Retrovirology

BioMed Central

Poster presentation

P19-03. Molecular mechanisms for enhancing the antigenicity of the carbohydrate epitope of the broadly neutralizing anti-HIV-1 antibody 2G12

Z Fulton*[1], KJ Doores[2], CN Scanlan[2], MR Wormald[2], RA Dwek[2], IA Wilson[1] and BG Davis[2]

Address: [1]Molecular Biology, The Scripps Research Institute, La Jolla, CA, USA and [2]University of Oxford, Oxford, UK
* Corresponding author

from AIDS Vaccine 2009
Paris, France. 19–22 October 2009

Published: 22 October 2009

Retrovirology 2009, **6**(Suppl 3):P323 doi:10.1186/1742-4690-6-S3-P323

This abstract is available from: http://www.retrovirology.com/content/6/S3/P323

Background

The broadly neutralizing antibody 2G12 is uniquely capable of recognizing the self-carbohydrate shield on the HIV-1 envelope glycoprotein gp120 and escaping immune tolerance. The preferred substrate of 2G12 is the Man4(D1)-arm of high-mannose glycans clustered on the gp120 outer surface. Remarkably, 2G12 has been shown to exhibit higher affinity for the non-self monosaccharide D-fructose than for D-mannose. D-fructose, in its pyranose form, resembles D-mannose, but with different substitutions at the anomeric and C-5 positions. These observations suggested other 'non-self' modifications to D-mannose may also enhance 2G12 binding. We consequently found that D-mannose with a C-6 methyl substitution binds 2G12 more strongly than both D-mannose and D-fructose. Moreover, introduction of this non-self modification to the terminus of the D1-arm creates the most potent monovalent 2G12 ligand known. We uncover here the molecular basis of this enhanced antigenicity, and the higher affinity of 2G12 for D-fructose over D-mannose, through high resolution crystallographic analyses.

Methods

Crystal structures of 2G12 in complex with the modified D-mannose and D1-arm, and D-fructose were determined to 1.75, 2.85, and 1.95 Å, respectively.

Results

The crystal structures of 2G12 in complex with the modified D-mannose and D1-arm revealed the C-6 methyl substitution enhances antigenicity by making additional hydrophobic contacts with the aromatic side chain of TyrL94. The D1-arm mimic otherwise adopts the same conformation as the natural D1-arm in complex with 2G12. The complex with D-fructose revealed the non-self monosaccharide is indeed bound in its pyranose form and its enhanced antigenicity is due to several additional H-bonds mediated by its C-5 hydroxyl.

Conclusion

The crystal structures reported here uncover different mechanisms for creating potent non-self monosaccharide antigens of 2G12. The fact the D1-arm mimic maintains the same interactions with 2G12 as the natural D1-arm is encouraging in terms of its potential as an immunogenic fragment to elicit a 2G12-like immune response.