**PE5**

**Differential effects of cell-surface CD4 and tetherin on ADCC mediated by non-neutralizing and broadly neutralizing anti-HIV antibodies: the role of Nef and Vpu**

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**Background:** The advent of monoclonal antibodies capable of broadly neutralizing HIV variants and recent demonstrations in humanized mice of how some of these antibodies can impact latent virus reservoirs in a Fc domain-dependent manner have rejuvenated interests in the area of humoral/innate immunity for HIV cure. HIV accessory proteins Nef and Vpu have been shown to promote escape from ADCC that is mediated by non-neutralizing antibodies by down-regulating CD4 and BST2/Tetherin. Indeed, the HIV receptor CD4 is down-modulated by both proteins, while BST2, which retains progeny virions at the cell surface, is down-regulated by Vpu. In doing so, the virus ensures that ADCC-mediating epitopes, including those transitionally exposed upon CD4-Env interactions, remain unmasked. Here, we:

1. delineated mechanistically the relative contributions of CD4 and BST2 to ADCC;
2. ascertained whether this mode of immune evasion is relevant to broadly neutralizing antibodies; and
3. assessed whether latently infected T cells, upon reactivation, are susceptible to ADCC.

**Methods:** Primary CD4+ T cells or T cells expressing only CD4, BST2, or both were infected with CCR5-tropic wild-type HIV or those deficient of Nef, Vpu or both proteins. Infected T cells were examined by flow cytometry for Env recognition by anti-HIV Env antibodies and susceptibility to ADCC.

**Results:** Shielding of infected T cells from ADCC induced by non-neutralizing antibodies is primarily dependent on Nef-induced CD4 down-regulation, BST2 provides a modulatory role. In marked contrast, BST2 down-modulation is crucial to prevent exposure of epitopes that are recognized by neutralizing antibodies, especially 10E8 and PG9. In fact, CD4 accumulation at the surface of infected cells was linked to significantly reduced Env recognition and ADCC by the PGT121 family. Further, T cells that are latently infected with nef- vpu- HIV were more susceptible to ADCC upon reactivation.

**Conclusions:** Non-neutralizing and broadly neutralizing anti-HIV antibodies can mediate efficient ADCC if relevant epitopes are exposed, although CD4 and BST2 contribution to this process is markedly different between these two classes of antibodies. Approaches aimed at neutralizing ADCC evasion by HIV Nef and Vpu would be important to the development of more robust anti-HIV responses and effective shock-and-kill strategies against latently infected cells.