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Novel Immune Regulatory Pathways and Their Role in Immune Reconstitution Syndrome in Organ Transplant Recipients with Invasive Mycoses

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Abstract

Immune regulatory pathways involving the newly discovered T regulatory (Treg) and Th17 cells are the principal targets of immunosuppressive agents employed in transplant recipients and key mediators of host inflammatory responses in fungal infections. These novel signaling pathways, in concert with or independent of Th1/Th2 responses have potentially important implications for yielding valuable insights into the pathogenesis of immune reconstitution syndrome (IRS) in transplant recipients, for aiding the diagnosis of this entity, and for achieving a balance of immune responses that enhance host immunity while curbing unfettered inflammation in IRS.

Keywords

Immune reconstitution syndrome; Fungal infections; Transplants

Introduction

Reduction or resolution of immunosuppression in immunocompromised hosts with opportunistic mycoses can trigger inflammatory reactions known as immune reconstitution syndrome (IRS) that mimic worsening disease expression [1–3]. IRS however, is often not recognized as an inflammatory entity with an immunologic basis and its occurrence is virtually always regarded as failure of therapy or relapse of infection [1]. Characterization of its biologic basis that is also poorly understood is pivotal in determining clinical or laboratory criteria that may be diagnostically useful and in devising therapeutic approaches for optimizing its management. This discussion focuses on current understanding of immune regulatory and signaling pathways that have potentially critical role in modulating inflammatory responses in IRS.

An Illustrative Case

A 52 year old renal transplant recipient presented seven months post transplant with an ulcerative skin lesion and a cavitary pulmonary mass. His immunosuppression comprised tacrolimus, mycophenolate mofetil, and prednisone. Biopsy of both lesions yielded *Cryptococcus neoformans* in culture and serum cryptococcal antigen was 1:256. A CT scan of the head and CSF analysis were unremarkable. Tacrolimus was withdrawn and prednisone dosage was reduced. Therapy with a lipid formulation of amphotericin B and 5 flucytosine was employed and converted to fluconazole 21 days later. Serum cryptococcal antigen had declined

to 1:64. Four weeks later, fever and confusion developed. An enhancing lesion in the left occipital lobe and an inguinal mass were documented. Serum cryptococcal antigen was 1:64. Biopsy of the inguinal mass showed well-formed granulomas with yeast forms visualized, but the cultures remained negative. Treatment with a lipid formulation of amphotericin B was resumed for “presumed failure of therapy” although failure was never microbiologically documented. An extensive work up failed to yield a new pathogen or an alternative etiology for the patient’s symptoms. Complete recovery eventually occurred after a protracted illness.

Discussion

This case fulfills the proposed criteria for defining IRS [1] and illustrates a complex and poorly understood entity that is becoming increasingly relevant in the management of invasive mycoses. Disease expression and outcomes in infectious diseases have typically been regarded as damage afflicted by the pathogen. Increasingly however, the host immune response is considered to play a critical role in microbial pathogenesis [4]. The tenets of “Damage Response Framework of Microbial Pathogenesis”, a conceptual paradigm that integrates host and pathogen interactions dictate that while host immunity is critical in facilitating the eradication of infection, an overly robust immune response may in fact be detrimental to the host [4]. Overzealous inflammatory responses may contribute to immune reconstitution syndrome (IRS) and poor outcomes in patients with opportunistic mycosis [1,4]. IRS associated with invasive fungal infections as been documented in diverse patient populations including, organ transplant recipients however, its pathophysiologic basis has not been fully defined [5–8].

Cytokine secreting regulatory T cells

A key mediator of immunity against pathogenic fungi are proinflammatory host responses due to adaptive T cell immunity [9,10]. Cytokine secreting T cells play a major role in the development of these antigen-specific adaptive immune responses [10,11]. Activation by cognate ligand causes precursor or naive CD4⁺ helper T cells (Th0) to differentiate into effector cells with distinct functional characteristics depending upon the cytokine milieu [12]. Historically, two major types of T helper cells, Th1 and Th2 have been recognized [9,12]. IL-12 driven differentiation through transcription factor T-Bet skews the development of Th0 cells towards Th1 [13]. These cells through production of their signature cytokine IFN- γ activate macrophages, promote NK cell induced cytotoxicity, and elicit proinflammatory responses [12]. IL-4 signal transduction by expression of GATA binding protein-3 (GATA-3) polarizes the differentiation of Th0 to Th2 cells that produce anti-inflammatory and immunosuppressive cytokines [14,15].

Thus, while inflammation is a protective antifungal host response, optimal outcomes in immunocompromised hosts with invasive mycoses are critically dependant upon achieving a fine balance between pro and anti inflammatory responses. Under activity of Th1 can result in failure to resolve infection however, inflammatory responses that ensue or continue unabated after the infection is mycologically controlled may worsen fungal disease and contribute to tissue damage [1,15]. Indeed, an imbalance characterized by an inadequate or excessive expression of either response can be detrimental to the infected host.

Th17 pathway and T regulatory cells

It has recently come to be recognized that potent inflammatory responses that were earlier considered to be due to Th1 may in fact be mediated by two completely separate lineages of T cells i.e., regulatory T cells (Tregs) and Th17 [15–20]. Emerging data show that transforming growth factor (TGF- β) depending upon the presence or absence of IL-6 can promote the differentiation of Th0 cells into two functionally distinct subsets of effector T cells [21] 22]

(Figure 1). In the presence of TGF- β , precursor T helper cells differentiate towards Tregs that are characterized by the expression of transcription factor foxhead box P3 (FoxP3), and in the presence of TGF- β and IL-6 towards Th17 cells [21–24]. FoxP3 is the master regulatory gene responsible for the function and development of Tregs [25,26]. Mice deficient in FoxP3 fail to generate CD25⁺CD4⁺ Tregs and succumb to a scruffy like inflammatory disorder [26,27]. Experimental data in animal models show that the development of Th17 and Tregs occurs in a mutually exclusive manner [16,22].

Role of Th17 and Tregs in transplant recipients with IRS

Biology and function of these cells novel immunoregulatory is gaining significant attention in the pathogenesis of a number of inflammatory diseases, anti tumor immunity, and immune disorders such as allograft rejection [15,17,18,28,29]. Th17 cells have been considered to play a role in the pathogenesis of collagen-induced arthritis, experimental allergic encephalitis, and other inflammatory conditions previously thought to be Th1-mediated [15,30]. Tregs on the other hand have anti-inflammatory characteristics and contribute to tolerance towards self and foreign antigens [26,31]. Accumulating evidence suggests that skewing of T-helper phenotype towards Th17 and Th1 is responsible for allograft rejection whereas differentiation towards Tregs and Th2 promotes graft tolerance [13,26,32–34]. Tregs have been documented in the peripheral blood of stable renal allograft recipients and within tolerated transplanted graft itself [35,36]. Indeed, induction of FoxP3 expression and generation of Tregs has been identified as a pivotal pathway in achieving enduring transplant tolerance [28,32].

Th17 pathway is also a major target of immunosuppressive agents employed in transplant recipients. Campath-1 H, a humanized CD52 antibody, antithymocyte globulin, and corticosteroids enhance FoxP3 expression and promote the development of Treg cells [37–40]. Calcineurin - inhibitor agents, tacrolimus and cyclosporine A on the other hand inhibit Tregs [41,42]. The suppressive effect of calcineurin-inhibitors on Tregs may be due to impaired IL-2 production due to these agents as IL-2 signaling is necessary for the generation and expansion of Tregs [43,44]. Rapamycin led to selective expansion of Tregs in one study [45] and neither enhancement nor inhibition of Tregs in two others [41,42]. In clinical setting, cumulative effect of an immunosuppressive regimen in transplant recipients with a functioning allograft reflects induction of tolerance by expansion and long-term maintenance of Tregs [41,42].

IRS in transplant recipients with opportunistic mycoses

Th1/Th2 responses have been recognized as important determinants of host susceptibility and outcome in medically important fungi e.g., *Candida*, *Cryptococcus*, and *Aspergillus* spp. [9, 10,46]. Depletion of Th1 enhances susceptibility to invasive fungal infections and an increase in Th2 compromises protective immunity and allows fungal pathogens to evade host defenses [47–49]. Pathogenic fungi *per se* have immunomodulatory characteristics and have the potential to inhibit Th1 while inducing Th2 response [50,51]. Emerging data now show functional activities of the Th17 pathway are a key contributor to the pathogenesis of fungal infections [20,52,53]. Th17 pathway was preferentially associated with inflammation and impaired antifungal resistance to *Candida* and *Aspergillus* [53]. In an experimental model, IL-23 and IL-17 increased the susceptibility of mice to *Candida* and *Aspergillus* infections by inhibition of protective Th1 immunity [53]. Antifungal activity of polymorphonuclear cells was inhibited even in the presence of IFN- γ suggesting that Th17 effector pathway prevailed over Th1 [53].

Treatment of fungal infections has been shown to revert host immunity towards an inflammatory phenotype [8]. It should be noted that several antifungal agents employed as therapy for fungal infections also have immunomodulatory effects. Amphotericin B

formulations, particularly amphotericin B deoxycholate promote the transcription and production of proinflammatory cytokines in murine and human immune cells [54–56]. Fungal β -D glucan through mammalian dectin-1 signaling can trigger potent inflammatory responses [57]. Echinocandins target fungal β -D glucan and therefore have the potential to modulate host immune response by altering β -D glucan surface content of the fungi [57,58].

Reversal of pathogen-induced immunosuppression, reduction or withdrawal of iatrogenic immunosuppressive agents and employment of effective antifungal therapy may be associated with a shift in immunologic repertoire towards physiologic or even pathologic proinflammatory responses leading to IRS (Figure 2). IRS in invasive fungal infections such as cryptococcosis and histoplasmosis typically presents as lymphadenitis, enhancing central nervous system lesions, and skin or soft tissue masses [1,59–61]. In a subset of patients with *Pneumocystis jiroveci* pneumonia and invasive pulmonary aspergillosis, worsening or symptomatic disease during receipt of appropriate therapy is also considered to be due to IRS [1,62,63]. There is no proven therapy for IRS. Current approaches using anti-inflammatory agents and corticosteroids as empirical treatment of symptomatic cases remain suboptimal [1].

Future prospects

Novel immune regulatory pathways involving Tregs and Th17 cells have significant implications for discerning the pathophysiologic basis of IRS. Interventions targeted to downregulate inflammation by manipulating regulatory T cells are increasingly proposed to be useful for the management of inflammatory and autoimmune disorders, for enhancement of tumor immunity, and for the establishment of transplant tolerance [15,28,64]. Experimental data show that antigen-specific Tregs expanded *in vitro* can be successfully used for the prevention and treatment of autoimmune disorders [31,64–66]. Such immunomodulatory approaches also have a potentially promising role for the treatment of IRS in opportunistic mycoses.

IRS remains a poorly understood entity and patient populations at risk for it in the current era are growing [67]. The diagnosis and management of IRS poses daunting challenges for care providers largely because its pathophysiologic basis has not been defined. Use of pharmacologic agents for the treatment of IRS such as corticosteroids that increase Tregs are associated with adverse sequelae and non-specific immunosuppressive effects [1]. Thus, investigations to assess the role of the novel immunoregulatory pathways have significant implications for optimizing outcomes in IRS associated with opportunistic mycoses not only in organ transplant recipients, but in other hosts as well.

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Figure 1.

Schematic diagram depicting T-cell differentiation. Depending upon the cytokine milieu i.e., IL-12, TGF- β plus IL-6, TGF- β or IL-4, the naive or precursor T helper cells (Th0) develop into Th1, Th17, Treg or Th2 cells, respectively via expression of their specific transcription factors T-Bet, retinoid orphan receptor (ROR) γ T, foxhead box protein (FoxP3), and GATA binding protein (GATA-3), respectively. IFN- γ and IL-17, the signature cytokines of Th1 and Th17 cells mediate proinflammatory responses whereas TGF- β , IL-10 and IL-4 production by Tregs and Th2 cells mediate anti inflammatory responses.

Figure 2.

Proposed model of immune responses leading to immune reconstitution syndrome in transplant recipients with invasive fungal infections.