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Kinetics of immune reconstitution and immune complications after cell and organ transplantation

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Abstract

In this review, we have focused on immune restoration after allogeneic hematopoietic stem cell transplantation (allo-HSCT) and solid organ transplantations (SOT). We discuss the kinetics of cytokine secretion during immune reconstitution phases that play a unique role in the connection between innate and adaptive immunity, therefore essential in normal and pathological immune reconstitution. We overview the importance of T cell immunity for antigen-specific immune reconstitution and the production of cytokines. We briefly touch upon a graft versus host disease and other immunopathology that accompany poor immune restoration after transplantation and discuss therapeutic interventions.

Abbreviation: NKG2D: Lectin-like type 2 transmembrane receptor encoded by gene Klrk1 (killer cell lectin-like receptor subfamily member 1; IRIS: Immune Reconstitution Inflammatory Syndrome

Introduction

Recent advances in solid organ and allogeneic hematopoietic stem cell transplantations (allo-HSCT) in the field of oncology have been attributed to stringent HLA matching between donors and recipients and impressive ranges of immunosuppressive therapy. However, new challenges have emerged, such as immune restoration disorders, which are represented by the unique symptomocomplexes of maladaptive recovery of the immune system. Patients eligible for transplant undergo high doses of chemo- or- radiation therapy, before transplantation, and prolonged iatrogenic immunosuppression afterward. Significant morbidity and mortality have reported in these patients due to viral infections, transplant rejection, graft versus host disease, or malignant disease relapse (Figure 1) [1]. During immune reconstitution, adequate interactions between innate and adaptive immunity are key players in maintaining the capacity to generate T cell populations that are able to control pathogens and to preserve peripheral tolerance.

Interaction between innate and adaptive immunity and immune reconstitution disorders

The fundamentals of immune system activation are complexed, they appear to begin with activation of innate phagocytic leukocytes (macrophages) by processed antigens. Activated macrophages secrete cytokines which are essential for communication between lymphocytes and macrophages, and play a unique role in macrophage M0 to M1/M2 polarization [2]. M1 type macrophages express CD86 and secrete inflammatory mediators like tumor necrosis factor-alpha (TNFA), IL1B, IL6, IL8, IL12, and IL23 [3,4]. M1 type is predominantly developed during acute infection when M0 macrophages are stimulated by cytokine interferon-gamma (IFNG), along with pathogen-associated molecular pattern molecules (PAMPs) [5]. Activated M1 macrophages concentrate to the site of infection and induce inflammation via nitric oxide (NO), reactive oxygen intermediates (ROI), and other damaging molecules. Subsequently, M1 polarizes into M2 type by IL4, IL10, IL13, and transforming growth factor-beta (TGFB), secreted by T cells. These macrophages phagocytose cellular debris to resolve inflammation and to facilitate wound healing [6,7]. M2 macrophages abundantly express mannose receptor, dectin-1, CD163, CD209, scavenger receptor A and B1, CCR2, CXCR1, and CXCR2. Additionally, M2 type exhibits different metabolic profiles: high production of ornithine and polyamines through the arginase pathway [8].

The proper switch between the M1/M2 phenotypes is important to the resolution of inflammation. It is controlled by T-helper (Th1/Th2) cells, effector T cells, and T-regulatory (Treg) cells [8-11]. However, in the settings of immunodeficiency, inappropriate macrophage polarization drives immune reconstitution pathology [12]. In the absence of IFNG signaling, macrophage activation by interferon alfa (IFN type II, IFNA) is likely to take over in T-cell- deficient patients with compromised IFNG responses [13]. IFNA displays protective anti-inflammatory functions via direct inhibition of pro-inflammatory cytokines, inductions of cytokine antagonists, or re-directing the signaling through negative feedback loops [14]. Thus, in the immunocompromised host, adjunct IFNG (IFN type II) and IFNA (IFN type I) treatments may allow the switch of the M1 polarization proinflammatory arm to the M2 polarization arm in order to control the inflammatory symptoms during post-transplantation immune reconstitution disorders.

Several animal model studies revealed that the induction of long-term allograft survival by the blockade of the CD28 and CD40 ligand T cell co-stimulation pathways is dependent on IFNG expression [15-17]. Through this mechanism IFNG limits expansion of activated T cells and facilitates long-term acceptance of transplanted organs. The pitfall, however, is that the excess of IFNG can promote vasculopathy

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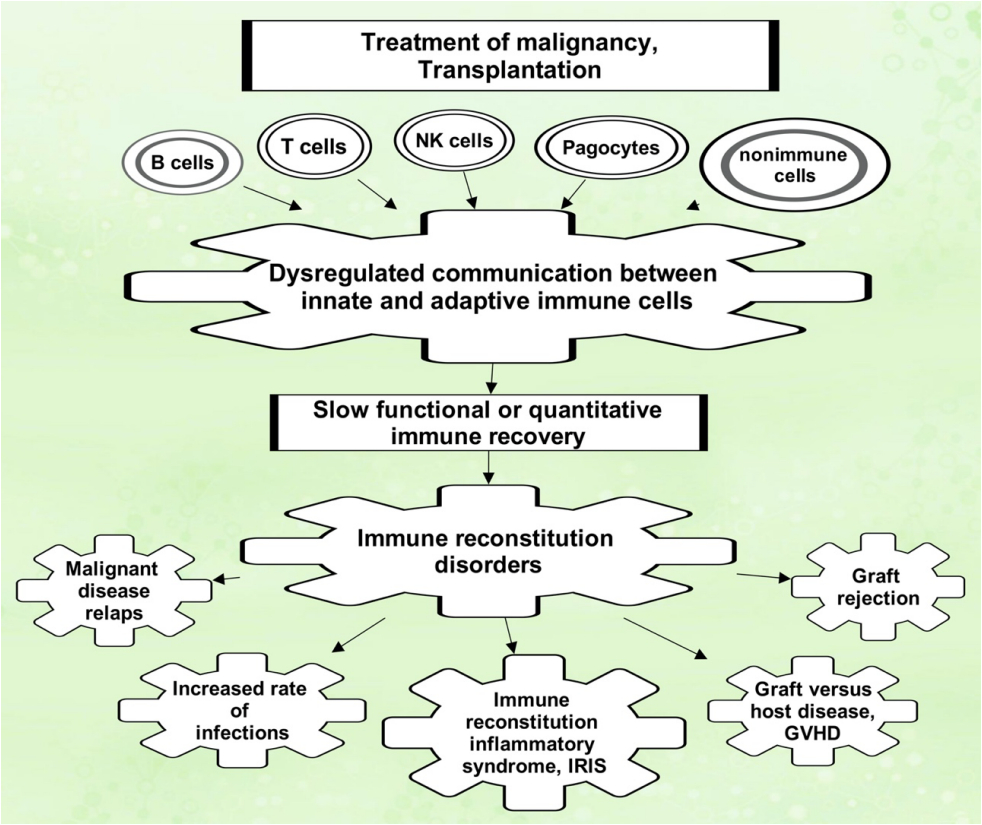

Figure 1. Immune complications after cell and organ transplantation

in solid organ recipients through immune cell activation and vascular remodeling [18,19]. Chronic rejection presents in the allograft vasculature as an immune-mediated, progressive vascular occlusion that results in ischemia and subsequent graft death [20]. Interleukin (IL33) is released from damaged or dying cells, triggers Th2-biased immune cell activation regulatory T cell and M2 macrophage expansion at the sites of graft rejection. By promoting T helper type 2 immunity, IL33 counterbalances IFNG-dominated Th type 1 immunity. It has been demonstrated that injections of IL33 reduce the formation of atherosclerotic plaques and vasculopathy, via driving the switch of a Th1 to Th2 in apolipoprotein E deficient animals [21], which suggests potential applicability of IL33 as biologics, in treating solid-organ recipients experiencing chronic allograph rejection. However, due to activation of NK cell-mediated hyper-cytotoxicity through CD95, granzymes, and perforins, IL33 usage is limited in the context of contact-dependent cardiac allograft rejection driven by abnormal IFNG production [22].

Natural killer (NK) cells are generally considered to be components of innate immune defense because they lack antigen-specific cell surface receptors [23]. NK cells have been recognized as major producers of cytokines such as IFNG in many physiological and pathological conditions [24]. NK cells also produce an array of other cytokines, both pro-inflammatory and immunosuppressive, such as TNFA and IL10, respectively. Also, they secrete growth factors such as GMCSF, GCSF, and IL3. In addition, NK cells are able to secrete chemokines, including CCL2, CCL3, CCL4, CCL5, and CXCL8 [25]. Recently, NK cells have been discovered to possess functions of an adaptive immune response. Immunological memory is a hallmark of adaptive immunity [26]. In vitro-activated NK cells (with cytokines IL12, IL15, IL18) and subsequently adoptively transferred into naïve mouse recipients have an enhanced ability to produce IFNG upon re-stimulation. These findings suggest that once activated mature NK cells may acquire stable, heritable properties that influence their behavior during subsequent infections [27]. Thus, NK cells appear to remember their past encounter with the antigens, which may be utilized as a future therapeutic strategy to combat post-transplantation immune reconstitution pathology [28,29].

Kinetics of innate and adaptive immune reconstitution in allo-HSCT recipients

Stem cell transplantation has become a lifesaving treatment for patients with immuno-hematological malignancies. For patients who undergo allo-HSCT, immune recovery is often accompanied by a high risk of infection-associated morbidity and mortality [30-38]. Allo-HSCT from HLA-matched sibling donors (MSD) generally provides the best clinical outcomes [39]. Banked umbilical cord blood (UCB) is a viable alternative for patients who don't have MSD [40].

To evaluate quantitative and qualitative immune recoveries several studies have been conducted [35,41-44]. In UCB recipients, slower T cell subset recovery with lower numbers of CD3+CD8+ (naïve and effector), CD3+CD4+ (naive and memory), and regulatory T cells were observed, than in MSD recipients, from day 60 to 1 year of observation [45]. Studies showed that sufficient IFNG production by CD4+ and CD8+ T cells toward viral antigens protects the recipients from reactivation of many latent viral diseases, particularly cytomegalovirus, CMV [46,47]. However, the rate of recovery and maturation of NK cells, and NK-driven IFNG production, did not significantly influence the occurrence of viral infections after allo-HSCT [48]. Higher frequency of viral infections and delayed immune T cell reconstitution was observed in UCB recipients [40,49-52]. It is hypothesized that

adaptive and innate immune cells synergize their effort to control latent infections in UCB stem cell transplant patients. Several studies showed rapid quantitative recovery of NK cells after transplantation, however, in the absence of thymic function and incomplete recovery of T cells, NK cells alone do not sufficiently function to combat infections unless combined with gene-modified virus-specific adaptively transferred T lymphocytes [53,54]. The excessive expansion of natural killer cells in *in vitro* assays has previously been reported to inhibit T cells' proliferation via p21 overexpression, and NKG2D-expressing NK cells exhibit cytotoxicity towards T helper cells, specifically Th17 cells [55]. However, we still need to understand *in vivo* communication between NK-, T-, and antigen-presenting cells during immune reconstitution in recipients who undergo various cellular treatment regimens [56-59].

Several studies showed that the incomplete ablation of NK cells in the graft resulted in the improvement of recipients' outcomes, but donor-recipient KIR ligand matching might be an even more efficient strategy for NK cell-mediated protection against CMV reactivation [29,60]. On the other hand, the expansion of Tregs inhibits pro-inflammatory responses in immune cells from the adaptive and innate compartments including NK cells and antigen-presenting cells (APCs) [61]. This is why *in vitro* expanded Tregs might be an attractive approach to achieve normal kinetics of immune reconstitution after transplantation [62-64]. Both options need to be further explored.

Treatment approaches for improvement of allogeneic HSCT immune recovery

It is very important for immune reconstitution that the grafts yield a sufficient amount of hematopoietic stem cells (CD34+ HSC). Mobilization of donors with granulocyte-colony stimulating factor (G-CSF) is the standard procedure for peripheral blood stem cell grafts in allo-HSCT. The addition of subcutaneous injection of drug plerixafor improves CD34+ HSC recovery from the graft, without altering the T and NK cell recovery, including Tregs cells, with anticipation to improve long-term transplant outcomes [65].

Post-transplantation, the adoptive transfer of T cells targeting the viral antigens during immune reconstitution can treat infections [66]. Adoptively transferred Epstein Barr virus (EBV) specific CD4+ and CD8+ T lymphocytes from the donor can reconstitute the patient's immune responses against EBV [54]. After allo-HSCT, cytomegalovirus (CMV)-specific T cells are used for the successful treatment of refractory CMV infections [67,68], and adenovirus-specific T cells from a donor are used for the treatment of patients with adenovirus infections [69]. Invasive fungal infections (especially aspergillosis) are another example of therapeutic applications of fungal specific T cell transfers [70]. Treatment with aspergillus-specific T cells has shown suppression of antigenemia and the prevention of invasive aspergillosis in many patients [71]. Hence, the adaptive cellular immune therapy has shown high efficacy in restoring the anti-infectious T cell immunity after allo-HSCT [72].

Many clinical studies test cytokine agonist-receptor complexes. Several studies have shown the benefit of IL15 analogs to restore immune homeostasis in transplant recipients. After allo-HSCT, immune activation was enhanced within 2 months with IL15/IL15R complexes and didn't increase the rate of adverse events [73]. Exogenous administration of IL7 has shown to boost antigen-specific T cell responses to viral infections [74]. A phase 1 clinical trial of recombinant human IL7 (hIL7) showed that CD3+, CD4+, and CD8+ counts are increased in hIL7-treated allo-HSCT recipients [75]. Hence, hIL7 carries a positive perspective for new treatment approaches to immune reconstitution disorders [59].

Kinetics of immune reconstitution and immune complications after solid organ transplantation

In solid organ transplantation (SOT), the proinflammatory responses triggered by the gradual decrease of immunosuppressive agents, but the continuation of antimicrobial and antiviral therapies are believed to be behind the development of post-transplant immune reconstitution pathology [65]. This pathology is presented in three forms; allograft rejection, graft versus host disease (GVHD), and immune reconstitution inflammatory syndrome (IRIS).

Th1 and Th17 cells are the primary mediators of allograft rejection. On the other hand, Tregs and Th2 cells promote graft tolerance [76-79]. The immunosuppressive regimens are the gold standard in transplant recipients to induce tolerance by downregulating Th1, Th17 cells, and upregulating Th2 cells, with or without Tregs expansion [80]. Combined immunosuppression with calcineurin inhibitors, mycophenolate mofetil, and steroids has emerged as a risk factor for cryptococcus (C.) neoformans-induced IRIS in adult SOT recipients. Calcineurin inhibitors like tacrolimus and cyclosporine A suppress Th1 cells and boost Th2 cell activity [81-83]. Also, they inhibit proliferation of Tregs (CD4+CD25+FoxP3+ cells) by blocking IL2 production [84,85]. By blocking IL2, immunosuppression causes a qualitative CD4+ deficiency, resembling the quantitative defect that characterizes HIV infection. Thus, the withdrawal of these anti-IL2 agents in SOT recipients could theoretically direct the balance toward pro-inflammatory responses of memory T cells, resembling the effect of CD4+ count comeback in HIV patients post ART. Moreover, calcineurin inhibitors and rapamycin inhibit Th17 cell generation [86-88]. Corticosteroids suppress Th1 cells and marginally promote Th2 cells and Tregs [89,90].

In the adult SOT population, immune reconstitution inflammatory syndrome (IRIS) has been reported as a paradoxical clinical deterioration following the initiation of antifungal regimens to combat opportunistic mycoses with a high incidence of graft failure in renal transplant recipients [91-95]. Typically, the patient shows an initial improvement, followed shortly by a deterioration similar to what was first described in HIV patients post ART [96,97]. Clinical findings of IRIS in SOT recipients are similar to those in patients with HIV with both local and systemic manifestations: painful lymphadenitis, high fever, central nervous system manifestations, and soft tissue infections [96, 98, 99]. In the adult SOT population, the C. neoformans is the pathogen most commonly associated with IRIS [91, 96]. Other reported pathogens include CMV and Mycobacterium tuberculosis [92,93].

The most significant determinant that impacts post-transplant quality of life is graft versus host disease (GVHD). In survivors of solid organ transplant, GVHD is a major cause of long-term morbidity and mortality. Contradictory evidence revealed that IL33 can either constrain or promote type 1 immune responses during GVHD [100-102]. The timing of IL33 administration and/or release may represent the crossroad that identifies the direction of immune response effectuated. IL33 infusion of recipients before the myeloablative conditioning regimens led to the expansion of populations of myeloablation resistant host Treg cells [103]. These IL33-expanded Treg cells constrained donor effector T cells to GVHD-targeted tissues and obviated GVHD [103]. When administered after allo-HSCT, IL33 inversely associated with exacerbation of acute GVHD-related lethality in mice [104]. Thus, the timing of treatment with IL33 may be beneficial for the outcomes if

the alloimmune response is driven away from the typical Th1 response towards a Th2 type immune response.

The prevention of chronic rejection of the allograft is still a preeminent challenge in SOT. Experimental and clinical data suggested a significant role for allospecific immune responses, particularly IFNG producing T cells in chronic rejection of the allograft [105-107]. The redirection of Th1 response towards Th2 immunity has been hypothesized to be a promoter for allograft survival and tolerance with less atherosclerosis [18,108,109].

Although IL33 treatment may be promising in chronic allograft rejection, it has been suggested that Th2 cytokines can promote acute graft dysfunction as both Th1 type and Th2 type cytokines are expressed in acute phase rejection [109-111]. Additionally, IL5 secreted by Th2 and eosinophils have been specifically described as potent mediators of acute graft rejection [112].

Summary

Adequate immune reconstitution after allo-HSCT or solid organ transplantation is the most important determinant for survival, as most life-threatening complications (e.g. viral infections, IRIS or GVHD) are associated with delayed immune function restoration and poor outcomes. The development of novel biotherapeutics and repurposing of existing drugs and biologics, with potentially more selective approaches for achieving the control over viral reactivations and durable graft tolerance, may in the future reduce the need for iatrogenic immune suppression post-transplantation.

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