Dynamics of B Cell Subpopulations in Pathogenic and Nonpathogenic SIV infections

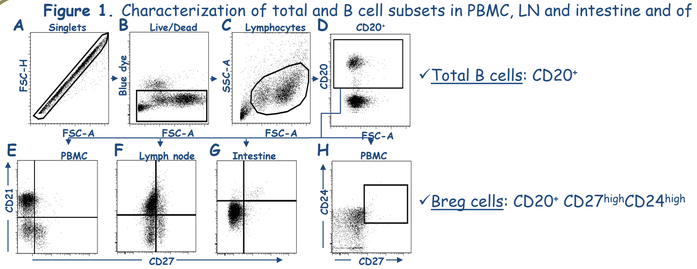
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Background: We compared and contrasted the dynamics of B cell subpopulations in mononuclear cells from blood, lymph nodes (LN) and intestine (INT) in progressive SIV infection of pigtailed macaques (PTMs) and in nonprogressive SIV infection of African green monkeys (AGMs) to elucidate the significance of B-cell changes observed in HIV/SIV infection.

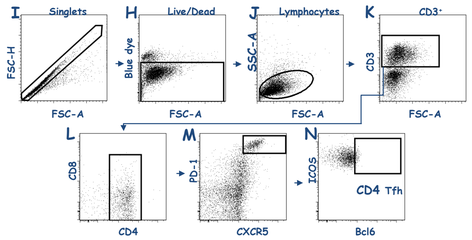
Methodology: We assessed the changes in total B cells, as well as of naïve, resting, activated and tissue-like memory B-cell subpopulations using a combination of CD20, CD27 and CD21 monoclonal antibodies. The dynamics of Bregs ($CD20^+CD24^{high}CD27^{high}$) were assessed by flow-cytometry. Activation, homing to the intestine, exhaustion and apoptotic status of total B cells were assessed as expression of Ki-67, TLR-2, $\alpha4\beta7$, PD-1 and Annexin V. CD4 T follicular helper (Tfh) cells were assessed with a combination of PD1, CXCR5, ICOS and Bcl-6. Binding anti-gp41 and neutralizing antibodies were assessed in the two species.

Figure 1. Characterization of total and B cell subsets in PBMC, LN and intestine and of Tfh in LN of PTMs and AGMs



✓Total B cells: $CD20^+$

✓Breg cells: $CD20^+$ $CD27^{high}CD24^{high}$



✓Naïve B cells: $CD27^-CD21^+$

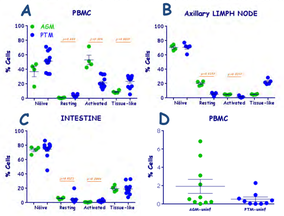
✓Resting memory B cells: $CD27^+CD21^+$

✓Tissue-like memory B cells: $CD27^+CD21^+$

✓Activated memory B cells: $CD27^+CD21^+$

✓ CD4 T follicular helper (Tfh): $CD4^+PD1h^{high}CXCR5^+ICOS^+Bcl\text{-}6^+$

Figure 2. Frequency of B cell subsets in PBMC, axillary LN and intestine in uninfected AGMs and PTMs



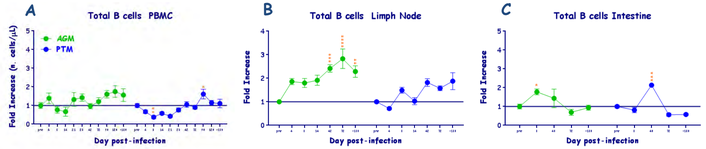
✓No significant differences were observed with regard to naïve B cells in any of the three compartments.

✓Significant differences were observed between the two species with regard to resting and activated memory B cells.

✓Significant differences in levels of tissue-like memory B cells were observed in PBMC.

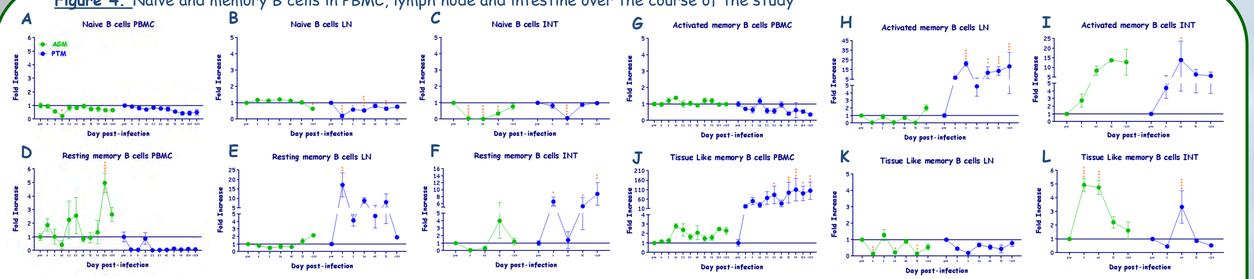
✓ No significant differences for Bregs in PBMC

Figure 3. Total B cells in PBMC, lymph node and intestine over the course of the study



✓Comparative assessment of changes in B cell populations occurring in SIVsab-infected AGMs and PTMs.

Figure 4. Naïve and memory B cells in PBMC, lymph node and intestine over the course of the study



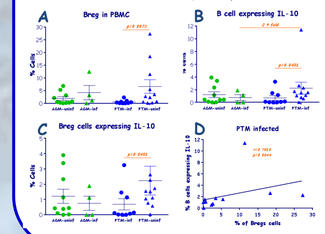
✓Similar changes in naïve B cells in pathogenic and nonpathogenic SIVsab infections

✓Resting memory B cell dynamics in PBMC and lymphoid tissues differed between pathogenic and nonpathogenic infections.

✓SIVsab pathogenic infection induced signficant increases in activated memory B cells in lymphoid tissue.

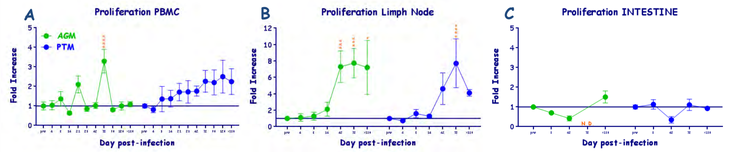
✓Signficant increases in peripheral tissue-like memory B cells were observed during chronic pathogenic infection.

Figure 5. Breg cell subset in PBMCs and expression of intracellular IL-10 in total B and Breg cells, positively correlated with frequency of total B-cells



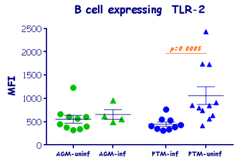
✓Bregs from PTMs significantly increase after SIVsab infection.

Figure 6. Activation status of total B cells from blood, lymph node and intestine over the course of the study



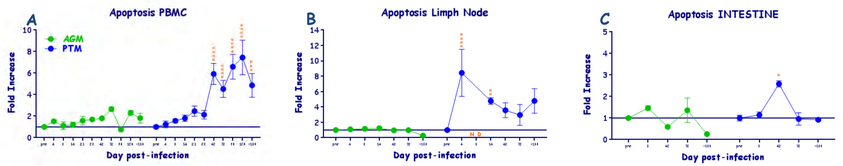
✓Increased levels of circulating B cell activation in pathogenic SIV infection

Figure 7. TLR2 expression on total B cells



✓TRL-2 increases significantly during chronic viremia in pathogenic infection.

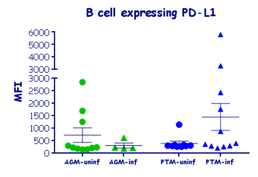
Figure 8. Apoptotic total B cells in blood, lymph node and intestine over the course of the study



✓Significant increase in levels of apoptotic circulating B cells during chronic pathogenic SIVsab infection of PTMs co

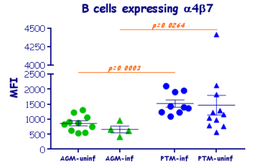
✓Only a transient significant increase in apoptosis during acute infection in the LN and gut tissues

Figure 9. Expression of PD-L1 on total B cells



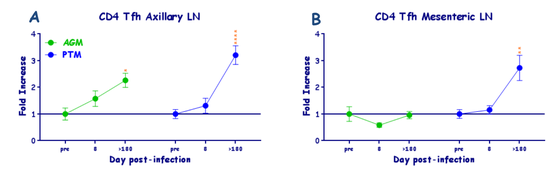
✓No significant differences in B cell PD-L1 expression were observed between PTMs and AGMs at baseline or during chronic infection.

Figure 10. Expression of homing marker $\alpha4\beta7$ on total B cells



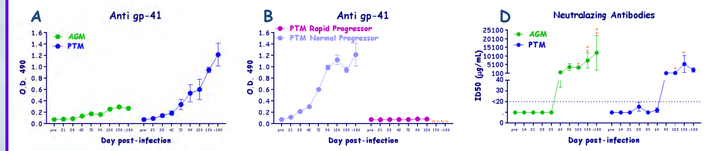
✓B cells from SIVsab-infected PTMs expressed significantly higher levels of the mucosal homing marker $\alpha4\beta7$.

Figure 11. Follicular helper CD4 T cells in axillary and mesenteric lymph nodes over the course of the study



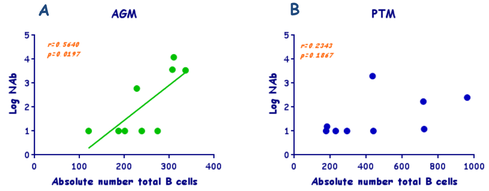
✓Follicular helper CD4 T cell populations increase in both pathogenic and non-pathogenic chronic infections.

Figure 12. Antibody responses and characterization of antibody maturation profile over the course of the study



✓High titers of binding antibodies in PTMs contrasted with low titers of anti-gp41 in AGMs.

Figure 13. Correlation of absolute count of total B cells vs. log of neutralizing antibodies



✓Only AGMs showed a positive correlation between B cells and Nab titers.

Conclusions: In AIDS-susceptible species, but not in nonprogressive hosts, SIV infection is associated with B cell dysfunction defined by loss of total and memory B cells, increased numbers of Bregs and increased B cell activation and apoptosis. These changes do not appear to be correlated with production of neutralizing antibodies, which is similar in both species. Yet, the rapid progressive infection is associated with a severe incapacity to mount an Ab response against gp41.