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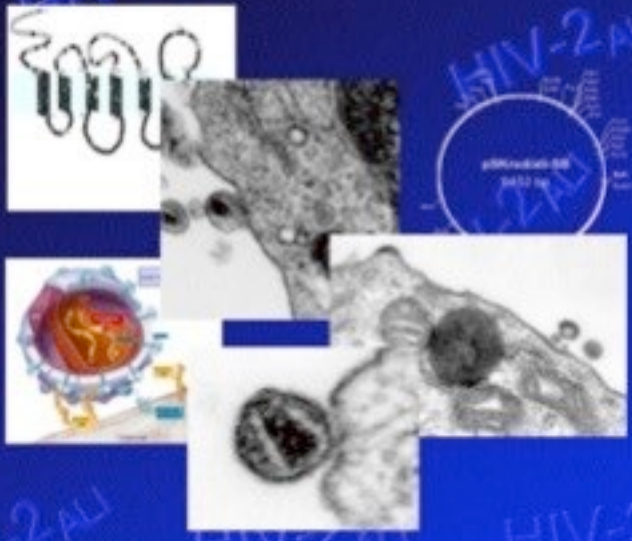
TROPISMO E INFECCIOSIDADE DO HIV-2

ESTUDO DAS INTERACÇÕES VÍRUS-CÉLULA DAS VARIANTES M-TRÓPICAS



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Title:

Tropism and infectivity of HIV-2
study of virus-cell interactions of macrophage-tropic variants

In this study, an HIV-2 (HIV-2ALI), that I isolated from an symptomatic patient was used as a model of HIV-2 interaction with host cells.
I deciphered the phenotypic and genotypic features of HIV-2ALI isolate.

The main objective of the work described in this thesis was to study the virus-cell interactions performed by M-tropic variants of HIV-2, using the primary HIV-2ALI strain as a model.

This virus is unable to productively infect any of the CD4+ cell lines tested. Accordingly viral replication cycle was analysed in order to identify the step responsible for this restricted tropism. The results showed that the abortive infection in those cell lines was due to a block at the level of virus entry into target cells.

The role of chemokine receptors in this phenotype was evaluated. From the results obtained it was evident that the presence of chemokine receptor CCR5 was sufficient to render cells susceptible to HIV-2ALI infection in vitro, independently of the presence of CD4 receptor.

Additionally, our results have revealed that HIV-2ALI has a low infectious potential in vitro in peripheral blood mononuclear cells when compared with other M-tropic and T-tropic viruses. Viral adsorption to target cells was identified as the step of replication cycle responsible for this low infectivity. Analysing the adsorption efficiency to several cell types, it was possible to conclude that this low adsorption efficiency, and consequently the low infectivity, could be overcome if high concentrations of CCR5 and CD4 receptors are present at cell surface. The results obtained also suggest that the low infectivity of HIV-2ALI was due to a low affinity to those cellular

receptors. Another important characteristic of HIV-2ALI was the inability to induce syncytia formation in peripheral blood mononuclear cells. As in the case of low infectivity, the presence of high levels of CCR5 and CD4 at target cell membrane could change this phenotype.

Since viral tropism, infectivity and syncytia formation are biological characteristics mediated mainly by the initial interactions between env gene glycoproteins and cellular receptors, we attempted to identify the regions of this gene that determined viral phenotype. With this aim several ALI-ROD quimeric viruses were constructed, replacing several regions of HIV-2ROD env gene by homologous regions of HIV-2ALI. The results demonstrated that HIV-2ALI phenotype was determined by regions spanning from conserved region C1 to the conserved region C4 of SU glycoprotein.

In conclusion, the phenotypic and pathogenic characteristics of HIV-2 M-tropic variants are determined by initial interactions between virus and target cell. These interactions involve the viral SU glycoprotein and cellular receptors, CD4 and CCR5. From this study it was possible to restrict the genetic determinants of this interactions to the region between C1 and C4 of the env gene. These interactions could also be responsible for the phenotypic differences between M-tropic and T-tropic variants, as well as for the less virulence observed for HIV-2 when compared to HIV-1.