

**POSTER 53****INDUCTION OF HIV-1 LATENCY AND REACTIVATION IN PRIMARY MEMORY CD4<sup>+</sup> T CELLS**

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HIV in infected individuals establishes a relatively small, but long-lived reservoir of latently infected cells. Latent infection is associated with low or no viral gene expression and, accordingly, is non-cytopathic. Indirect evidence for the lack of cytopathicity from latent proviruses stems from the observation that the half-life of this reservoir is in the order of months to years. Latent viruses undergo reactivation, giving rise to new productive infections that carry full pathogenic potential. The cell type that harbors this long-lived, latent viral reservoir is thought to consist of quiescent memory T cells. We present a novel ex-vivo model for the study HIV latency as well as its reactivation. This model faithfully recapitulates salient features of the in vivo latent reservoir. For example, latent proviruses in this system are devoid of any detectable gene expression, yet, they are perfectly competent for gene expression when reactivated by a number of external stimuli. This model uses primary, human CD4<sup>+</sup> lymphocytes and viral integration is polyclonal. This powerful, yet straightforward model allowed us to (i) assess the relative permissiveness of various CD4<sup>+</sup> cell subsets to harbor latent proviruses; (ii) explore signaling pathways that may preclude the establishment of latent infections and/or induce reactivation of latent proviruses; and (iii) explore the use of select agonists and antagonists of the relevant signaling pathway(s) to experimentally manipulate latency and reactivation.

Our results confirm and extend the notion that latency in the T-cell memory reservoir is concomitant with little or no viral gene expression. We also confirm the notion that latent viruses have no intrinsic defects that would hinder viral gene expression. Instead, lack of detectable gene expression stems from the presence or absence of signal transducers and transcription factors that are naturally regulated in response to various T-cell differentiation programs. Knowing the pathways that underlie the outcome of an infection (whether latent or productive), and those that allow reactivation, will enable us to rationally design antiviral drugs for preventing the establishment of, or eliminating, latent HIV-1 that could be applied as adjuvant therapy in the context of conventional antiretrovirals.

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