Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title: Investigation of a Human Virus Tumor Gene through a Chimera Virus Mouse Infection Model

Synopsis:

OBJECTIVE
This project is focused on a single protein, kLANA (latency-associated nuclear antigen), of a major human tumorogenic virus, Kaposi's sarcoma associated herpesvirus (KSHV). kLANA is vital for KSHV to establish latent infection, hence tumorigenesis. What is proposed here is the utilization of an innovative virus chimera model system recently developed in our laboratory to investigate specific molecular functions of kLANA in vivo.
BACKGROUND
KSHV latently infects tumor cells and its genome persists as a multicopy episome. LANA acts on KSHV terminal repeat (kTR) DNA to mediate episome persistence, for which it is essential. LANA also mediates KSHV episome DNA replication and exerts important transcriptional and growth effects. Hence, kLANA is vital to latent infection and, therefore, tumor cell viability. There is no available animal model for KSHV. We have used Murid Herpesvirus 4 (MHV-4) that encodes a LANA homologue (mLANA) as a model system for pathogenesis studies.
EXPERIMENTAL STRATEGY
The strategy is to use the MuHV-4 kLANA chimera model to engineer specific mutations in kLANA functional motifs and investigate their physiological impact on virus induced lymphoproliferation and persistence in mice.
SIGNIFICANCE
Our recente discovery that, despite more than 60 million years of evolutionary divergence between KSHV and MuHV-4, that kLANA can functionally substitute for mLANA in MuHV-4 chimeric virus. Our model provides a means to assess future kLANA targeting through strategies such as small molecule inhibition towards virus eradication and associated tumor treatment. More broadly, our work successfully tests the concept of functional substitution of a human pathogen gene into a model pathogen to allow in vivo investigation. Previously, such chimeric viruses were felt to be non-viable due to evolutionary divergence. These findings also have the potential to be applied to other human pathogens, which lack small animal models.

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Remunerated or volunteer training:
Could be remunerated if student has more than 16 mark for first cycle studies