Tudor et al. Retrovirology 2010, 7(Suppl 1):P23
http://www.retrovirology.com/content/7/S1/P23

RETROVIROLOGY

POSTER PRESENTATION Open Access

The immunoglobulin CH1 constant region modulates antigen binding affinity and functional activities of the broadly neutralizing 2F5 HIV specific antibody

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From 16th International Symposium on HIV and Emerging Infectious Diseases
Marseille, France. 24-26 March 2010

Background

The ability of the heavy chain constant region (CH) to affect antibody affinity and specificity could be at the origin of a stronger or weaker memory response, depending on the isotype. Using as a model the broadly neutralizing human mAb 2F5, directed against the membrane proximal region (MPER) of the HIV-1 envelope transmembrane subunit gp41, we investigated the interplay between 2F5 isotype and functional activity.

Methods

A 2F5 IgA isotype was constructed from the 2F5 IgG1. Functional monomeric 2F5 IgA and IgG1 were expressed in CHO cells and their immunochemical characteristics and anti-HIV-1 in-vitro activity were evaluated.

Results

As compared to 2F5 IgG1, 2F5 IgA sharing identical VH and VL domains but in a different CH context: (i) binds with higher affinities gp41 and MPER peptides; (ii) has an increased capacity at inhibiting endocytosis of HIV-1 by dendritic cells; (iii) has an increased HIV-1 neutralizing activity in lymphocytic CD4+ T cells; (iv) blocks more efficiently HIV-1 transcytosis across epithelial monolayers in-vitro and normal human rectal mucosa, but (v) has lower ADCC activity. Epitope mapping with a 7 mer epitope library shows that 2F5 IgA recognizes essentially the same hexapeptide epitope as its IgG counterpart.

Discussion

These results show that the CH region can fine-tune the specificity of an antibody, by modulating its binding affinity to the antigen and the neutralizing activity of variable-region of otherwise identical antibodies. The determinant role of CH region on affinity and specificity changes our understanding of vaccine responses. In the context of HIV-1, which is mainly transmitted sexually, these results strongly suggest that raising a mucosal humoral IgA based response will be superior to an IgG one in blocking HIV-1 transmission.

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Published: 11 May 2010

doi:10.1186/1742-4690-7-S1-P23
Cite this article as: Tudor *et al.*: The immunoglobulin CH1 constant region modulates antigen binding affinity and functional activities of the broadly neutralizing 2F5 HIV specific antibody. *Retrovirology* 2010 **7**(Suppl 1):P23.

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