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Characterization of HIV specific T cell responses during acute and early HIV-1 subtype C infection

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ABSTRACT

It is not known what kind of T cell immunity is required to be effective at containing viral replication and abating HIV-1 disease progression. While most studies have examined HIV-1 specific T cell responses in chronic infection, consideration of how these responses evolve during acute and early stages of HIV-1 infection and their influence on viral set point and the course of disease represent important information for understanding potential vaccine induced T cell immunity. To this end, a cohort of 53 individuals identified during acute HIV-1 subtype C infection was followed over the first year of infection to: a) determine whether the magnitude and breadth of HIV-1 specific T cell responses at 3 month post infection were correlated with viral set point at 12 months, b) characterize the hierarchy of HIV-1 specific T cell responses and associated temporal patterns of responses related with viral set point and disease progression, c) study the impact of the polyfunctional nature of CD8+ T cell profiles during acute/early HIV-1 infection that provide for selection of CTL escape mutations, and d) study the dynamics and kinetics of plasma mediators of apoptosis (Fas, TNF-RII and TRAIL) during acute/early HIV-1 infection and associate with viral set point and disease progression. Comprehensive T cell recognition patterns across the complete HIV-1 subtype C proteome were measured using the IFN-γ ELISPOT assay. The polyfunctional nature of CD8+ T cells was measured by simultaneous analysis of IFN-γ, TNF-α, MIP-1β, IL-2, perforin and CD107 using polychromatic flow cytometry. Plasma levels of apoptosis mediators-Fas, TNF-RII and TRAIL were assessed using ELISA. The magnitude and breadth of IFN-γ ELISPOT responses at 3-months post infection were correlated with

viral set point at 12 months post infection. A strong and diverse pattern of T cell recognition was observed at 3 months post infection, with the recognition of Nef, Gag and Pol being immunodominant as early as 3 weeks post infection. Over 6 months, there was a 23% chance of an increased response to Nef for every week post infection ($p=0.0024$), followed by non-significant increase to Pol (4.6%) and Gag (3.2%). Responses to Env and regulatory proteins appeared to remain stable. The magnitude of T cell responses fluctuated widely over the first year of infection and three distinguishing temporal patterns of T cell recognition could be observed: persistent, lost and new. Relating these patterns of T cell recognition with disease progression showed that the proportion of persistent T cell responses were significantly higher ($p=0.0037$) in slow progressing (85%) compared to rapid progressing (20%) individuals. New T cell responses tended to associate with rapid progression ($p=0.06$) and lost responses, which were associated with autologous sequence escape (88%) had no bearing on disease progression. The median time to autologous viral escape was found to be directly associated with time to loss of IFN-γ ELIPSOT responses ($r=0.61$, $p=0.019$), where 80-100% of responses that were lost occurred at an average of 14 weeks (95% C.I: 4.4-24 weeks) after epitope escape. In four of these individuals, (I) the total magnitude of epitope-specific CD8+ T cells was associated with the time of viral escape mutant selection and (II) there was no association between the polyfunctional nature of CD8+ T cells, perforin expression or memory maturation with selection of early or late viral escape mutant epitopes. In addition, the magnitude and polyfunctionality of early and late mutating epitope specific CD8+ T cells were significantly reduced ($p=0.003$) over time following selection of viral escape mutants. A further analysis of twenty-one

individuals for plasma levels of TRAIL, TNF-RII and Fas showed a significantly elevated levels of TNF-RII in acute/early infection and was associated with changes in viraemia and CD4+ and CD8+ T cell activation over the first year of infection. Overall, the findings presented in this thesis provides an insight on the character of T cell immunity in the containment of viraemia in acute HIV-1 infection and also highlights the rapidity of T cell evolution and the likely unpredictable nature of T cell recognition patterns during acute to early infection.