HERPES SIMPLEX VIRUS TYPE 1 INFECTION DISTURBERS ERAD MACHINERY TO FAVOR ITS VIRAL REPLICATION

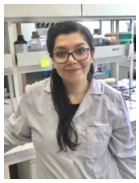
Cinthia Mella, MSc, PhD (c), UACh, CHILE
Hianara Bustamante, PhD, UACh, CHILE
Salamín Marukel, PhD, UACh, CHILE
Paula Salazar, BSc, UACh, CHILE
Luis Leyton, BSc, UACh, CHILE
Patricia Burgos, PhD, USS, CHILE
Carola Otth, PhD, UACh, CHILE

Abstract

Statement of the Problem: Herpes simplex virus type 1 (HSV-1) is a neurotropic virus that causes a latent persistent infection in humans, and affect to two thirds of the population under 50 years of age. It has been shown that during productive infection HSV-1 triggers endoplasmic reticulum (ER) stress, due to the overload of viral proteins that must be synthesized at ER. However, the impact of HSV-1 infection on ER Associated Degradation (ERAD) is yet unknown. The purpose of this study is investigate the impact of HSV-1 infection on ERAD function. **Methodology & Theoretical Orientation:** We infected H4 neuroglioma cells with HSV-1 and analyzed the intracellular levels of EDEMs proteins, ER Lectins that participate in the recognition of misfolded glycoproteins, the E2 Ube2j1with a role in the ubiquitylation of the ERAD cargoes, and VCP/p97, key in the retrotraslocation of the cargoes from the ER lumen towards the cytosol for cargoes degradation. Moreover, we analyzed key proteins involved in the quality control of newly synthesized proteins such as Calnexin, GRP78 and GRP94. The protein levels were evaluated by immunoblotting and the mRNA levels were analyzed by RT-qPCR. To investigate whether ERAD components could have an impact on HSV-1 viral replication, we performed TCID50 assay in H4 cells depleted in EDEM1. **Findings:** We found that HSV-1 reduces in specific manner the levels of the ERAD proteins, and surprisingly does not alter those proteins that work in ER folding. RT-qPCR and immunoblotting analysis showed that such down regulation was due to a post-transcriptional event. In cells with reduced expression of EDEM1 was detected a significant increase in HSV-1 viral replication efficiency. **Conclusion & Significance:** Altogether, this study elucidated the contribution of ERAD function as a crucial pathway to prevent HSV-1 replication, and identified to EDEM1 as a key protein hijacked by HSV-1 to favor its own replication. **Funding:** FONDECYT 1180936

Recent Publications

1. Bustamante H.A. González A.E. Cerda-Troncoso C. Shaughnessy R. Otth C. Soza A. Burgos P.V. (2018) "Interplay Between the Autophagy-Lysosomal Pathway and the Ubiquitin-Proteasome System: A Target for Therapeutic Development in Alzheimer's Disease". Frontiers in Cellular Neuroscience 12:126.
2. Acuña Hinrichsen, F. D., Muñoz, M., Hott, M., Martin, C., Mancilla Sierpe, E. K., Salazar, P., ... & Otth, C. (2018). Herpes Simplex Virus Type 1 Enhances Expression of the Synaptic Protein Arc for Its Own Benefit. Frontiers in cellular neuroscience, 12, 505.
3. Otth C, Leyton L, Salamin M, Acuña-Hinrichsen F, Martin C, Concha MI. (2016). Herpes Simplex Virus Type 1 Neuronal Infection Elicits Cellular and Molecular Mechanisms of Neuroinflammation and Neurodegeneration in in vitro and in vivo Mice Models. In. Handbook of Infection and Alzheimer's Disease. Ed. Miklossy, J. Publisher: IOS Press. ISBN 978-1-61499-706-1
4. Otth C, Acuña-Hinrichsen F, Leyton L, Maritn C, Concha M. (2016). Herpes simplex virus type 1 at the central nervous system. Herpesviridae. Publisher: InTech. ISBN 978-953-51-4824-1. Pag. 11-30.
5. Cinthia Mella, Gustavo Medina, Sandra Flores-Martin, Zorayda Toledo, Rosa Simaluiza, Guillerno Pérez-Pérez, Heriberto Fernández. Interaction between zoonotic bacteria and free living amoebas. A new angle of an epidemiological polyhedron of public health importance?. Archivos de Medicina Veterinaria, 48, 1, ISSN: 0301-732X, Editorial: Facultad Ciencias Veterinarias UACh, 2016



Biography

Dr © is a Microbiologist interested in host-pathogen interactions. Her current work consists in examining the cellular and molecular effects of a neurotropic virus in neuronal cells during infection, with a particular focus in neurodegenerative and inflammation processes, using Herpes Simplex Virus Type 1 as a study model. Her research points the effect of HSV-1 infection in the function and expression of Kallikrein-related peptidases, with important focus in the physiological effect of viral infections at the Central Nervous System.

Email: cinthiamellar@gmail.com