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The Role of Cytokines and Cellular Receptors in the Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome

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ABSTRACT

Tuberculosis (TB) is the most prevalent opportunistic infection in patients with acquired immunodeficiency syndrome (AIDS) and the major reason for morbidity and mortality. In this review, we focus on pathological immune restoration in AIDS patients after antiretroviral therapies (ART) initiation. This manuscript discusses the importance of T cell immunity for antigen-specific immune reconstitution and the production of cytokines, which are divided into 2 subgroups: interferons (IFN), and interleukins (IL). We overview the role they play in connection between innate and adaptive immunity during immune restoration. We describe how hypercytokinemia produced by innate and adaptive immune cells, leads to the manifestations of tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) in AIDS patients during the recovery of CD4+ T cells on ART. We conclude with a brief synopsis of treatment approaches.

Immune Reconstitution Inflammatory Syndrome in AIDS Patients

Tuberculosis (TB) is the most prevalent opportunistic infection in late-stage HIV-infected individuals and the major reason for morbidity and mortality [1]. Furthermore, the risk of TB- associated IRIS remains a major clinical concern, after patients initiate antiretroviral therapy [2]. The foremost common clinical features of TB-IRIS are fever and worsening respiratory symptoms with pulmonary infiltrates, mediastinal lymphadenopathy, and pleural effusions.

Extrapulmonary TB-IRIS manifestations include acute nephropathy, intracranial tuberculomas, tuberculous meningitis, skin or visceral abscesses, osteomyelitis, epididymo-orchitis [3,4]. Rates of morbidity and mortality attributable to paradoxical tuberculosis associated IRIS is higher in resource limited settings where diagnostic and treatment options are restricted [5-8]. The manifestations of TB-IRIS occur within 3 months of ART initiation, re-initiation, or regimen change because of treatment failure. The British HIV Association has issued guidelines for starting the TB treatment with ART according to CD4+ cell count. If the CD4+ cell count is greater than 200 cells/μl, ART is started 6 months after completing TB treatment. If CD4+ cells are in the range of 100-200; ART is started 2 months after starting TB treatment. If CD4+ cell count is less than 100, both anti-tuberculosis drugs and ART can be started together [9].

Kinetics of Innate and Adaptive Immune Reconstitution in TB-IRIS

Kinetics of cytokine expression and secretion in blood and cerebrospinal fluid (CSF) during immune reconstitution in TB-AIDS patients have been described [10-12]. Peripheral blood mononuclear cells from patients co-infected with HIV and Mycobacterium tuberculosis (MTB) demonstrated increased blood levels of the innate pro-inflammatory cytokines IL1, IL6, IL8, and TNFA (tumor necrosis factor alfa) in vitro after stimulation with heat-killed MTB [13,14]. Patients with TB-IRIS have shown increased levels of IL6 and IL18 and low levels of IL27 before ART commencement, followed by the expansion of inflammatory monocyte subsets and inflammasome activation during IRIS events [15-19].

Numerous cytokines increase in plasma and serum after ART initiation, such as CRP (C- reactive protein), granulocyte-colony stimulating factor (GCSF), interleukins IL1B, IL1RA, IL6, IL8, IL18, TNFA and soluble tissue factor [20]. The foremost consistently elevated cytokines during TB-IRIS events are IL6, TNFA, and IFNG (interferon gamma) [21].

Abnormal frequencies of chemokine receptor expression on CD4+ T cells is associated with TB-IRIS. For example, an increase in CXCR3+CCR6−CD4+ T cells and a decrease in CXCR3-CCR6+CD4+ Th17 lymphocytes have been reported in TB-IRIS cases from pre-ART to 6 weeks of post-ART initiation [22]. Along with these cytokines, the pre-ART increases in plasma concentrations of IL10, monocyte chemoattractant protein 1 (MCP1/CCL2), and eotaxin render TB patients susceptible to TB-IRIS and early mortality. Thus, dyscytokinemia during immune

reconstitution created by innate and adaptive immune cells is behind IRIS symptoms [14,16].

### Recovery of T Helper Cells and TB-IRIS Events

Several studies assessed baseline and CD4+ T cell count kinetics in patients who developed IRIS and compared with those who died from other causes after ART initiation [23]. The recovery of CD4+ T cells was similar in patients who developed TB-IRIS and survived, as compared to patients with uneventful recovery on ART. In the early stages of immune restoration, CD4+ T cell memory dominated phenotype is observed in TB-IRIS patients, which confers protection against mycobacterium tuberculosis reinfection/reactivation or relapse [24-26]. IRIS patients reconstitute a higher proportion of helper CD4+ T cells during 6 months post-ART as compared to non-IRIS patients [27]. These CD4+ T cells (together with CD8+ T cells) secrete higher IFNG in response to TB antigens and many other pro-inflammatory cytokines which may lead to cytokine storm [28,29]. The assessment of CCR5 and CXCR3 expressions on T cells to investigate the role of Th1 responses in TB-IRIS, before and after ART showed that TB-IRIS patients had higher proportions of CCR5+CD4+ T cells at week 6, which also associated with high viral loads. There was also an increase in the proportion of CD4+ T cells co-expressing CCR5+ and CXCR3+ in the TB-IRIS group compared with the non-TB-IRIS group [30,31].

Cells of the Innate Immune System in IRIS

Innate immune cell types, including natural killer (NK) cells and myeloid cells, are also linked to TB-IRIS development [25,32,33]. There are major differences between the kinetics of favorable immune reconstitution and that which is accompanied with IRIS. Activation of cytotoxic NK and T cells in peripheral blood mononuclear cell population (PBMCs) from IRIS patients resulted in a higher expression of cytotoxic mediators (perforin and granzyme B) [34]. Higher NK cell degranulation capacity in IRIS patients before ART and after 2 weeks of TB treatment initiation has been reported in IRIS patients, followed by decreased expression of NK cell activating- receptors (NKp30, NKp46, NKG2D (NK group 2D)) [33]. NK cell activity is controlled by cytokines (mainly IL12, IL15, IL18, and IFNA) and by a complex repertoire of activatory and inhibitory receptors. It has been shown that NK/T cells have a unique phenotype of effector T cell receptor subunits expression, which enhances effector functionality with higher degranulation potential [35,36]. The expression of killer cell immunoglobulin-like receptors (CD158a) was higher in TB-IRIS than non-IRIS patients before ART, but the expression of NKG2D (CD314+) on NK/T cells was lower in HIV-TB patients after ART initiation [37].

The activation of the inflammasome by monocytes and macrophages may play a role in systemic inflammation via the production of nitric oxide (NO), IL1 and IL18 in patients who develop TB-IRIS after commencing ART [38-40]. Moreover, live mycobacterium tuberculosis and MTB antigens are known to activate (NOD-, LRR- and pyrin domain-containing protein 3) NLRP3 and inflammasome cascade, causing significant damage to target cells and tissues [40-42]. Thus, it is not surprising that immune activation occurs via NLR-inflammasome pathways, representing exaggerated innate cells' response toward ongoing viral replication and microbial antigens. It had been recently shown that the inflammasome pathway drives CD4+ T cell depletion in HIV infection and delayed immune reconstitution. In TB-IRIS patients with symptoms of deterioration of the central nervous system, the increased inflammasome activation may represent a peripheral biomarker of brain inflammation that crosses the blood-brain barrier [16,17,43-45]. These research reports discussed the inflammasome pathway as a driver of CD4+ T cell depletion in HIV1 infection that delayed immune reconstitution

and played a critical role in IRIS pathogenesis [46].
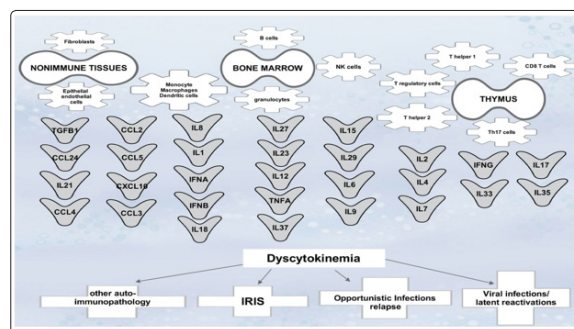
Figure 1: Dyscytokinaemia that leads to or accompanies the tuberculosis-associated immune reconstitution disorders.

Treatment Approaches to Combat IRIS

Since hypercytokinemia discussed above is a major driver of IRIS symptoms, corticosteroid therapies have demonstrated improved outcomes due to increased transcription of anti-inflammatory mediators and decreased transcription of proinflammatory cytokines and chemokines [47]. However, corticosteroids have been shown to decrease T-cell survival by enhancing apoptosis [48]. The use of prednisone to treat TB-IRIS, cut down acute symptoms in the short term [49,50]. The addition of short duration of IFNG or IFNA to prednisone treatment was useful to bring back impaired communication between innate and adaptive immune branches [51-54]. The serum concentration of cytokines such as IL10, IL12p40, IFNG, and chemokine CXCL10 decreased during 4 weeks of prednisone therapy, but increased in the placebo group, further emphasizing a pathological role for hypercytokinemia in TB-IRIS (figure 1) [47].

Neutralization of IL6 with a monoclonal antibody decreased disease pathology and extended survival in preclinical models, yet to be confirmed in phase 1 studies in humans [21]. Anti-TNF agents such as antibodies, chloroquine or thalidomide can be useful if administered with ART to prevent or treat TB-meningitis and TB-IRIS [54,55]. Other drugs such as pentoxifylline and hydroxychloroquine had also been used to treat IRIS patients, with some reported benefits [56- 58]. Leukotriene antagonist, Montelukast, has shown successful outcomes in treating steroid-refractory IRIS patients [59,60]. Leukotrienes trigger broad antimicrobial, proinflammatory effects due to leukocyte (neutrophil particularly) recruitment to sites of inflammation, and amplification systemic immune responses [61,62]. Montelukast reduces leukotriene-driven inflammatory response without creating significant immunosuppression. Formal clinical trials need to be conducted to define the success of these therapies, and assess the effectiveness and the duration of treatment required. Since M. tuberculosis infection increases CCR5+ expression on T cells and CCR5+CD4+ T cells accumulate in the lung during TB-IRIS, a CCR5 inhibitor therapy could be considered as a therapeutic strategy to prevent pulmonary TB-IRIS in HIV- infected patients when given ART.

Conclusion and future prospective

Dyscytokinemia (figure 1) plays a major role in the pathogenesis of immune reconstitution disorders [63]. Cytokines, that are produced by T, NK, NK/T cells, and innate immune cells play a profound role in managing the immune responses. As discussed above, abnormal frequencies of chemokine receptor expression, and high levels of IL6, IL10, TNFA, and IFNG represent the signature of TB-IRIS. Since hypercytokinemia is a major driver of IRIS pathogenesis, immunotherapies have shown to improved patients' symptoms.

Conflict of Interests

The authors declare no conflict of interest.

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