Tolerant DCs induced upon exposure to HTLV-1-infected T cells

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Introduction and Objectives: Human T-cell leukemia virus type-1 (HTLV-1) is the etiological agent of adult T-cell leukemia/lymphoma (ATLL). ATLL is one of the most aggressive blood cancers described to date, and the available treatments show limited efficacy. ATLL progression is associated with a low CD8+ T-cell response, and an increase in the number and activity of regulatory T-cells as well as in the levels of anti-inflammatory cytokines such as TGF-B and IL-10. However, how this immunotolerant status is induced is not completely understood. Infection of innate immune cells, such as dendritic cells (DCs) by HTLV-1 impairs several innate functions, such as the secretion of anti-inflammatory cytokines, and the ability to sustain T-cell proliferation, suggesting that HTLV-1 might also induce suppressive DCs. We thus aimed at analyzing the tolerant properties of HTLV-1-exposed DCs, and at identifying the viral determinants required to induce these properties.

Methods: Human primary monocyte-derived dendritic cells (MDDCs) were cultured with cell-free HTLV-1 virions, or co-cultured with HTLV-1 chronically infected T-cell lines producing infectious viral particles or not (C91-PL or C8166 cells, respectively). HTLV-1-exposed MDDCs were then stimulated by different TLR agonists, and MDDC activation was monitored by measurement of CD86 surface expression.

Results: We show that neither cell-free HTLV-1 virions nor HTLV-1-infected T-cells activate MDDCs. In addition, MDDCs exposed to HTLV-1-infected T-cells are unresponsive to secondary stimulation through TLR3 and TLR4 receptors but not to TLR2 and TLR7 receptors. Importantly, induction of this tolerant phenotype in HTLV-1-exposed MDDCs requires cell-to-cell contacts between MDDCs and infected T-cells, rather than viral particle production.

Conclusion: Our results demonstrate that cell-to-cell contacts between DCs and HTLV-1-infected T-cells induce a TLR3/4-specific tolerance in DCs, without the need for transfer of infectious viral particles. The possible molecular mechanisms induced in DCs upon exposure to HTLV-1 infected T-cells will be discussed.

Keywords : HTLV-1, dendritic cell, tolerance, T cells, cell-cell contact
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