Herpes simplex virus paralyzes dendritic cell migration

Herpes simplex virus (HSV) is a very successful human pathogen, known for its high sero-prevalence and the ability to infect a wide range of different cell types, including dendritic cells (DCs). Since directed DC migration to areas with high lymphocyte density is essential for the induction of potent immune responses, e.g. upon viral infections, interference with DC migration constitutes an attractive target to hamper antiviral immunity. To investigate whether HSV-2 modulates distinct hallmarks of DC biology, human monocyte-derived mature DCs (mDCs) were infected with HSV-1 strain 17 or HSV-2 strain G. At different time points post infection, cells were analyzed for the (i) initiation of viral protein expression by performing Western blot analyses, (ii) transwell migration and (iii) adhesion capability, as well as (iv) chemokine receptor expression and β2 integrin activity via flow cytometry. Here we demonstrate that HSV-2 induces mDC adhesion and thereby negatively interferes with mDC migration, very similar to its family member HSV 1. In particular, infection of mDCs revealed inhibited CCL19- as well as CXCL12-directed transwell migration using fibronectin-coated membranes. However, the respective chemokine receptors, CCR7 and CXCR4, were stably expressed on HSV-2-infected mDCs 4 hpi, the time point at which migration was already significantly inhibited. Considering this, reduction of transwell migration capability was caused by induction of mDC adhesion on β2 integrin-specific ligands via LFA-1, due to its constitutive activation on infected mDCs. This in turn was based on HSV-2-mediated proteasomal degradation of the negative regulator of β2 integrin activity, CYTIP, whereas the positive regulator of β2 integrin activity, cytohesin-1, remained stably expressed. In conclusion, the here presented data extend and strengthen recent reports regarding CYTIP degradation, induction of adhesion and reduction of migration in the context of an HSV-1 or HCMV infection (Theodoridis et al., 2011; Grosche et al., 2017). Therefore, hampering antigen delivery to SLOs and thus inhibiting the induction of a potent antiviral immune response seems to be evolutionary conserved among different members of the herpesviridae.

Keywords : Herpes simplex virus, dendritic cells, adhesion, migration
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