Evolution of epitope-specific CD8+ T cell responses with viral escape during Acute Subtype C HIV-1 infection

Catherine Riou³, Mandla Mlotshwa³, Melissa-Rose Abrahams³, Deniz Chopersa³, Michael Liu⁴, Milu Goonetilleka³, Florette Treurnicht³, Koleka Milisana³, Andrew McMichael², Carolyn Williamson¹, Salim Abdool Karim³, Olivi M Gray² and the CAPRISA 002 study team.

¹Division of Immunology, University of Cape Town, South Africa. ²Division of Virology, University of Cape Town, South Africa. ³University of Oxford, United Kingdom. ⁴Centre for the AIDS Program of Research in South Africa (CAPRISA), University of KwaZulu Natal, South Africa.

Introduction

- Dissecting the specificity of CD8+ T cell responses during acute and early stage of HIV-1 infection, and how these epitope-specific responses evolve with viral diversity represent important information for understanding potential vaccine-induced immunity.
- We recently described some of earliest T cell responses that occur during acute/early subtype C HIV-1 infection and how these change over time in relation to autologous viral escape and early disease progression (Mlotshwa et al 2010).
- A subset of these individuals were analyzed in more detail to characterize the functional profiles of CD8+ T cells that target transmitted and mutant epitopes in 5 participants.

Methods

- A complete dissection of IFN-γ T cell responses across the entire expressed HIV-1 subtype genome undertaken using a panel of 400 autologous peptides for each participant arranged in pool-matrix format allowed use to identify putative epitopes peptides, after deconvolution. Single epitopes were confirmed in a follow-up IFNg ELISPOT.
- For each individuals, transmitted and mutant epitopes (defined on longitudinal viral sequencing) were used in an ICS assay to evaluate the magnitude and functional profiles (IFNγ, TNFα, CD107, MIP1α and Perforin) of epitope-specific CD8+ T cell responses before and after viral escape.

Table 1 Epitope sequence used in the ICS to study multifunctional profiles of CD8+ T cells

<table>
<thead>
<tr>
<th>Epitope Sequence</th>
<th>IFNγ+</th>
<th>TNFα+</th>
<th>CD107+</th>
<th>MIP1α+</th>
<th>Perforin+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results 1

Magnitude of CD8+ T cell responses overtime towards early (<20 weeks PI) and late (>20 weeks PI) escape HIV epitopes.

Results 2

Functionality of CD8+ T cell responses towards early (<20 weeks PI) and late (>20 weeks PI) escape HIV epitopes, BEFORE escape.

Results 3

Longitudinal analysis of multifunctional profiles and magnitude of wild type (transmitted) and mutant epitopes before and after sequence evolution.

Acknowledgements

We would like to thank National Institute for Communicable Disease, AIDS Immunology Vaccine Lab staffs and the Clinic staffs at CAPRISA. This study was supported by CAPRISA which forms part of the Comprehensive International Program of Research on AIDS (CIPRA) funded by the National Institute of Allergy and Infectious Disease (NIAID), National Institutes of Health (NIH) and the US Department of Health and Human Services (DHHS) (grant R1 U19 AI51794).

Conclusions

Overall, the magnitude and polyfunction of mutant-specific responses were lower as compared to transmitted-specific responses. However, some mutant epitopes can present similar magnitude and polyfunction as compared to transmitted epitopes prior to escape. Overtime both transmitted and mutant responses decrease and no emergence of mutant-responses were observed after mutation occurred.

In this study, we have shown the following key findings:
- Magnitude, more than polyfunctionality, of HIV-specific CD8+ T cell responses appear to play a role in CTL-dependent epitope escape.
- Mutant epitopes can be recognized at low frequency prior to escape and the quicker escape occurs.
- Mutant epitopes can be recognized at low frequency prior to escape and the quicker escape occurs.
- Overall, the stronger and faster response toward mutant epitopes appears to play a role in CTL-dependent epitope escape.
- Mutant epitopes can be recognized at low frequency prior to escape and the quicker escape occurs.
- Overall, the stronger and faster response toward mutant epitopes appears to play a role in CTL-dependent epitope escape.