promote the activation and growth of endothelial cells and the expression of adhesion molecules, release of angiogenic molecules

HIV/AIDS and HHV

- Like HHV-6, HHV-7 has been found in peripheral blood of 83% of healthy HIV-seronegative subjects but only in 3% of HIV-positive patients

- '' To our knowledge, no association between HHV-7 and HIV infection has been demonstrated in vivo, and the absence of the HHV-7 genome from the plasma of all of our HIV-infected patients, irrespective of clinical conditions, does not support a role for this virus in HIV infection ''

(Brocollo 2002)

Francesco BroccoloCLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, Nov. 2002, p. 1222–1228

”We observed that CMV (primarily), EBV, and HHV-8 were the most commonly detected viruses, presumably due to reactivation in the context of severe immunosuppression, while no significant reactivation of HHV-6 or HHV-7 was demonstrated at any stage of HIV/AIDS”

HHV-6 as modifier of CMV replication

- HHV-6 stimulates secretion of TNF-alpha. Association between TNF-alpha and subsequent CMV antigenaemia in liver transplant recipients has been reported (Fietze 1999)
- Early HHV-6 reactivation leads to delayed reconstitution of CMV-specific T-helper immune response in SCT recipients (Wang 2002)

From the studies of HIV/AIDS

- HHV-6 as cofactor in HIV disease progression (transactivation of HIV promoters by HHV-6 genes)
- Induction of CD4 in HHV-6 infected CD8+NK cells

(Clark 2000)

From the studies of CMV

- From transplant population (renal and liver) – association between seroconversion, detection of HHV-6 DNA in PBMC or detection of HHV-6 and CMV DNA in serum and CMV infection, reactivatin and disease severity was observed

(Dockrell 1997, Humar 2002)

From the studies of HCV

- Data are conflicting:
  - HHV-6 viraemia in HCV positive liver transplant recipients is associated with increased risk of early fibrosis (Singh 2002)
  - No any effect of HHV-6 on HCV (Razonable 2002, Humar 2002)

Immunosuppressive and immunomodulatory effects of HHV-6 and HHV-7 (Boech 2003)

Beta-herpesvirus	Setting	Reported effect
HHV-6	Solid organ transplantation	↑ risk of CMV infection and more severe CMV disease, organ rejection
	Stem cell transplantation	↑ risk of CMV infection
	HIV infection	HIV disease progression in adults and in children (after vertical transmission)
	Hepatitis C (after liver transplantation)	More severe cirrhosis
HHV-7	Solid organ transplantation	↑ risk of CMV infection and disease, organ rejection

Limitations of clinical importance

- No selective HHV-6, HHV-7 suppressive trials have been performed
- Small studies on SOT, SCT and HIV/AIDS patients population

Thank you!

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