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Poxvirus and vaccines

Summary

The main objectives of our laboratory are geared to understand molecular basis in the pathogenesis of infectious agents and their interaction with the host cell, as well as to use this knowledge in the development of vaccines that might be effective against viral (HIV, hepatitis C) and parasitic diseases (malaria and leishmaniasis), using vaccinia virus as a model vector system.

In the period 2005-2006 we have made the following observations.

1) Defined the structure of one of the more complex virus, Intracellular Mature Vaccinia Virus (IMV) at the resolution between 4 and 6 nm, using cryomicroscopy and electron tomographic reconstruction (Cyrklaff, M et al 2005).

2) Identified Wiskott-Aldrich Syndrome

protein as needed for vaccinia virus pathogenesis (Guerra et al, 2005).

3) Explained how alphaviruses, like Sindbis (SV) and Semliki Forest virus (SFV), escape the interferon-induced ds-RNA dependent protein kinase (PKR) inhibitory antiviral effects by a novel mechanism that overpasses the requirement for eIF2 (Ventoso et al, 2006), identified ATF-3 as a novel PKR-induced molecule that triggers apoptosis (Guerra et al, 2006), identified the tumor supresor ARF as antiviral by promoting PKR release from its binding to nucleophosmin (Garcia, M et al, 2006); we also wrote a review on the impact of PKR in celll biology (García et al, 2006).

4) Developed potential vaccines against leishmaniasis (Pérez-Jiménez et al, 2005) and against HIV/AIDS (Gómez et al, 2006a, 2006b).

5) As a result of our findings, three patent applications have been submitted.

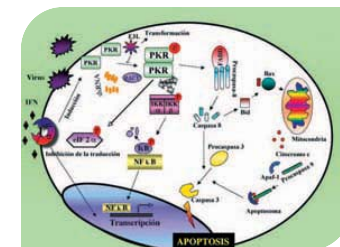


Figure 1: Mode of action of the protein kinase PKR, an antiviral and antiproliferative regulator.

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Selected publications

Cyrklaff, M., Risco, C., Fernández, J. J., Jiménez, M. V., Esteban, M., Baumeister, W. and Carrascosa, J. L. (2005). Cryo-Electron tomography of vaccinia virus. *Proc. Natl. Acad. Sci. USA* 102, **2772-2777**.

Ventoso, I., Sanz, M. A., Molina, S., Berlanga, J. J., Carrasco, L. and Esteban, M. (2006). Translational resistance of late alphavirus mRNA to eIF-2 alpha phosphorylation: a strategy to overcome the antiviral effect of protein kinase PKR. *Genes Development* 20, **87-100**.

Guerra, S., López-Fernández, L. A., García, M. A., Zaballos, A. and Esteban, M. (2006). Human gene profiling in response to active protein kinase PKR in infected cells: involvement of the transcription factor ATF-3 in PKR-induced apoptosis. *J. Biol. Chem* 281, **18734-18745**.

García, M. A., Gil, J., Ventoso, I., Guerra, S., Domínguez, E., Rivas, C. and Esteban, M. (2006). The impact of protein kinase PKR in cell biology: from antiviral to antiproliferative action. *Microb. Mol. Biol. Reviews* 70, **1032-1060**.

García, M. A., Collado, M., Muñoz, C., Mathew, A., Arroyo, J., Esteban, M., Serrano, M. and Rivas, C. (2005). Antiviral action of tumour suppressor ARF. *The EMBO Journal* 25, **4284-4292**.

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