Modulation of the IL-6 Signaling Pathway in Herpes Simplex Virus type-1-infected Mature Dendritic Cells

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In order to avoid viral infections, the human organism must be protected from the continuous threat via its immune system. Dendritic cells (DCs) are the most potent antigen presenting cells and play a pivotal role in the induction of protective adaptive immune responses. Thus, DCs represent interesting targets for virus-induced immune-evasion strategies including the degradation of functionally important molecules. Previously, our group has shown that Herpes simplex virus type-1 (HSV-1) does not only downmodulate the expression of CD83, a functionally very important protein, on directly-infected mature DCs (mDCs), but also on their un-infected “bystander” cells, via the release of non-infectious light- (L-) particles, lacking the viral genome. Within the present study, we investigated whether HSV-1-derived L-particles also modulate the IL-6 signaling pathway in mDCs, i.e. the IL-6Rα and the downstream molecule STAT3. Monocytes were isolated from human PBMCs and differentiated into mDCs using a cytokine cocktail. Subsequently, mDCs were mock- or HSV-1-infected (MOI 0.65) and harvested at 0-24 hpi for analyses of IL-6Rα expression on directly infected and uninfected “bystander” mDCs via flow cytometry. To further analyze STAT3 protein expression levels, mDCs were mock- or HSV-1-infected (MOI 2), harvested at 0-24 hpi and subjected to Western blot analyses. Here we show that HSV-1 reduces the expression levels of IL-6Rα as well as STAT3 of directly-infected mDCs. Mechanistically, the HSV-1 immediate-early gene product ICP27 and the tegument protein viral host shutoff (vhs) are involved in this proteasome-dependent STAT3 degradation. Noteworthy, not only directly-infected but also their uninfected “bystander” mDCs displayed reduced IL-6Rα expression levels, however, in a timely-delayed manner. Co-culture experiments revealed that L-particles, derived from directly HSV-1-infected mDCs, very likely transmit these effects to their uninfected counterparts via a phagocytosis-independent manner. The present work shows that HSV-1-derived L-particles transport viral proteins to uninfected “bystander” DCs, induce the downmodulation of functionally important proteins, such as IL-6Rα and STAT3, and thereby hamper DC-mediated antiviral immune responses.

Keywords : Herpes simplex virus type-1, dendritic cells, IL-6 signaling
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