

Poster presentation

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PI9-03. Molecular mechanisms for enhancing the antigenicity of the carbohydrate epitope of the broadly neutralizing anti-HIV-1 antibody 2G12

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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.