Picker: MHC II and MHC E-Restricted CD8+ T Cells and Control of HIV

OVERVIEW

In the past decade, we have demonstrated in rhesus models that persistent SIV vaccine vectors based on the ubiquitous β-herpesvirus cytomegalovirus (RhCMV/SIV vectors) elicit and indefinitely maintain systemic high frequency, circulating and tissue-resident effector memory T cell (TEM) responses that can intercept and stringently control a highly pathogenic, AIDS-causing SIV very early, if not immediately, after exposure. Moreover, these responses not only maintain this control over the long term, but actually clear the infection to the degree that protected animals are not distinguishable from non-SIV-exposed animals by state-of-the-art analysis at necropsy. During the course of these investigations, it was determined that these T_{EM}-type responses are associated with unprecedented array of SIV epitope-specific CD8+ T cell responses (3-fold the breadth of conventional responses) that were restricted by MHC class II (MHC II; two-thirds of responses) and non-classical MHC E (one-third of responses) proteins, rather than the conventional polymorphic MHC class I (MHC I) presentation. Also in contrast to conventional CD8+ T cell responses, many of the unconventional viral epitopes targeted by these responses were common to most or even all monkeys, despite the fact that these monkeys were out-bred and quite genetically heterogeneous. These highly unusual CD8+ T cell responses were found to be due to deletion of 2 genes, UL128 and UL130, in the fibroblast-adapted CMV vector compared to wildtype CMV, and repair of these 2 genes completely reversed the recognition properties back to conventional characteristics.

Given that HIV and SIV have evolved to evade conventional CD8+ T cell responses, it's possible that the unconventionally targeted CD8+ T cell responses elicited by the UL128/UL130-deleted CMV vectors account for their demonstrated efficacy against SIV challenge. It is also noteworthy that since the discovery of these responses in UL128/UL130-deleted CMV vector-vaccinated monkeys, careful and specific scrutiny of CD8+ T cell responses in humans and monkeys with spontaneous (e.g., not vaccine-related) HIV or SIV control has led to the identification of minor, but unequivocal, MHC II-restricted, HIV- or SIV-specific CD8+ T cell populations. This finding raises the question of whether these spontaneous (e.g., non-CMV vector-elicited) unconventional CD8+ T cell responses might have contributed to the viral control in these subjects. Evidence of the importance of these unconventional responses would have implications for HIV vaccine development, both to inform the clinical development of CMV vectors and to develop alternative methods to generate these responses. Consequently this consortium effort was established to determine 1) the mechanisms responsible for generation of unconventionally targeted CD8+ T cell responses, 2) the functional implications of unconventional epitope recognition by CD8+ T cells, and most importantly, 3) whether unconventionally targeted SIV- or HIV-specific CD8+ T cells manifest enhanced *in vivo* viral control compared to conventionally targeted CD8+ T cell response.

This grant is led by Louis Picker, MD (Oregon Health & Science University (OHSU)/Vaccine and Gene Therapy Institute), with participation of John Altman, PhD (Emory University, tetramer development), Bruce Walker MD (Ragon Institute of MGH, MIT, and Harvard), and Mark Davis (Stanford University, systems immunology). The award was received in September 2014 with an initial agreement length of 3 years.

RESEARCH OBJECTIVES

1.) Determine the contribution of unconventionally targeted, SIV-specific CD8+ T cells (MHC II- and/or MHC E-restricted) to RhCMV/SIV vector efficacy

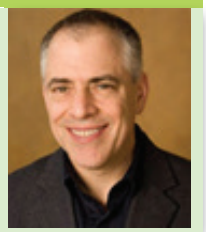
2.) Compare the phenotypic and functional differentiation of unconventional vs. conventional epitope-specific CD8+ T cells elicited by strain 68-1 and strain 68-1.2 RhCMV/SIV vectors vs. controlled SIV infection

3.) Characterize the TCR repertoire and developmental origin of unconventionally targeted CD8+ T cells elicited by strain 68-1 RhCMV/SIVgag vectors

4.) Determine the strain 68-1 RhCMV-mediated mechanism(s) that direct the development of unconventionally targeted CD8+ T cells and prevent conventional epitope recognition

5.) Identify and characterize MHC II-restricted CD8+ T cells in HIV-infected individuals

Grant at a Glance



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