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PERSONS WITH RESIDUAL VIREMIA ON ART HAVE HIGHER FREQUENCIES OF MYELOID-DERIVED SUPPRESSOR CELLS

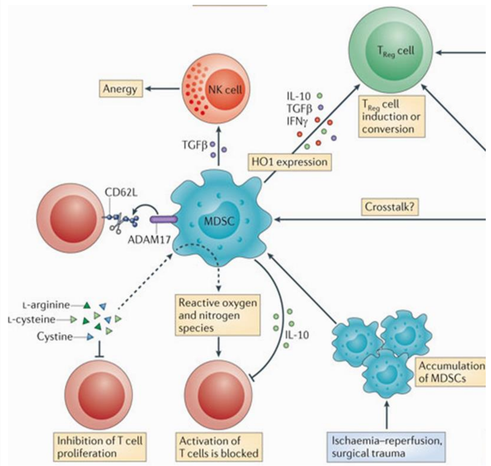
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BACKGROUND

- Myeloid derived suppressor cells (MDSC) a heterogenous population of immature and mature cells with immunosuppressive function that expand during inflammatory conditions. They have various mechanisms of immune suppression, including production of arginase.
- This regulatory function can be necessary to check immune drive, but provides opportunities for diseases to take advantage of decreasing immunity.
- In pathological conditions such as cancer or certain infections, expansion of these cells could worsen clinical status.

- Although MDSC can suppress chronic inflammation and immune activation in chronic HIV despite viral suppression on ART, MDSC could also suppress HIV-specific immune responses, thus facilitating HIV persistence. MDSC can also increase regulatory T cell activity as well as dependence on IL-6, IL-10, TNF-a, and other cytokines.
- Human MDSC derive from various sources and have different phenotypes:
  - o Classic MDSC (cMDSC): Lineage-, CD33+, HLA-DR-
  - o Monocytic MDSC (mMDSC): CD3/19/56-,CD33+, HLA-DR-, CD14+, CD11b+
  - o Granulocytic MDSC

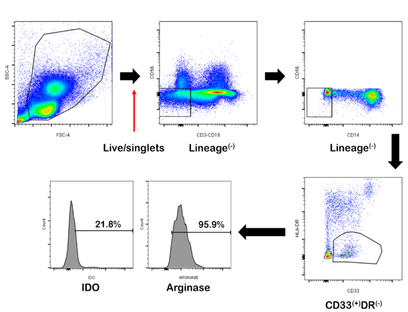


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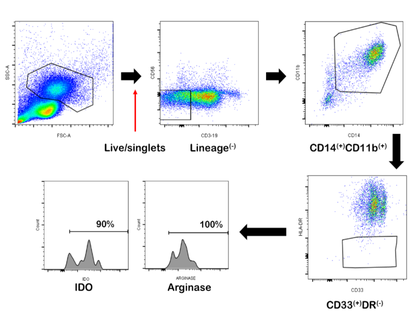
STUDY DESIGN AND METHODS

- 225 participants of ACTG A5321 were evaluated by flow cytometry for % cMDSC and mMDSC of all live cells.
- Levels of HIV DNA, cell-associated RNA, and inflammatory markers were evaluated, as well as % inflammatory monocytes (which migrate towards inflammation sites and contribute via inflammatory cytokine production).
- Ratio of %mMDSC to %inflammatory monocytes (iMono) was calculated to characterize anti-inflammatory (mMDSC) vs. pro-inflammatory (iMono) cell relationships, and was used to evaluate associations with residual HIV viremia, HIV DNA and RNA, intact proviral DNA, and soluble factors of inflammation.

cMDSC Gating Strategy



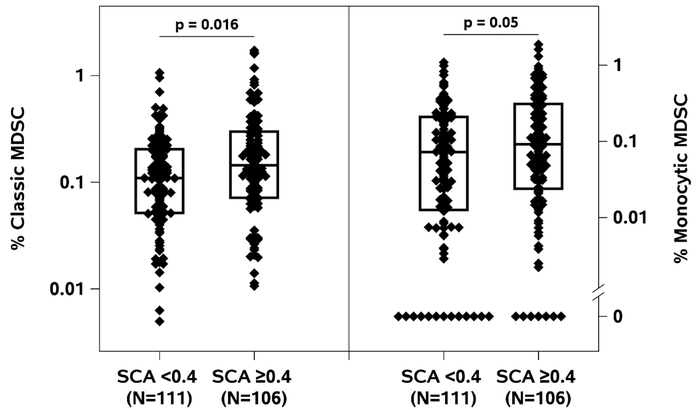
mMDSC Gating Strategy



CONCLUSIONS

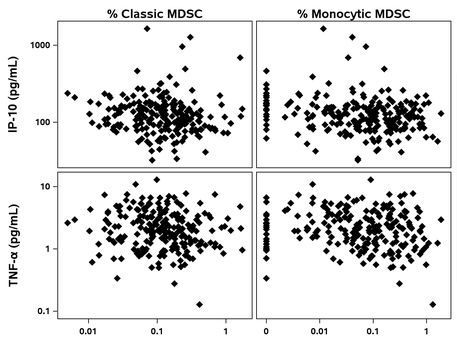
- **Higher myeloid-derived suppressor cell (MDSC) frequencies are associated with residual viremia despite long-term ART, and with lower soluble markers of inflammation.**
- **This suggests that MDSC inhibit virally suppressive HIV-specific immune responses, and targeting MDSC could potentially boost this immune reactivity. Indeed, targeting MDSC-receptor tyrosine kinases has been shown to increase immune function against tumor growth.**
- **Although reversing MDSC-mediated suppression could be beneficial in achieving HIV remission in ART, blockade could also result in increased levels of systemic inflammation.**

INDIVIDUALS WITH RESIDUAL VIREMIA HAVE HIGHER %cMDSC and %mMDSC

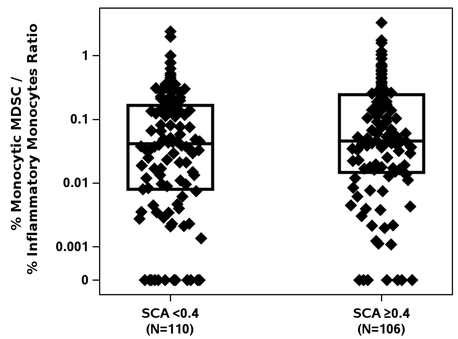


- Both %cMDSC and %mMDSC were higher in individuals with residual HIV viremia vs. no detectable residual viremia:
- cMDSC = 0.14% vs. 0.11%, p=0.016
- mMDSC = 0.09% vs. 0.07%, p=0.05

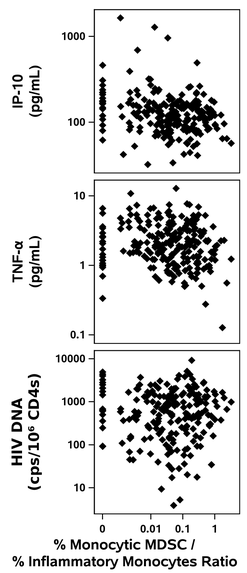
INFLAMMATORY CYTOKINES AND MDSC LEVELS ARE NEGATIVELY CORRELATED



- IP-10 negatively correlated with both % cMDSC and mMDSC (r= -.18, p=0.008, and = -.23, p<0.001, respectively).
- TNF-alpha also exhibited this trend (r= -.15, p=0.021, and = -.15, p=0.024, respectively).
- Results were adjusted for pre-ART HIV RNA.



- Higher ratios of mMDSC to iMonocytes negatively correlated with levels of IP-10 and TNFa (r= -0.24, p<0.001, r= -0.15, p=0.028, respectively).
- There was no significant correlation between mMDSC/iMono ratio and HIV persistence.



PARTICIPANT DEMOGRAPHICS

Characteristic	N=225	
Age at A5321 entry (years)	Median Min, Max	49 23, 74
Sex	Male Female	186 39
Years on ART at A5321 entry	Median Min, Max	7 4, 16
A5321 entry CD4+ T cell count (cells/mm^3)	Median Min, Max	681 116, 1554
Pre-ART plasma HIV-1 RNA (log$_{10}$cps/mL)	Median Min, Max	4.6 2.8, 6.7
A5321 entry HIV-1 RNA (cps/mL)	<40 cps/mL	225 participants

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