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HIV: Current Research

Perspective

Nef-Mediated Protection of Infected Cells from Immunological Clearance

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DESCRIPTION

The long-term survival of latently HIV-infected cells is the greatest hurdle to obtain HIV cure or remission, with the latter defined as a condition in which combination Antiretroviral Treatments (cART) might be terminated without risk of viremia recrudescence. These viral reservoirs, which mostly consist of long-lived resting memory CD4+ T cells that carry integrated replication-competent HIV in a largely transcriptionally quiescent state, can reawaken at any time to create infectious virions. Those with smaller latent HIV reservoirs should be more receptive to cure, remission, and/or posttreatment virological control, therefore identifying clinical, immunological, and other reservoir size factors is a top goal.

It is now well documented that starting cART early reduces the size of the latent HIV reservoir, and that the set-point viral load and length of viral suppression on cART are further positive and negative predictors of reservoir size, respectively. Immunological factors are also involved. The homeostatic proliferation and clonal growth of latently HIV-infected CD4+ T cells have a direct impact on the size and dynamics of the latent HIV reservoir, and data suggests that early antiviral immune responses may also regulate reservoir development and persistence. A recent longitudinal investigation of an acute infection cohort found that key cytokine levels before treatment linked with HIV DNA levels after 96 weeks of cart. Furthermore, a previous analysis of the cohort studied in this study found baseline HIV-specific granzyme B responses, primarily contributed by Human Leukocyte Antigen- I (HLA-I) restricted CD8+ T cells, to be significant negative correlates of reservoir size at 48 weeks post-cART, as measured in terms of HIV proviral loads and replication-competent viral Infectious Units Per Million CD4+ T cells (IUPM).

The finding that early HIV-specific adaptive immune responses correlate with reservoir size raises the possibility that viral characteristics that aid in evasion of such responses may potentially impact reservoir creation and persistence. The HIV accessory protein Nef is an example of such a component. By downregulating cell surface HLA-A and B as well as CD4, Nef avoids host adaptive immunity. The former function allows infected cells to avoid HLA-restricted CD8+ T-cell responses, whereas the latter function allows infected cells to avoid Antibody-Dependent Cellular Cytotoxicity (ADCC) by reducing cell surface Env's ability to transit to its CD4-bound conformation, which is required for ADCC epitope exposure.

People carrying Nef sequences with a strong immune evasion function would have bigger reservoirs due to Nef-mediated protection of infected cells from immunological clearance since main Nef sequences varied in their capacity to downregulate CD4 and, in particular, HLA. The recent discovery that pharmacologic suppression of Nef improves CD8+ T-cell-mediated clearance of latently HIV-infected cells in vitro lends evidence to Nef's function in HIV reservoir maintenance. Given the worldwide genetic variety of HIV (pandemic group M strains now consist of 9 subtypes and 96 circulating recombinant forms), modulatory effects of HIV genotype/phenotype variation on latent reservoir size are possible. In support of this, a recent study found that HIV reservoir sizes in Uganda (where subtypes A and D predominate) were three times less than in the United States (where subtype B predominates), with the variations not clearly due to demographic or clinical variables. HIV subtype B Nef sequences had the greatest CD4 and HLA downregulation activities of any major group M subtype, leading to the idea that enhanced within-host Nef activity may play a critical role in the establishment of bigger reservoirs in subtype B-infected people.

The study performed HIV subtyping and assessed within-host Nef function among 30 individuals with acute/early (6 months) infection who participated in a clinical trial comparing standard and intensive cART and who had previously been assessed in detail for their clinical, immunological, and reservoir size characteristics in order to identify novel virological correlates of HIV reservoir size. The date of cART beginning, but not the first treatment regimen, was found to be a significant predictor of HIV reservoir size at 48 weeks post-cART in the original experiment. A later analysis that included all individuals, independent of treatment, found HIV-specific CD8+ granzyme B responses directed against Tat/Rev, Env, Gag, and Vif, as well as proteome-wide, to be additional negative indicators of reservoir size. Through the findings it can be identified that the HIV subtype and Nef-mediated immune evasion function as unique predictors of reservoir size in early-treated patients, hence supporting virological features as essential modulators of the HIV reservoir.

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