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POSTER PRESENTATION

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HIV-1 Tat protein induces the production of IDO in human monocyte derived-dendritic cells through a direct mechanism: effect on T cells proliferation

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Background

During HIV-1 infection, an increase of indoleamine 2,3 dioxxygenase (IDO) expression, and dendritic cells (DC) dysfunction were often associated with AIDS disease progression [1].

Materials and methods

In this work, we investigated the effect of Tat recombinant protein from HIV-1 Lai and SF-2 strains on the expression of IDO, in Monocyte-derived dendritic cells (MoDCs) generated following 5 days of culture in the presence of GM-CSF and IL-4. IDO expression was analysed by SDS-PAGE and western blotting, intracellular labelling or by measuring kynurenine production by Ehrlich's assay. The capacity of Tat-treated MoDC to stimulate T cell proliferation was analysed by following CFSE dilution in the presence or absence of IDO inhibitor (1-methyl-tryptophane).

Results

We show that Tat induces IDO protein expression and activity in a dose dependent manner by acting at the cell membrane level. Using different Tat-fragments, we show that the N-Terminal domain, Tat 1-45, but not the central region, Tat 30-72, is sufficient to induce the expression of active IDO. Tat protein is also able to induce several cytokines in MoDCs, including IFN- γ , a strong inducer of IDO. In order to understand whether IDO is induced directly by Tat protein or indirectly following IFN- γ production, complementary experiments were performed and showed that: i) at the kinetic level, Tat induced IDO expression before the production of

IFN- γ ii) treatment of MoDCs with Tat-conditioned medium was unable to stimulate IDO expression, iii) coculture of MoDCs in a transwell cell system did not allow IDO expression in MoDCs not previously treated by Tat, iv) direct contact between Tat-treated and untreated MoDCs was not sufficient to induce IDO expression in a Tat-independent manner, and v) treatment of MoDCs in the presence of IFN- γ pathway inhibitors, Jak I and Ly294002, inhibited IFN- γ -induced IDO but had no effect on Tat-induced IDO. At the functional level, our data showed that treatment of MoDCs with Tat led to the inhibition of their capacity to stimulate T cell proliferation. This impairment was totally abolished when the stimulation was performed in the presence of 1MT, an inhibitor of IDO activity, arguing for the implication of the kynurenine pathway.

Conclusions

By inducing IDO, Tat protein may be considered, as a viral pathogenic factor, in the dysregulation of the DC functions during HIV-1 infection.

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