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γδT cells are ADCC effectors in elite HIV controllers

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Background

Elite controllers have immune responses capable of modulating HIV replication. Our goal is to understand the role for gamma/delta T cells in controlling HIV. These rare individuals maintain undetectable plasma virus loads with few or no signs of disease progression despite not using antiretroviral therapy. High frequencies of "protective" MHC haplotypes implicated Class I-restricted cytotoxic T lymphocytes as one mechanism for virus control but this cannot explain the majority of individuals who do not carry these MHC alleles. Neutralizing antibodies are generally absent among elite controllers, but serum antibodies are active in antibody-dependent cellular cytotoxicity (ADCC) against target cells decorated with HIV Env glycoprotein. ADCC requires Fc receptor-expressing, cytotoxic effector cells to mediate destruction of HIV-infected targets; the nature of ADCC effectors has not been described for elite HIV controllers.

Methods

Cellular immunology studies with PBMC from elite controllers (designated by us as natural virus suppressors) and matched uninfected controls.

Results

We noted previously (Riedel, et al., AIDS 23:1955, 2009) that elite controllers have levels of gamma/delta T cells higher than matched controls, in sharp contrast to extensive depletion of this subset expected for individuals with HIV infection and disease. The Vgamma2Vdelta2+ subset is highly activated in elite controllers; these cells express CD56, a marker for cytotoxicity, and CD16, the Fc gamma receptor IIIa that is used for ADCC. In vitro studies demonstrated potent ADCC against Env-decorated cell targets using human monoclonal antibodies with expanded gamma/delta effector cells from elite controllers.

Discussion

A distinguishing feature among elite controllers is the preservation of activated Vgamma2Vdelta2+ T cells capable of mediating ADCC. These studies encourage the development of immunotherapies to activate gamma/delta T cells, enhance the effector component of ADCC, promote virus clearance and slow disease progression. The combination of ADCC antibodies and potent effector cells corresponds to durable control of viremia and disease. Early depletion of gamma/delta T cells in HIV disease may eliminate an important subset needed for ADCC and, despite strong antibody responses, allow HIV to persist with progressing disease.

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