RĪGAS STRADIŅA UNIVERSITĀTE

ERAF EIROPAS REĢIONĀLĀS ATTĪSTĪBAS FONDS

IEGULDĪJUMS TAVĀ NĀKOTNĒ

EIROPAS SAVIENĪBA

"Promotion of International Cooperation Activities of Riga Stradiņš University in Science and Technologies", Agreement No. 2010/0200/2DP/2.1.1.2.0/10/APIA/VIAA/006

HHV6 and HHV7
Similarities and Differencies

13.10.2011. Riga
I. Jaunalksne

HHV-6/HHV-7

- Roseolovirus genus of b herpesvirinae subfamily
- Genomes are 160-162kb in size

- HHV-6 and HHV-7 share limited nucleotide homology and antigenic cross-reactivity

- 90-99% of adults had been infected by both viruses
- HHV-6A and HHV-6B u 100 share 79.9% identity

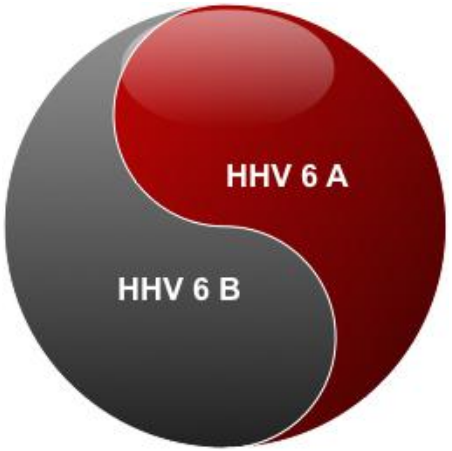
HHV- 6 Cell Tropism

- Lymphocytes -
- CD4+, activated CD4 + cells apear to be the preferance target for fully permissive replication
- CD8+- HHV-6A, but not HHV-6B

- NK cells- HHV6A/B
- Mo- HHV6A/6B
- CD34+ - HHV6A could infect, but not produce viral progeny

- Epithelial cells
- Endothelial cells
- Fibroblasts

HHV-6 Cell Tropism



- Oligodendrocytes
- Fetal astrocytes

- HHV6A have greater neurotropism that HHV6B

- HHV6B – Mo/Macrophages more than CD4+ cells, epithelial cells that line tonsilar crypts

HHV-6

- CD 46 – (glycoprotein)- cellular receptor
- Is expressed on the surface of all nucleated cells
- CD46 is a receptor for complement

HHV- 6 Immunomodulation

- Downregulates CD3 in infected cells
- Downregulates CD46 in infected cells

- Upregulates chemokine receptor CCR7 in infected cells
- Downregulates CXCR4

- Downregulates MHC class I in infected dendritic cells
- Reduces IL-2, IFNg,TNFa,Il-1b

HHV- 6 Immunomodulation

- Downregulates proliferation
- Downregulates IL-15, therefore NK cell cytotoxicity
- Stimulate IL-10, IL-12 expression

HHV6 Persistence In The Host

- In the salivary glands (transmission way)
- Mo

- Bone marrow progenitors
- HHV6A more frequently detected in CSF

- HHV6B more frequently detected in PBMC compared with HHV6A, HHV6B is prevalent in tonsills

HHV-7

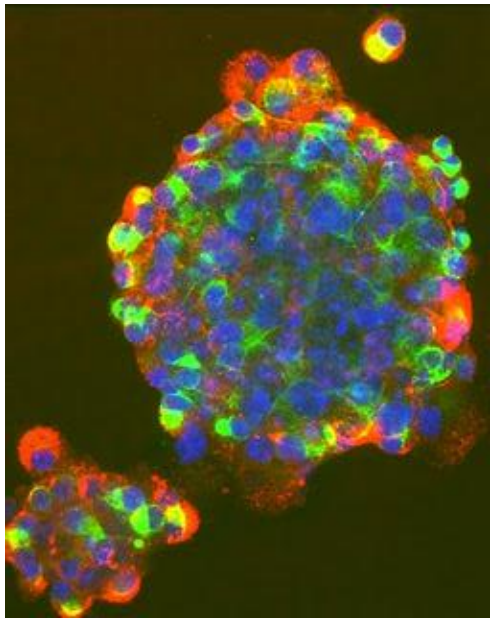
- Share with HHV6 30- 60% amino acid sequences
- HHV7 has been detected in over 50% of PBMC (lymphoid and non lymphoid cells)
- Latency in CD4+ cells
- CD4 is the receptor for HHV7
- HHV7 is detectable in salivary glands, but cultured from saliva only HHV6B and HHV7

HHV7

- HHV7 primary infection most offen occures after HHV6 infection

- Roseola is less frequent than in HHV6 infection

Stem Cells



- HHV6/7 affect stem cell growth
- HHV7 – inhibits the growth of granulocyte, monocyte,erytroid, megacarocyte progenitors
- HHV6-has less effect on progenitors, inhibits more differentiated progenis.
- HHV-6 inhibit ability to respond to growth factors- GMCSF, IL-3, block the ability of monocytes differentiate to macrophages

T Lymphocytes

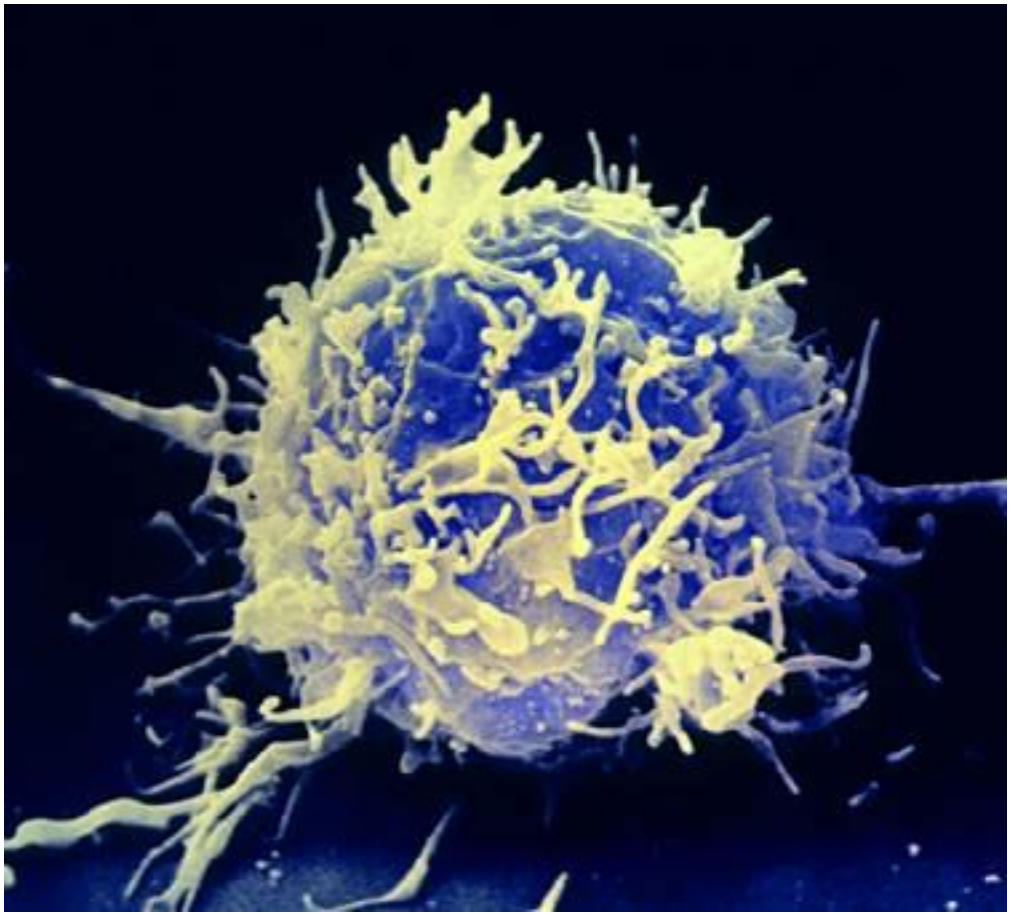
- HHV6A can induce cell fusion via CD46 receptor in the absence of viral protein synthesis.
- HHV7-induces formation of giant multinucleated CD4 T cells, possibly due to polyploidization of infected cells because of intererupted cell cycle.
- HHV6A/B affects almoust all major lymphoid cellular subsets including CD4+ and CD8+ positive T cells.
- HHV6A- replicates and kills CD4+ , CD8 + cells equally

T Lymphocytes

- HHV 6B predominantly replicates and depletes CD4+ cells
- CD4+ is upregulated after HHV6A/6B infection
- CD3 was downregulated only in infected cells
- HHV6A –showed a stronger effect on CD3 expression in CD4 Ly than HHV6B
- HHV7 uses CD4 as its cellular receptor, CD4 but not CD 3 expression is reduced after HHV7 infection

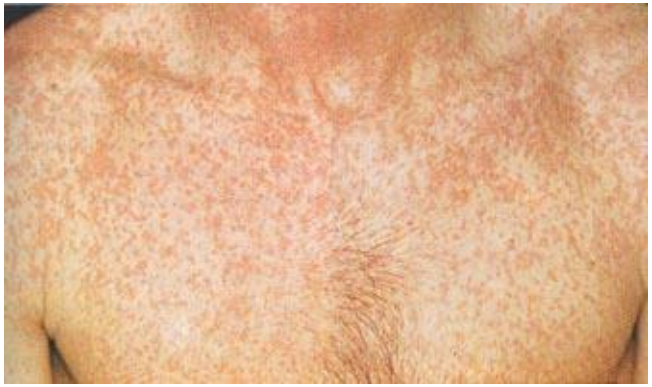
T Lymphocytes

- HHV6/HHV7 infected Ly lose their ability to proliferate and to kill virus infected cells



HHV-6/HHV-7 clinical onset

- Acute febrile disease of infants
- Fever for few days



- Maculopapular rash that resolves spontaneosly (exanthema subicum, roseola infantum)

HHV-6/HHV-7 clinical onset

Primary infection may give:

- Otitis, gastrointestinal or respiratory distress-womiting,diarhea, hepatitis (hepatosplenomegaly), cough, pneumonitis, myocarditis, seizures, myelosupression

- HHV-7 – fever, (with or without) rash, mimic HHV6
- Primary infection in adults rare/ symptoms severe

HHV-6/HHV-7 clinical onset

- Primary infection
- Persistence
- Reactivation/immunodeficiency

transplantation, tumor, HIV/AIDS, myloma, kaposi sarkoma,

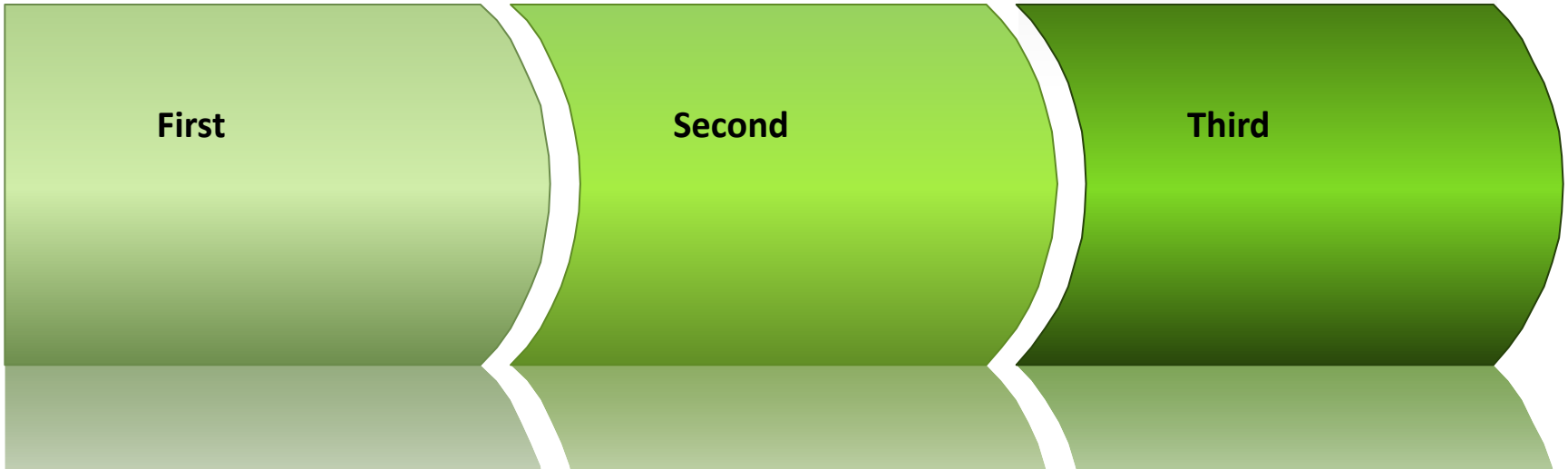
hr. fatigue syndrom, fibromialgia,temporal lobi epilepsy, MS, Graves disease

Ig M ab

- Develop after 5-7 days onset of clinical symptoms, reached they titers in 2-5 weeks,

- Dissapear after 2 month post infection

- HHV7 primary infection of HHV6 naive individuals induces IgM ab that can neutrolize
- both HHV6 and HHV7 –there is no IgM response to either virus when HHV7 infection follows HHV6



Ig G ab

- Appears 10 days till 2 weeks after onset of clinical symptoms, remain at measurable levels for many years
- HHV6 specific IgG4 was detected in all bone marrow transplant recipients-
- Marker of HHV6 reactivation????

HHV6 and HHV7 similarities

- Both are related to subfamily of Herpesviridae
- Genetic content and biological properties are similar
- Both live in humans

- The main transmission way is throught saliva
- Both causes infection in early childhood

- After primary infection latency is established
- Reactivation is caused by immunosupression
- Reactivation result depend on immunodeficiency degree

HHV6 Differencies

- There are 2 subtipes- HHV6A, HHV6B
- HHV6 binds to CD46

- Replication in salivary glands are observed for HHV6B, but not for HHV6A, it is more neurotropic
- Early childhood infections are caused by HHV6B

- HHV6A is related to adults primary infection and is more neurotropic –related to central nervous system disorders

HHV7

- HHV7 binds to CD4
- Causes infection in early childhood, later than HHV6B
- Clinically mimics HHV6 B infection

References

1. Arvin A.,Campadelli-Fiume G.,Mocarski E. HHV-6A,6B and 7: immunobiology and host response. Human Herpesviruses: Biology, Therapy and immmunoprophylaxis. Cambridge: Cambridge University Press, 2007, 1-24,

2.Cormelli C.,Jacobson S.,Viruses and Multiple Sclerosis.Viral immunology.2000,8 (1):255-267,

3.Duncan A.C.,GriffithsP.D.Human herpesvirus 6:relevance of infection in the immunocompromised host.British Journal of Haematology, 2003,120,3,384-395,

4.Jannello A.,Debbeche O.,Martin E,Attalan L.H., Samarani,Ahmad A. Viral strategies for evading cellular immune responses of the host. Journal of Leukocyte Biology,2006, 79,16-35,

5. Hall C.B., Caserta M.T., SchnabelK.C.,Boettrich C.,Mc Dermott M.P.Lofthus G.K.,Jennifer A.,Dewhurst C., Dewhurst S. Congenital infections with human herpes virus 6 (HHV6) and human herpesvirus 7 (HHV7). The Journal of Pediatrics,2004, 145, 472-477,

6. Yoshikawa T.,Black I,.B.Jhira M.,Suzuki K., Suga S.,Lida K.,SaitoY.,Asohuma K.,Tanaka K.,Asano Y.Comparison of Specific serological assays for diagnosing human herpesvirus 6 infection after liver transplantation.Clinical Diagnostic Laboratory Immunology, 2001,8 (1):170-3,

7. Leite J.L., Bufalo N.E., Santos R.B.,Romaldin J.H., Ward L.S.Hormones. International Journal of Endocrinology and metabolism. 2011,9,

8. Šedy J.R., Spear P.G.,Ware C.F. Cross-regulation between herpesviruses and the TNF superfamily members.Nature Review of Immunology, 2008, 8 (11),:861-873,

9.Torigoe S., KumatoT.,Koide W.,Taya K.,Yamanishi K.,Clinical manifestation s associated with human herpesvirus 7 infection. Archive diseases of children. 1995,72 (6): 518-519

Thank you!

RĪGAS STRADIŅA UNIVERSITĀTE

ERAF
EIROPAS REĢIONĀLĀS ATTĪSTĪBAS FONDS

IEGULDĪJUMS TAVĀ NĀKOTNĒ

EIROPAS SAVIENĪBA

"Promotion of International Cooperation Activities of Riga Stradiņš University in Science and Technologies", Agreement No. 2010/0200/2DP/2.1.1.2.0/10/APIA/VIAA/006