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Commentary

HIV vaccines: Unmasking myeloid derived suppressor cells

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Correlates of HIV control remain unknown, but several pieces of evidence point to a role of $CD8^+$ *T*-cells. To this point initial HIV vaccine strategies sought to induce broadly neutralizing antibodies, however recent approaches also aim to expand $CD4^+$ helper T-cells (**Th**) to support B- and $CD8^+$ *T*-cell development and to promote polyfunctional $CD8^+$ cytotoxic T lymphocytes (**CTLs**) that can kill reactivating cells harboring virus [1]. However, increased inflammation during HIV infection drives myeloid derived suppressor cell (**MDSC**) and T regulatory cell (**Treg**) expansion and upregulation of inhibitory molecules, resulting in decreased T-cell function and exhaustion [1]. Subsequently a barrier to an effective HIV vaccine has been immunosuppression of T-cells [2,3].

In this article of EBioMedicine, Li et al., [4] investigate the role of MDSC, Treg and immune checkpoint blockade on T-cell function during prophylactic and therapeutic DNA vaccination in a murine model of chronic HIV infection (EcoHIV). Previously [5] the authors reported amplification of anti-viral T-cell responses generated by a DNA vaccine (sPD1-$p24_{fc}$). This vaccine expressed HIV-1 Gag p24 fused to soluble PD-1 (**sPD-1**) which binds to PD-L1 and/or PD-L2 on dendritic cells (**DCs**) and blocks the inhibitory pathway, thus promoting T-cell activation. Here, the authors reveal that similar to infection in humans, EcoHIV infection results in expansion of MDSC and Treg cells and upregulation of inhibitory molecules (PD-1, Tim-3) on T-cells, resulting in decreased T-cell function and chronic infection [4]. In contrast, prophylactic DNA vaccination with sPD1-$p24_{fc}$ reduced viral burden and restored some anti-viral $CD8^+$ *T*-cell activity, however, was unable to reduce Treg and MDSC frequency, nor prevent immune exhaustion. Although this strategy was able to subvert the EcoHIV infection, the use of the sPD1-$p24_{fc}$ vaccine as a therapeutic or tandem as a prophylactic plus therapeutic was less successful. In addition, the authors demonstrate that myeloid cells, including MDSC, may harbor EcoHIV virus, and are resistant to CTL-mediated killing, thus further contributing to chronic infection. To overcome this barrier, the author's combine their prophylactic sPD1-$p24_{fc}$ vaccine, to enhance T-cell responses, and use an anti-GR-1 antibody to deplete MDSCs. This method was effective in reducing viral burden in the mice, virus in myeloid populations, and inhibitory molecules on $CD8^+$ *T*-cells. In the absence of global immunosuppression, prophylactic pre-clinical and clinical vaccine candidates generate anti-HIV T-cell responses, however many have failed to show protection [1]. Additionally, massive expansion of immunosuppressive MDSC after cART treatment interruption stifles vaccine-induced $CD8^+$ *T*-cell responses generated during chronic, albeit virally-suppressed infection [6]. Therefore, MDSC ablation during other stages of EcoHIV infection and in conjunction with a therapeutic vaccine are worth investigating.

Pre-clinical HIV models have demonstrated a role for vaccine-induced MDSCs in mitigating vaccine immunogenicity or exacerbating infection [2,7], but also in preventing initial mucosal viral spread [8]. Two phenotypic subsets of MDSCs have been characterized in cancer and viral infections, monocytic (**M-**) and granulocytic/polymorphonuclear (**G-/PMN-LIKE**) MDSCs. Both subtypes are reported to increase in people living with HIV (**PLWH**) – higher frequencies are positively associated with increased HIV viral load and lower CD4 nadir [9]. In this report, MDSC are identified by GR-1 which does not discriminate these two subsets and thus M-MDSC and G-MDSC (and potentially neutrophils) would be depleted by the anti-GR-1 antibody. As the authors report greater expansion of M-MDSC, but infection of both MDSC subsets, further investigation is needed to distinguish between the roles of M-MDSC and/or G-MDSC on T-cell immune suppression and viral persistence in this system.

This study begins to unmask the complex and Janus-like nature of MDSCs during HIV viral infection: reducing antiviral $CD8^+$ *T* cell responses or limiting $CD4^+$ proliferation and HIV viral targets. The results by Li et al., [4] further suggest the need to deplete, block or reduce MDSC activity, expansion, and/or recruitment in order to enhance T-cell responses generated by therapeutic or prophylactic HIV vaccine strategies. Beyond directly targeting $CD8^+$ *T*-cells in the context of primary vaccination/booster immunizations, the effects of regulating MDSC suppressive effects on $CD4^+$ Th/T follicular (**Tfh**) cells and various antigen presenting cells (**APCs**) should be further examined. In addition to myeloid APCs and DCs, B-cells may also present retroviral antigens – in another murine retrovirus (LP-BM5) immunodeficiency model, monocytic, but not granulocytic, MDSCs strongly inhibited antigen presentation by B-cells, in part through a

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novel checkpoint blockade ligand VISTA [10]. With single pronged HIV vaccine strategies outdated, ongoing future vaccine platforms should focus on combinatorial efforts to overcome the complex HIV immune environment.

Contributors

MAO wrote the first draft of the manuscript. MAO and WRG co-edited the manuscript.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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