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VIRUS-HOST INTERACTIONS

8.05

Exploiting Lipid Metabolism by HSV-1: a Challenge to Rethink New Therapies for Alzheimer's Disease

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Herpes simplex virus-1 (HSV-1) establishes a life-long latent infection and can enter the brain via retrograde axonal transport. Recurrent reactivation of HSV-1 may lead to neurodegenerative disorders, including Alzheimer's disease (AD), although the underlying mechanisms have not been fully elucidated yet. Lipids constitute the bulk of the brain dry mass and alteration of lipid metabolism is a key component in AD. Recently, CMS121 was shown to protect transgenic AD mice by reducing cognitive loss and inflammation. Interestingly, FAS (fatty acid synthase), a key enzyme in the synthesis of lipids that is increased in AD patients, was identified as a target of CMS121. FAS inhibition through CMS121 protects against lipid peroxidation and neuroinflammation, linking perturbed lipid metabolism to neurodegeneration. Considering that cellular lipid metabolism plays a pivotal role in viral infection and that the mechanisms for the metabolic reprogramming by HSV-1 are still poorly understood, we aim at dissecting the host metabolic pathways modulated by HSV-1 in a neuronal-like cell line to identify crucial pathways that might be targeted to prevent HSV-1-driven AD. Specifically, we found an increase in both *de novo* synthesis and lipid storage following HSV-1 infection. In addition, we demonstrated that the anti-AD compounds targeting lipid metabolism (*i.e.* CMS121, C75) impaired HSV-1 infectivity. Moreover, to better understand the link between FAS and HSV-1 infectivity, we suppressed FAS expression by short hairpin RNA (shRNA) (shFASN) and validated the results obtained with the compounds, ruling out any off-target effects. Overall, our data unveil new aspects of HSV-1-AD interplay and uncover new potential targets to rethink new possible therapies.

8.06

Comparison of HEp-2 and Vero cell responses reveal unique proapoptotic activities of the herpes simplex virus type 1 alpha0 gene transcript and product

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HSV-1 induces and then later blocks apoptosis in infected cells. The immediate early viral gene alpha0, which synthesizes the ICP0 protein, is necessary and sufficient for HSV-1-induced apoptosis in human epithelial (HEp-2) cells. While ICP0 protein synthesis is not necessary for HSV-1-induced apoptosis in infected HEp-2 cells, evidence suggested that it might be needed in infected African green monkey kidney (Vero) cells. Here, we determined specific aspects of alpha0 needed to trigger apoptosis in these two cell types. HEp-2 cells transfected with alpha0 expressing plasmids generating full-length, truncated, or no detectable (multiple stop codons) ICP0 protein died through apoptosis. Thus, ICP0 protein is not necessary for alpha0-induced apoptosis and that alpha0 mRNA alone has apoptotic induction properties in HEp-2 cells. We next investigated the primary structure of alpha0's mRNA to better define its proapoptotic ability. Since alpha0 is one of the few HSV-1 genes that are spliced, we transfected cells with a plasmid expressing an ICP0 cDNA copy, pcDNAICP0. Cells transfected with pcDNAICP0 underwent apoptosis at a level equivalent to those transfected with the genomic copy of alpha0, indicating that neither splicing events nor introns are required for the apoptotic function of alpha0 in HEp-2 cells. Since HSV-1-induced apoptosis in Vero cells requires protein synthesis early in infection, proteins synthesized with immediate early kinetics may facilitate apoptosis. Vero cells were transfected with plasmids producing either full-length ICP0 or ICP0 truncated at codon 212. Full-length ICP0, but not truncated ICP0, induced apoptosis in Vero cells. Together, these results suggest that alpha0 gene expression triggers apoptosis, but ICP0 protein is needed to facilitate apoptosis in Vero cells. Additionally, ICP0's facilitation activity may lie in its carboxyl-terminal domain. These results demonstrate that alpha0's mRNA and protein possess proapoptotic properties. The requirement for ICP0 protein during HSV-dependent apoptosis appears to be cell type specific.