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MDSC: a new player in HIV immunopathogenesis

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Myeloid-derived suppressor cells (MDSCs) were initially described more than 2 decades ago as bone marrow suppressor cells in mice with metastatic lung tumors [1]. In the past several years, there has been increasing interest in their role in cancer immune regulation [2,3]. MDSCs are a heterogeneous group of immature and progenitor myeloid cells that undergo expansion during pathologic conditions and are characterized by their strong immunosuppressive ability [4]. This is manifested as a dampening of cytotoxic reactivity of both natural and adaptive immunity, that is, natural killer (NK) and NKT cells, and CD4⁺ and CD8⁺ T cells, respectively. Unlike MDSCs in mice which can be identified using co-expression of Gr-1 and CD11b [5], a number of different markers have been used to identify this population in humans. In some cancer studies, they have been identified as lineage negative (Lin[−]) human leukocyte antigen DR expression negative (HLA-DR[−]) cells that express the common myeloid marker CD33, whereas other studies defined them as CD11b⁺CD14⁺CD15⁺ and HLA-DR[−] cells which express arginase-1 [6]. Recently Zhao *et al.* [7] described that specific members of the S100 protein family are expressed in MDSCs and that these may be useful markers in identifying this cell population. Apart from the phenotype, the mechanisms of suppression continue to be investigated. Some studies have attributed MDSC-suppressive ability to their expression of arginase-1 [8,9] and inducible nitric oxide synthetase (iNOS), whereas others point to the production of reactive oxygen species [10]. An important issue that is currently being studied is the interaction of MDSCs with other immune cells, particularly regulatory T cells (Tregs). MDSCs can induce the expansion or recruitment of Tregs, which can be an important mechanism for immune suppression [11–13].

Conflicts of interest

There are no conflicts of interest.

In this issue of *AIDS*, Vollbrecht *et al.* describe for the first time, MDSCs, identified as the CD11b⁺CD14⁻CD33⁺CD15⁺ cell population in HIV-1 infection [14]. The cross-sectional study showed elevated frequencies of MDSCs in HIV-1-infected antiretroviral therapy (ART)-naïve patients compared to healthy controls. There was a significant positive correlation, albeit modestly, to plasma HIV-1 viremia, and a modest negative correlation with CD4⁺ T-cell counts. The authors report a rapid drop in MDSC frequencies upon starting ART. The authors showed that isolated MDSCs inhibited the proliferation of Gag/Nef-stimulated CD8⁺ T cells. Moreover, the authors report a significant increase in Treg frequencies during co-incubation experiments with MDSCs, as well as a significant positive correlation with Tregs, defined as CD4⁺CD25⁺FOXP3⁺ T cells.

The role of immunoregulatory cell populations in HIV-1 infection continues to be an important field of investigation. The results from Vollbrecht *et al.*'s study show a possible deleterious effect of MDSCs as they inhibit HIV-1-induced proliferation of CD8⁺ T cells. Yet, the immunosuppressive ability of MDSCs may be beneficial in curbing the damaging effects of persistent immune activation and consequent systemic inflammation associated with chronic HIV-1 infection. However, there are several important issues that should be considered in MDSC studies in HIV-1 infection. First, similar to studies on Tregs in HIV-1 infection, an important impediment is the lack of a specific marker(s) for MDSCs. Indeed, investigations of MDSCs in various cancers have used different combinations of markers [6]. Thus, contrasting results on MDSC frequency and function in HIV-1 infection could be affected by methodological differences in MDSC identification. Second, although there were significant modest correlations between peripheral MDSCs and plasma HIV-1 viremia and CD4⁺ T-cell counts in the studies of Vollbrecht *et al.*, it will be important to evaluate MDSCs in tissues especially since it has been shown that the in-vivo suppression of MDSCs is limited to the inflammatory site [15]. Gut mucosal or lymph node specimens should be obtained to further evaluate the possible role MDSCs play in HIV-1 infection. Third, as in cancer studies, the specific mechanism of suppression that MDSCs use to inhibit HIV-1-specific immune responses, including their interaction with Tregs, should be investigated as this information will be helpful in designing HIV-1 immunotherapeutic strategies. In the same manner, these cells should be considered in the interpretation of immunotherapy studies. We have shown that the frequency of MDSCs, defined as Lin⁻HLA-DR⁻CD33⁺ cells, is markedly elevated in HIV-1-infected patients receiving a dendritic cell-based HIV-1 vaccine [16]. The lack of efficacy of some immune-based therapies and vaccines may be due to the expansion or the increased function of immunoregulatory cells [17], including MDSCs. This finding has also been recognized in the cancer vaccine field. In a phase I prophylactic trial using mucin 1 peptide antigen and polyinosinic-polycytidylic acid stabilized with polylysine and carboxymethylcellulose adjuvant in individuals at high risk for developing colorectal cancer, nonresponsiveness to the vaccine has been linked to an increase in the frequency of MDSCs [18].

With an increasing number of HIV-1 studies focusing on HIV-1-associated persistent immune activation and HIV-1 cure, the role of immunoregulatory cell populations become more important. As with Tregs, MDSCs may be important in decreasing levels of immune activation and systemic inflammation, but at the same time, may substantially inhibit the

effects of different immunotherapeutic strategies. Also, since cytotoxic T-cell responses appear important in killing reactivated cells that harbor the latent HIV-1 provirus in HIV-1 cure studies [19], dampening the effects of MDSC suppression could be vital in purging the latent HIV-1 reservoir. This possibly is noteworthy especially since histone deacetylase inhibitors, which are used to activate HIV-1 reservoirs in these studies, have been shown in murine studies to expand MDSCs [20]. As such, it is important to further define the complicated immunoregulatory network at work in HIV-1 infection. Identification of specific pathways or interactions between these immunoregulatory cells may provide the vital key to designing highly effective HIV-1 immune-based strategies.

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