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S Tenzer[1], E Wee[6], A Burgevin[2], G Stewart-Jones[6], L Friis[6], K Lamberth[3], C Chang[6], M Harndahl[3], M Weimershaus[2], J Gerstoft[4], N Akkad[2], P Klenerman[6], L Fugger[6], EY Jones[6], AJ McMichael[6], S Buus[3], H Schild[1], P van Endert[2] and AK Iversen*[5,6]

Address: [1]University of Mainz, Mainz, Germany, [2]INSERM, Unité 580, Université Paris-Descartes, Paris, France, [3]University of Copenhagen, Copenhagen, Denmark, [4]Rigshospitalet, The National University Hospital, Copenhagen, Denmark, [5]Oxford University, Oxford, UK and [6]Wellcome Trust Centre for Human Genetics, Oxford University, Oxford, UK

* Corresponding author

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Background

Cytotoxic T cells (CTL) play a key role in limiting human immunodeficiency virus (HIV)-1 replication. However, although the cellular immune response in HIV-infected individuals can potentially target multiple virus epitopes, the same few are repeatedly recognized. Here we investigated the factors determining observed CTL response hierarchies in Gag p17 and p24.

Methods

We used constitutive and immuno-proteasomal digestion assays, transporter associated with antigen processing (TAP) binding assays, endoplasmatic reticulum aminopeptidase (ERAAP) trimming assays, HLA binding assays, T cell cloning and ELISpot assays to evaluate the contribution of each of these factors to final epitope presentation and recognition. Key findings were further examined using structural analyses.

Results

We show that CTL-immunodominance in regions of HIV-1 p17- and p24-Gag correlates with epitope abundance, which is influenced strongly by proteasomal digestion profiles, TAP-affinity and ERAAP-mediated trimming, and moderately by HLA affinity. Structural and functional analyses demonstrate that proteasomal cleavage-preferences modulate the number and length of epitope-containing peptides, thereby affecting T cell response avidity and clonality. Cleavage patterns were affected by both flanking and intra-epitope CTL-escape mutations.

Conclusion

Our analyses show that antigen processing shape CTL-response hierarchies, that viral evolution modify cleavage patterns, and suggest strategies for in vitro vaccine optimization.