Establishment, maintenance and reactivation from latency of the Herpes Simplex Virus type 1 (HSV-1)

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INTROUCTION

Herpes Simplex Virus 1 (HSV-1) is able to perform latency in the nucleus of sensory neurons (where replication and gene expression take place) after primary infection in skin or mucosa, from where it travels through its free nerve endings to the bilateral Trigeminal Ganglia (TG) of the Peripheral Nervous System (PNS) by retrograde microtubule-associated axonal transport. The objective of the current study is to review the existing knowledge about the elements that take part in establishment, maintenance and reactivation from latency in HSV-1 [1] [2].

RESULTS

ESTABLISHMENT.

Selective site of entry. **VP16** is a structural tegument protein and a transcriptional activator of Intermediate Early (IE) genes. However, the virus is unable to initiate lytic infection when entering by distal axons (using animal models) *(Figure 1),* because VP16 is transported independently from capsids after the uncoating and it does not reach the cell nucleus, thus avoiding IE gene expression [1].

Latency-Associated Transcript. Major LATs are part of HSV-1 genome, and are highly expressed in latently infected neurons. they encode **microRNAs**, which repress IE gene expression by an antisense mechanism [3].

ProMyelocytic Leukemia Nuclear Bodies. **PML-NBs** are proteinaceous structures that associate with HSV-1 DNA and inhibit its transcription *(Figure 2)* [2].

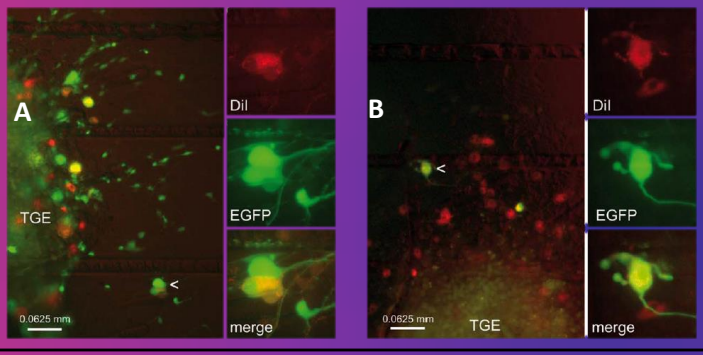

Fig. 1: HSV-1 infection of the trigeminal ganglia explants (TGEs). EGFP- positive neurons with DiI counterstaining indicate lytic infection of HSV-1. **A)** Direct nfection of the ganglia allows VP16 to reach easily the cell nucleus, which increase lytic infection levels. **B)** Infection by distal axons shows less EGFP-positive neurons [1].

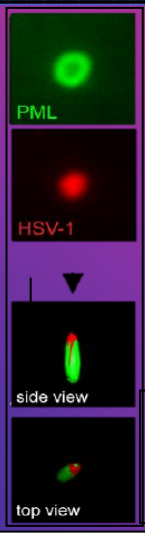

Fig. 2: PML-NBs associated with HSV-1 genomes in SC16/lip mice infected TG sections stained by immuno-FISH. The HSV-1 DNA signal is located within the PML-NBs [2]

MAINTENANCE.

PML-NBs remain associated with HSV-1 genomes even after replicative infection has ceased, suggesting that they play a role in the maintenance of latency. (*Figure 2*) [3].

Major LATs have anti-apoptosis properties and the capacity to repress gene expression, leading to the maintenance of latency, as observed in a study that showed reduction of infected-cell populations in long-term latency when LAT-negative virus was regarded [3].

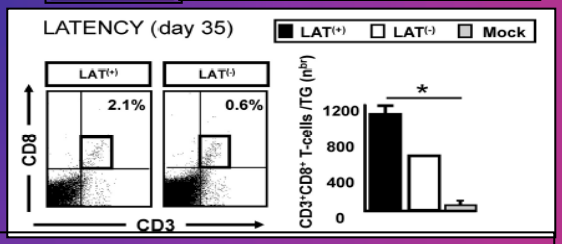

Fig. 3: Higher percentages and numbers of total CD8 T cells detected in LAT$^+$ TG compared to LAT$^-$ TG during latent HSV-1 infection [4]

REACTIVATION.

HSV-1 antigen (Ag)-specific leukocytes, which inhibit reactivation, are found in association with neurons during HSV-1 infection [4] [5]. Major Histocompatibility Complex class 1 (MHC-1) is upregulated by **major LATs** in the infected cells of C57BL/6 mice, which attracts CD8 T cells *(Figure 3).* CD8 T cells, in turn, express a marker of exhaustion, PD-1 (induced by its ligand in infected neurons, PD-L1, upregulated by major LATs), leading to functional exhaustion of CD8 T cells. Human models, in contrast, show immunocompetent TG with no exhaustion phenotype. [5]

Infected Cell Protein- 0 (ICP0), an IE gene and a regulatory protein, can induce proteasome-dependent degradation of HSV-1 repressive nuclear factors [1]. Centromeres are docking sites for HSV-1 genomes and repress them, which in consequence leads to decreased LAT levels [2]. Thus, ICP0 is not repressed by the LAT-derived microRNA anymore (see establishment), and it has developed an anti-centromere activity, leading to the release of viral genome [2]. Since ICP0 acts as a potent activator of gene expression, all these processes that result in its synthesis induce de-repression of the entire genome, favouring reactivation [2].

CONLCUSION

Data show a complex but regulated network of interactions between HSV-1 and its host. Mouse models are the most used but display low efficiency of reactivation of HSV-1, different epitope recognition by CD8 T cells and functional and phenotypic exhaustion of these cells. Those features are not found in human models. Therefore, mouse is not representative of human HSV-1 infection, and how each element affects latency cannot be fully elucidated, because of the differences in HSV-1 cycle observed when different human, animal or *in vitro* models are examined.

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