EXPANSION OF MYELOID-DERIVED SUPPRESSOR CELLS IN ART-SUPPRESSED HIV-INFECTED PATIENTS

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Background. The existence of HIV reservoirs represents the main obstacle to cure HIV. The role of the immune system at maintaining and regulating this viral persistence remains largely unknown. Here, we studied the role of the myeloid-derived suppressor cells (MDSC), a heterogeneous population of immature myeloid cells with high immunosuppressive effects on the HIV reservoir.

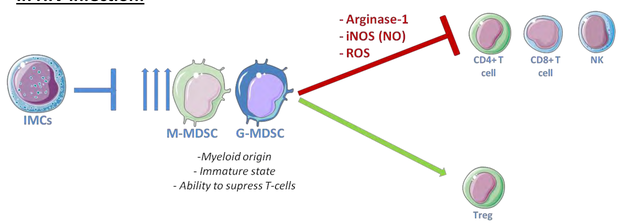
Methods. Samples from n=14 ART suppressed and n=8 heathy controls were included in this study. Frequency of two subpopulation of MDSC (CD3-, CD33+, CD11b+, HLA-DRlow), M-MDSC (CD14+) and G-MDSC (CD14-), was assessed by multiparametric flow cytometry, as well as immune activation in $CD4^+$ and $CD8^+$ T cells (markers CD38 and HLA-DR). The functional status of MDSC was assessed by the expression of Indoleamine 2,3-dioxygenase (IDO) and Arginase-1 (ARG-1). Total HIV DNA and intracellular HIV RNA were quantified by qPCR in purified $CD4^+$ T cells. P24 expression and MDSC infiltration in B cell follicles within lymph nodes of n=2 chronic infected patients was measured by immunohistochemistry.

Results. ART suppressed patients presented significantly higher proportions of M-MDSC compared to healthy controls (0.24% and 0.78 in healthy and ART-suppressed donors, respectively). Importantly, this expanded M-MDSC population showed higher expression of IDO and ARG-1 (MFI of 488 and 628 for IDO, 533 and 685 for ARG-1 in healthy controls and ART-suppressed, respectively), two enzymes highly related with the immunosuppressive capacity of the MDSC. Moreover, the percentage of MDSC in ART suppressed patients positively correlated with the activation of $CD4^+$ and $CD8^+$ T cells (rho=0.7839 p=0.0025 for $CD4^+$, and rho=0.709 p=0.0098 for $CD8^+$), which in turn correlated with intracellular HIV DNA (rho=0.6726 p=0.00331 for $CD4^+$, and rho=0.7421 and p=0.0140 for $CD8^+$) and HIV-RNA (rho=0.8778 p=0.0042 for $CD4^+$, and rho=0.8374 and p=0.0095 for $CD8^+$). Additionally, infiltration of MDSC in B cell follicles was preferentially observed in association with the expression of p24 (rho=0.4445 p=0.0056).

Conclusion. Overall, in ART-suppressed patients, MDSC might be an important player in the preservation of the HIV-reservoir. Finding new therapeutic strategies to modulate the immunosuppressive actions of the MDSC might significantly impact the HIV reservoir.

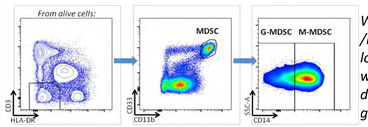
Myeloid-Derived Supressor Cells (MDSC) → *are a heterogeneous population of cells that expand during cancer, inflammation and infection, and that have a remarkable ability to suppress T-cell responses.*

In HIV infection:

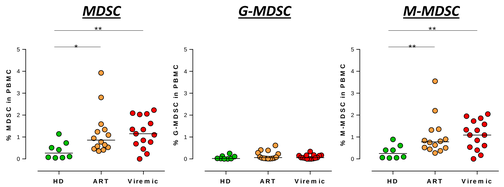


Qin A. et al. 2013 JVI
Vollbrecht T. et al. 2012 AIDS

✓ **MDSC are expanded in HIV-infected patients, even in ART suppressed patients**

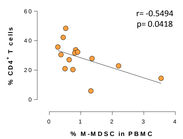


We defined MDSC as CD3-/HLA-DR- or low/CD33+/CD11b+, and we used CD14 to distinguish monocytic and granulocytic subpopulation.

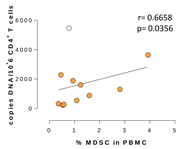


HIV infected patients present higher levels of total MDSC and monocytic MDSC (M-MDSC), even after start ART suppressive treatment. We didn't observe changes in granulocytic MDSC (G-MDSC).

CD4⁺ T cells

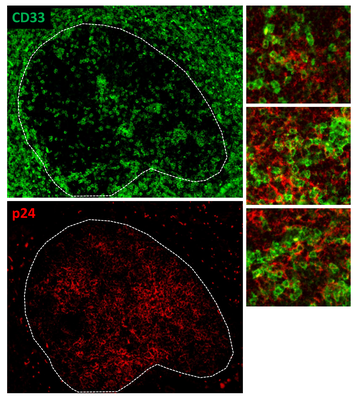


HIV-DNA



Percentage of M-MDSC negatively correlates with percentage of $CD4^+$ T cells. And total MDSC with intracellular viral DNA.

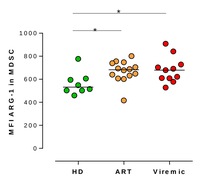
✓ **Infiltration of $CD33^+$ cells in B cells follicle is related with infection level**



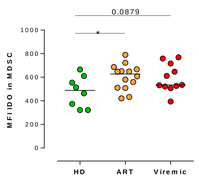
We measured the absolute number of $CD33^+$ cells in B cell follicle of human lymph node, and we correlated this with the MFI of p24 in the same follicle.

✓ **MDSC from HIV infected patients overexpress Arginase-1 and IDO**

Arginase-1



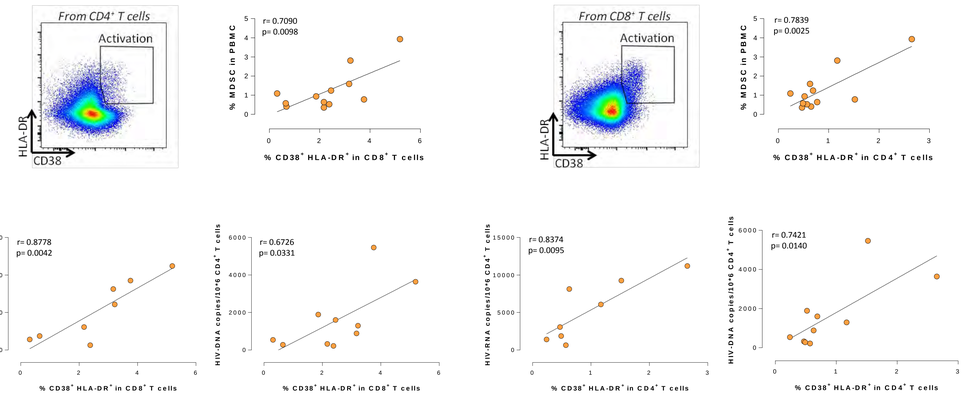
IDO



We measured by flow cytometry MFI of arginase-1 (ARG-1) and Idoleamina 2,3-dioxygenase (IDO) in MDSC. In both, viremic and ART suppressed patients an increase of MFI of both enzymes was detected.

✓ **Immune activation of T cells correlates with MDSC and intracellular HIV RNA and HIV DNA**

Immune activation in $CD8^+$ T cells



Immune activation in $CD4^+$ T cells

Immune activation in $CD4^+$ and $CD8^+$ T cells was assesed by the expression of HLA-DR and CD38. The activation of both population positively correlates with the percentage of MDSC and with the intracellular number of copies of HIV RNA and HIV DNA.

- ❖MDSC are expanded in HIV infected patients and overexpress Arginase-1 and IDO enzymes.
- ❖ Proportion of MDSC in ART suppressed patients correlates with immune activation, that at same time is related with the number of copies of HIV RNA and HIV DNA.
- ❖In human lymph node MDSC could be implicated in the infection level of B cell follicle.

Immunosuppressive activity of MDSC could participate in the maintaining of HIV reservoir

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