Rapid Gut-Homing of Plasmacytoid Dendritic Cells During Acute SIV Infection

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Abstract

Introduction Lentivirus infections are characterized by a rapid loss of mucosal CD4+ T cells and breakdown of the gut mucosa. In addition, multiple studies have shown that IFN-α-producing plasmacytoid dendritic cells (pDC) are activated early after lentivirus infection, but despite the importance of the gut mucosae in HIV/SIV pathogenesis, little is known about pDCs in these tissues during acute infection.

Methods This planned sacrifice study included a total of 21 rhesus macaques — six naïve and six infected with SIVmac239 sacrificed at 14 days post-infection, and nine infected with SIVmac239 sacrificed in chronic stage disease. Animals had colorectal and lymph node biopsies prior to infection, were followed longitudinally by blood collection and full tissue collections were performed at necropsy. Phenotypic and functional analyses were performed using polychromatic flow cytometry.

Results During acute SIV infection the frequency of pDCs in blood declined rapidly, as early as day 3 post-infection, with an ~5-fold loss by day 14, inversely correlating with viral load ($R = -0.55$, $p < 0.001$). Furthermore, when compared to naïve controls, pDC frequencies in animals sacrificed at day 14 post-infection were reduced 5- to 10-fold in lymphoid organs including liver and spleen, but were generally unchanged in lymph nodes. This overall loss in blood and vascular organs coincided with 2- to 8-fold increases in pDCs in colon and jejunum. Of note, when comparing individual animals pDC frequencies in colorectal tissue at day 14 sacrifice were between 6- and 12-fold greater than pre-infection colorectal biopsies. Also, as early as day 6 the gut-homing receptor, α4β7, increased significantly over baseline on circulating pDCs, peaking at ~day 10 post-infection and suggesting a likely mechanism for increased gut-homing. Interestingly, in all chronically infected animals, pDC numbers remained significantly elevated in the mucosa, regardless of viral load. Clinically, re-distribution of pDCs was significantly associated with markers of activation and correlated with loss of CD4+ T cells in the gastrointestinal tract ($R = -0.603$, $p < 0.001$), indicating a potential mechanism of pDC-induced depletion.

Conclusions Herein we demonstrate acute and permanent accumulation of pDCs in the gastrointestinal tract during SIV infection. While pDC accumulation in the mucosa could aid in virus control, over-production of IFN-α derived from these cells could also contribute to increased immune activation, inflammation, and CD4+ T cell death in the gut mucosa commonly associated with progressive lentivirus infections.

SIV infection of rhesus macaques

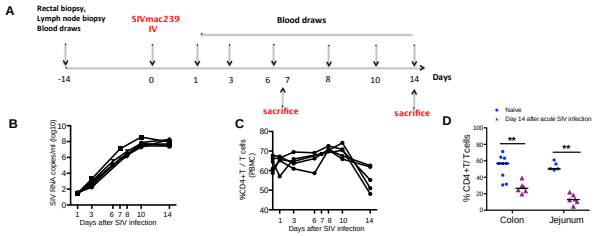


Figure 1. Plasma viral load and CD4+T cell dynamics in acute SIV infection. (A) Schedule of blood and tissue collection in acute SIV infected macaques. (B) Kinetics of plasma viral load during acute SIV infection. Percentages of CD4+ T cells among total CD3+ T cells in blood (C), colon and jejunum (D). Statistical comparisons are between naive and acutely infected macaques at the indicated time points. Mann-Whitney *U* test; * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Circulating pDCs have increased proliferation, but no significant change in apoptosis

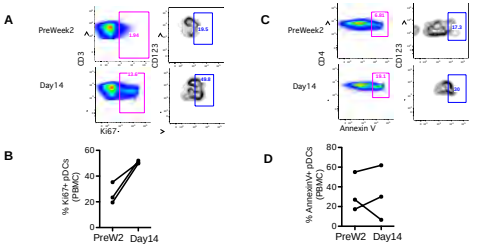


Figure 3. SIV-induced proliferation of pDCs. (A) Representative flow cytometry plots showing Ki67 expression in circulating pDCs. (B) Frequency of Ki67 expression in circulating pDCs was compared between pre-infection biopsies and at day 14 post-infection sacrifice. (C) Representative flow cytometry plots showing Annexin V expression on circulating pDCs. (D) Frequency of Annexin V expression in circulating pDCs were compared between pre-infection biopsies and at day 14 post-infection sacrifice.

Rapid depletion of pDCs from circulation, but accumulation in gut after SIV infection

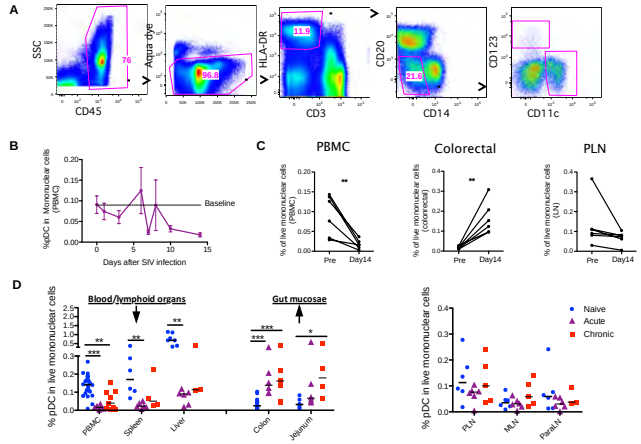


Figure2. Depletion of pDCs from circulation, but accumulation in intestinal mucosae during SIV infection. (A) Representative gating strategy to identify pDCs among mononuclear cells. (B) Means and standard deviations of circulating pDC frequencies from six animals following acute SIV infection. (C) Frequencies of pDCs among mononuclear cells in tissues were compared between pre-infection biopsies and at day 14 post-infection sacrifice. (D) Frequency of pDCs among mononuclear cells in tissues were compared between naive, and acutely and chronically SIV-infected rhesus macaques. PLN, peripheral lymph nodes; PaLN, paracolonic lymph nodes; MLN, mesenteric lymph nodes.

Trafficking is a potential mechanism for pDC accumulation in gut mucosae

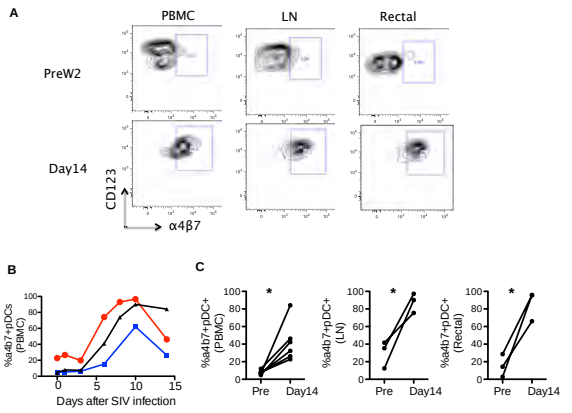


Figure4. Rapid gut-homing of pDCs after acute SIV infection. (A) Representative flow cytometry plots showing demonstrating α4β7 expression on pDCs in PBMC, LN and rectal tissue. (B) Dynamic of α4β7 expression on circulating pDCs. (C) α4β7 expression on pDCs were compared between pre-infection biopsies and at day 14 post-infection sacrifice.