Hcmv pathogenesis and modulation of the immune system by hcmv

Science, Biology

Infection in immunocompetent individuals usually unnoticed. After primary infection of different cell types for example epithelial cells of the liver, lungs, kidney, salivary glands, large intestine, placenta endothelial cells, smooth muscle cells, fibroblasts, neuronal cells and myeloid cells (Sinzger et al., 1995), HCMV stays latent in CD34+ myeloid progenitors, from which reactivation and replication can occure (Soderberg, 2006).

Despite the fact that a healthy immune framework controls HCMV replication, the infection can neither be eliminated by immune functions nor by antiviral medications. Upon failure or diminished efficiency of particular immune capacities, opportunistic HCMV infections may prompt extreme or even deadly illness.

Immune control of primary and latent HCMV infection is stored out in a various ways (Reddehase, 2000), with noticeable roles for type I and type II interferons, NK cells, and CD8+ but also CD4+ T-cells, while antiviral antibodies are basic to limit dissemination of intermittent infection (Sylwester et al., 2005). Even if a healthy immune framework effectively controls disease, HCMV prompts lasting changes in the structure of immune cell populations. Consistently extending CD8+ T-cells particular for a few HCMV epitopes overwhelming the memory CD8+ T-cell population is a sign of CMV infection and not seen in other viruses (Sylwester et al., 2005).

In the elderly HCMV particular CD8+ T-cells may cover over 20% of circulating CD8+ cells (Ouyang et al., 2003), a phenomenon called “ memory inflation”. In addition, a higher recurrance of HCMV particular CD4+ T-cells can be seen in HCMV positive people. These cells display a CD4+/CD28

phenotype and are classified as terminally separated effector memory cells (Van Leeuwen et al., 2004). Recently, a role for HCMV in early aging of the immune framework or “ immune risk phenotype” (IRP), estimated as upset CD4: CD8 ratios, was connecting HCMV to immunosenescence (Wikby et al., 2002) and weakened responsiveness to immunization (Pawelec et al., 2012), with possible impact seen in young adults (Turner et al., 2014). Also, induction of IL-6 and TNF has been described in HCMV-positive people (Pawelec et al., 2012).

Furthermore, HCMV infection results in expansion of a NK cell subset expressing activatory CD94/NKG2C receptors in vivo and in vitro (Guma et al., 2006). Autonomously, HCMV induces the extension and separation of killer cell immunoglobulin like receptor (KIR) expressing natural killer cells, manifesting as steady imprints in the NK cell repertore. HCMV actuated training by inhibitory KIRs is advancing a clonal like extension of NK cells, causing predisposition for self-particular inhibitory KIRs (Beziat et al., 2013). In vitro examination a HCMV driven developmental capability of extra natural killer cell subpopulations descriped by inhibitory KIR2DL1 and KIR2DL3 and activatory KIR3DS1 receptors (Charoudeh et al., 2013).

Once infected, cells turn out to be firmly controlled by HCMV, expressing various controllers of the cell cycle, apoptosis, cell signaling pathways, antigen presentation. The expression profile of infected cells turns out to be greatly adjusted by HCMV because of transcription of HCMV genes, great manipulation of cellular transcriptome due to HCMV encoded transcription

elements and expression of HCMV miRNAs which influence both HCMV and host transcription design.

The virus encodes a number of proteins that manipulate the Class I and Class I human leuckocyte antigen (HLA) response, interfere with natural killer cell (NK) cell activities, control and manipulate the cell cycle, inhibit apoptotic pathways and modulate inflammatory pathways including the matrix metalloproteinase pathway and cellular adhesion molecules. Based upon data from the Rhesus CMV model, the Class I HLA manipulation genes may serve as facilitators of reinfection (Hansen et al., 2010) through NK cells and via antibodies that recognize key surface glycoproteins such as gB and gH either singly or, as recently described, as part of multiprotein viral surface complexes (Revello et al., 2010). Sequence variability across the large viral genome generates extensive viral strain diversity (Renzette et al., 2013), which may allow reinfection of the infected person by another strain of CMV (non-primary infection) (Mocarski et al., 2007).

Patients with the late-onset primary antibody deficiency (common variable immune deficiency disease), the combination of CMV replication in target organs such as gut and kidney together with a hyper reactive CD8 T-cell immune response can yield tissue inflammation (Marashi et al., 2011). Interestingly, this inflammatory disease can be reduced by anti-CMV therapy using ganciclovir and by inhibiting tumour necrosis factor (TNF) through infliximab.