Members of the HIV prevention research community gathered in Cape Town, South Africa in October 2014 for the inaugural HIV Research for Prevention (HIV R4P) conference on AIDS vaccine, microbicide and antiretroviral-based prevention science. Although prophylactic approaches were the primary focus of the meeting, multiple abstracts describing work in human studies, acute HIV infection, and animal models provided insight relevant to HIV eradication.

**Human intervention studies: therapeutic vaccine and early ART**

Harriet Robinson and colleagues [1] reported results of a Phase I open-label trial of GOVX-B11, a DNA/MVA prime-boost regimen, in HIV-infected patients on ART. Volunteers received four vaccinations at intervals of 8 weeks: two of pG2/J57 DNA followed by two of MVA/HIV62B. Eight weeks after the last immunisation, and following an efavirenz washout where indicated, participants entered a 12-week treatment interruption. Eight of nine volunteers completed all vaccinations, which were well tolerated. The investigators reported augmented cellular and humoral HIV-specific responses with vaccination. Gag-specific CD8+ T cells were boosted over pre-vaccination levels in seven of the eight volunteers (P<0.05), whereas Gag-specific CD4+ T cells were boosted in five (P=0.2). Six and five of the eight patients elicited previously undetectable CD8+ and CD4+ T cell responses, respectively, to Gag epitopes. Gp120 or gp41-specific antibody responses were boosted in three and two of eight patients, respectively. Excluding one acute seroconverter, the median reduction in HIV-1 RNA at weeks 2, 6, and 12 compared to pre-ART levels was –2.2, –1.3 and –0.8 log10 copies/mL. There was no comparator placebo arm and all volunteers resumed ART following treatment interruption.

Alexandra Schuetz and colleagues [2] investigated the impact of very early ART on HIV-specific cellular responses. For 28 Thai patients treated during acute HIV infection (11 in Fiebig stages I or II [FI/II] and 17 in Fiebig stage III [FIII]), IFN-γ intracellular cytokine staining pre-ART and 6 and 24 months post-ART was performed. HIV-specific T cell responses were detected in acute infection (pre-ART) only among volunteers in stage FI; however, after 6 months of ART both groups demonstrated similar frequency of both CD8+ and CD4+ T cell responses. Of patients treated in FI/II, 55% demonstrated CD8+ T cell Gag-specific responses at 6 months, while a CD4+ T cell Gag-specific response was reported in 18%. Among FIII patients, these responses were 47% and 23%, respectively. The frequency of Gag-specific CD8+ T cell responses was maintained 24 months post-ART, largely among patients who initiated ART in FIII. The study did not include volunteers who did not initiate ART. The authors postulated that development of cellular responses despite suppressive ART may be due to viraemia, albeit declining, immediately following ART initiation, or due to ongoing viral replication in privileged sites.

**Characterisation of acute infection**

The impact of the replicative capacity of transmitted HIV viruses on the early immune inflammatory milieu and establishment of the viral reservoir was described by Prince et al. [3]. Investigators measured plasma cytokines as well as cellular markers of activation (CD38+HLA-DR+), exhaustion (PD-1) and proliferation (Ki-67) at the time of seroconversion. These data were associated with measures of cell-associated viral DNA in CD4+ memory T cell subsets. Results demonstrated that replicative capacity was positively correlated with plasma levels of inflammatory cytokines and with activation of both CD8+ and central memory CD4+ T cells (P=0.01 and P=0.002, respectively). Replicative capacity was also positively correlated with proliferation and with the level of cell-associated viral DNA in central memory CD4+ T cells (P=0.003 and P=0.01, respectively). The authors observed that cellular immune activation, proliferation, exhaustion and cell-associated viral DNA in central memory CD4+ T cells were all associated with the rate of disease progression and concluded that the replicative capacity of the transmitted virus plays an integral role in HIV-1 immunopathology. Presented results also suggest an impact of replicative capacity on the early development of the latent reservoir.

Gustavo Kijak and colleagues [4] conducted HIV single-genome sequencing (SGS) and targeted deep sequencing (TDS) of plasma obtained from volunteers sampled early and frequently during acute HIV infection to describe cryptic multiple infections. The investigators evaluated seven high-risk volunteers in Thailand and East Africa, all HIV negative at study entry with subsequent HIV nucleic acid conversion documented by twice-weekly testing. Beginning at days 2–7 post nucleic-acid conversion, they employed HIV SGS and TDS (Ion Torrent), finding that, in six of seven volunteers, pre-peak viremia SGS profiles were consistent with infection by a single transmitted founder virus. However, TDS revealed additional variants in four of these volunteers. Full-length genetic distances between major and minor variants were consistent with acquisition of multiple viruses from the same donor. Viral populations evolved at dramatic rates; however, patterns varied substantially. Intervariant recombinants were detected from day 21 onwards and both major and minor variants acquired CTL escape mutations. The authors concluded that minor variants can occur that are undetectable by SGS and that these variants contribute to viral evolution, with implications for HIV vaccine and cure strategies.

Zaza Ndhlou and colleagues [5] investigated CD8+ T cell responses in acute HIV infection among female volunteers in KwaZulu Natal, South Africa. Pre-infection and early HIV infection longitudinal samples (days 1–160 post Fiebig I) were examined to describe the initial T cell response via intracellular cytokine staining (CD4, CD8, Ki-67, Bcl-2, CD38, HLA-DR), IFN-γ ELISPOT, and class I tetramer-staining assays. Results demonstrated that acute HIV infection rapidly induced activation and expansion of HIV-specific CD8+ T cells, with more than 90% becoming activated by day 14 post Fiebig I, upregulating CD38, HLA-DR, and Ki–67. At peak activation, HIV-specific CD8+ T cells selectively expressed high levels of the pro-apoptotic marker CD95, low anti-apoptotic molecule BCL-2 and failed to...
upregulate the IL-7 receptor. Overnight incubation of peak activation CD8+ T cells resulted in high levels of spontaneous cell death compared to cells collected after the resolution of T cell activation. Activated CD8+ T cells were also less responsive to ex vivo stimulation compared to specimens collected after resolution of activation. The authors concluded that acute HIV infection induces massive CD8+ T cell expansion and postulated that the disappearance of early responses may result from persistent antigen-stimulation that leads to apoptosis of virus-specific cells. They suggest that strategies to block apoptosis may strengthen early immune responses to HIV infection.

Animal studies

Alejandro Balazs and colleagues [6] described a vectored immunoprophylaxis (VIP) approach to achieve long-lived broadly neutralising antibody (bNAb) expression in BLT humanised mice. Mice infected with the REJO.c transmitted molecular founder HIV strain were treated with ART for 5 weeks followed by intramuscular injection of VIP expressing the bNAb VRC07 or luciferase. Following VIP administration, the investigators observed a sharp rise in the blood concentration of VRC07 in the blood. Mice expressing the bNAb demonstrated a rapid decline in viral load to undetectable levels as well as an increase in CD4+ T cells over 4 weeks. These effects persisted for the remaining 8 weeks of the study. In comparison, mice expressing luciferase demonstrated increasing viral loads and decreases in CD4+ T cells. The authors concluded that VIP expressing VRC07 is sufficient to suppress actively replicating transmitted founder virus and that these results support further development of this strategy for use in HIV-infected patients.

Rama Amara and colleagues [7] examined the follicular immune response in controller versus non-controller rhesus macaques in the context of a DNA/MVA SIV vaccine challenge study. The macaques were vaccinated and then challenged intrarectally with SIVmac251. Animals with viral load below 1,000 copies/mL at set-point were defined as controllers. All controllers (n=19) were vaccinated, while the non-controller group (n=18) consisted of both vaccinated and unvaccinated macaques. Following the challenge, investigators observed an enrichment of SIV+ PD-1hi CD4+ T cells in the lymph nodes and rectum of non-controllers but not controllers. A higher frequency of Gag CM9 Tet+ CD8+ T cells was demonstrated in the lymph nodes of controller macaques compared to the non-controllers. The authors noted that a significant fraction of antiviral CD8+ T cells in the controller macaque co-expressed CXCR5, which is required for homing to B cell follicles/germinal centres (GC). The frequency of Tet+ CXCR5+ granzyme B+ cells was also higher in the lymph nodes of controller macaques. Immunofluorescence staining revealed co-localization of CD8+ T cells with PD-1 bright cells in IgD-GC of controller but not non-controller macaques. CXCR5+ CD8+ T cells from the controller macaques restricted the anti-CD3 driven expansion of CM9 peptide pulsed T follicular helper cells in vitro, indicative of killing potential. The authors concluded that this novel subset of antiviral CD8+ T cells may contribute to enhanced control of pathogenic SIV infection by inhibiting GC of lymphoid sites and limiting SIV replication in T follicular helper cells in a vaccine setting.

Disclaimer

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