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Mechanisms, Consequences, and Treatment of Chronic Inflammation in HIV Disease

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Disease-induced activation and inflammation take a major toll on human health and are associated with premature aging and increased mortality [1,2]. In fact, some evidence suggests the increase in human lifespan over the past century may be due, at least in part, to decreased incidences of chronic inflammation caused by infectious diseases. Chronic herpes virus infections such as CMV and EBV have both been associated with increased immune activation and immunosenescence [3], and a burgeoning body of evidence indicates chronic inflammation induced by HIV disease has a similar effect [4,5]. Interestingly, increased inflammation and aging due to HIV occur even during combination antiretroviral therapy (cART)-mediated viral suppression. These findings leave us with 3 primary questions. (i) What are the long-term consequences of ongoing immune activation and inflammation? (ii) What are the underlying cause(s)? and (iii) How do we treat?

Generalized immune activation has long been recognized as a primary feature of HIV/AIDS pathogenesis [6,7]. Even before the cART era over-activation of the adaptive and innate immune systems was associated with increased disease progression and subsequent patient death. Activation and expansion of non-HIV-specific T cells is well documented, and generalized T-cell activation more effectively predicts $CD4^+$ T-cell decline and clinical disease progression than plasma viral loads [8]. Increased activation of innate dendritic and natural killer (NK) cell populations and increased soluble inflammatory mediators (TNF-α, IFN-α) are also common in progressive HIV disease, and many of these same features of chronic immune activation have been documented in pathogenic SIV-infected macaque models [9-11]. Interestingly, even in HIV patients who have effective cART-mediated viral suppression markers of chronic activation persist and life expectancy is still 10 years less than normal healthy controls. Indeed, even in virally suppressed patients, 2/3 of deaths are not AIDS-related, but rather are associated with other chronic disease states including cardiovascular diseases, non-AIDS-related cancers, and liver and kidney failure [12]. Collectively, these features link HIV-induced persistent inflammation to a premature aging phenotype, even in cART-treated patients. A key role for systemic immune activation in HIV pathogenesis is further supported by the observation that natural hosts of SIV, such as sooty mangabeys and African green monkeys, which fail to develop immunodeficiency and AIDS despite high levels of virus replication have surprisingly low levels of immune activation in chronic disease [13].

Despite investigation, the mechanism(s) of chronic immune activation are not entirely clear. However, several causes have been posited in observational studies, clinical trials and further studied in nonhuman primate (NHP) models. (i) Ongoing productive HIV replication below the limit of detection of most clinical assays could be driving immune activation [14]. In fact, HIV-infected persons with undetectable plasma viremia typically have readily detectable HIV RNA in rectal samples and using newer ultrasensitive techniques often have very low levels of detectable RNA in plasma [15]. This ongoing virus replication in sites such as the gut likely induces significant immune changes in cytokine networks, cell activation and trafficking, among others. (ii) Permanent disruption of the gastrointestinal barrier and associated gut epithelia apoptosis contributes to microbial translocation, a process whereby microbial products such as lipopolysaccharide (LPS) breach the damaged mucosal barrier and activate lymphocytes systemically [5,16]. Interestingly, although microbial translocation declines during virus-suppressive cART, it does not normalize, indicating a need to potentially treat microbial translocation directly. (iii) Early and sustained virus-induced dysregulation of $CD4^+$ Tregulatory (Tregs) cells can result in a permanently over-activated immune system due to lack of immunomodulation [17]. Indeed Tregs are both infected and depleted in HIV and SIV disease, resulting in higher levels of immune activation, but this is generally reversible with cART or by blocking Treg function in NHP models. However, the general lack of understanding of the mechanisms and consequences of chronic immune activation highlight a critical need for more research.

With the advent of cART, HIV-infected persons are living longer than ever with the eventual goal of a manageable chronic infection with a normal life span. However, as discussed herein, lentiviruses can still induce a chronic inflammatory state associated with co-morbidities and increased mortality. Therefore, future treatment of HIV/AIDS will have to include not only antivirals, but also anti-inflammation strategies. Treatment of HIV patients with COX-2 inhibitors has shown promise for decreasing inflammation, but is still in the early stages of testing [18]. Recently, a trial was performed using statins as an intervention for HIV-associated cardiovascular disease, but failed to demonstrate efficacy [19]. Other trials to directly treat inflammation in HIV patients include using rifaximin, mesalamine, and lisinopril are ongoing [20]. Alternatively, some research has focused on addressing the cause(s) of immune activation directly. One such approach aims to restore gut homeostasis and gut microflora using probiotics in conjunction with antiretroviral therapies. In a NHP model the damage and systemic effects of gut epithelial breakdown and microbial translocation were abated, at least in part, by probiotic therapy [21]. Furthermore, in small studies of untreated HIV patients, probiotics resulted in increased CD4 counts [22,23]. In conclusion, although significant progress has been made to delineate mechanisms of chronic immune activation, additional research is necessary. There also remains a critical need for the development of novel modalities to treat both the underlying causes and the long-term effects of chronic HIV-induced inflammation.

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