

# Herpesvirus-induced glycans

Selectin ligands and related carbohydrate structures on the surface of the infected cell

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- I. Nyström K, Nordén R, Muylaert I, Elias P, Larson G, Olofsson S. Induction of sialyl-Lex expression by herpes simplex virus type 1 is dependent on viral immediate early RNA-activated transcription of host fucosyltransferase genes. *Glycobiology* 2009 Aug;19(8):847-59.
- II. Nordén R, Nyström K, Olofsson S. Activation of host antiviral RNA-sensing factors necessary for herpes simplex virus type 1-activated transcription of host cell fucosyltransferase genes FUT3, FUT5, and FUT6 and subsequent expression of sLe(x) in virus-infected cells. *Glycobiology* 2009 Jul;19(7):776-88.
- III. Nordén R, Nyström K, Aurelius J, Brisslert M, Olofsson S. Virus-induced appearance of the selectin ligand sLex in herpes simplex virus type 1-infected T cells: Involvement of host and viral factors. *Glycobiology*. 2013 Mar;23(3):310-21.
- IV. Nordén R, Nyström K, Adamiak B, Halim A, Nilsson J, Larson G, Trybala E, Olofsson S. Involvement of viral glycoprotein gC-1 in expression of the selectin ligand sialyl-Lewis X induced after infection with herpes simplex virus type 1. *APMIS*. 2013 Apr;121(4):280-9.

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UNIVERSITY OF GOTHENBURG

# Herpesvirus-induced glycans

## Selectin ligands and related carbohydrate structures on the surface of the infected cell

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### Abstract

Human herpesviruses are usually acquired early in life and are widely distributed in the population. A common feature of all human herpesviruses is that they persist in the host after the primary infection. Thus, the host immune system resolves the acute stage of the infection but these viruses have evolved means to remain in a state of latency in some cells from which they occasionally reactivate into a state of replication. A functional immune system will clear these episodes and the clinical manifestations are therefore usually mild or absent. On the other hand, when the immune system is dysfunctional the herpesviruses pose a serious threat. Especially cytomegalovirus (CMV) and Epstein-Barr virus (EBV) are associated with severe infections in transplant patients and other immunosuppressed patients, where infiltration of virus-infected leukocytes into organ tissue can give rise to pneumonia, hepatitis and renal failure.

The mechanism behind organ colonization of herpesvirus-infected leukocytes is not clear. However, the normal pathway for leukocyte transmigration over the endothelial wall is well characterized and involves interaction between carbohydrate binding proteins, selectins, and selectin ligands, including the Lewis antigen sialyl Lewis X (sLeX). The selectin ligands are therefore potential targets in viral pathogenesis and we have previously demonstrated that several herpesviruses can in fact activate the cellular pathway for synthesis of sLeX and related structures. In this work we aimed at defining the mechanism behind herpesvirus-induced selectin-ligand expression using herpes simplex virus type 1 (HSV-1) as a model virus. Moreover, we aimed at establish a model system for studying the effects of CMV and EBV infections on selectin ligand synthesis in leukocytes.

We determined that sLeX expression in HSV-1 infected fibroblasts depends on viral RNA transcription and the cellular protein kinase R, an antiviral protein complex that detects small double stranded RNA fragments generated by transcription of HSV-1 genes. We also found that the mechanism for HSV-1-induced expression of sLeX in T-lymphocytes was dependent on viral early protein synthesis, contrary to the situation in fibroblasts. Selectin ligands are expressed on glycoproteins in the cell and we found that sLeX can also be displayed on virus-encoded glycoproteins in fibroblasts. Preliminary data suggests that CMV and EBV also can manipulate the cellular machinery for selectin-ligand synthesis in leukocytes.

Patients with suppressed immune system are always at risk of developing severe CMV or EBV disease and are therefore carefully monitored for viral DNA in the blood. Unfortunately the viral load does not always correlate to disease progression and the patients risk severe complications. It is possible that selectin-ligands comprise a new set of diagnostic tools that can be used in parallel with traditional PCR based methods for better prediction of CMV/EBV disease progression. It is also possible that selectin-ligands are new targets for antiviral treatment and several substances, which block interaction with selectins, are already in clinical trials for evaluation of their anti-metastatic potential.

**Keywords:** Herpesviruses, HSV-1, CMV, EBV, sialyl Lewis X, Lewis Y, selectin, PKR

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