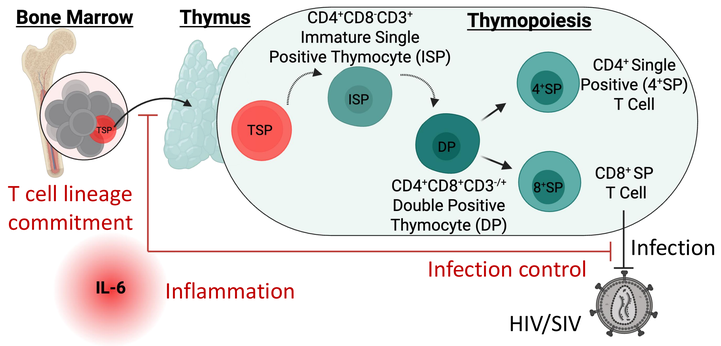
IL-6 Inhibits T-Cell Lineage Commitment of Hematopoietic Stem and Progenitor Cells During Pathogenic Retroviral Infection

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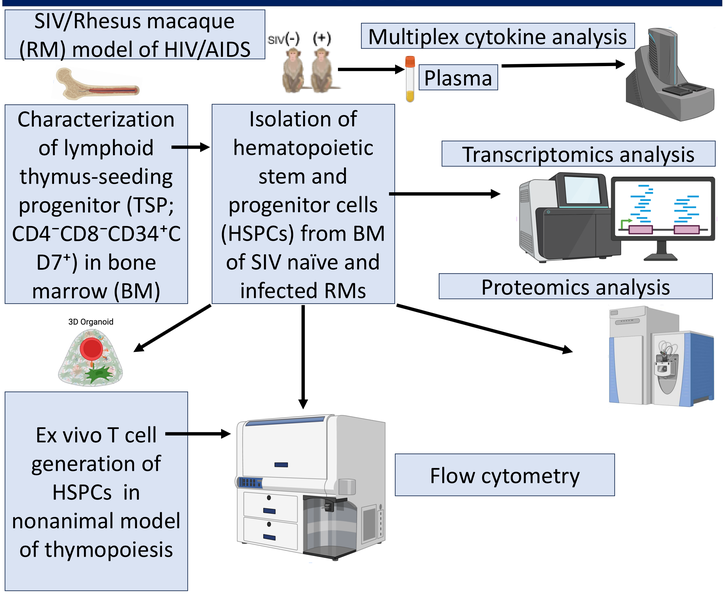
Introduction



Hypothesis

Pathogenic inflammation driven emergency hematopoiesis restricts pre-thymic T cell lineage commitment of progenitors in bone marrow causing paucity of T cells, thereby directly impairing viral control.

Methods



Analyses:

- Phenotypic profiling of TSPs and HSPCs in BM
- Phenotypic profiling of ex-vivo T cell potential of HSPCs
- Phenotypic profiling of TSPs under SIV infection
- Multiplex profiling of inflammation signatures in plasma
- Transcriptomic and proteomic profiling of HSPCs in BM
- Ex-vivo thymopoiesis under inflammatory condition

- ❑ Inflammation antagonizes T cell lineage commitment of progenitors in bone marrow.
- ❑ Pre-thymic T cell restriction drives viral control failure.
- ❑ Interleukin-6 is the mechanistic driver.

Results

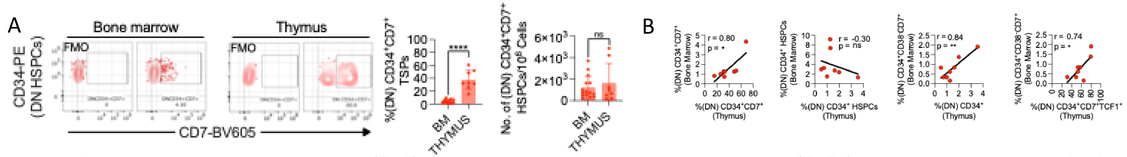


Figure 1. Frequency of bone marrow (BM) lymphoid thymus seeding progenitors (TSPs) broadly identified by CD4-CD8- double negative (DN) CD34+CD7+ markers in BM and thymus (A). Correlation of frequency of progenitors between BM and thymus (B). Pearson correlation coefficient and P value are shown.

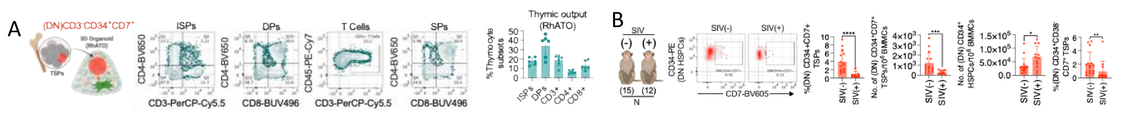


Figure 2. T cell developmental potential of BM derived (DN) CD34+CD7+ TSPs in *ex vivo* model of thymopoiesis (A). Impact of SIV infection on frequency of TSPs in BM, and the number of TSPs as well as HSPCs in BM (B).

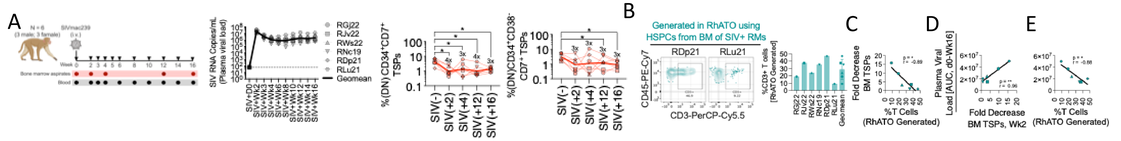


Figure 3. Longitudinal tracking of plasma viral load (PVL) and frequency of TSPs in BM of six RMs (A). Frequency of ex-vivo generated T cells from HSPCs isolated from RMs at week 16 post infection (B). Correlation between fold drop in frequency of TSPs in BM and ex vivo generated T cells (C). Correlation between PVL and fold drop in TSPs (D) or frequency of ex vivo generated T cells (E).

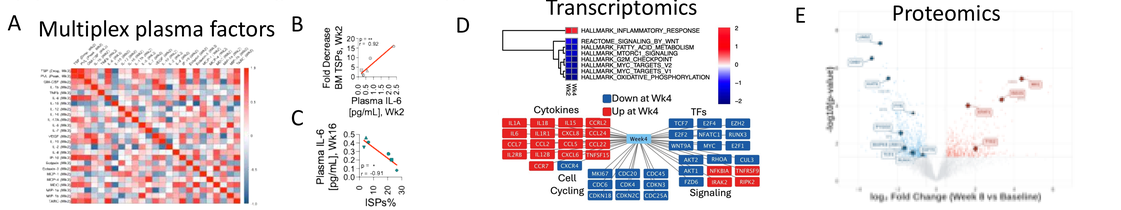


Figure 4. Correlation matrix between plasma signatures of inflammation, fold drop in frequencies of TSPs, and PVL (A). Correlation between drop in %TSPs and plasma IL-6 (B). Correlation between plasma IL-6 and ex vivo T cell potential (C). Pearson correlation coefficient and P value are shown. Representative transcriptomic (D) and proteomic (E) profile of HSPCs in BM of SIV infected RMs compared with SIV naïve RMs.

Results

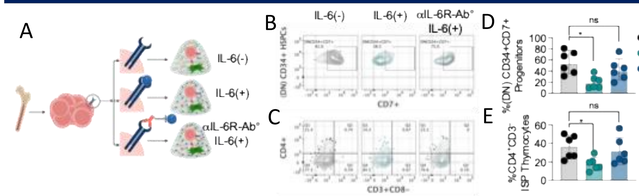


Figure 5. Experimental design (A). Representative flow plots showing frequency of TSPs (B) and ISPs (C). Bar graph showing quantitation of frequency of TSPs (D) and CD4+CD3- (ISPs) early thymocytes (E).

Conclusions

- ❖ Expression of CD7 identifies TSPs in BM and thymus of RMs.
- ❖ Both, proportion of TSPs and HSPCs T cell differentiation potential were significantly reduced early upon SIV infection.
- ❖ Reduction in CD38- TSPs highly correlated with reduced T cell generative potential of BM HSPCs
- ❖ Reduction in CD38- TSPs and T cell potential highly correlated with loss of viral control.
- ❖ Plasma IL-6 highly correlated with reduced T cell potential.
- ❖ Transcriptomic and proteomic profile of HSPCs showed upregulation of inflammatory pathways with parallel downregulation of pathways associated with T cell development.
- ❖ Ex vivo exposure of model of thymopoiesis to IL-6 paralleled in vivo findings, showing significant reduction in TSPs.
- ❖ Ex vivo blockade of IL-6 receptor prevented IL-6 mediated restriction of T cell committed differentiation of HSPCs.

Summary

We show that inflammation, particularly IL-6, restricts T cell lineage commitment of bone marrow progenitors. This pre-thymic restriction causes reduced T cell generative ability of HSPCs in BM. Importantly, this reduced T cell potential directly correlates with loss of viral control early after infection.

Acknowledgements

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