Role of Monocyte/Macrophage Activation and Recruitment to Mucosal Sites in SIV Immune Activation /Inflammation and Pathogenesis

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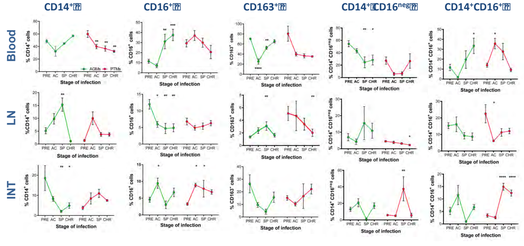
Background: Although monocytes/macrophages (Mo/Ma) can be infected by HIV/SIV, may play a role in virus transmission at mucosal sites and may represent a major reservoir for HIV/SIV, their role in HIV/SIV pathogenesis is incompletely elucidated.

Goal: To understand Ma contribution to SIV pathogenesis by comparing and contrasting dynamics, recruitment to lymphoid and mucosal tissues and function of Mo/Ma and their subsets between progressive and nonprogressive NHP models of AIDS. To determine if Mo/Ma may be responsible for development of HIV-/SIV-related comorbidities (i.e., cardiovascular).

Design: A total of 13 PTMs and 34 AGMs were IV-infected with 300 TCID50 of SIVsab. Blood, LNs and intestine were collected prior to infection (PRE), at viral peak (AC), set point (SP) and chronic infection (CHR).

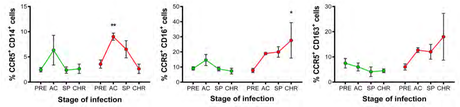
Methods: Flow cytometry to assess changes in Mo/Ma subsets (CD14, CD163, CD16, CD14+CD16-, CD14+CD16+), mobilization (CCR5, α4β7, CCR7), immune activation (CD80, CD86, Ki67, TF), apoptosis (cas-3), cytokine production (IL-6, IL-10, IL-12, TNF-α) and phagocytic capacity of Mo/Ma. ELISA, to measure soluble Mo activation markers (sCD14, sCD163, TF). IHC, to quantify tissue Ma (CD16, CD163, CD68, HAM56).

Monocyte/Macrophage Dynamics

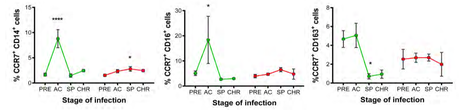


Different Patterns of Mo/Ma Homing in Pathogenic and Nonpathogenic SIVsab Infections

Increased CCR5 Mo expression supports Mo/Ma homing to the gut of SIV-infected PTMs

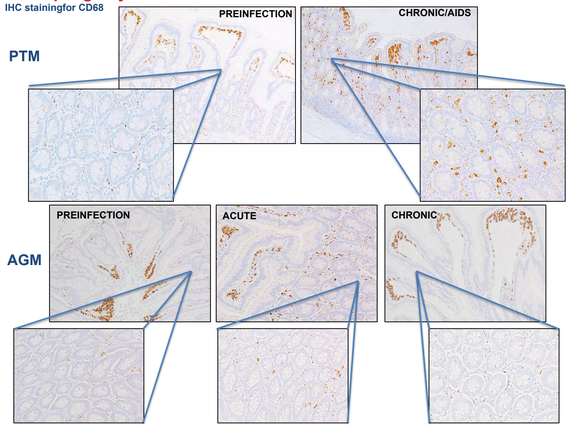


Increased CCR7 Mo expression supports Mo/Ma homing to AGM LNs



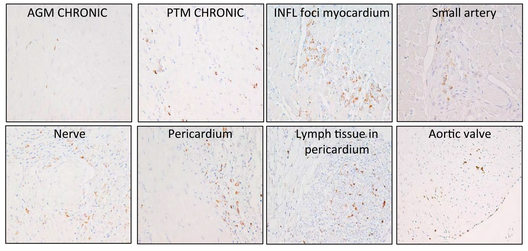
Macrophage Dynamics in the INT of SIVsab-infected PTMs and AGMs

IHC staining for CD68



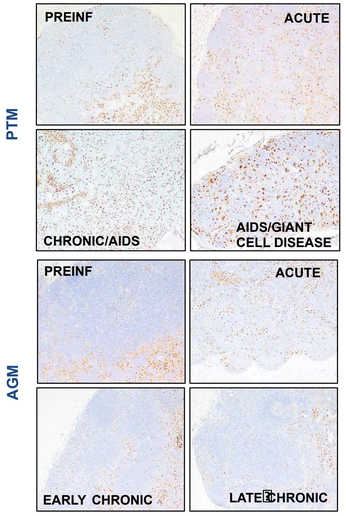
Macrophage Infiltration in the Heart of SIVsab-infected NHPs

IHC staining for CD68



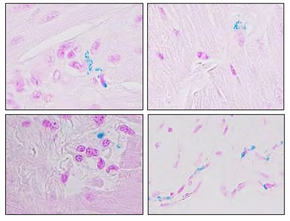
Macrophage Dynamics in the LNs of SIVsab-infected NHPs

IHC staining for CD68

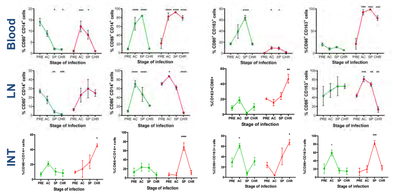


Macrophage Migration and Infiltration in the Heart of SIVsab-infected PTMs with AIDS

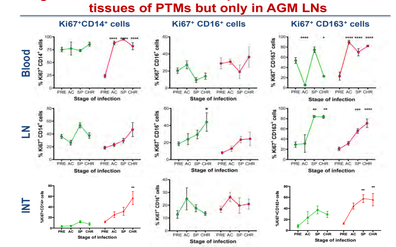
IRON-OXIDE MICROPARTICLES INJECTED 68 HOURS PRIOR TO NECROPSY



Increased expression of Mo/Ma activation markers in circulation and at mucosal sites in PTMs

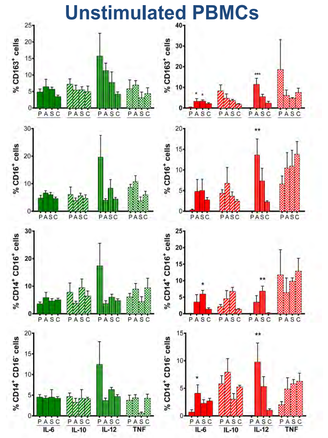


Significant increases in Mo/Ma proliferation in blood and tissues of PTMs but only in AGM LNs

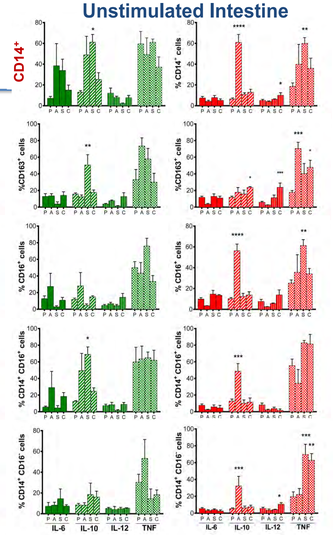


Increases in IL-6, IL-12 and TNF production by Mo and mucosal Ma in PTMs but not in AGMs

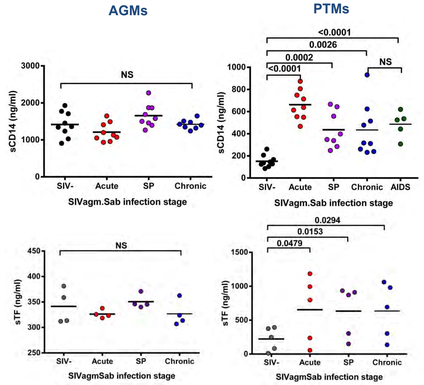
Unstimulated PBMCs



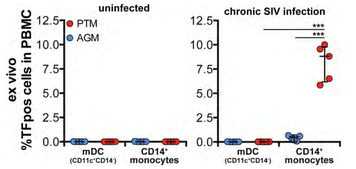
Unstimulated Intestine



Increased levels of sCD14 and sTF in SIVsab-infected PTMs but not in AGMs



Increased TF expression on circulating CD14+ Mo of chronically infected PTMs



Conclusions

- Progressive SIV infection is associated with Mo recruitment and Ma infiltration in mucosal and non-mucosal tissues.
- Ma are highly activated and produce high levels of proinflammatory cytokines in SIVagm-infected PTMs.
- Ma represent the main immune cell type expressing TF in progressive infection, suggesting a critical role in HIV-/SIV-related hypercoagulability.
- Mo/Ma may contribute to the increased IA/INFL and cardiovascular comorbidities that distinguish progressive from nonprogressive SIV infection.