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REVIEW ARTICLE

AN UPDATE ON THE ROLE OF CYTOKINES IN HIV INFECTION: IMMUNOMODULATION PATHWAYS

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Abstract

HIV immune activation plays an important role in the immune pathogenesis of this disease. The mechanisms that drive this immune activation are partially defined and may be the result of multiple factors. Although the introduction of concomitant antiretroviral therapy (cART) has improved life expectancy in HIV-infected individuals, some sustained immune activation occurs in these patients when plasma HIV RNA levels are 'undetectable'. There is evidence that A better understanding of immune activation pathways should be of value in developing complementary therapies to restore the immune system in HIV-infected patients. This paper describes cytokine-mediated pathways of immune activation of her CD4 and CD8 T-cell pools during HIV infection.

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Introduction:-

HIV infection: Pathogenesis

HIV infection targets the immune system and causes immunodeficiency in an immune-stimulating environment. The molecular mechanisms driving the pathogenesis of HIV infection are not fully understood and may consist of multiple factors. The acute phase of HIV- or SIV-infected rhesus monkeys (RM) is characterized by a sharp decline in peripheral CD4 T cell numbers and a significant reduction in CD4 + CCR5 + memory T cells (Brenchley et al., 2004; Mehandru et al., 2004; Mehandru et al., 2004). al. ., 2004; Li et al., 2005; Mattapallil et al., 2005). In the chronic phase, sustained depletion of CD4 T cells coupled with continued HIV replication leads to the development of AIDS. Depletion of CD4 T cells by direct HIV infection only partially explains the depletion of the CD4 T cell pool, and various bystander mechanisms have been described as contributing to CD4+ T cell death (Haase, 1999). .

B cells, NK cells, monocytes, macrophages, and T cells (HIV and non-HIV-specific CD4 and CD8 T cells) show evidence of immune activation (Brenchley et al., 2006; van Grevenynghe et al., 2011). Specifically in the T-cell compartment, immune activation is evidenced by increased T-cell proliferation (Kovacs et al., 2001; Hazenberg et al., 2000) and increased expression of cell surface activation markers such as HLA-DR and CD38 (Kestens et al., 1994). Several studies have found that this immune activation correlates better with clinical disease progression than does CD4 T-cell counts or HIV RNA levels (Hazenberg et al., 2003), suggesting that immune activation contributes to disease pathogenesis has been hypothesized to be an important factor in Her studies of SIV infection in natural hosts, sweety monkeys (SM) and African green monkeys (AGM), have contributed to a better understanding of the

role of immune activation in retroviral infections. In these animals, primary acute infection is associated with a moderate, transient decline in peripheral blood CD4 T cells associated with severe depletion of CD4 T cells in mucosal tissues such as the gut-associated lymphoid tissue (GALT) and lungs (Gordon et al., 2007; Pandrea et al., 2007). The chronic phase of infection is characterized by low immune activation despite high viraemia. In contrast, in non-human primates (such as rhesus monkeys (RM)) that develop AIDS-like disease after SIV infection, the chronic phase of infection is similar to that seen in one HIV infection characterized by activation associated with immunity. Observed in humans (Chahroudi et al., 2012).

The introduction of concomitant antiretroviral therapy (cART) has improved life expectancy in people living with HIV. Despite plasma levels of HIV RNA being "undetectable" (generally <50 copies/mL) after initiation of therapy, accumulating data show evidence of sustained low but sustained immune activation increase. This sustained immune activation can take many forms. Its clinical importance is strongly suggested by the increased risk of all-cause mortality associated with elevated levels of soluble markers of inflammation and coagulation such as IL-6, sCD14 and D-dimer. A better understanding of the signaling pathways involved in immune activation pathways during HIV infection should aid in the development of adjunctive therapies that may put the immune system into quiescence (Kuller et al. , 2008).

HIV: T cell immune activation

Multiple forces may be responsible for destroying the immune system of HIV-infected patients. An unresolved paradox in HIV-infected patients is that both CD4 and CD8 T cells are activated, while the CD4 T cell pool is depleted and the CD8 T cell pool is expanded.

Increased activation of CD4 and CD8 T cells can be measured by in vitro and in vivo proliferation, examination of expression of nuclear antigens such as Ki67, measurement of DNA content, or labeling with DNA precursors (Sieg et al., 2005). In vitro and in vivo labeling studies in HIV-infected patients show that the expansion of both CD4 and CD8 T-cell pools is directly related to the level of HIV viremia and is significantly reduced after initiation of cART has been shown (Mohri et al., 2001). However, these previous studies did not explain selective depletion of CD4 T cells and expansion of CD8 T cells.

CD4 T cell immune activation is driven by the homeostatic response to lymphopenia as well as HIV-induced inflammation

The homeostatic response of the CD4 T-cell pool may be regulated to allow only a limited degree of expansion per individual cell to maintain repertoire diversity (Surh and Sprent, 2008; Asquith et al., 2009). Lymphopaaenic conditions, such as HIV-induced lymphopaenia, post-bone marrow transplantation, and CD4 T-cell idiopathic lymphopaenia, are associated with robust proliferation of T cells in response to elevated levels of homeostatic cytokines such as IL. There is a homeostatic response that is reflected. -7 (Malaspina et al., 2007). This process, triggered in response to changes in pool size, is thought to restore steady-state levels of CD4 T cells (Mackall et al., 1997).

HIV-induced lymphopenia: the role of interleukin 7 (IL-7)

Serum and tissue IL-7 levels during HIV-induced lymphopenia have been shown to strongly correlate with the degree of CD4 T cell depletion (Napolitano et al., 2001). IL-7 is a member of the common gamma chain (γc) family of cytokines that includes IL-2, IL-15, and others. IL-7 is present in most tissues and produced by a variety of cells including:

Fibroblastic reticular cells (FRCs) in T-cell areas of lymphoid organs. thymic, liver and intestinal epithelial cells; fibroblasts; keratinocytes; and dendritic cells (Rochman et al., 2009). Studies have shown that IL-7 plays a critical role in naive and memory T cell homeostasis by regulating survival, proliferation, and repertoire diversity (Fry et al., 2005). IL-7 is a heterodimeric IL-7 receptor (IL-7R) to transmit the signal. Binding of IL-7R by IL-7 regulates Janus kinase signaling transducers and activators of transcription (JAK-STAT) (primarily JAK1, JAK3 and STAT5), phosphatidylinositol 3-kinase (PI3K) and Src family kinase signals activates transduction pathways (Mazzucchelli and Durum, 2007).

HIV-induced lymphopenia and associated elevated IL-7 levels lead to upregulation of death receptor Fas expression in naive T cells and increased susceptibility to Fas-mediated apoptosis in CD127-expressing T cells have been suggested to play a role (Rethi et al., 2008).

A key component of CD4 T cell homeostasis is the circulation of cells through lymphoid organs where they have the opportunity to encounter cognate antigens or receive survival signals from homeostatic cytokines (Takada et al., 2009). Lymphoid organs in chronically HIV-infected patients and pathogenic SIV-infected non-human primate species show increased fibrosis, suggesting that these relationships may change in the context of HIV infection (van Grevenynghe et al., 2008). Lymphoid tissue-mediated homeostatic changes, including exposure to IL-7 and other survival signals, may be involved in the depletion of CD4 and CD8 naïve (Zeng et al., 2011) and memory (van Grevenynghe et al., 2008) T cells . It is worth noting that this process can be at least partially reversed by cART (Zeng et al., 2012).

The role of Type-I IFN and the HIV-induced inflammatory environment

Type I IFNs are a group of cytokines that exhibit antiviral and immunomodulatory properties during viral infection (Bekisz et al., 2004) [85]. Type I IFNs are also involved in immunopathogenesis in HIV infection. In vitro, plasmacytoid dendritic cells from healthy controls were induced to secrete type I IFNs by infectious or non-infectious HIV (Herbeuval et al., 2006)[86], and the primary CD4 T cell death receptor (DR5/TRAIL) may increase expression (Herbeuval et al., 2007). A type I IFN-dependent increase in the enzyme 2,3-dioxygenase (IDO) in plasmacytoid dendritic cells has been detected in lymphoid tissues of HIV-infected patients (Boasso et al., 2007).

Taken together, chronic exposure to type I IFNs may be involved in the pathogenesis of HIV infection. A role for chronic exposure to type I IFNs and immunopathogenesis in HIV infection has also been established in studies of non-pathogenic SIV infections (SM and AGM). Strong transcriptional profiles of genes associated with IFN type I signaling have been reported in chronically HIV-infected individuals. Genes involved in type I IFN signaling that have been associated with naive and memory -CD4 and -CD8 T cell subsets to understand the differential effects of HIV infection and interferon exposure on immune activation of CD4 and CD8 T cells analyzed the transcriptional profile of Both CD4 and CD8 T cells from viraemic HIV-infected individuals showed increased mRNA transcripts associated with type I IFN signaling (Rotger et al., 2011).

IFN-alpha and therapy

The introduction of cART has improved life expectancy for people living with HIV. Antiretroviral therapy can reduce plasma HIV levels below 50 copies/mL for long periods of time, but viral replication levels return to baseline within weeks after treatment is discontinued in HIV-infected patients what appears to be a paradox in the clinical management of is the antiviral activity of this cytokine when administered antitumor therapeutically. Similarly, when administered to patients with early stages of HIV infection, IFN-α exhibits a stronger antiretroviral effect than that of the first approved antiretroviral drug, zidovudine (AZT) (Tavel et al., 2010). Also noteworthy is the fact that the hepatitis C patient responds better to IFN-α in patients with less IFN-related gene activation in her pretreatment (Lempicki et al., 2006). Moreover, IFN-α may have therapeutic benefit in some her HIV-infected patients, but only in those patients who do not have high levels of her IFN-α in vivo at the start of treatment. HIV-infected patients can receive lifelong treatment for the infection. Growing data clearly support evidence of viral persistence and sustained immune activation in patients receiving antiretroviral therapy despite 'undetectable' plasma HIV levels (Buzon et al., 2010). This persistent intracellular HIV reservoir appears to be present in multiple anatomical sites, including peripheral lymphoid tissue, the gastrointestinal tract, and the central nervous system (Chomont et al., 2011).

Conclusion:-

The immune system of HIV-infected patients is characterized by immunodeficiency that occurs as part of immune activation. The CD4 T cell pool decreases while the CD8 T cell pool expands. Homeostatic cytokines such as IL-7 and pro-inflammatory cytokines such as IFN-α are elevated and may play important roles in some of the pathological aspects of HIV infection. A better understanding of the role of these and other cytokines in the development of HIV infection will not only advance our knowledge of HIV pathogenesis and treatment, but also our understanding of the role of cytokines in health and disease. .

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