Plasmacytoid dendritic cell phagocytosis of IgG anti-p24 associates with control of HIV infection

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Introduction

- Elucidating mechanisms of immune control in HIV controllers will facilitate the development of therapeutic HIV vaccines
- The failure of vaccine-induced $CD8^+$ T-cell responses to prevent/control HIV infection in clinical trials has renewed interest in antibodies
- IgG antibodies towards HIV Gag proteins are associated with control of HIV infection but the mechanisms are unclear
- Gag specific antibodies may inhibit HIV replication by inducing accessory cell responses (e.g. NK cells, plasmacytoid dendritic cells) via Fcγ receptors
  - Isotype diversification of IgG antibodies may affect the activation of FcγRs
- Gag antibodies activate NK cells poorly, so we are investigating opsonising antibodies that activate pDC

Summary and Conclusions

- The magnitude of opsonizing antibody responses against HIV p24 that induce phagocytosis by pDC was highest in controllers, particularly viraemic controllers
- Opsonizing antibodies to HIV p24 are phagocytosed by pDC via FcγRIIa
- Isotype diversification (skewing towards IgG2) of IgG antibodies to HIV p24 is greater in HIV controllers, particularly viraemic controllers
  - Isotype diversification may enhance opsonophagocytosis
- The effect of opsonizing antibodies on downstream pDC activation events (IFNα & TNFα production, upregulation of co-stimulatory molecules) should be investigated

Results

Fig 1: Phagocytosis of opsonized p24-coated beads is more uniform in Gen 2.2 cells than THP-1 cells

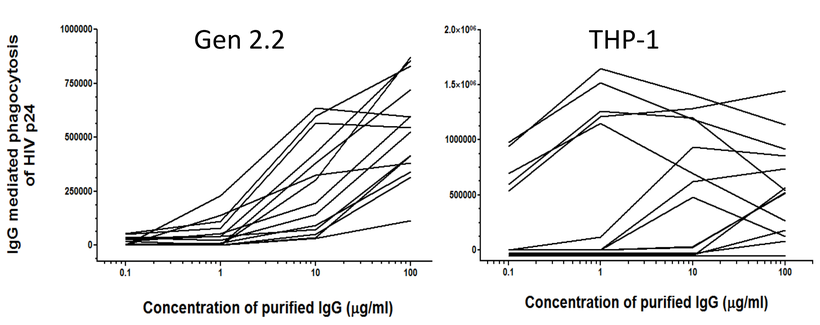


Fig 2: Phagocytosis of opsonized p24-coated beads by Gen 2.2 cells occurs via FcγRIIa

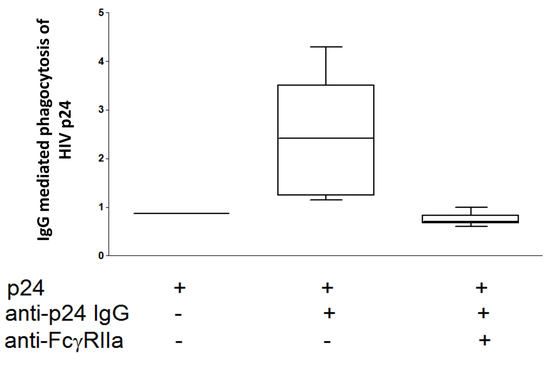


Fig 3: Opsonizing antibodies to HIV p24 are higher in controllers than non-controllers, particularly viraemic controllers

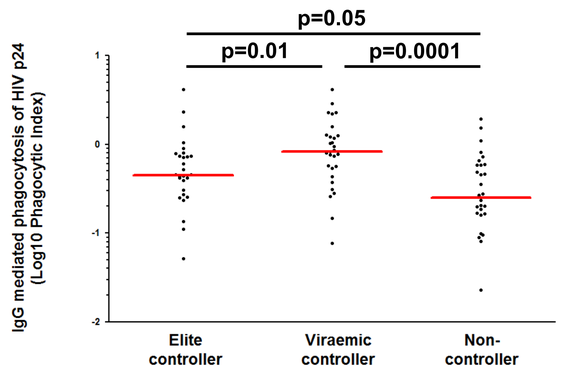


Fig 4: Both IgG1 and IgG2 antibodies to native HIV p24 were detected and correlated with opsonizing antibody responses to HIV p24

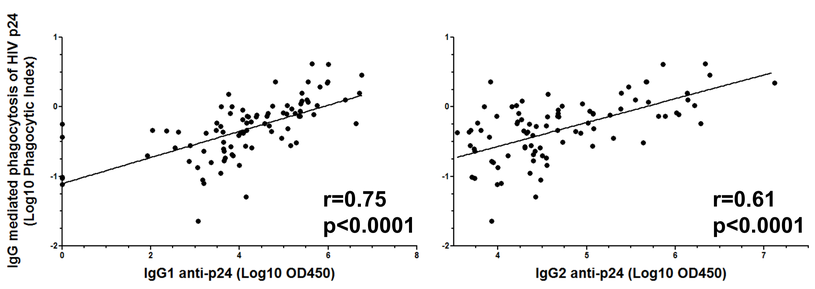
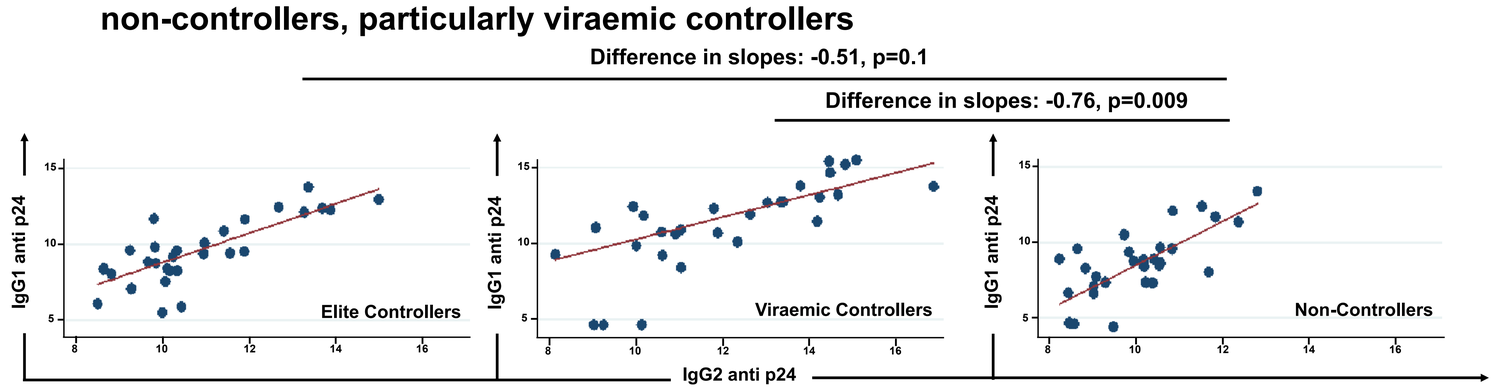
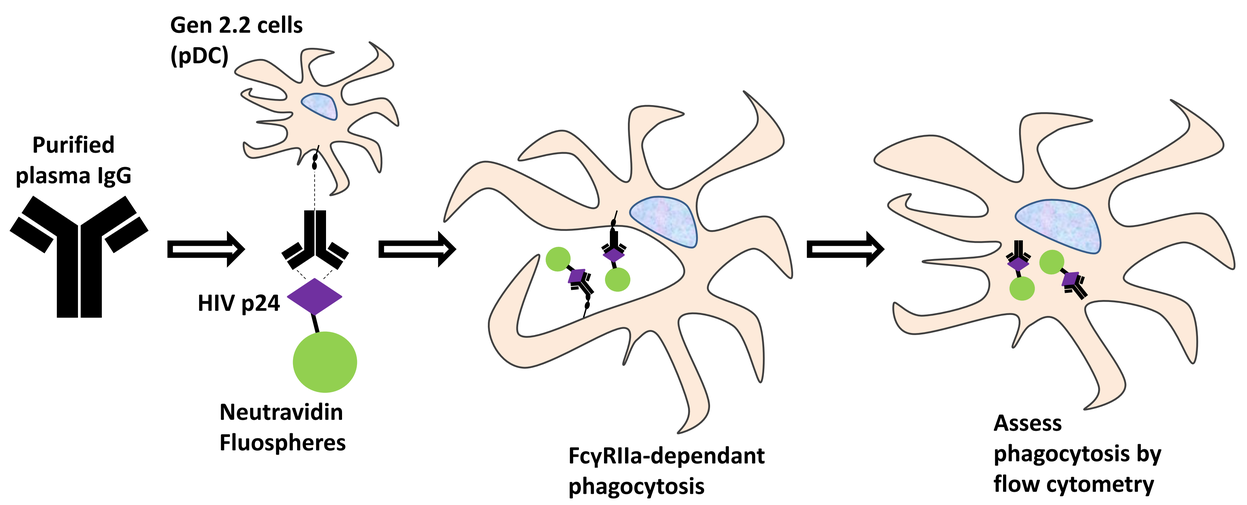


Fig 5: Isotype diversification of IgG antibodies to HIV p24 (indicated by the slope of the line of IgG1 vs IgG2 antibodies being skewed towards IgG2) was greater in controllers than non-controllers, particularly viraemic controllers



Methods

- Plasma samples were obtained from ART-naïve HIV patients enrolled into the SCOPE study, UCSF:
  - 30 elite controllers (HIV RNA <50 copies/mL for >12 months)
  - 29 viraemic controllers (>50 but <2000 HIV RNA copies/mL for >12 months)
  - 30 non-controllers (HIV RNA >10,000 copies/mL)
- Opsonising antibodies to HIV p24 were measured by a phagocytosis assay using Gen 2.2 cells (pDC cell line)
- Isotype diversification of IgG antibodies to HIV p24 was assessed by comparing IgG1 vs IgG2 ratios as assayed by ELISA



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