

Network: Infection and Inflammation: from Pathogen-induced Signatures to Therapeutic Target Genes

Project: Identification of Cellular Targets in HSV-1 Infected Dendritic Cells Using Functional Genomics in order to Establish New Antiviral Therapies

Alexander Steinkasserer - Friedrich Alexander University, Erlangen-Nuremberg –
alexander.steinkasserer@derma.imed.uni-erlangen.de

Results/Project Status

Herpes simplex virus type 1 (HSV-1) is able to establish latency in infected individuals. In order to characterize potential new immune escape mechanisms mature Dendritic Cells (DC) were infected with HSV-1 and total cellular RNA was isolated from infected and mock-infected populations at different time points. RNA profiling on Affymetrix Human Genome U133A arrays demonstrated a dramatic down-regulation of the migration-mediating surface molecules CCR7 and CXCR4, an observation that could be further confirmed by Reverse-Transcriptase Polymerase-Chain-Reaction (RT-PCR) and FACS analyses. Furthermore, migration assays revealed that upon infection of mature DC, CCR7- and CXCR4-mediated migration towards the corresponding CCL19- and CXCL12 chemokine gradients is strongly decreased. Noteworthy, the infection of immature DC with HSV-1 prior to maturation, lead to a failure of CCR7

and CXCR4 up-regulation during DC maturation and as a consequence also induced a block of their migratory capacity. Additional migration assays with a vhs mutant virus, lacking the virion host shutoff (vhs) gene which is well known to degrade cellular mRNAs, suggested a vhs-independent mechanism. These results indicate that HSV-1 infected mature DC are limited in their capacity to migrate to secondary lymphoid organs, the areas of antigen presentation and T-cell stimulation. Thus, inhibiting an antiviral immune response. This represents a novel, not yet known mechanism of HSV-1 to escape the human immune system.

Lit.: 1. Prectel et al., J Gen Virol. 2005, 86(Pt 6):1645-57

Fig 1A

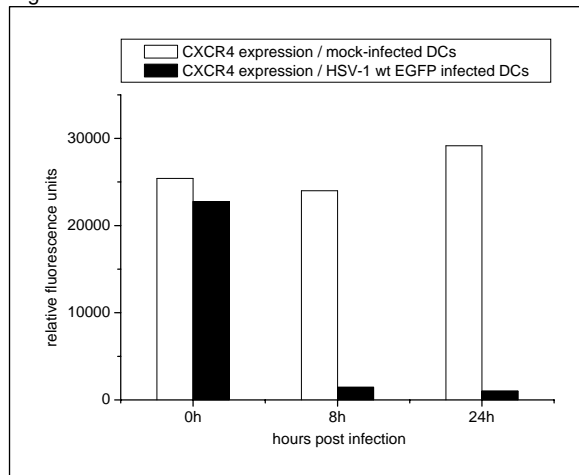


Fig 1B

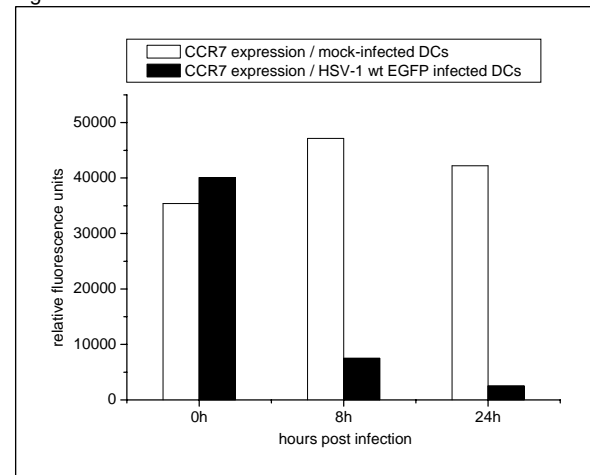


Fig 1: HSV-1 infection of mature DC induces dramatic changes in the CXCR4 (A) and CCR7 (B) expression.

Fig 2A

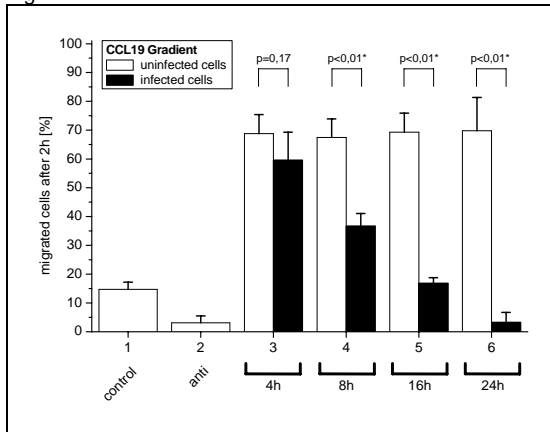


Fig 2B

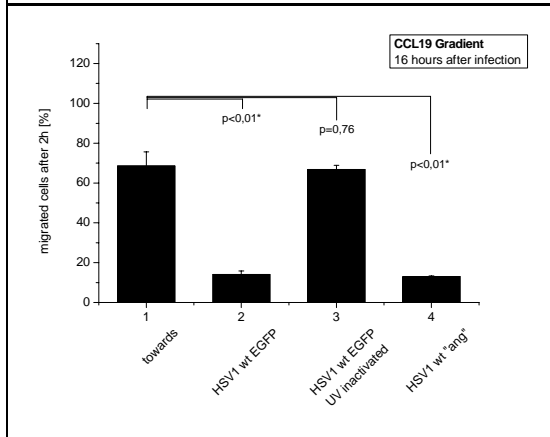
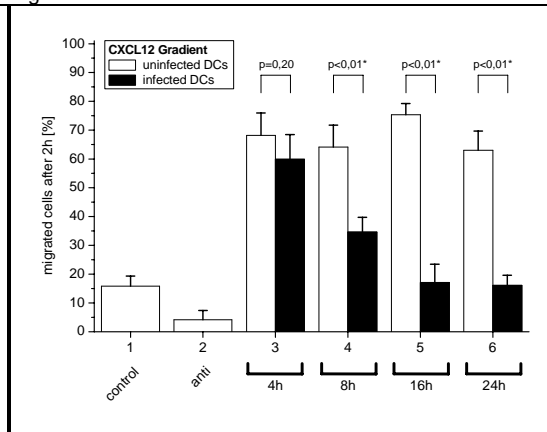


Fig 2C

Fig 2: HSV-1 infected DC lose their ability to migrate towards chemokine gradients.

Fig 3A

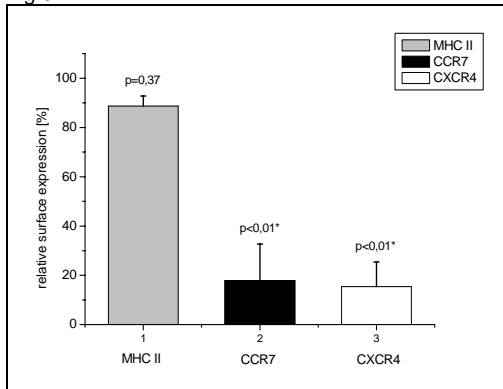


Fig 3B

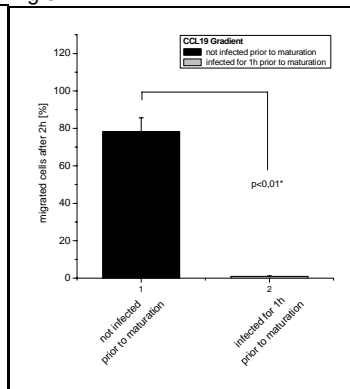


Fig 3C

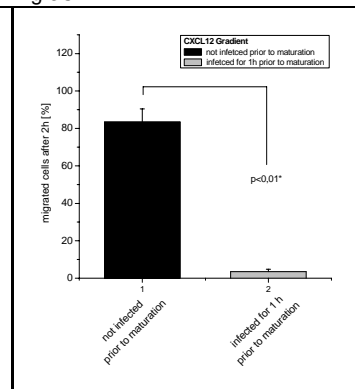


Fig 3: Infection of immature DC with HSV-1 prior to maturation leads to loss of CCR7 (A) and CXCR4 (B) surface expression and loss of migration capability (C).