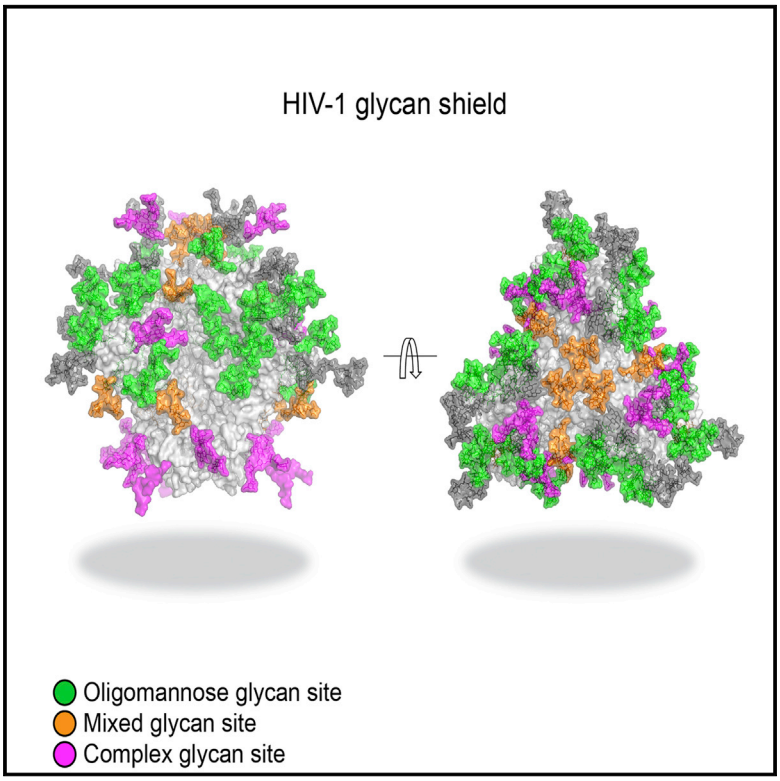
Article

Cell Reports

Composition and Antigenic Effects of Individual Glycan Sites of a Trimeric HIV-1 Envelope Glycoprotein

Graphical Abstract



Highlights

- Quantitative, site-specific N-glycan analysis of a soluble HIV-1 Env trimer
- A map of the extremes of simplicity and diversity at individual glycan sites
- The fine structure of the mannose patch area of the Env trimer
- How individual glycan sites influence HIV-1 Env-pseudovirus neutralization

Authors

Anna-Janina Behrens, Snezana Vasiljevic, Laura K. Pritchard, ..., John P. Moore, Katie J. Doores, Max Crispin

Correspondence

katie.doores@kcl.ac.uk (K.J.D.), max.crispin@bioch.ox.ac.uk (M.C.)

In Brief

Behrens et al. present detailed, quantitative, site-specific analyses of N-glycosylation sites of a soluble recombinant HIV-1 envelope glycoprotein trimer. The results highlight structural and antigenic details of the glycan shield that will be valuable for designing next-generation HIV-1 Env vaccines and understanding virus neutralization by broadly active antibodies.

Behrens et al., 2016, Cell Reports *14*, 2695–2706
March 22, 2016
http://dx.doi.org/10.1016/j.celrep.2016.02.058

CellPress

Cell Reports
Article

Composition and Antigenic Effects of Individual Glycan Sites of a Trimeric HIV-1 Envelope Glycoprotein

Anna-Janina Behrens,[1] Snezana Vasiljevic,[1] Laura K. Pritchard,[1] David J. Harvey,[1] Rajinder S. Andev,[2] Stefanie A. Krumm,[2] Weston B. Struwe,[1] Albert Cupo,[3] Abhinav Kumar,[1] Nicole Zitzmann,[1] Gemma E. Seabright,[1] Holger B. Kramer,[4] Daniel I.R. Spencer,[5] Louise Royle,[5] Jeong Hyun Lee,[6] Per J. Klasse,[3] Dennis R. Burton,[7,8] Ian A. Wilson,[6,9] Andrew B. Ward,[6] Rogier W. Sanders,[3,10] John P. Moore,[3] Katie J. Doores,[2,*] and Max Crispin[1,*]
[1]Oxford Glycobiology Institute and Department of Biochemistry, University of Oxford, South Parks Road, Oxford OX1 3QU, UK
[2]Department of Infectious Diseases, Faculty of Life Sciences and Medicine, King's College London, Guy's Hospital, London SE1 9RT, UK
[3]Department of Microbiology and Immunology, Weill Cornell Medical College, New York, NY 10021, USA
[4]Department of Physiology, Anatomy and Genetics, University of Oxford, South Parks Road, Oxford OX1 3QX, UK
[5]Ludger, Ltd., Culham Science Centre, Abingdon, Oxfordshire OX14 3EB, UK
[6]Department of Integrative Structural and Computational Biology, International AIDS Vaccine Initiative (IAVI) Neutralizing Antibody Center and CAVD, Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery, The Scripps Research Institute, La Jolla, CA 92037, USA
[7]Department of Immunology and Microbial Science, IAVI Neutralizing Antibody Center and CAVD, Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery, the Scripps Research Institute, La Jolla, CA 92037, USA
[8]Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology and Harvard University, Boston, MA 02142, USA
[9]Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA 92037, USA
[10]Laboratory of Experimental Virology, Department of Medical Microbiology, Center for Infection and Immunity Amsterdam (CINIMA), Academic Medical Center of the University of Amsterdam, 1105 AZ Amsterdam, the Netherlands
*Correspondence: katie.doores@kcl.ac.uk (K.J.D.), max.crispin@bioch.ox.ac.uk (M.C.)
http://dx.doi.org/10.1016/j.celrep.2016.02.058

SUMMARY

The HIV-1 envelope glycoprotein trimer is covered by an array of N-linked glycans that shield it from immune surveillance. The high density of glycans on the trimer surface imposes steric constraints limiting the actions of glycan-processing enzymes, so that multiple under-processed structures remain on specific areas. These oligomannose glycans are recognized by broadly neutralizing antibodies (bNAbs) that are not thwarted by the glycan shield but, paradoxically, target it. Our site-specific glycosylation analysis of a soluble, recombinant trimer (BG505 SOSIP.664) maps the extremes of simplicity and diversity of glycan processing at individual sites and reveals a mosaic of dense clusters of oligomannose glycans on the outer domain. Although individual sites usually minimally affect the global integrity of the glycan shield, we identify examples of how deleting some glycans can subtly influence neutralization by bNAbs that bind at distant sites. The network of bNAb-targeted glycans should be preserved on vaccine antigens.

INTRODUCTION

The trimeric HIV type 1 (HIV-1) envelope glycoprotein (Env) is the sole target for broadly neutralizing antibodies (bNAbs) produced by the immune system during infection and is, therefore, a focus of vaccine design. In numerous studies, bNAbs provide passive protection from viral challenge to non-human primates (Hessell et al., 2010; Mascola et al., 2000; Moldt et al., 2012). Many of these bNAbs recognize epitopes that are wholly or partially composed of glycan structures (Blattner et al., 2014; Calarese et al., 2003; Falkowska et al., 2014; Garces et al., 2014; Huang et al., 2014; Kong et al., 2013; McLellan et al., 2011; Mouquet et al., 2012; Pancera et al., 2013; Pejchal et al., 2011; Scanlan et al., 2002; Scharf et al., 2014; Walker et al., 2011). HIV-1 Env is among the most heavily glycosylated proteins known, with glycans making up ~50% of its total mass (Lasky et al., 1986). These abundant glycans have long been considered to shield the trimer from immune surveillance by occluding relatively conserved protein surfaces (Wei et al., 2003); while this concept remains valid, it is also now evident that the glycan shield itself can be a target for bNAbs. Defining the detailed composition of the glycan shield will increase our understanding of bNAb epitopes and how HIV-1 is neutralized and, thus, help the rational design of Env-based vaccine immunogens.

The Env trimer is composed of three gp120 and three gp41 subunits. Analyses of monomeric gp120 proteins have revealed the presence of under-processed N-glycans that remain in oligomannose form ($Man_{5-9}GlcNAc_2$) because steric constraints impede the actions of the endoplasmic reticulum (ER) and Golgi α-mannosidases (Bonomelli et al., 2011; Doores et al., 2010; Go et al., 2013; Leonard et al., 1990; Zhu et al., 2000). These oligomannose-type glycans are mainly localized to a highly conserved area of the gp120 outer domain, the so-called "intrinsic mannose patch,"