

Latent herpes simplex virus infections of sensory neurons of the human peripheral nervous system

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Research question and background

Herpes simplex virus type 1 (HSV-1) is an endemic human herpesvirus worldwide that establishes a lifelong latent infection of neurons in the trigeminal ganglion (TG), allowing intermittent reactivation resulting in recurrent disease in some persons. Studies in HSV-1 animal models suggest a central role of TG-infiltrating virus-specific CD8 T-cells to control reactivation. In humans, however, the functional properties and fine specificity of intra-TG T-cell responses remain enigmatic. Both primary and recurrent disease can result in clinical disorders of variable severity or even death, emphasizing the unmet need for preventive and therapeutic vaccines. The aims of our HSV-1 studies were to characterize the functional properties and HSV-1 antigens recognized by T-cells infiltrating HSV-1–infected human TG.

Methods and tissues used

The Dutch Brain Bank has developed a unique infrastructure enabling researchers to obtain unprocessed blood and brain tissues of deceased donors with a very short post-mortem interval (<8 hrs). In our HSV-1 studies we used molecular (e.g. [RT-]qPCR), immunological (e.g. flow cytometry, and phenotypical and functional analyses of TG-derived T-cell cultures) and in-situ analysis platforms (e.g. immunohistochemistry and in-situ tetramer stainings) on paired human cadaveric blood and TG specimens.

Results and conclusion

We characterized the HSV-1 proteins recognized by virus-specific CD4 and CD8 T-cells recovered from human HSV-1–infected TG. T-cell clusters, consisting of both CD4 and CD8 T-cells, surrounded neurons and expressed mRNAs and proteins consistent with in-situ antigen recognition and antiviral function. HSV-1 proteome-wide scans revealed that intra-TG T-cell responses included both CD4 and CD8 T-cells directed to one to three HSV-1 proteins per person. HSV-1 protein ICP6 was targeted by CD8 T-cells in 4 of 8 HLA-discordant donors. In-situ tetramer staining demonstrated HSV-1-specific CD8 T-cells juxtaposed to TG neurons. Intra-TG retention of virus-specific CD4 T-cells, validated to the HSV-1 peptide level, implies trafficking of viral proteins from neurons to HLA class II-expressing non-neuronal cells for antigen presentation. The diversity of viral proteins targeted by TG T-cells across all kinetic and functional classes of viral proteins suggests broad HSV-1 protein expression, and viral antigen processing and presentation, in latently infected human TG. Collectively, the human TG represents an immunocompetent environment for both CD4 and CD8 T-cell recognition of HSV-1 proteins expressed during latent infection. HSV-1 proteins recognized by TG-resident T-cells, particularly ICP6 and VP16, are potential HSV-1 vaccine candidates.