McMichael: HLA-E restricted CD8 responses induced by CMV vaccines

OVERVIEW

Despite very significant but partial success of drug based approaches and public health measures, there are still over 2 million new HIV-1 infections per year. Therefore an effective prophylactic vaccine is very badly needed. Attempts have also been made to design vaccines that stimulate HIV-1 specific CD8+ T cells, but no protection has been seen in three trials, STEP, Phambili, and HVTN505, using adenovirus-5 vectors to deliver antigen. The level and breadth of CD8+ T cell responses stimulated were not high and, in each case, much of the response was focused on variable epitopes in Env, Gag, and Pol. Recent experiments from Louis Picker's group have raised the possibility that the right kind of vaccine-induced CD8+ T cells could protect. In rhesus monkeys he used a Rhesus CMV vector RhCMV68-1 to deliver SIV genes as a vaccine. When these animals were challenged mucosally a year after vaccination, 53% of those infected were able to clear virus completely. The virus was eradicated by CD8+ T cells; however the T cell responses are very atypical with the CD8+ T cell responses against multiple epitopes that are even in magnitude and are restricted by either MHC-II or MHC-E. These results are strikingly different from all previous monkey-SIV protection experiments even in the presence of strong and broad classical CD8+ T cell responses. Therefore it seems likely that these unique T cell responses are important to the clearance of virus by CD8+ T cells.

These results from the Picker group raise the following important questions:

1.) Can these T cell responses be elicited in humans?

2.) What atypical antigen processing pathways are important for priming these T cells and why are the T cell responses so broad?

3.) Have they played a part in elite control and could they account for apparent lack of infection in some very highly HIV-exposed individuals?

4.) Are similar responses elicited by immunogens other than RhCMV68.1?

Our laboratory has extensive experience in characterizing the biological functions of HLA-E, for example demonstrating that the normal function of HLA-E is to present an HLA-Ia signal peptide to the NKG2A/CD94 and NKG2C/CD94 receptors on natural killer (NK) cells. We also determined the first structure of HLA-E bound to the signal peptide VL9 (15) and showed that the identical peptide sequence in the signal peptide of HCMV UL40 subverted NK cell recognition of HCMV infected cells. We are therefore well placed to explore the role of HLA-E in HIV-1 infection. The studies proposed here will complement the vaccine program that is ongoing in Louis Picker's laboratory.

This grant is led by Andrew McMichael, MD (University of Oxford), in a collaborative association Louis Picker, MD (Oregon Health and Sciences University). The award was received in July, 2015 with an initial agreement length of 3 years.

Grant at a Glance

Principal Investigator
Andrew McMichael, MD

Grantee Institution
University of Oxford, Oxford, UK

Project Title
HLA-E restricted CD8 responses induced by CMV vaccines

OPPID
11133649

Grant Award
Up to $556,000, awarded in July, 2014

RESEARCH OBJECTIVES

1.) Identification of HLA-E binding peptides in HIV-1.

2.) Identification of peptides presented with HLA-E in HIV-1 infected cells.

3.) Analysis of whether the two allotypes of HLA-E differ in their peptide presentation and level of expression.

4.) Identification of HLA-E restricted CD8+ T cells in HIV seronegative and infected donors and vaccine recipients. This will span the following subject types:

   a.) Naïve CD8+ T cells in healthy HIV-1 negative blood donors

   b.) HIV-infected individuals

   c.) Donors who have been highly exposed to HIV-1 but have not become chronically infected

   d.) Volunteers who have received HIV-1 vaccines including BCG based vaccines

5.) Analysis of the phenotype of HLA-E restricted CD8+ T cells.

6.) Analysis of how these findings relate to Rhesus monkeys.

PROGRESS

1.) We have developed HLA-E-peptide binding and expression assays that have led to identification of 3 HIV derived binding peptides.

2.) We have eluted HIV-1 peptides from HLA-E on PBMC and cell lines and identified putative epitopes.

3.) HLA-E*0103 is expressed at higher levels than HLA-E*0103 and appears to bind more peptides.

4.) We have established a CD8 T cell repertoire assay that detects primary CD8 T cell responses in HIV-negative donors, including responses to (non-HIV) epitopes restricted by HLA-E.

5.) We have determined the crystal structure of HLA-E bound to a non-canonical Mycobacterial epitope peptide.

6.) We have shown that HCMV UL40 and RhCMV Rh67 serve similar functions in expressing MHC-E on CMV infected cells when TAP is blocked..