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Psychological distress, killer lymphocytes and disease severity in HIV/AIDS

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Abstract

Immunocellular mechanisms that account for the association between psychosocial risk factors and increased susceptibility to faster progression of HIV/AIDS are largely unknown. This study used structural equation modeling to test the hypothesis that enumerative and functional alterations in killer lymphocytes mediate the relationship between higher levels of psychological distress (defined by perceived stress, anxiety and depressive symptoms) and greater HIV disease severity (defined by HIV-1 viral load and T-helper ($CD4^+$) cell count), independent of standard demographic and various HIV-related covariates. Participants were 200 HIV-1 seropositive adults on combination antiretroviral therapy (ages 20–55 years; 67% men; 62% black; 84% AIDS). The data fit a psychoimmune model in which the significant relationship between higher distress levels and greater disease severity was mediated by diminished natural killer (NK) cell count and cytotoxic function, as well as increased cytotoxic ($CD8^+$) T-cell activation. Overall the findings indicated that the psychoimmune model accounted for 67% of the variation in HIV disease severity. In contrast, the data did not support a reverse directionality mediation model, where greater HIV disease severity predicted greater distress as a function of killer lymphocyte status. In sum, the psychoimmune associations of the final model are physiologically consistent and suggest that distress-related alterations in killer lymphocyte immunity may play a role in the biobehavioral mechanisms linked with HIV-1 pathogenesis.

Keywords: Anxiety; Cytotoxic T-cell activation; Depression; Distress; Helper T-cell; HIV/AIDS; Natural killer cell; Viral load

1. Introduction

A growing body of evidence supports an association between specific psychological variables and greater susceptibility to HIV disease progression (Cole and Kemeny, 2001; Ironson et al., 2005b; Kemeny, 2003; Leserman, 2003b). However, the immunocellular mechanisms that mediate the relationship between psychological factors and indices of HIV disease severity remain largely unknown (Kemeny, 2003; Kopnisky et al., 2004; Segerstrom and Miller, 2004; Sloan et al., 2007). HIV infects immune cells with CD4 surface receptors, primarily T-helper cells, and disease progression is signaled by a T-helper cell count decrement, an HIV viral load expansion, and the occurrence of clinical symptoms of

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immunodeficiency (Vergis and Mellors, 2000). The severity of disease is indicated by the magnitude of viral load expansion and T-helper cell count depletion, and by the type of clinical conditions that have been diagnosed (Centers for Disease Control and Prevention, 1992). In HIV spectrum disease there may be a long interval, possibly 10–20 years, between initial infection and the onset of serious immunodeficiency symptoms during which HIV viral replication is largely restrained (Vergis and Mellors, 2000). During this period of clinical latency, millions of HIV virions may be produced and eliminated by the immune system daily (Ho et al., 1995). This rather remarkable feat is accomplished, in part, by the facilitation of cytotoxic or "killer" lymphocytes, including Natural killer (NK) cells and cytotoxic ($CD8^+$) T-cells (Dines et al., 2004; Fortis and Poli, 2005; Gandhi and Walker, 2002; Levy et al., 2003; Whiteside and Herberman, 1994). Notably, poorer functional responsiveness of NK and cytotoxic T-cells has been associated with greater risk of progressive HIV immunodeficiency and mortality (Ullum et al., 1999).

Both NK and cytotoxic T-cells have the capacity to kill HIV-infected cells directly (Gandhi and Walker, 2002; Whiteside and Herberman, 1994). The NK cells, in addition to serving as the primary cytotoxic effectors of the innate immune system anti-viral response, are also instrumental in coordinating the adaptive immune system anti-viral response (Fortis and Poli, 2005; Whiteside and Herberman, 1994). The latter response may include the direct activation of cytotoxic T-cells via secretion of interferon (IFN)-γ, as well as the indirect action of soluble factors such as β-chemokines, which inhibit viral entry into T-helper cells by CCR5 coreceptor antagonism (Fortis and Poli, 2005; Kottilil et al., 2003; Levy et al., 2003; Oliva et al., 1998). As HIV disease worsens, the number of NK cells decreases along with their cytotoxic function (NKCC), whereas the cytotoxic T-cell subset undergoes an expansion that is associated with an increase in cytotoxic T-cell activation, reflected by the expression of CD38 and HLADR cell surface antigens on these cells (Cole and Kemeny, 2001; Giorgi et al., 2002, 1993; Savarino et al., 2000; Sousa et al., 2002). Therefore, both NK cells and cytotoxic T-cells may influence HIV disease severity directly, via the ability to lyse and kill HIV-infected cells, and NK cells may also influence disease severity indirectly via chemokine-mediated viral replication inhibition and cytotoxic T-cell activation.

To date, there is a paucity of information regarding the immunocellular mechanisms that may mediate the relationship between psychological factors and indices of HIV disease severity. Several different psychosocial factors have been linked to accelerated HIV disease progression, including greater subjective life stress, pessimistic cognitive appraisals about disease progression and mortality, avoidant and emotionally inexpressive (Type C) coping strategies, persistent depressive symptoms, inhibited personality characteristics, and lower perceived social support (Cole et al., 1996; Cook et al., 2004; Ickovics et al., 2001; Ironson et al., 2005a,b; Leserman et al., 2002; Reed et al., 1999; Solano et al., 2002). Studies have hypothesized that the linkage between psychological and immunological functioning is a result of a bidirectional communication between the central nervous system and immune effector cells, via sympathetic neurotransmitters, cytokines and hypothalamic–pituitary–adrenal hormones (Black, 1988; Schneiderman et al., 1999; Segerstrom and Miller, 2004). Findings from our laboratory studies of HIV-infected and seronegative persons have indicated that acute mental stress induces a mobilization of specific killer lymphocyte subsets and functions, but HIV-seropositive subjects displayed less stress-induced increase in NK cell numbers and NKCC, and greater mobilization of cytotoxic T-cells, particularly activated cytotoxic T-cells (Hurwitz et al., 2005). Assuming that these HIV serostatus response differences meaningfully reflect a disease-related difference in psychoneuroimmunological regulation, these findings would suggest that an association between greater perceived psychological distress and worsened HIV disease severity may be mediated directly or indirectly by differences in the regulation of NK and cytotoxic T-cells.

Previously, in HIV-infected but non-AIDS defined men and women, we have shown that HIV viral load moderates the relationship between psychological distress—measured by subjective perceptions of life stress, HIV/AIDS-related anxiety and depressive symptoms—and specific immunocellular subsets, namely T-helper memory cells and B-cells (Motivala et al., 2003). The present study sought to extend these findings by evaluating in AIDS-defined as well as pre-AIDS subjects the hypothesis that functional and enumerative alterations in killer lymphocytes mediate the relationship between higher levels of psychological distress and greater HIV disease severity, indexed by HIV-1 viral load and T-helper cell count. Because it is also plausible that HIV disease severity and related immunocellular alterations, such as killer lymphocyte activation and inflammatory cytokine production, can influence cognitive, affective, somatic and behavioral function (Brabers and Nonnett, 2006; Levy et al., 1989), this study also tested a reverse directionality hypothesis wherein variation in psychological distress was predicted by HIV disease-related alterations in killer lymphocytes. These hypotheses were evaluated using a structural equation modeling (SEM) approach, which controlled for numerous demographic and HIV-relevant variables.

2. Methods

2.1. Participants

Participants were drawn from the pre-intervention assessment of the Miami Selenium for Heart and Immune Health Trial (ISRCTN #22553118; Hurwitz et al., 2007). A convenience sample of HIV-1 seropositive men and women residing in Miami-Dade, Broward and Palm Beach counties of Florida were recruited between 2001 and 2005 using newspaper advertisement, flyer distribution at HIV/AIDS clinics and support groups, and physician and chain referrals. As described, the cohort