Herpesvirus-induced expression of sLe^x and related O-linked glycans in the infected cell

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i Mikrobiologens föreläsningssal, Guldhedsgatan 10A, Göteborg

fredagen den 5 oktober, 2007

av
Kristina Nyström

Fakultetsopponent:
Professor Jacques Le Pendu
INSERM, Universite de Nantes

This thesis is based on the following papers:

I. Mårdberg K, Nyström K, Tarp MA, Trybala E, Clausen H, Bergström T, Olofsson S. Basic amino acids as modulators of an O-linked glycosylation signal of the herpes simplex virus type 1 glycoprotein gC: functional roles in viral infectivity*. Glycobiology 2004; 14(7):571-81.*

II. Nyström K, Biller M, Grahn A, Lindh M, Larson G, Olofsson S. Real time PCR for monitoring regulation of host gene expression in herpes simplex virus type 1-infected human diploid cells*. J Virol Methods 2004; 118(2):83-94.*

III. Nyström K, Grahn A, Lindh M, Brytting M, Mandel U, Larson G, Olofsson S. Virus-induced transcriptional activation of host FUTgenes associated with neo-expression of Le^y in cytomegalovirus- and sialyl-Le^x in varicella-zoster virus-infected diploid human cells. *Glycobiology 2007; 17(4): 355-366.*

IV. Nyström K, Elias P, Larson G, Olofsson S. Herpes simplex virus type 1 ICP0-activated transcription of host fucosyltransferase genes resulting in neo-expression of sialyl-Le^x in virus-infected cells. *In Manuscript.*

Herpesvirus-induced expression of sLe^x and related O-linked glycans in the infected cell

Kristina Nyström
Department of Infectious Medicine, Göteborg University, 2007

Abstract

Lewis antigens constitute a family of fucosylated carbohydrate antigens (glycotopes), involved in leukocyte homing and related immunological phenomena. These glycotopes are only expressed restrictedly in normal cells, but are induced at appropriate occasions. It is well established that many tumors "hijack" Lewis glycotopes for e.g. extravasation and metastasis, and recent data indicate that also human retroviruses may use a similar strategy for colonization of distal tissues. The overall goal of the present thesis was to explore the prerequisite for this phenomenon to occur in cells infected with herpesviruses, a virus family where persistent infections and immune evasion are important hallmarks.

Using confocal immunofluorescence, neo-expression of Lewis antigens was found on cells infected with herpes simplex virus type-1 (HSV-1), varicella-zoster virus (VZV), and cytomegalovirus (CMV). However, whereas the neurotropic viruses VZV and HSV-1 induced sialyl Lewis x (sLe^x), CMV induced Lewis y (Le^y) at the surface of the infected cells. Real time RT-PCR methods for transcriptional analysis of all known human fucosyltransferase genes (FUT) were developed to determine the mechanism behind virus-specific induction of different glycotopes. The herpesviruses investigated were all able to induce transcription of FUT3, FUT5 and FUT6 relevant for sLe^x and Le^y synthesis whereas only CMV induced FUT1, necessary for Le^y expression. In most cases the transcriptional activity of these genes was several orders of magnitude larger in virus-infected cells compared to uninfected cells.

The viral factors causing neo-expression of glycotopes were explored using FUT5 and the HSV-1 infected cell as a model system. It was found that the transcripts of the immediate early viral gene, designated ICP0, was able to induce FUT5 transcription without assistance of the translated gene product. This finding explained the extremely early occurrence of host FUT5 RNA, detectable as early as one hour post infection. However, several other viral factors were engaged in regulation of the FUT5 transcription downstream the ICP0 induction. The viral glycoprotein gC-1 was identified as a probable candidate as a carrier of O-linked glycans and important regulatory elements of the O-glycosylation sequon of gC-1 were characterized. These regulatory elements were decisive for the social behavior of virus-infected cells in culture.

The conclusion of the present work is that herpesviruses possess powerful mechanisms for viral control of the expression of selectin ligands and similar glycotopes, of relevance for tumor metastasizing and tissue invasion of human transforming retroviruses. sLe^x and Le^y constitute targets for development of cancer chemotherapy, but further investigation is necessary to determine whether this approach is applicable also for treatment of herpesvirus-infections.

Keywords: HSV-1, CMV, VZV, O-linked glycans, Lewis antigens, ICP0

ISBN: 978-91-628-7271-7