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Immunopathogenesis of immune reconstitution disease in HIV patients responding to antiretroviral therapy

Luc Kestens[a], **Nabila Seddiki**[b], and **Paul R. Bohjanen**[c]

[a]Immunology Unit, Department of Microbiology, Institute of Tropical Medicine, Antwerpen, Belgium

[b]National Centre For HIV Epidemiology and Clinical Research, University of New South Wales and Centre For Immunology, Darlinghurst, Australia

[c]Center for Infectious Diseases and Microbiology Translational Research, Departments of Microbiology and Medicine, University of Minnesota, Minneapolis, Minnesota, USA

Abstract

Purpose of review—The aim of this article is to review the most recent literature regarding the immunopathogenesis of pathogen-associated immune reconstitution disease and to discuss the role of immune activation and various effector molecules and cells such as macrophages, effector and regulatory T cells, and natural killer cells in immune reconstitution disease.

Recent findings—Many HIV patients receiving antiretroviral treatment develop immune reconstitution disease, which is characterized by exaggerated inflammatory immune responses to replicating or dead pathogens. In the majority of these cases, immune reconstitution disease is associated with restoration of pathogen-specific cellular immune responses involving $CD4^+$ or $CD8^+$ effector T cells. The precise conditions that trigger immune reconstitution disease have not yet been identified. Immune reconstitution disease patients have overt immune activation, which may be due to poor homeostatic control after the fast initial immune recovery in patients receiving antiretroviral therapy. Poor homeostatic control in immune reconstitution disease patients may be linked to unbalanced restoration of effector and regulatory T cells.

Summary—Although the precise mechanism of immune reconstitution disease is not well understood, it is probably related to rapid restoration of pathogen-specific immune responses and poor homeostatic control that promote exaggerated immunopathological responses, especially if viable pathogens or pathogen debris are present at high concentrations.

Keywords

antiretroviral treatment; HIV/AIDS; immune reconstitution; immunopathogenesis; IRD; IRIS

Introduction

A considerable number of HIV patients who are receiving antiretroviral therapy (ART) develop extensive inflammatory responses within the first weeks or months after starting treatment, a phenomenon referred to as immune reconstitution disease (IRD) [1]. Two distinct, but overlapping clinical scenarios of IRD are commonly seen: unmasking IRD and paradoxical IRD [2,3•]. In ‘unmasking’ IRD, patients with advanced immune suppression prior to ART

Correspondence to Professor Dr Luc Kestens, Immunology Unit, Department of Microbiology, Institute of Tropical Medicine Antwerpen, Nationalestraat 155, B-2000 Antwerpen, Belgium, Tel: +32 3247 6229; fax: +32 3247231; e-mail: lkestens@itg.be .

are unable to mount an effective immune response against the viable pathogenic organisms that are present, but improving immunity after ART allows previously unrecognized pathogens to evoke an inflammatory response (unmasking). In contrast, 'paradoxical' IRD is the clinical worsening of an infection that was previously successfully treated and is caused by exaggerated activation of the immune system against persisting antigens present as dead organisms or debris following the initiation of ART. It is currently unknown whether the 'unmasking' and 'paradoxical' forms of IRD occur via the same pathophysiological mechanisms.

IRD has been associated with a variety of mycobacterial, viral, fungal and parasitic infections [3•,4]. We currently do not know if all inflammation associated with IRD occurs via the same mechanism, regardless of the inciting pathogen, or if distinct mechanisms exist for different opportunistic pathogens.

This review focuses on the immunopathogenesis of pathogen-associated IRD whereby patients with advanced HIV experience clinical worsening due to exaggerated inflammatory responses to occult, latent, or previously treated infections. The aim of this review is to discuss the putative role of various effector molecules and immune cells such as macrophages, T cells, regulatory T cells (Tregs), and natural killer cells in IRD associated with a variety of different pathogens.

Pathogenesis of immune reconstitution disease

Although data are limited, the inflammatory response associated with IRD appears to be cellmediated and anti-gendriven [1]. The development of IRD requires advanced HIV infection with severe immune damage, improving immunity in response to ART, the presence of inciting antigens that trigger an immune response and the apparent loss of normal homeostatic control of immune responses, resulting in an overexuberant inflammatory response. The strongest predictor for the development of IRD, however, is a low $CD4^+$ T-cell count prior to starting ART [5,6]. In AIDS patients, damage to homeostatic control mechanisms [7], followed by rapid ART-associated restoration of pathogen-specific immune responses, could promote exaggerated inflammatory responses, especially if viable pathogens or pathogen debris are present at high concentrations. Nevertheless, it is intriguing that restoration of pathogen-specific immunity is uneventful in some patients but leads to severe immunopathology in others.

Immune correlates of immune reconstitution disease

The identification of laboratory markers that facilitate early recognition of IRD would be very useful either to prevent IRD, or to diagnose IRD and monitor treatment. Furthermore, they could provide a better insight in the immunopathogenesis of IRD, although their association with IRD may be indirect or even nonspecific.

Several serological indicators of IRD have been described since it was first recognized. In particular, plasma levels of the pro-inflammatory cytokine IL-6 are elevated during IRD, irrespective of the provoking pathogen and responding immune cells [1,8]. The source of IL-6 in IRD is not precisely known but it may be derived from activated macrophages [1]. We might anticipate that levels of other serum markers of inflammation, such as C-reactive protein (CRP) and other pro-inflammatory cytokines such as TNF-α), IL-1, IL-8, will also be increased in IRD but prospective studies are needed to assess their predictive value in IRD. Although increased serum levels of soluble CD30 (sCD30) have been associated with higher HIV viral loads and history of cytomegalovirus (CMV)-associated IRD [9], high sCD30 levels are probably a better indicator of ineffective ART in general than of IRD [10]. Increased levels of IFN-γ, human interferon-inducible protein 10 (IP-10) and mono-kine induced by IFN-γ (MIG) have been reported in patients who developed *Mycobacterium tuberculosis* IRD after starting ART [11]. High levels of IL-2 and IL-7 cytokines were also detected in *Mycobacterium*

avium complex (MAC) IRD patients (Seddiki *et al*., unpublished data). These two cytokines, which are known for their role in high cell turnover, may certainly play a role in the exuberant T-cell responses observed in these patients (Fig. 1).

Genetic predisposition

IRD has been associated with distinct human leucocyte antigen (HLA) profiles and regulatory cytokine gene polymorphisms. For instance, it was shown several years ago that patients with CMV retinitis or encephalitis IRD frequently carry HLA-B44 and an ancestral haplotype HLA-A2, B44, DR4 [12]. In addition, patients who have experienced herpes virus IRD rarely carry IL-12B-3'UT whereas patients with mycobacterial IRD rarely carry TNF-α-308*2 and IL-6–174*G [13]. As these alleles are linked to low cytokine production, these observations tend to confirm the role of the Th1 cytokine IL-12 in CMV IRD [14] and the role of the pro-inflammatory cytokines IL-6 and TNF-α in mycobacterial IRD. These and other genetic markers may be useful for identifying patients who have genetic susceptibility to IRD.

Role of effector T cells

T cells play important roles in host defense and immunopathology associated with mycobacterial, viral, fungal, and parasitic infections. Although IRD is often associated with $CD4^+$ Th1-mediated immunopathology, mainly mycobacterial infections, there are indications that both $CD4^+$ and $CD8^+$ effector T-cells are involved in IRD pathogenesis. Indeed, preliminary data from microarray analysis of gene expression are in support of the important role of T-cell activation in IRD pathogenesis (P.R. Bohjanen, unpublished results). We hypothesize that the effectors cells involved in IRD are similar to the effector cells that play a role in the normal immune responses to specific pathogens (Table 1) [11,14–19,20•,21–51] but, in IRD, these responses are exaggerated.

Mycobacterium tuberculosis-associated immune reconstitution disease—Most tuberculosis (TB)-IRD develops within the first 3 months of ART and can occur as 'unmasking' or 'paradoxical' IRD [52]. TB-IRD occurs during the period when redistribution of memory T cells occurs [53]. Patients with TB-IRD have restored skin test responses to TB antigens and increased numbers of TB-specific CD4 T cells [11]. These findings suggest that Th1 cells are not only important in protection and TB granuloma formation but also in TB-IRD [16,54]. Similar to TB-IRD, Th1 cells may also be involved in IRD associated with nontuberculous mycobacterial infections (Table 1).

Viral immune reconstitution disease—Most patients with viral IRD involving CMV, hepatitis B virus (HBV), hepatitis C virus (HCV), JC virus, varicella zoster virus (VZV), herpes simplex virus (HSV) and human herpes virus-8 (HHV-8) also have restored T-cell responses [34]. In viral infections, $CD8^+$ T cells in particular are involved in protection and immunopathology. These cells are probably also implicated in viral IRD associated with CMV [34], HSV and VZV [27,28], JCV [41], HHV-8 [30,32] and HBV and HCV IRD [39]. The precise contribution of the different T-cell subsets in viral IRD pathogenesis, however, is much less clear than in mycobacterial infections (Table 1). For instance, interaction between $CD4^+$ and $CD8^+$ T cells appears to be pivotal in CMV end-organ disease development [35] and both $CD4^+$ and $CD8^+$ T cells contribute to the formation of viral vesicles in HSV and VZV skin lesions [55].

Cryptococcal immune reconstitution disease—*Cryptococcus neoformans* is the fungal pathogen most commonly associated with IRD [46]. The high susceptibility of HIV-1 patients to *C. neoformans* suggests that CD4 T cells are important in protection against *C. neoformans*. Antigen-stimulated $CD4^+$ T cells produce IFN-γ that activates phagocytosis of

C. neoformans by macrophages, and $CD4^+$ T cells have a direct cytotoxic effect on C. neoformans [44]. The precise effector mechanisms involved in cryptococcal IRD are not known but it is likely that CD4 T cells and IFN-γ are involved.

Pneumocystis pneumonia immune reconstitution disease—CD8 T cells are the primary effector cells responsible for host tissue inflammatory damage in *Pneumocystis* pneumonia (PCP), and alveolar macrophages, $CD4^+$ T cells, $CD8^+$ T cells, and even γδT cells have important roles in PCP defense [47]. Recent data from animal models provide evidence that $CD4^+$ T cells, and in particular, Th2 cytokines such as IL-4, IL-5 and IL-6 contribute to respiratory disease in PCP-associated IRD, whereas CD8 T cells modulate the CD4 T-cell- and eosinophil-mediated pulmonary pathology [48,56].

Schistosome immune reconstitution disease—A few cases of IRD have been described in HIV patients co-infected with parasitic helminths such as *Schistosoma mansoni* [50]. These patients developed eosinophilia, enteritis or colonic inflammatory polyposis after antire-troviral treatment. The immunopathology of schistosomiasis is mainly linked to the granulomatous immune response around trapped eggs in host tissues [57]. HIV infection appears to reduce egg excretion [58], possibly as the result of reduced granuloma formation. ART may restore granuloma formation around trapped eggs resulting in IRD. As granuloma formation around the eggs requires functional $CD4^+$ T cells [59], it is likely that these cells play a role in schistosome IRD. Other parasitic infections such as leishmaniasis, strongyloidiasis, cryptosporidiosis and toxoplasmosis have also been associated with IRD [50].

Role of regulatory T cells

Tregs maintain homeostasisby suppressing other immune cells and thereby preventing collateral damage from inflammatory responses. The balance between allowing the immune response to clear infections and preventing immunopathology is delicate, and it is possible that IRD is the result of an unbalanced immune reconstitution of effector and regulatory T cells in patients receiving ART. In addition, Tregs could be defective in either numbers or function in maintaining homeostasis in patients with IRD. Interestingly, $CD4^+CD25^+CD127^{lo}$ $FoxP3^+$ Tregs have been found to expand significantly in HIV-1 infected patients who developed mycobacterial IRD after ART, compared with healthy controls and to HIV^+ patients who did not develop IRD (Seddiki, personal communication). Furthermore, the ratio of Tregs to effector/memory subsets was higher in IRD-patients (Seddiki *et al*. unpublished). High IL-2 levels, found in IRD patients, probably promote the survival of Tregs. The suppressive function of Tregs, however, was found to be compromised in patients with IRD, suggesting that these Tregs were unable to function efficiently (Seddiki *et al*., unpublished data). This defect was correlated with the failure of Tregs to suppress the secretion of a number of inflammatory cytokines and chemokines including IL-6, IL-4, TNF-α and IFN-γ. In contrast, IL-10 production was found to be relatively low in some patients with mycobacterial IRD, suggesting that an imbalance in inflammatory and regulatory cytokines might explain the aberrant immune responses observed (personal communication).

An interesting view on the possible role of Tregs and systemic bacterial lipopolysaccharides (LPS) in TB IRD was published recently [20•]. Subjects that do not develop IRD could have normal Tregs or have developed tolerance (anergy) to persistent LPS/tubercle antigens. In contrast, those individuals with defective Tregs or those with enormous plasma LPS could be vulnerable to IRD.

Role of natural killer cells

Natural killer cells belong to the innate immune system and have the capacity to be activated by virus-infected cells. Stimulation of natural killer cells, however, is partially dependent on cytokines produced by activated CD4 T cells such as IL-2, IFN-γ and IL-15. The activity of natural killer cells is determined by the expression of cell-surface molecules (killer immunoglobulin-like receptors; KIRs), which activate or inhibit their function. Patients with CMV IRD were indeed found to carry significantly more activating KIRs encoded by the KIR genes 3DS1 and 2DS5 than controls [36], suggesting that natural killer cells may have a role in herpes IRD.

The role of macrophages

Macrophages require intact Th1-type responses to be activated and establish immunity to chronic intracellular bacterial infections like TB and chronic intracellular parasitic infections such as leishmaniasis. Consequently, these infections are well known opportunistic infections associated with HIV. Most patients with TB-IRD have restored TB-specific CD4 T cells [11] but little is known about macrophage function in these patients. Inappropriate activation of macrophages could contribute to the immunopathogenesis of TB IRD [18,19] and *Leishmania* IRD.

Role of leukotrienes

Leukotrienes are inflammatory mediators released by mast cells. Interestingly, several cases of IRD, associated with urticarial vasculitis, secondary syphilis and tuberculosis were successfully treated with the leukotriene receptor antagonist montelukast, a drug used to treat asthma, suggesting that leukotrienes maybe involved in the immunopathogenesis of some types of IRD [60,61].

Predictors of immune reconstitution disease

Since the first cases of IRD, studies have tried to identify clinical and laboratory predictors of IRD. A low CD4 count (< 100 cells/μl) at the initiation of treatment has been identified as one of the best predictors of IRD. Other parameters, however, such as a history of more frequent opportunistic infections, higher CD8 counts and lower hemoglobin levels were also recognized as being predictors of IRD associated with MAC, CMV, MTB and *Cryptococcus* [62]. The authors suggest that the higher number of CD8 cells may reflect a higher level of immune activation. As $CD8^+$ T cells are mainly implicated in viral infections, the predictive power of CD8 T-cell count can probably be improved when used in the context of the prediction of viral IRD.

Conclusion

IRD is the result of an exaggerated cellular immune response to living or dead pathogens or debris. IRD is associated with restoration of pathogen-specific effector T cells and regulatory T cells. Tregs may be suppressed, however, by the disrupted cytokine environment because of impairment of the homeostatic control mechanisms. Apart from this fact, it is not clear which factors or combination of factors trigger IRD. These factors could be pathogenrelated (antigen load), genetic or immune related such as for instance the diversity of pathogen-specific T cells during immune restoration. Although data are still very scarce, macrophages and natural killer cells are also suspected to play a role in IRD.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 527).

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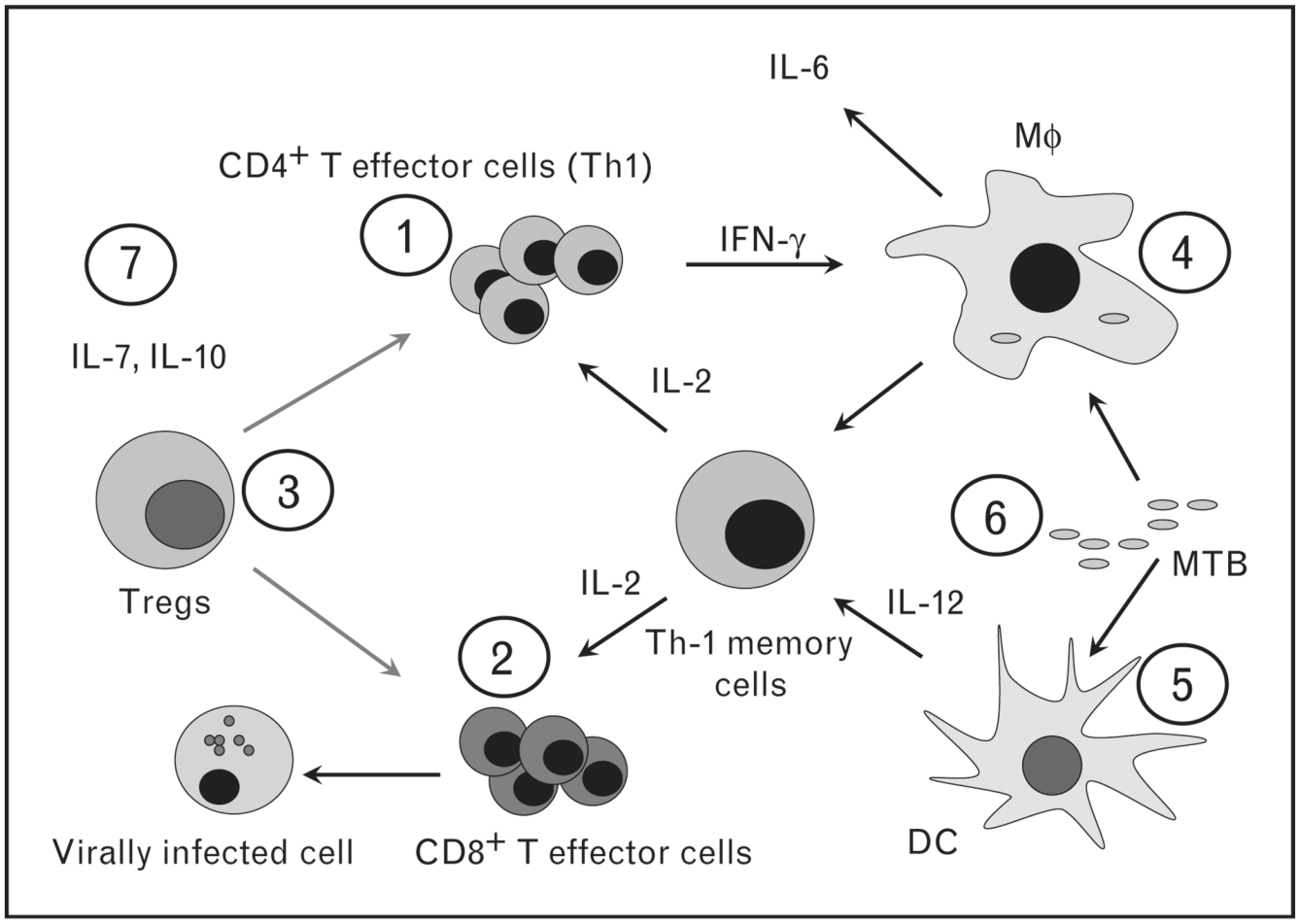

Figure 1. The immunopathogenesis of immune reconstitution disease is not precisely known but there are indications that various players are involved

CD4 T cells (1) are involved in mycobacterial and other granulomatous immune reconstitution disease (IRD) whereas $CD8^+$ T cells (2) are more frequently associated with viral IRD. IRD could be the consequence of unbalanced reconstitution of overactivated T cells and regulatory T cells (Tregs) (3). Direct activation of monocytes (4) and dendritic cells (5) during immune reconstitution, in particular by living or dead mycobac-teria or antigenic debris could be a possibility (6). Antigen load (6) during immune restoration may be a determining factor as well. Finally, the cytokine environment (7) during immune restoration, IL-7 and IL-10 in particular, both important in T-cell homeostasis, could have a pivotal role in the IRD. MTB, *Mycobacterium tuberculosis*; Mϕ, macrophage.

Table 1

Effector mechanisms in immune restoration disease

Pathogen	Immunopathology	Effector cells and cytokines	References
Bacteria			
Mycobacterium tuberculosis (MTB)	Lymphadenopathy, pulmonary manifestations, systemic inflammatory responses etc.	CD4 T cells, macrophages?, Tregs?, LPS?	[11,15–19,20•]
Mycobacterium avium complex (MAC)	Lymphadenitis, pulmonary granulomatous responses	CD4 T cells?	[21,22]
Mycobacterium leprae	Borderline disease and type 1 reactions	CD4 T cells?	[23]
Other mycobacteria	Lymphadenopathy, pulmonary manifestations,	CD4 T cells?	[24]
Viruses			
Herpes simplex virus (HSV)	Dermatological manifestations	CD8 T cells, IL-6	[25,26]
Varicella zoster virus (VZV)	Dermatological manifestations	CD8 & CD4 T cells	[27,28]
Human herpes virus 8 (HHV-8)	Kaposi sarcoma flare	CD8 T cells?, IFN-γ, TNF-α	[29–32]
Cytomegalovirus (CMV)	CMV retinitis, immune recovery uveitis	CD8 T cells, NK cells, CD4 cells (IFN-γ), IL-6 (macrophages), IL-12, Treg deficiency?	[14,33–37]
Hepatitis B virus (HBV)	Inflammatory flares and elevated liver enzymes	CD8 T cells, Tregs?	[2,38]
Hepatitis C virus (HCV)	Inflammatory flares and elevated liver enzymes	T cells, cytokines, Tregs?	[38,39]
JC virus (JCV)	Progressive multifocal leukoencephalopathy (PML)	CD8 T cells	[40–43]
Fungi			
Cryptococcus neoformans	Central nervous system cryptococcosis	CD4 T cells, IFN-γ, macrophages	[44–46]
Pneumocystis carinii	Pneumonia	CD8 T cells, CD4 T (Th2), IL-4, IL-5, IL-6	[47,48]
Parasites			
Leishmania spp.	Visceral, cutaneous and mucosal leishmaniasis, post kala-azar dermal leishmaniasis	CD4 T cells and IFN-γ?, macrophages?	[49]
Schistosoma mansoni	Colitis and polyposis, granuloma formation around eggs	CD4 T cells?	[50,51]

IL, interleukin; LPS, lipopolysaccharide; NK, natural killer; Th2, T helper type 2; TNF, tumour necrosis factor; Tregs, regulatory T cells.