Acute HIV-1 infection: targeting the regulator

Gregg Dean  NORTH CAROLINA STATE UNIVERSITY

In this issue of Blood, Jiang and colleagues describe the use of humanized rag2⁻/⁻γC⁻/⁻ mice to demonstrate the preferential infection and depletion of Tregs during acute HIV-1 infection.

The role of regulatory T cells (Tregs), phenotypically defined as CD4⁺CD25⁺FoxP3⁺, has been the subject of intense investigation with regard to HIV-1 pathogenesis. Treg numbers have been variably reported to be increased, decreased, or unchanged during HIV-1 infection. Likewise, contradictory studies have concluded Tregs to be beneficial or detrimental to the host based on correlations between clinical status and Treg number. These discrepancies are most likely multifactorial.

First, the phenotypic definition of Tregs has differed among studies and suppressor function, the gold standard assay for Tregs, has often not been demonstrated. Furthermore, studies differ in the tissues evaluated and there may be important differences in Treg percentages between blood, lymph nodes, and mucosa-associated lymphoid tissues. Undoubtedly, whether patients are being treated with antiretroviral drugs is a confounding factor but perhaps the stage of disease is more important.

It is becoming evident that whether Tregs are increased or decreased and whether that is good or bad for the host may depend on clinical stage. For instance, it could be envisioned that rapid induction of a Treg response during acute infection may blunt the antiviral immune response and permit persistent infection. On the other hand, increased Tregs during chronic infection may suppress the systemic inflammation associated with disease progression. Finally, the wild card is whether Tregs themselves are preferential targets of HIV-1 infection and a potential reservoir during chronic disease. Resolution of these questions will undoubtedly require numerous experimental approaches and systems, but in the present report, Jiang et al validate a valuable in vivo model system and begin to answer some of these critical questions.

The authors had previously reported that Tregs express the HIV-coreceptor CCR5 and are highly susceptible to HIV infection and replication. They also found that FoxP3 enhances gene expression from the HIV-1 long terminal repeat by specifically binding NF-κB. These observations were important but required corroboration in an in vivo model system. After demonstrating the presence of Tregs phenotypically and functionally in the lymphoid tissues and blood of humanized rag2⁻/⁻γC⁻/⁻ mice, the authors used a highly pathogenic CCR5/CXCR4 dual tropic HIV-1 strain to infect the mice. Tregs were preferentially and productively infected by HIV-1 and were depleted. Based on increased levels of active caspase 3 in the Treg population, Jiang et al propose the depletion is due to infection-induced apoptosis.

Myeloma research goes 3D

Diane F. Jelinek  MAYO CLINIC

In this issue of Blood, Kirshner and colleagues describe the development of an exciting 3-dimensional model system that appears to support in vitro expansion of primary human myeloma cells and provides a physiologically relevant platform on which to test the therapeutic efficacy of antimyeloma drugs.

Currently, the arsenal of experimental tools available to study the biology and drug susceptibility of primary human myeloma cells is significantly restricted by the lack of in vitro model system(s) that permits reproducible growth of primary myeloma cells, including the putative cancer stem cell compartment. Investigators in this field have long struggled with this limitation and have concluded that this experimental hurdle largely reflected the ill-defined, yet critical, dependence of primary myeloma cells on signals uniquely provided by the bone marrow microenvironment and the failure of various in vitro systems to provide this support. Indeed, it is not without coincidence that the vast majority of human myeloma cell lines established to date derive from patients who have progressed to extramedullary disease, implying that success in this arena is tied to the relative emancipation of at least a subset of primary myeloma...
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